5 November 2025
EMA/CHMP/309212/2025
Committee for Medicinal Products for Human Use (CHMP)

Austedo

International non-proprietary name: Deutetrabenazine

Procedure No. EMEA/H/C/006371/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

Abbreviation or Specialist Term	Explanation
5-HT_{2B}	5-hydroxytryptamine receptor 2B
^{14}C	Carbon-14 labelled
α-HTBZ	Alpha-dihydrotetrabenazine
β-HTBZ	Beta-dihydrotetrabenazine
ADME	Absorption, distribution, metabolism, and excretion
ADR	Adverse Drug Reaction
AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
AMPT	α-methyl-p-tyrosine
ANCOVA	Analysis of covariance
AUC	Area under the plasma concentration-time curve
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 hours postdose
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
BA	Bioavailability
BARS	Barnes Akathisia Rating Scale
BCRP	Breast Cancer Resistance Protein
BE	Bioequivalence
BSEP	Bile salt export pump
BCRP	Breast cancer resistance protein
BID	Twice daily
C-D	Carbon-deuterium bond
CDQ-24	Craniocervical Dystonia Questionnaire
C_{avg}	Average concentration
$C_{avg,ss}$	Steady-state average concentration
CGIC	Clinical Global Impression of Change
CHO	Chinese hamster ovary cells
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed plasma concentration
$C_{max,ss}$	Steady-state maximum observed plasma concentration
CMC	Carboxymethyl Cellulose
CMH	Cochran-Mantel-Haenszel
C_{min}	Minimum observed plasma concentration
$C_{min,ss}$	Steady-state minimum observed plasma concentration
COPD	Chronic Obstructive Pulmonary Disease

Abbreviation or Specialist Term	Explanation
CNS	Central nervous system
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CV	Respiratory and Cardiovascular
CYP	Cytochrome P450
DA or D	Dopamine
DART	Developmental and reproductive toxicity
DCP	Dyskinesia in Cerebral Palsy
DTBZ impurity (SD-996)	DTBZ diastereomer (SD-996); SD-996
DTBZ impurity (SD-997)	SD-997
Deuterated α-HTBZ	Deuterated Alpha-HTBZ; d_6-α-HTBZ; d_6-Alpha-HTBZ; SD-948; α-dihydrodeutetrabenazine (DHTBZ); M6 from DTBZ
Deuterated β-HTBZ	Deuterated Beta-HTBZ; d_6-β-HTBZ; d_6-Beta-HTBZ; SD-949; β-dihydrodeutetrabenazine (DHTBZ); M5 from DTBZ
Deuterated [+]-α-HTBZ	Deuterated [+]-Alpha-HTBZ; TEV-56257; SD-948-200
Deuterated [−]-α-HTBZ	Deuterated [−]-Alpha-HTBZ TEV-56260; SD-948-100
Deuterated [+]-β-HTBZ	Deuterated [+]-Beta-HTBZ; TEV-56259; SD-949-200
Deuterated [−]-β-HTBZ	Deuterated [−]-Beta-HTBZ TEV-56258; SD-949-100
Deuterated M1	Deuterated 2-methylpropanoic acid-β-HTBZ; d_6-M1; SD-1021
Deuterated M4	Deuterated monohydroxytetrabenazine; d_6-M4; SD-1018
DMSO	Dimethyl Sulfoxide
dP/dtmax	Maximum rate of change
HPLC	High-performance liquid chromatography
DDI	Drug-drug interaction
DRA	Dopamine Receptor Antagonists
DTBZ	Deutetrabenazine
EC_{50}	Half maximal effective concentration
ECGs	Electrocardiograms
ECHA	European Chemical Agency
eCTD	Electronic Comon Technical Document
EM	Extensive/intermediate metabolizers
E-R	Exposure-Response
ERA	Environmental Risk Assessment
ESS	Epworth Sleepiness Scale
ESS	Effective Sample Size
FDA	United States Food and Drug Administration
FOB	Functional Observational Battery (evaluations)
GD	Gestational day

Abbreviation or Specialist Term	Explanation
GLP	Good Laboratory Practice
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale - Anxiety Subscale (HADS-A)
HD	Huntington's Disease
HED	Human Equivalent Dose
HEK293	Human embryonic kidney cells
hERG	Human ether-à-go-go-related gene
HPBL	Human Peripheral Blood Lymphocytes
HPLC-MS/MS	High-performance liquid chromatography tandem mass spectrometry
5-HT	Serotonin
ICH	International Council on Harmonisation
IC_{50}	Half maximal inhibitory concentration
ISS	Integrated Summary of Safety
ITRS	Interactive Technology Response System
IR	Infrared
ITT	Intent-to-Treat
ITTPB	Intent-to-Treat Post-Baseline
K_i	Inhibitory constant
LC/MS	Liquid chromatography/ Mass spectrometry
LOCF	Last observation carried forward
LVP	Left ventricular pressure
M1	2-methylpropanoic acid β-HTBZ
M4	Monohydroxytetrabenazine
MAA	Marketing Authorisation Applications
MAOIs	Monoamine oxidase inhibitors
MATE	Multidrug and toxin extrusion
MCID	Minimal Clinically Important Difference
mCDQ-24	Craniocervical Dystonia Patient-Reported Questionnaire
MDCKII	Madin-darby canine kidney strain II cells
MDR1	Multidrug resistance protein 1
MEC	Molar Extinction Coefficient
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measurements
MoCA	Montreal Cognitive Assessment
MRHD	Maximum Recommended Human Dose
mITT	Modified ITT
NCA	National Competent Authority

Abbreviation or Specialist Term	Explanation
NOAEL	No Observed Adverse Effect Level
N	Number of participants
n	Number of participants in subgroups
NE	Norepinephrine
NOEL	No Observed Effect Level
Non-deuterated α-HTBZ	Non-deuterated Alpha-HTBZ; d_0-α-HTBZ; d_0-Alpha-HTBZ; SD-946; α-dihydrotetrabenazine**;** M6 from TBZ
Non-deuterated β-HTBZ	Non-deuterated Beta-HTBZ; d_0-β-HTBZ; d_0-Beta-HTBZ; SD-947; β-dihydrotetrabenazine**;** M5 from TBZ
Non-deuterated M1	Non-deuterated 2-methylpropanoic acid-β-HTBZ; d_0-M1; SD-1027
Non-deuterated M4	Non-deuterated monohydroxytetrabenazine; d_0-M4; SD-1026
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
$-OCD_3$	Trideuteromethoxy groups
$-OCH_3$	Trihydromethoxy groups
OCT	Organic cation transporter
PBT	ECHA's persistence, bioaccumulation and toxicity
PGIC	Patient Global Impression of Change
P-gp	P\ -glycoprotein
PK	Pharmacokinetic
PND	Postnatal day
PM	Poor metabolizers
PR	Prolonged release
PT	Preferred Term
QD	Once daily
QSAR	Quantitative Structure-Activity Relationship
QTcF	QT interval corrected for baseline heart rate using the Fridericia correction
SAP	Statistical Analysis Plan
SD-990	Diastereomer of TBZ
SE	Standard Error
SOC	System Organ Class
$t_{½}$	Half-life
t_{max}	Time to maximum observed drug concentration during a dosing interval
$t_{max,ss}$	Time to maximum observed drug concentration during a dosing interval at steady state
TBZ	Tetrabenazine
TBZ diastereomer (SD-990)	SD-990
TD	Tardive Dyskinesia

Abbreviation or Specialist Term	Explanation
TDRM	Total Drug Related Material
TFC score	Total Functional Capacity score
TMC score	Total Maximal Chorea score
TQT study	Thorough QT study
TS	Tourette Syndrome
VPC	Visual Predictive Check
UHPLC	Ultra high-performance liquid chromatography
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States of America
USPI	United States Prescribing Information
VMAT2	Vesicular Monoamine Transporter, Type 2

1. Background information on the procedure

1.1. Submission of the dossier

The applicant TEVA GmbH submitted on 7 March 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Austedo, through the centralised procedure under Article 3(2)(a) - New Active Substance of Regulation (EC) No 726/2004.

The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 May 2023.

The applicant initially applied for the following therapeutic indication: treatment of tardive dyskinesia in adults.

Thereafter, in the course of the procedure the applicant agreed to revise the proposed therapeutic indication to treatment of moderate to severe tardive dyskinesia in adults.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC (full mixed application) [marketing-authorisation application dossiers where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references) of Directive 2001/83/EC, as amended].

1.3. Information on paediatric requirements

Pursuant to Article 13 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0205/2023, dated 14 June 2023, on the granting of a (product-specific) waiver for deutetrabenazine tablet (EMEA-002052-PIP02-23) for the treatment of tardive dyskinesia.

The waiver applies to all subsets of the paediatric population from birth to less than 18 years of age.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance deutetrabenazine (DTBZ) contained in the above medicinal product to be considered as a new active substance (NAS), as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union (EU).

1.6. Scientific advice

The applicant did not seek scientific advice from the CHMP. Teva only requested national scientific advice from the National Competent Authorities (NCAs) of Germany, Sweden and The Netherlands for the potential Huntington's disease (HD) indication and development program, between 2016 and 2017, on the new active substance status of DTBZ and the adequacy of the non-clinical and clinical development programme to support a MAA of DTBZ for treatment of HD-associated chorea, considered relevant for the TD development programme.

In addition, Teva received FDA advice during DTBZ development programme (including the programme for the osmotic PR formulation QD).

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Fátima Ventura** Co-Rapporteur: **Alexandre Moreau**

The application was received by the EMA on	7 March 2024
The procedure started on	28 March 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	27 June 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	8 July 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 July 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 December 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	10 February 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2025
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	27 February 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 April 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	9 May 2025
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	20 May 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting	19 June 2025

a marketing authorisation to Austedo on	
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS) on	19 June 2025

1.8. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Paolo Gasparini** Co-Rapporteur: **Peter Mol**

The applicant submitted written notice to the EMA to request a re-examination of Austedo CHMP opinion of 19 June 2025 on	26 June 2025
The CHMP appointed Paolo Gasparini (IT) as Rapporteur and Peter Mol (NL) as Co-Rapporteur on	24 July 2025
The applicant submitted the detailed grounds for the re-examination on	22 August 2025
The re-examination procedure started on	23 August 2025
The CHMP Rapporteur's re-examination assessment report was circulated to all CHMP members on	22 September 2025
The CHMP Co-Rapporteur's assessment report was circulated to all CHMP members on	24 September 2025
The CHMP Rapporteur circulated the Rapporteurs' Joint Assessment Report on the detailed grounds for re-examination to all CHMP members on	8 October 2025
The detailed grounds for re-examination were presented by the applicant during an oral explanation before the CHMP on	15 October 2025
The CHMP, in light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion on the new active substance (NAS) claim and, in its final opinion, concluded that deutetrabenazine is not a NAS as claimed by the applicant on	16 October 2025
A revised opinion was adopted by the CHMP in order to improve clarity and consistency in the assessment of the applicant's grounds for re-examination.	5 November 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Tardive dyskinesia

Tardive dyskinesia (TD) is a disabling, potentially irreversible, delayed onset, hyperkinetic movement disorder in which predisposed patients experience abnormal involuntary movements resulting from chronic or even episodic exposure to dopamine receptor antagonists (DRAs), such as antipsychotics and some antiemetics.

Cessation of the DRA, reduction of the DRA to the lowest efficacious dose for controlling the underlying condition, or switching to a different DRA (e.g., from first to second-generation antipsychotic) is the first-line therapeutic approach in TD. However, these actions do not guarantee the resolution of TD and they risk compromising the stability of the underlying condition for which the DRA is being used.

There is a limited number of treatment approaches for TD, available inconsistently across the EU. These options have inherent limitations, leaving a high unmet need in this patient population for new efficacious treatments with a favourable safety profile, including not compromising the stability or control of the underlying disorder.

2.1.2. Epidemiology and risk factors

The risk of treatment-emergent TD with newer-generation antipsychotics is lower than with first generation antipsychotics which is in line with the observed global mean prevalence in adults of 30% for first-generation antipsychotics exposure versus 21% for second-generation antipsychotics exposure. Despite the decreased use of first-generation antipsychotics, the incidence of TD remains high in the antipsychotic-treated population. The steady rise in patients treated with antipsychotics may contribute to the continued high incidence and impact of TD. The symptoms of TD result in high patient burden as they are often persistent and disabling. The uncontrollable movements have a significant impact on quality of life and adversely impact emotional, professional and social well-being. Moreover, TD impacts how patients manage their underlying condition, which can interfere with effective treatment. The prevalence of TD in adults is estimated to be 21% in patients taking second-generation antipsychotics versus 30% in those exposed to first-generation antipsychotics.

2.1.3. Aetiology and pathogenesis

The mechanisms underlying the pathogenesis and pathophysiology of TD are unclear. It appears that chronic dopamine D2-receptor antagonism causes changes in striatal circuits, which leads to a state of dopaminergic hyperactivity.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The clinical manifestations of TD include chorea, dystonia, akathisia, and stereotyped behaviours generally of the tongue, lower face and jaw, and extremities (but sometimes involving the pharyngeal, diaphragmatic, or trunk muscles). TD can persist for years after discontinuation of the offending agent,

although some patients can experience partial or complete remission of symptoms a few years after discontinuation of the causative agent.

2.1.5. Management

The therapeutic goal for the treatment of TD is to reduce involuntary movements and improve quality of life. There are several treatment approaches for TD available in the EU. However, these options have inherent limitations, leaving a high unmet need in this patient population.

Cessation of the DRA, reduction of the DRA to the lowest efficacious dose for controlling the underlying condition, or switching to a different DRA (e.g., from first to second-generation antipsychotic) is the first-line therapeutic approach in TD. However, these actions do not guarantee the resolution of TD and they risk the stability of the underlying condition for which the DRA is being used, rendering this approach infeasible for many patients. Dyskinesia may even increase when the product which caused it is reduced or changed to another.

Tiapride hydrochloride, a selective dopamine D2 and D3 receptor antagonist, is an approved treatment for TD in several European countries although it has an undesirable side effect profile, including parkinsonism and hyperprolactinemia, only transient efficacy, a complicated dosing schedule, and a duration of use that is limited to only a few months. In addition, other therapies have been used off-label with varying degrees of success (amantadine, levetiracetam, piracetam, clonazepam, propranolol, vitamin B6, tetrabenazine in some countries and Ginkgo biloba).

A known therapeutic target for the treatment of TD is VMAT2 (Vesicular Monoamine Transporter, Type 2) that mediates re-uptake of dopamine and other monoamines from the cytosol into presynaptic vesicles in the terminals of dopaminergic neurons, such as in the basal ganglia. Tetrabenazine (TBZ) is a reversible VMAT2 inhibitor that is widely approved in the EU for the treatment of HD-associated chorea. TBZ is also approved for the treatment of moderate to severe TD in a small number of European countries. However, TBZ is known to have poor tolerability and requires frequent dosing, which may impact treatment adherence and persistence. Poor tolerability may also lead to suboptimal efficacy of treatment.

<u>Unmet need</u>

Considering the limitations described above, there is an unmet need for new efficacious treatment options for TD in the EU that have a favourable safety profile and that do not compromise the stability or control of the underlying disorder.

2.2. About the product

DTBZ and the major circulating metabolites (deuterated α-dihydrotetrabenazine [HTBZ] and deuterated β-HTBZ) of DTBZ, are reversible inhibitors of VMAT2, resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores. While the precise mechanism of action by which DTBZ exerts its effects in the treatment of TD is unknown, it is believed to be related to its effect as a depletor of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals.

DTBZ is structurally related to TBZ. DTBZ incorporates two trideuteromethoxy groups (-OCD3) at the 9- and 10-positions, while two trihydromethoxy groups (-OCH3) exist at the corresponding positions in TBZ.

The -OCD3 groups confer a greater resistance to enzymatic modification, resulting in a slower metabolism and an improvement of the pharmacokinetic (PK) properties of DTBZ compared to TBZ. While the incorporation of the -OCD3 groups improves the PK properties, the substitution of hydrogen by deuterium does not change the primary and secondary pharmacology. *In vitro* binding and functional studies have shown high binding affinity and functional effect of DTBZ and its deuterated metabolites α-HTBZ and β-HTBZ to the primary target VMAT2. These studies also demonstrated that the selective deuterium substitution did not alter the basic pharmacological profile of DTBZ and its deuterated metabolites compared to TBZ and its corresponding nondeuterated metabolites.

The initially claimed indication for Austedo was "Treatment of tardive dyskinesia in adults". Thereafter, within the responses to the clinical efficacy major objections (MO), the applicant agreed to restrict the therapeutic indication to *"treatment of moderate to severe tardive dyskinesia in adults",* as requested by CHMP.

Austedo dosing should be determined individually for each patient, based on adequate reduction of tardive dyskinesia symptoms and tolerability.

2.3. Type of Application and aspects on development

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as prolonged-release tablets containing 12 mg, 24 mg, 30 mg, 36 mg, 42 mg and 48 mg of deutetrabenazine as active substance.

Other ingredients of the tablet core are: butylhydroxyanisole (E 320), butylhydroxytoluene (E 321), macrogol high-molecular-mass 200K, macrogol high-molecular-mass 5000K, hypromellose 2910, sodium chloride, allura red AC (E 129), magnesium stearate, cellulose acetate, macrogol 3350, hydroxypropylcellulose.

Ingredients of colour film-coating are: poly(vinyl alcohol), titanium dioxide (E 171), macrogol 3350, talc. Colour agents for the different strengths are: for Austedo 12 mg: indigo carmine (E 132), for Austedo 24 mg: indigo carmine (E 132), allura red AC (E 129), for Austedo 30 mg: sunset yellow FCF (E 110), for Austedo 36 mg: indigo carmine (E 132), sunset yellow FCF (E 110), allura red AC (E 129), for Austedo 42 mg: sunset yellow FCF (E 110), allura red AC (E 129), for Austedo 48 mg: allura red AC (E 129).

Ingredients of the printing ink are: shellac, iron oxide black (E 172), propylene glycol.

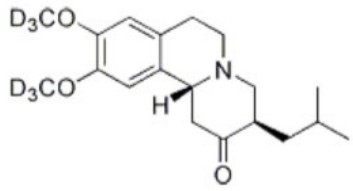
The product is available in PVC/PCTFE/PVC-Aluminium blisters as described in section 6.5 of the SmPC.

2.4.1. Active Substance

2.4.1.1. General Information

The chemical name of deutetrabenazine is (*RR*, *SS*)-1, 3, 4, 6, 7, 11b-hexahydro-9, 10-di(methoxy-d_3)-3-(2-methylpropyl)-2*H*-benzo[a]quinolizin-2-one corresponding to the molecular formula $C_{19}H_{21}D_6NO_3$. It has a molar mass of 323.462 g/mol and the following structure:

Figure 1: Active substance structure



The chemical structure of deutetrabenazine was elucidated by a combination of NMR, FTIR, MS, UV and elemental analysis. The solid-state properties of the active substance were measured by DSC, XRPD, and TGA. All results are consistent with the proposed chemical structure of deutetrabenazine.

The active substance is a white to slightly yellow crystalline powder, it is slightly hygroscopic. Deutetrabenazine is practically insoluble in water, but its solubility increases at pH values lower than its pKa (6.3). The solubility values as stated in the dissolution method development report, covering the physiological pH range in the gastrointestinal tract, are consistent with the ionization properties of the active substance.

Deutetrabenazine [(*RR*, *SS*)-configuration i.e. racemic mixture of *RR* and *SS* enantiomers] converts to the diastereomers [(*RS*, *SR*)-configuration] under acidic or basic conditions. The diastereomer is also known as related substance SD-996. Enantiomeric purity is controlled routinely by HPLC.

Polymorphism has been observed for deutetrabenazine. Deutetrabenazine has two known polymorphic forms. The polymorphism of deutetrabenazine was investigated using solvent and non-solvent-based recrystallization methods. Characterization of crystal forms produced during the screening were analysed using XRPD, TGA, DSC, moisture balance, FT-Raman spectral analysis, and FTIR.

The applicant claimed new active substance (NAS) status for deutetrabenazine based on indent 1 of the of Annex I of Chapter 1 of Volume 2A of the Notice to applicants. The CHMP evaluated the justification provided and whereas it is acknowledged that deutetrabenazine as such has not been previously authorised in the EU, it is an isotopologue of the authorised tetrabenazine. In deutetrabenazine 6 hydrogen atoms have been replaced by 6 deuterium atoms and is therefore considered a derivative of tetrabenazine. Replacement of hydrogen by deuterium (which is a naturally occurring isotope of hydrogen) does not constitute a different elemental structure compared to tetrabenazine and therefore the therapeutic moiety that patients are exposed to is considered the same. Therefore, the NAS claim for deutetrabenazine was not accepted based on its molecular structure (indent 1 of the of Annex I of Chapter 1 of Volume 2A of the Notice to applicants). A NAS claim under indent 2 is discussed further in the NAS AR.

2.4.1.2. Manufacture, process controls and characterisation

The active substance is obtained from a single manufacturer. A satisfactory QP declaration has been provided.

Deutetrabenazine is synthesized in four main steps/stages using well defined starting materials with acceptable specifications. Each stage intermediate is dried, packaged, and stored until needed for the next processing stage.

The starting materials used in manufacture of deutetrabenazine have defined chemical properties and structures and contribute significantly to the structure of deutetrabenazine. The starting materials are

separated from the final active substance at least by two synthetic steps. The adequateness of the proposed specifications for each starting material is supported by CoAs for three batches each...

Control of the critical steps and intermediates were established to ensure the identity, purity, and quality of each intermediate. Adequate in-process controls are applied during the synthesis. The batch analysis data for intermediates used for the primary finished product batches comply with the proposed specifications. The isolated intermediates underwent a stability study for 6 months at ambient temperature (3 batches for each intermediate); the stability results demonstrate there is no change after 6 months at ambient temperature.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The primary packaging material complies with Commission Regulation (EU) 10/2011, as amended.

2.4.1.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

The active substance specification includes tests for: description (visual), identification (IR, HPLC, XRPD), water content (KF), residue on ignition (Ph. Eur.), elemental impurities (Ph. Eur), related substances (HPLC), residual solvents (GC), assay (HPLC), deuterium content (1H NMR) and methyl iodide content (GC).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. The limit for genotoxic impurity methyl iodide is set below the threshold of toxicological concern according to ICH M7 and is thus considered acceptable. Limits for residual solvents are set in line with ICH Q3C, limits for elemental impurities are according to ICH Q3D.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Regarding the method for water content, even if a pharmacopoeial method has been used, the applicant should verify the method and deliver the corresponding verification data post-approval since deutetrabenazine is not monographed in Ph. Eur. (quality recommendation 2). Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on 15 batches manufactured at various scales were provided. The results are within the specifications and consistent from batch to batch.

2.4.1.4. Stability

Stability data on four commercial scale batches of the active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* description, identification, water content, related substances, assay, and deuterium content. The analytical methods used were the same as for release and are stability indicating. All tested parameters were within the specifications.

Photostability testing following the ICH guideline Q1B was performed on one batch. Changes to the active substance are not observed when the samples were wrapped in aluminium foil or packaged in bags. Therefore, the packaging materials used for deutetrabenazine active substance are adequate to protect the active substance from light.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months at room temperature in the proposed container.

2.4.2. Finished medicinal product

2 . 4 . 2 . 1 . Description of the product and Pharmaceutical Development

Austedo prolonged-release osmotic system tablets 12 mg, 24 mg, 30 mg, 36 mg, 42 mg and 48 mg are developed for once daily oral administration.

Tablets are round, bilayer, film-coated with a colour coating, a black colour printing unique to each dose strength on one side and a precise laser-drilled hole on one side.

The tablets are comprised of immediate-release and prolonged-release components that release the active substance in a controlled and sustained manner over a period of 24 hours. The core tablet consists of a swellable non-active layer and a prolonged release active layer. The release mechanism of the tablet is depicted in Figure 2 and the tablet itself in Figure 3. Uptake of water via the semi-permeable membrane swells the non-active core tablet layer, the resultant build-up of osmotic pressure slowly pushing the remaining active substance through the laser-drilled orifice.

Figure 2: Depiction of the release mechanism of the tablet

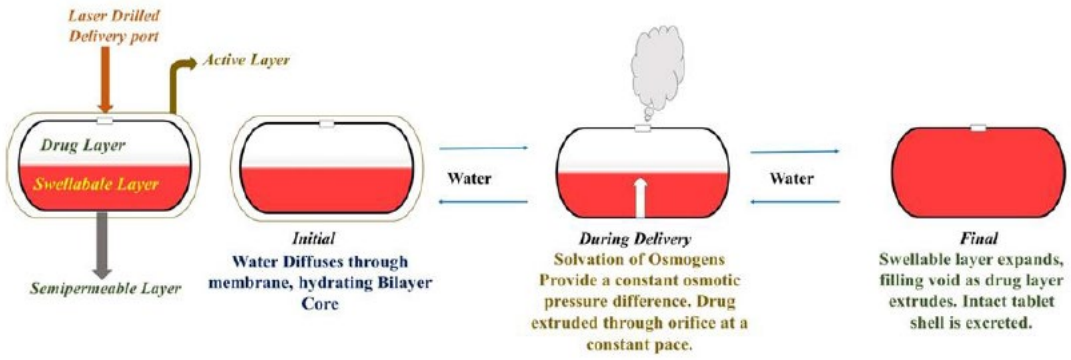
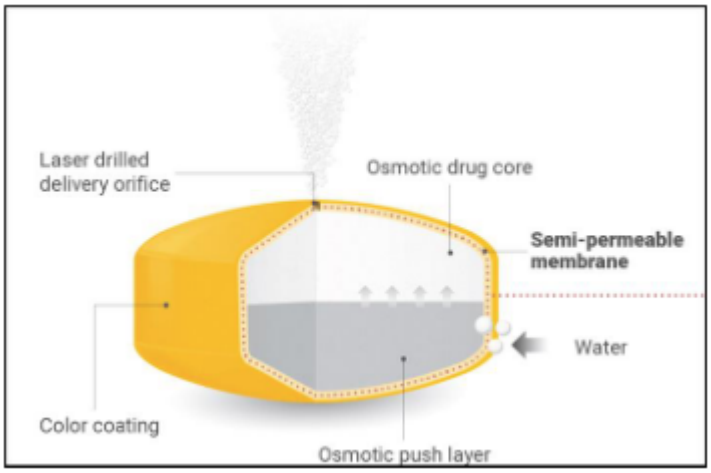


Figure 3: Schematic representation of the osmotic tablet



The composition of the Austedo prolonged-release tablets is presented, along with function of ingredients and quality reference standards, in .

The aim of pharmaceutical development was to develop a tablet that will deliver the active substance, deutetrabenazine, in a controlled manner, use safe, commonly accepted excipients that will support the manufacture of stable, homogeneous, and robust tablets and to select excipients that will enhance active substance solubility and stability.

The active substance particle size has been justified, and it is appropriately controlled.

Compatibility of the active substance and the excipients has been evaluated and proven with binary mixtures and further demonstrated by the available stability studies data.

The functions of excipients used in the finished product are well explained. All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards except the Opadry II film coating colour systems and the Opacode black imprinting ink that are tested according to in-house specifications that have been described and found acceptable. There are no novel excipients used in the finished product formulation.

Risk assessments of formulation components and formulation variables guided the studies that were conducted to evaluate the effect of excipients on finished product CQA (assay, content uniformity, dissolution and degradation products) and determine the optimized levels of excipients that led to final formulation.

The bilayer core formulation was extensively explored and studied to have a balanced combination of rate controlling polymers both in active and push layers, an osmotic agent and other excipients so that it works efficiently once a semi-permeable prolonged-release coating is applied on top of these cores. An optimized bilayer core with an optimized prolonged-release coating was one of the goals of formulation development program. The composition of each layer of the tablet was optimised.

The composition of the prolonged release coating was investigated by design of experiments (DOEs) to understand the impact of varying polymer levels on active substance release. These studies used a core tablet of composed of 100% active substance.

Further prototype batches were then manufactured. In this manner, the formulation of a tablet with the desired release profile, i.e. an immediate release component and a prolonged release component was optimised.

Five clinical bioequivalence studies were performed with prolonged-release tablets containing 6 mg (not applied for in the MAA), 12 mg, 24 mg, 36 mg, and 48 mg of deutetrabenazine, demonstrating

bioequivalence. The 30 and 42 mg tablets were compared with the 24 mg and 48 mg tablets in comparative in vitro dissolution studies in biorelevant media (pH 1.2, 4.5 and 6.8). Dissolution rates were found to be comparable (similarity factor f2 > 50) between strengths and considering the equivalent release mechanisms, the various tablet strengths are considered to bioequivalent.

No overages are used for deutetrabenazine core tablets. Overages are proposed for coating components in the immediate-release active substance coating, prolonged-release coating, seal coating and colour film as well as for colour coating suspension.

The effect of alcohol on finished product dissolution was evaluated for different strengths of deutetrabenazine prolonged-release tablets in 0.1 HCl with different concentrations of ethanol (0%; 5%; 20%; 40%). The dissolution profiles obtained reveal that there was no alcohol-induced dose dumping effect evident in any of the deutetrabenazine prolonged-release tablets evaluated.

The dissolution conditions were justified based on achieving sink conditions and low sample-to-sample variability.

In the initially submitted dossier, the CHMP considered that discriminatory power had not been adequately demonstrated resulting in a major objection. In response, the applicant explained that the discriminatory nature of the method had been investigated with respect to material attributes, formulation changes and process changes. The discriminatory power of the dissolution method was adequately demonstrated, and the major objection is resolved.

Relevant manufacturing process steps were subjected to risk assessment. The medium and high risks on finished product CQAs were identified. Several studies were then conducted to understand the effect of relevant process variables in finished product CQAs and define the optimized target and ranges of process parameters to minimize those risks.

Deutetrabenazine prolonged-release tablets are packaged in PVC/PCTFE/PVC-Aluminium blisters blister packs. The materials comply with Ph. Eur. and EC requirements. The suitability of selected container closure system is properly addressed with regard to compatibility, and protection against moisture. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

In terms of secondary packaging, the treatment initiation pack (containing Austedo 12 mg, 24 mg, 30 mg, 36 mg, 42 mg, and 48 mg prolonged-release tablets) blisters are included in wallet cards which are placed in a card box. The maintenance packs (Austedo 24 mg, 30 mg, 36 mg, 42 mg, 48 mg prolonged-release tablets), blisters are included in a card box as secondary packaging.

2.4.2.2. Manufacture of the product and process controls

The finished product is manufactured at sites for which satisfactory GMP documentation has been provided.

The manufacturing process for deutetrabenazine prolonged-release tablet consists of multiple unit operations. The process consists of manufacturing of active and inactive granules blends and compression into bilayer tablets. The further process involves the successive application of different coatings and laser drilling. Finally, the tablets are printed and packed. The process is considered to be non-standard.

The narrative description manufacturing process of deutetrabenazine prolonged-release tablets was presented for the different steps, which includes information on equipment, process parameters (target/range) and in-process controls (IPCs).

Relevant information of Critical Process Parameters (CPPs) for Austedo tablets, including acceptance criteria (target and range), description of studies conducted for their establishment and outcomes on the criticality assessment weres presented.

The list of all IPCs with acceptance criteria and reference to methods of analysis was provided. The IPCs are considered acceptable for this type of manufacturing process and pharmaceutical form.

The hold times of the different intermediates are defined. They have been established based on intermediate hold time stability studies data of primary batches and hold times used during process validation. Supportive hold time data for some intermediates were not available during the procedure. The applicant has committed to generate these data in the next production run and in case the results impact on the approved intermediate hold times, to submit a variation to amend the hold times accordingly**.** (quality recommendation 3).

Process validation was carried out on three consecutive production scale batches of 6 (strength which is not applied for in the MAA), 12 and 24 mg tablets. A validation protocol was submitted for the other strengths with formal validation planned post-approval. Since the process is non-standard, this was not considered acceptable resulting in a major objection. In response, the applicant provided validation reports for 3 consecutive production scale batches of the 30, 36, 42, and 48 mg strengths which was considered acceptable. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.4.2.3. Product specification, analytical procedures, batch analysis

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), tablet size, identification (HPLC, IR), identification for colorant titanium dioxide, identification for specific colorants (HPLC), assay (HPLC), uniformity of dosage units by content uniformity (HPLC), degradants (HPLC), BHA/BHT content (HPLC), dissolution (HPLC), water content (KF), and microbial tests (Ph. Eur.).

Skip testing is applied for identifications of colorants and for microbial tests and found acceptable.

The in-house methods used for identification of deutetrabenazine (by FTIR), identification of colorant - titanium dioxide (by chemical reaction), identification of colorant – specific colour (by HPLC), BHA and BHT content (by HPLC), identification of deutetrabenazine, assay, content Uniformity (by HPLC), degradation products (by HPLC) and dissolution (by HPLC) in the finished product are described. The full analytical validation reports are presented and support their suitability for their intended use.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The suitability of the Ph. Eur. methods for determination of microbiological contamination in the finished product has also been documented and proven. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Information provided on the four specified degradation products in the finished product is acceptable. None of these degradation products have structural alerts for mutagenicity.

With regard to presence of residual solvents in the finished product, solely class 3 solvents are used but are removed during the manufacturing process as confirmed by data collected.

The potential presence of elemental impurities in the finished product was assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

Batch analysis results were provided for three commercial scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

2.4.2.4. Stability of the product

Stability data from three commercial scale batches of each strength of finished product stored for up to 36 months (12 mg and 24 mg) respectively 18 months (30 mg, 36 mg, 42 mg and 48 mg) under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Furthermore, intermediate stability conditions (30 ºC/65% RH) were assessed for batches with attributes not meeting the stability specifications criteria under accelerated stability conditions.

Tablets were tested for: description, assay, degradants, BHA/BHT content, dissolution, water content, and microbial tests. Methods were identical to those used for release. The stability indicative nature of the HPLC methods used for assay and degradation products in the finished product has been demonstrated by the forced degradation studies.

For the 12 mg strength tablet, OOS results for degradants were observed after 6 months at 40 ºC /75% RH. However, the 12 mg tablets complied with the specification after 12 months at 30°C/65%RH and 36 months at 25 °C/60 %RH. The claimed shelf-life of 36 months with storage instruction "do not store above 30 °C" can be accepted.

For the 24 mg strength tablet, complied with the specification after 6 months at 40 °C/75% RH and 36 months at 25 °C/60% RH. The claimed shelf-life of 36 months, without special storage conditions is acceptable.

For the 30 mg, 36 mg, 42 mg and 48 mg tablet strengths, all measured parameters complied with the specifications after 6 months 40 °C/75% RH and 18 months at 25 °C/60% RH. The claimed shelf-life of 24 months without special storage conditions is acceptable in line with ICH Q1E extrapolation principles.

Holding time stability studies were performed with bulk tablets under controlled storage conditions (room temperature 15 – 30 °C and humidity NMT 70%) to reflect the real conditions during real storage and transportation of the bulk product). Bulk hold times are acceptable.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results of photostability study show that Austedo tablets are photostable.

Based on the available stability data, the proposed shelf-life of 3 years for the 24 mg strength as maintenance pack and 2 years for, 30 mg, 36 mg, 42 mg, 48 mg strengths as maintenance packs as well as for the treatment initiation pack as stated in the SmPC (section 6.3) is acceptable. The 12 mg prolonged-release tablets should not be stored above 30 °C, therefore, the treatment initiation pack (containing Austedo 12 mg, 24 mg, 30 mg, 36 mg, 42 mg, and 48 mg prolonged-release tablets) should not be stored above 30 °C. There are no special precautions for storage for maintenance packs (Austedo 24 mg, 30 mg, 36 mg, 42 mg, 48 mg prolonged-release tablets).

2.4.2.5. Adventitious agents

The only material from animal origin is the shellac glaze in Opacode Black Ink. The shellac material is derived from insects, however insects are not implicated in BSE/TSE. No other components or raw materials used in the manufacturer of deutetrabenazine prolonged-release tablets are from animal or human origin. The information provided as acceptable.

2.4.3. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Two major objections were raised on the discriminatory nature of the dissolution method and missing process validation data for 30-48 mg strengths. These were resolved by provision of additional data demonstrating that the method can discriminate between formulation and process variables, and that the manufacturing process for all strengths is sufficiently robust.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. These points are put forward and agreed as recommendations for future quality development.

2.4.4. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.5. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. A validation report for a reagent method should be provided.

2. The applicant should verify the active substance water content method and provide the corresponding verification data.

3. The applicant should perform hold time studies in the next production run and if the results impact the approved intermediate hold times, submit a variation to amend the hold times accordingly.

2.5. Non-clinical aspects

2.5.1. Introduction

DTBZ, a reversible inhibitor of the vesicular monoamine transporter type 2 (VMAT2), is proposed as once daily osmotic prolonged release (PR) formulation for the treatment of TD in adults. VMAT2 is a membrane protein that transports monoamine neurotransmitters such as dopamine from the cytosol into presynaptic vesicles. Reversible VMAT2 inhibitors decrease the uptake of monoamines into synaptic vesicles and subsequently deplete monoamine stores. The depletion of dopamine in presynaptic neurons mediates the *in vivo* efficacy of VMAT2-inhibitors in hyperkinetic movement disorders such as TD.

DTBZ is structurally related to the VMAT2 inhibitor TBZ. Deuterium is a naturally occurring, non-radioactive, stable isotope of hydrogen which, due to the presence of a neutron, has twice the mass as hydrogen. DTBZ incorporates two trideuteromethoxy groups (-OCD_3) at the 9- and 10-positions, whereas two trihydromethoxy groups (-OCH_3) exist at the corresponding positions in TBZ.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Data from competitive binding assays indicate that deuterated and non-deuterated α-HTBZ and β-HTBZ metabolites have similar binding affinities for VMAT2, with Ki values showing minimal differences, attributed to random variability. Deuterated α-HTBZ and β-HTBZ had Ki values of 3.8 nM and 22 nM, respectively, compared to 3.1 nM and 20 nM for their non-deuterated counterparts. Further assays identified the [+] enantiomers of α-HTBZ and β-HTBZ as the active moieties with significantly lower Ki and IC50 values compared to the [−] enantiomers. Follow-up functional studies confirmed these findings, showing that the [+] deuterated α-HTBZ and β-HTBZ inhibited human VMAT2 with IC50 values of 6.4 nM and 21 nM, respectively, whereas the [−] enantiomers exhibited much higher IC50 values.

Additionally, minor metabolites M1 and M4 were characterized and found to have 63-fold lower VMAT2 affinities, deeming them non-active.

Overall, DTBZ's efficacy is attributed to the [+] metabolites, despite DTBZ itself not being an active moiety due to its rapid metabolism and low clinical exposure.

The applicant did not perform *in vivo* pharmacodynamic studies with DTBZ.

Overall results from the pharmacological studies identified the deuterated metabolites [+]-α-HTBZ and [+]-β-HTBZ as the active moieties inhibiting VMAT2 and demonstrated that the substitution of hydrogen by deuterium does not change the primary or the secondary pharmacology of DTBZ relative to that of TBZ.

TBZ demonstrated efficacy in several published pharmacological animal studies, particularly in the context of monoamine depletion. By inhibiting VMAT2, TBZ reduces the loading of dopamine (DA) into presynaptic vesicles, thereby modulating dopaminergic transmission. Pettibone et al (1984) demonstrated that the peripheral administration of TBZ (2 mg/kg) to rats caused reductions in levels of DA, norepinephrine (NE) and serotonin (5-HT). These reductions were near maximal at 15 minutes post dose and lasted at least two hours after TBZ administration. Among the three monoamines, DA was particularly sensitive to TBZ, with levels in the striatum and hypothalamus decreasing by 70-75% shortly after administration, indicating a strong impact on this monoamine. In contrast, hypothalamic NE demonstrated relative resistance, with reductions not exceeding 25%, even at higher doses of TBZ,

suggesting regional differences in sensitivity. The depletion of NE and 5-HT occurred to a similar extent across various brain regions, but the timing and dosage of TBZ administration significantly influenced the degree of depletion. Mehvar et al (1986) also demonstrated the in-vivo efficacy of TBZ on monoamine depletion. Their study showed that TBZ, administered via intraperitoneal injection to rats at 3 mg/kg, along with its major metabolite, HTBZ, significantly reduced monoamine levels. This effect was more pronounced on DA compared to NE and 5-HT. The pharmacologic effects of TBZ peaked within 0.5 hours post-administration, and while DA levels tended to be higher than baseline 12 hours after injection, the other monoamines returned to baseline levels within 5 hours. The study also highlighted that the monoamine-depleting activity of TBZ is closely related to the higher serum and brain concentrations of its metabolite, suggesting that the effects observed after TBZ administration are primarily due to the formation of HTBZ rather than the parent drug itself.

2.5.2.2. Secondary pharmacodynamic studies

The secondary pharmacology screen for the deuterated forms of α-HTBZ and β-HTBZ showed no substantial activation of secondary targets, except for binding to Sigma and serotonin 5-HT7 receptors, which exhibited an antagonistic effect for deuterated [-]-HTBZ metabolites. DTBZ administered within the recommended clinical dose range resulted in clinical exposure levels of both deuterated α-HTBZ and β-HTBZ that are insufficient to significantly engage the sigma receptors. The IC50 values for binding of deuterated α-HTBZ and β--HTBZ metabolites to the sigma receptor exceed the clinical exposure by 25-fold and 4-fold, respectively, at the highest clinical dose (based on the Maximum observed plasma concentration [Cmax) free fraction]. The 5-HT7 receptor, a G-protein coupled serotonin receptor, plays roles in mood regulation, circadian rhythm, and cognition. While 5-HT7 antagonism has shown antidepressant and anxiolytic effects in animal models, no approved drugs selectively target this receptor. However, the clinical implications of selective 5-HT7 inhibition remain uncertain, requiring further research. The off-target binding activities of the deuterated α-HTBZ and β-HTBZ did not differ systematically from their non-deuterated forms. The absence of unexpected toxicity in non-clinical safety studies with DTBZ further supports these findings. The minor human metabolites M1 and M4 do not contribute to VMAT2 efficacy and are unlikely to affect off-target activity.

2.5.2.3. Safety pharmacology programme

Stand-alone in vivo central nervous system (CNS), respiratory and cardiovascular safety pharmacology studies have not been performed with DTBZ. However, assessments were made during the GLP-compliant 3-month repeated dose toxicity studies in rats and juvenile rats. In the 3-month study, rats received DTBZ or TBZ orally, with functional observational battery evaluations showing no significant differences in most parameters between test and control groups, except for increased grooming noted in the TBZ group. Catalepsy, a common reaction to dopamine-reducing drugs like TBZ, increased with TBZ dosage, reaching significance at 30 mg/kg/day. DTBZ, at the same dose, showed comparable catalepsy effects to TBZ, indicating similar pharmacological responses.

The juvenile toxicity study identified DTBZ-related effects, such as higher rearing counts and resistance to handling, at doses ≥5 mg/kg/day, with no effects observed at 2.5 mg/kg/day. Despite these findings, no adverse effects on auditory startle response or learning and memory were noted at any dosage level.

In vitro studies on the cardiovascular system demonstrated significant inhibition of hERG potassium channel current by deuterated α-HTBZ and β-HTBZ, with IC50 concentrations well above predicted Cmax values after DTBZ administration in humans. However, no in vivo cardiovascular or respiratory safety pharmacology studies were conducted for DTBZ. A GLP-compliant study was conducted to evaluate the effects of TBZ on respiratory parameters in freely moving conscious rats using whole body plethysmography (XENAZINE NDA 21894 FDA Summary Basis of Approval, Pharmacology Review(s) Part 2, 2008). The results of the study are described below.

TBZ was administered by oral gavage to male Sprague Dawley rats at 0, 5, 15 or 30 mg/kg. The animals were acclimated to the plethysmography box for 30 minutes prior to two 15-minute intervals of baseline readings. Changes in tidal volume, respiratory rate and minute volume were recorded and averaged over 15-minute intervals for 4 hours post dose. In all groups there was a transient small increase in the respiratory parameters during the first 15 minutes post dose, which was considered to be related to the dosing procedure. The dose-related initial increase in respiratory rate was followed by a sustained decrease that had not resolved by the end of the 4-hour recording period. A TBZ-related increase (up to 45%) in tidal volume was noted at all doses tested (with statistical significance relative to controls at ≥15 mg/kg). At 30 mg/kg, the tidal volume had not returned to baseline at the end of the 4-hour observation period. The tidal volume increases were not considered clinically significant. A dose-related initial increase in minute volume was observed with a return to baseline or slightly below over the observation period (the secondary decrease was greater at 5 and 15 mg/kg than at 30 mg/kg).

Cardiovascular effects of TBZ in dogs

A GLP-compliant study was conducted using radiotelemetry to assess the potential cardiovascular effects of TBZ in conscious dogs (XENAZINE NDA 21894 FDA Summary Basis of Approval, Pharmacology Review(s) Part 2, 2008). The results of the study are described below.

TBZ was administered via oral capsule to non-naïve male beagle dogs at 0, 5, 10, or 20 mg/kg using a cross-over design with at least 7 days between dosing periods. The animals were radio telemetrically instrumented and assessed for effects on blood pressure (systolic, diastolic and arterial), heart rate, left ventricular pressure (LVP) and maximum rate of change in LVP (dP/dtmax) and electrocardiograms (ECGs) (RR, QRS, PR, QT and QT interval corrected for baseline heart rate using the Fridericia correction (QTcF) intervals and height of the R-wave and visual inspection) relative to baseline. Parameters were assessed at 2 intervals, 15 minutes apart, prior to dosing (nominally, 30 and 15 minutes prior to dosing), then at 0, 15, 30, 45, 60, and 90 minutes post dose and hourly up to 22 hours post dose.

TBZ was associated with clinical observations of "subdued, exhibited staggering gait, tremors and emesis" in one animal at approximately 3 hours after receiving the high dose. Subsequent observations in this animal indicated "some improvement" at approximately 5 hours post dose and by 12 hours post dose only slightly subdued behaviour was noted. The only treatment-related blood pressure effect was a small transient increase in the high dose group (20 mg/kg) at 90 minutes post dose, which was attributed to a large increase in motor activity in a single animal.

The FDA also indicated that there was a transient increase in mean arterial pressure for the low dose group (5 mg/kg) at 45-90 minutes post dose and for the 20 mg/kg group at the later time points of 11 to 14 hours post dose. There was a dose-related increase in heart rate, starting with a slight increase at 5 mg/kg. At 10 mg/kg, the increase in heart rate had an onset of 3 hours post dose, increased through 9 hours post dose, and returned to baseline at 11 hours post dose. At 20 mg/kg, the increased heart rate (described as tachycardia by the sponsor) was noted after 90 minutes through 4 hours post dose, with a return to baseline by 10 hours post dose. None of these changes were statistically significant. The only TBZ-related left ventricular effect was a small transient increase in LVP at

20 mg/kg at 90 min post dose, which was attributed to a large increase in motor activity of a single animal.

In addition, FDA noted an increase in LVP at 5 mg/kg at 90 min post dose, and an increase at 10 mg/kg at 6-7 hours and 17 hours post dose. There was no "noticeable change" in maximum rate of change in left ventricular pressure (dP/dtmax) compared to vehicle in the low dose group (5 mg/kg). The mid-dose (10 mg/kg) produced an increase (not statistically significant) in dP/dtmax (beginning at 4 hours, peaking at 7 hours, remaining increased through 9-10 hours post dose, and returning to near baseline by 11 hours post dose). The applicant noted an additional transient increase at 19 and 22 hours post dose, which they attributed to 2 animals (associated with increased motor activity in these animals). At 20 mg/kg, an increase in dP/dtmax was observed (peaking at 90 minutes, remaining increased though not at peak levels through 10 hours post dose). Teva attributed the degree of increase to one animal; however, more modest increases were noted in the others.

In addition, the FDA noted increases at 5 mg/kg at 90 minutes post dose and 16 hours post dose. The ECG waveform assessment noted by the sponsor indicated that, "*Expected changes in the RR interval (corresponding to changes in heart rate) were observed. There were no noticeable changes in the corrected QT interval QTcF between pre-dose and post-dose values on any dosing occasion.*"

The FDA suggested that there was a treatment, although not dose-related, increase in QTcF when compared to the vehicle control. A qualitative visual examination of the ECG waveform was conducted for each animal at each time point that a cardiovascular assessment was determined. According to Teva, "*No morphological changes - pre or post dose were observed.*" The applicant concluded that treatment-related positive chronotropic (increase in heart rate) and inotropic (increase in dP/dtmax) effects observed at ≥10 mg/kg may be due to sympathetic stimulation.

Overall, TBZ was not associated with adverse cardiovascular effects *in vivo*.

2.5.2.4. Pharmacodynamic drug interactions

Drug interaction information in the product label for DTBZ related to non-clinical pharmacodynamic interactions are based on the product label for TBZ. This information is documented accordingly in the SmPC.

2.5.3. Pharmacokinetics

The non-clinical pharmacokinetic (PK) programme included studies conducted with DTBZ, deuterated α-HTBZ, deuterated β-HTBZ and other minor metabolites. Absorption of DTBZ has been characterised in vitro, in stand-alone PK studies, and toxicokinetic evaluations within toxicology studies. The whole-body distribution, excretion, and the blood-to-brain ratio of [14C] DTBZ total drug related material (TDRM) was evaluated in rat. In addition, toxicokinetics of the minor human deuterated metabolites M1 and M4 were evaluated in rodents and in PK studies in dogs and rabbits.

Validated high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) methods were applied to measure the concentrations of various test analytes, including DTBZ and its deuterated and non-deuterated metabolites, in plasma and dose formulations from toxicology studies. These methods also quantified minor metabolites and impurities in formulations with carboxymethyl cellulose (CMC) or Dimethyl Sulfoxide (DMSO). All methods met FDA GLP validation criteria for sensitivity, selectivity, carryover, recovery and matrix effect, calibration reproducibility, accuracy, precision, and stability. Additionally, radiochemical methods for [14C]-DTBZ and [14C]-TBZ were developed for rat distribution and excretion studies, and qualified HPLC-MS/MS methods were used for in vitro metabolism studies.

In vitro evaluations of DTBZ and its deuterated α-HTBZ and β-HTBZ metabolites demonstrated high permeability and indicated no interaction with MDR1 and BCRP transporters at clinically relevant concentrations. While in Phase 1 studies, deuterium substitution in DTBZ increased the half-lives and approximately doubled the AUC values of deuterated α-HTBZ and β-HTBZ compared to TBZ, rodents did not show the same consistent effects from deuteration as humans, likely due to species differences in CYP enzymes. Repeated-dose studies in rats and mice revealed comparable half-lives and AUC values for deuterated and non-deuterated metabolites, with no accumulation noted. Juvenile rats exhibited higher exposures than adults, and in a PK study in adult Beagle dogs, AUC and t½ values for DTBZ and α-HTBZ were similar after a 1 mg/kg oral dose of DTBZ and TBZ, but the AUC for β-HTBZ was 3.2- and 2.7-fold greater in males and females, respectively, after DTBZ compared to TBZ. After a single oral dose of DTBZ and TBZ to CD-1 and CF-1 mice and New Zealand White rabbits, the Cmax and AUC values of DTBZ and the deuterated M1 and M4 minor metabolites were similar (in general no more than 2-fold different) compared with TBZ and the corresponding non-deuterated metabolites. No relevant gender differences were found.

In a radiolabelled tissue distribution study in Lister Hooded rats, [14C]-DTBZ-related radioactivity was primarily found in the uveal tract, urinary bladder, small intestine, and liver, peaking at 1-hour post-dose and declining thereafter. By seven days, most radioactivity had been eliminated, with remaining concentrations in the uveal tract, kidney cortex, liver, pigmented fur, nasal mucosa, and thyroid gland, and by 21 and 35 days, it was only measurable in the uveal tract and pigmented fur. In Sprague Dawley rats, a single oral dose showed blood-to-brain partition ratios of 1 or higher between 1 to 8 hours post-dose, with faster decline in the brain than blood, indicating no accumulation in the brain.

Human studies showed comparable distribution of radioactivity in blood and plasma with no preferential binding. DTBZ and its deuterated metabolites were not substrates for human MDR1, BCRP, OATP1B1, OATP1B3, or OCT1 transporters. The extent of plasma protein binding of deuterated α-HTBZ for human, monkey, dog, rat, and mouse plasma proteins were in the range of 55% to 85%, which were comparable to deuterated β-HTBZ binding, ranging from 48% to 85%, with no concentration dependency. The extent of plasma protein binding of DTBZ and deuterated α-HTBZ and β-HTBZ was similar to TBZ and the non-deuterated α-HTBZ and β-HTBZ, measured under the same concentrations.

The comprehensive non-clinical metabolism data of DTBZ are consistent with the metabolic profiles observed in humans, with no additional structurally-related metabolites of DTBZ relative to TBZ. Deuterated human circulating metabolites were either represented in rats treated with DTBZ or represented in humans, by non-deuterated human metabolites following administration of TBZ. Introduction of deuterium in DTBZ and the deuterated HTBZ metabolites attenuates O-linked demethylation of the HTBZ metabolites by human CYP2D6, without affecting the absorption, distribution, or excretion.

The prolonged half-lives of deuterated HTBZ metabolites observed in humans were not observed in rats, where absorption, distribution, metabolism, and excretion of DTBZ were similar to TBZ, with no impact on the safety evaluation.

Data in healthy subjects who are poor CYP2D6 metabolizers showed that the exposure to deuterated α HTBZ and deuterated β HTBZ would be increased similarly to taking strong CYP2D6 inhibitors (maximum exposure increased 2 fold and total exposure approximately 4 fold). This information is documented in the SmPC (section 4.2, 4.5 and 5.2).

A dedicated PK study to assess the effect of hepatic impairment on the PK of DTBZ and its active metabolites was not conducted. In addition, patients with TD who had impaired hepatic function were excluded from pivotal clinical trials. Since DTBZ is extensively metabolised in the liver, and due to the potential increase in systemic exposure, the use of DTBZ in patients with hepatic impairment is contraindicated (see SmPC section 4.3).. As the approval of the current DTBZ PR tablets is based on a

bridging / extrapolation approach, and in the absence of new PK data (either with the IR and PR formulations) allowing to lift this contraindication, it appears more appropriate and prudent to maintain the same recommendation in DTBZ SmPC in order to guarantee a consistency between available SmPCs of the different pharmaceutical forms. In the opposite case, the actual SmPC would introduce a different and unjustified recommendation of use (not recommended versus contraindicated). Although the lack of data in a specific subgroup of patients is not an automatic reason for a contraindication, it is considered that, taking into account the specific nature and knowledge of this dossier, the actual information (contraindication) is acceptable to avoid misinterpretation by prescribers regarding any clinical advantage or flexibility that the new formulation would have over the existing one.

After administering [14C]-DTBZ to rats, about 60% of the radioactivity was primarily excreted via faeces, with approximately 30% via urine up to 120 hours post-dose. Similarly, administering an equal oral dose of [14C]-TBZ to rats resulted in recovery of radioactivity to the same degree and in equal proportions across various excreta compartments, suggesting that deuteration did not affect excretion mechanisms.

DTBZ and the deuterated α-HTBZ and β-HTBZ metabolites seem devoid of DDI potential at the maximal therapeutic exposures. On the other hand, concomitant use of strong CYP2D6 inhibitors (e.g., quinidine, antidepressants such as paroxetine, fluoxetine and bupropion) showed to increase the systemic exposure to the active dihydro-metabolites of deutetrabenazine by approximately 3 fold. This information is documented accordingly in the SmPC (section 4.5).

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

A non-GLP single dose toxicity study was conducted in rats with administration by oral gavage of vehicle, DTBZ or TBZ (both at 2.5 or 15 mg/kg), in suspensions of 0.5% carboxymethyl cellulose (CMC) in distilled water. Animals were observed until scheduled necropsy on day 14. Toxicity was assessed based on food consumption, body weights, clinical observations, clinical pathology parameters, organ weights and gross pathology. A subset of animals was used for toxicokinetic analysis of deuterated and non-deuterated α-HTBZ and β-HTBZ in plasma over the course of 12 hours after dosing.

No specific toxicological concern arose from these data.

2.5.4.2. Repeat dose toxicity

Repeated dose toxicity studies with administration of DTBZ comprised two studies in rats, a non-pivotal study with 2 weeks duration and a pivotal study with treatment for 13 weeks (studies **SD-809-NC-006** and **SD-809-NC-025**, respectively). In both studies, administration was done twice a day and, in addition to a vehicle control group, a group treated with TBZ was also included. In both studies, DTBZ and TBZ were administered by oral gavage as suspensions in 0.5% CMC with 0.1% polysorbate 80 (Tween™ 80) in distilled water. In the 2 weeks study the two daily doses were administered separated by approximately 12 hours; in the 13-week study, the doses were administered approximately 8 hours apart, except on the days prior to and days of blood collection, as appropriate, when the doses were administered 12 hours.

In the 2 weeks non-pivotal study, animals were observed until the scheduled necropsy on day 14 (with first day of dosing on day 0). Toxicity was assessed based on clinical observations, food consumption, body weights, clinical pathology, organ weight, and gross pathology. For TK analysis (deuterated and

nondeuterated α-HTBZ and β-HTBZ metabolites), blood was collected at 0.5, 1, 2, 4, 8, and 12 hours after the first daily dose administration on study days 0 and 13 from a subset of animals.

In the 13 weeks pivotal study, animals were observed until scheduled necropsy on day 28 (interim phase) or day 91 (main phase). Toxicity was assessed based on clinical observations, food consumption, body weights, functional observational battery (males) (FOB; comprised of handling, open field, sensory, neuromuscular, and physiological observations), clinical pathology, ophthalmic examinations, macroscopic and microscopic pathology, organ weights, and histological organ examination at the interim and main necropsy. Blood was collected from a subset of animals for DTBZ, TBZ, deuterated α-HTBZ, and deuterated β-HTBZ plasma concentration and toxicokinetics assessment. Blood samples for toxicokinetics were collected from all animals in satellite TK vehicle control group at approximately 1 hour after the first daily dose administration and from 5 animals/sex/group/time point in satellite TK doses groups at approximately 0.5, 1, 3, 6, and 12 hours after the first daily dose administration on study days 0, 34 (study week 4), and 91 (study week 13).

Findings after both single and repeated oral doses of DTBZ included reduced body weight gain in males, CNS-related clinical observations in males and females, changes in reproductive organ weights, oestrous cycle arrest, and mammary hyperplasia in females. Reduced body weight gain in male rats after DTBZ dosing was like what previously observed with TBZ and considered adverse in the 14-day study, and at the 1-month interim phase of the GLP-compliant 3-month repeat dose study, at doses ≥30 mg/kg/day and at doses ≥10 mg/kg/day after 3 months. Clinical signs in the non-GLP and the GLP studies included partial eye closure, tremors, hypoactivity/lethargy, flattened body posture and rigid tone, all of which were noted in rats treated with TBZ in the present studies and in studies conducted in support of Xenazine® approval (US FDA 2008).

Partial eye closure is an expected pharmacological effect of VMAT2 inhibition due to reduced sympathetic tone in the autonomic ganglia controlling eyelid opening. Tremors (male only) were considered adverse in severity at 50 mg/kg/day in the 14-day study but not at 30 mg/kg/day in the 3-month repeated dose study. Clinical signs persisted for the duration of each study but showed clear intradose attenuation each day. By contrast, test article-related effects on body weight gain were most pronounced the first week of each repeat dose study with subsequent recovery. Mammary hyperplasia and oestrous cycle arrest at the proestrus phase in Study SD-809-NC-025 were considered an expected physiological consequence of reduced CNS dopamine with attendant disinhibition of prolactin. Oestrous cycle effects in female rats were noted with TBZ in studies supporting Xenazine® approval (HSDB 2019).

Equal doses of DTBZ and TBZ had similar effects on body weight gain in pregnant rats and were both negative for foetal toxicities, similar to results described in Xenazine® United States Prescribing Information (USPI) (HSDB 2019).

Adverse clinical observations after repeated oral doses of DTBZ in juvenile rats consisted of tremors and hyperactivity/changes in motor activity. Similar changes in motor findings were also observed in adult rats that were administered DTBZ or TBZ. Changes in motor behaviour and other CNS-related effects are likely related to the pharmacological action of the drug, with changes in central dopamine neurotransmission. Predose hyperactivity was observed with DTBZ and TBZ doses of 10 and 30 mg/kg/day after approximately 12 days of dosing in adults. Tremors were noted after 30 and 50 mg/kg/day DTBZ and TBZ in adult males in Study SD-809-NC-006, with the effects at 50 mg/kg/day considered adverse. In the 3-month GLP toxicology study (Study SD-809-NC-025), non-adverse tremors were observed in all males and approximately 50% of females at 30 mg/kg/day and sporadically in those dosed with 10 mg/kg/day. Thus, clinical observations were qualitatively the same in juveniles dosed with DTBZ and adults dosed with DTBZ and TBZ although they were observed at lower doses. Similarly, adult humans and children experience qualitatively similar adverse events (AE) after oral administration of DTBZ.

2.5.4.3. Genotoxicity

There were no genotoxicity signals in the bacterial and mammalian *in vitro* assays of deuterated α-HTBZ and deuterated β-HTBZ, or DTBZ containing diastereomer SD-996. There were no positive signals in an *in vivo* micronucleus assay conducted in male and female mice.

The applicant pointed out that *"in studies conducted to support Xenazine® approval (HSDB 2019), TBZ and the nondeuterated HTBZ metabolites were clastogenic in the in vitro chromosome aberration assay in Chinese hamster ovary or lung cells in the presence of metabolic activation with rodent S9 when tested at concentrations up to 2.5 mM that produced evidence of cytotoxicity."* The lack of similar findings in the current studies with DTBZ is attributed to the *in vitro* test systems, the ICH-compliant dose limit of 1mM and the lack of observed cytotoxicity. For completeness, although previously conducted *in vivo* micronucleus tests with TBZ (in rats and mice) produced generally similar results to DTBZ in mice, there were some equivocal responses in female rats.

Additional studies were conducted to evaluate M4 and the disproportionate human metabolite M1, both minor metabolites, representing on average 9.1% (M1) and 5.2 % (M4) of total circulating drug-related material when compared to the $AUC_{0-\infty}$ values for total drug related material. M1 and M4 were negative in bacterial reverse mutation and M1 was negative in *in vitro* chromosomal aberration studies.

2.5.4.4. Carcinogenicity

Carcinogenicity studies have not been conducted with DTBZ.

The Applicant believes that carcinogenicity bioassays are not required based on the following weight of evidence, indicating that, like TBZ, DTBZ does not present a carcinogenic risk:

- DTBZ and its deuterated metabolites did not show binding or functional effects in a large panel of off target sites (secondary pharmacology) at clinically relevant concentrations. DTBZ and its deuterated metabolites were highly specific to their target VMAT2 (primary pharmacology), a target that has not been associated with carcinogenic potential;
- Genotoxicity studies of DTBZ and its deuterated metabolites were consistently negative for mutagenic or clastogenic potential. This is consistent with the negative genotoxicity results for TBZ and its non-deuterated metabolites;
- No pre-neoplastic or neoplastic changes were observed in the 3-month toxicology study of DTBZ in rats at the highest dose tested (30 mg/kg/day);
- Qualitative structure activity relationship (QSAR) evaluation (Report DRK23-3092) revealed a negative predictive outcome;
- The deuterium-carbon substitution (for hydrogen-carbon) in DTBZ does not alter the binding pharmacology, PK in rodents or safety of DTBZ or its deuterated metabolites relative to TBZ and its non-deuterated metabolites, indicating that the following carcinogenicity data for TBZ / non-deuterated 9 O-desmethyl-β-HTBZ would be applicable to DTBZ:
    - No increase in tumours was observed in p53+/- transgenic mice treated orally with tetrabenazine (5, 15, and 30 mg/kg/day) for 26 weeks;
    - No increase in tumours was observed in Tg.rasH2 transgenic mice treated orally with the major human metabolite, 9-desmethyl-β-DHTBZ (20, 100, and 200 mg/kg/day), for 26 weeks (Xenazine® US Prescribing Information, 2019, as referenced in HSDB 2019);

- Chronic toxicology studies with TBZ, including a 26-week study in rats and a 9-month study in dogs (Xenazine® FDA pharmacology review PharmR_P1, US FDA Pharm Tox Review 2008), did not reveal any pre-neoplastic or neoplastic lesions.

2.5.4.5. Reproductive and developmental toxicity

No stand-alone fertility and early embryonic development studies with DTBZ were conducted. Reference is made to the 13 weeks repeated dose toxicity study and to juvenile animal toxicity studies conducted with DTBZ.

Effects on mating and fertility indices were assessed in rats in the 3-month repeat-dose toxicology study with DTBZ (study **SD-809-NC-025**) and in juvenile toxicology studies with DTBZ (study **SD-809-NC-055**) or with DTBZ and deuterated β-HTBZ (study **DS-2017-035**).

No specific toxicological concern was identified in this regard after reviewing data submitted by the Applicant. The fertility and early embryonic development data for DTBZ, derived from the 3-month repeated dose toxicity study and from the two juvenile toxicity studies in rats, are similar to the fertility effects reported to TBZ, with the main effects being dose-related disruption of oestrus cyclicity, reported in the adult studies but not in the juvenile toxicology studies, with no effects on mating or fertility in both males and females.

Embryo-foetal development studies with administration of deutetrabenazine comprised two studies in rats, one non-pivotal (dose range-finding study) and the other pivotal (studies **SD-809-NC-051** and **SD-809-NC-052**, respectively). In both studies, administration was done twice a day by oral gavage. In addition to a vehicle control group, a group treated with TBZ was also included in the pivotal study. DTBZ and, as applicable, TBZ, were administered as suspensions in 0.5% carboxymethyl cellulose (CMC) with 0.1% polysorbate 80 (Tween™ 80) in distilled water. In the non-pivotal study, the two daily administrations were done approximately 6 hours apart; in the pivotal study, approximately 6 hours apart or, on the days of blood sample collection, approximately 8 hours apart.

Embryo-foetal assessment resulted in no embryo-foetal toxicities and similar maternal effects after DTBZ and TBZ exposure. It is expected that additional embryo-foetal development, fertility, and pre- and post-natal development results would likely mimic what has been documented for TBZ.

Pre- and post-natal development studies of DTBZ were not conducted, but based on all other existing pharmacology, PK and toxicology data, it is expected that results would mimic those reported for TBZ, outlined in the public domain (Pharmacology review, US FDA Pharm Tox Review 2008 and HSDB 2019). In that study, premated female CD®(SD)IGSBR rats were administered TBZ once daily via oral gavage, from GD 6 through lactation day (LD) 20 at doses of 0, 5, 15, or 30 mg/kg/day. An increase in stillbirths and offspring postnatal mortality was observed at 15 and 30 mg/kg/day and delayed pup maturation was observed at all doses. A no-effect dose for pre- and post-natal developmental toxicity in rats was not identified. The lowest dose tested (5 mg/kg/day) was less than the MRHD on a mg/m^2 basis. A NOEL for findings in the F_0 dams may not have been achieved, based on an effect on pup retrieval data at the lowest dose tested (despite lack of clinical observation in the dams). It was not possible to ascribe the effect to dam or pup, because of difficulty distinguishing between dam and pup effects. The NOEL for F_1 perinatal pup survival was 5 mg/kg/day (approximately 0.48× the MRHD on a mg/m^2 basis). There were treatment-related delays in the pinna unfolding (30 mg/kg/day), hair growth (all doses), eye opening (30 mg/kg/day), vaginal opening (all doses) and preputial separation (≥15 mg/kg/day). Therefore, a NOEL for development was not established.

Based on the overall pharmacology, PK, and toxicology similarities between DTBZ and TBZ (notably in the fertility and embryo-foetal developmental endpoints), it is anticipated that a pre-and post-natal

developmental toxicity study with DTBZ would obtain results similar to those reported for TBZ. Given the lack of an identified NOEL in the TBZ pre- and post-natal developmental study (with a low dose below the MRHD on a mg/m^2 basis), the conduct of a dedicated pre- and postnatal developmental toxicity study with DTBZ appeared to be of very limited value.

In terms of juvenile studies, there were no test item-related (deuterated β-HTBZ or DTBZ) adverse effects on clinical observations, body weights and body weight gains (deuterated β-HTBZ only), food consumption, ophthalmologic findings, behaviour (open field observations, motor activity, auditory startle and learning and memory), clinical pathology (haematology, clinical chemistry and coagulation), femur lengths, organ weights, sexual maturation, oestrus cycling, mating and fertility, Caesarean section parameters, sperm morphology, motility and counts, macroscopic (including counts of corpora lutea and implantations for the reproductive females) and microscopic post-mortem evaluations. As noted in all previous toxicology studies of DTBZ, there were DTBZ-related reduced male body weights and body weight gains observed during the treatment and early post-treatment periods. Based on these data, the systemic and reproductive NOAEL for deuterated β-HTBZ was determined.

2.5.4.6. Toxicokinetic data

The Applicant provided toxicokinetic data for studies conducted with DTBZ as well as for published studies performed with TBZ. For DTBZ, toxicokinetic data were obtained for two repeated dose toxicity studies in rats (2-week and 13-week studies), an *in vivo* micronucleus assay in mice, an embryo-foetal development study in rats and three studies in juvenile rats (one of which also involved administration of deuterated β-HTBZ); these included data for the metabolites deuterated α-HTBZ and β-HTBZ, in the case of the non-pivotal 2-week repeated dose toxicity study in rats, and for DTBZ and metabolites deuterated α-HTBZ and β-HTBZ, in the case of the other studies.

For TBZ, data was provided for a 9-month repeated dose toxicity study in dogs, a fertility study in rats and an embryo-foetal development study in rabbits and a carcinogenicity study in mice; these included data for TBZ and its metabolites α-HTBZ and β-HTBZ, in the case of the 9-month study in dogs and embryo-foetal development in rabbits, and for the metabolites only in the case of the fertility and the carcinogenicity studies.

Regarding studies conducted with DTBZ, in the pivotal 13-week repeated dose toxicity study with administration of DTBZ to rats, systemic exposures (AUC and C_{max}) to deuterated α-HTBZ were markedly higher than to DTBZ and deuterated β-HTBZ, in both males and females, with a higher difference in males. Systemic exposure to deuterated α-HTBZ increased with dose levels and was higher in males, compared to females. A higher systemic exposure to the deuterated α-HTBZ metabolite, compared to DTBZ and deuterated β-HTBZ, was also observed in the embryo-foetal developmental study in rats and studies conducted in juvenile rats. In the *in vivo* micronucleus assay in mice, systemic exposure to deuterated α-HTBZ was also higher than to DTBZ or deuterated β-HTBZ, but the difference was less marked than that observed in rats.

The Applicant also provided tables with information on safety exposure margins based on animal studies conducted with DTBZ and published studies performed with TBZ. Safety margins were determined based on exposure to (D)TBZ and also its metabolites (deuterated) α-HTBZ and β-HTBZ.

Regarding studies conducted with DTBZ, based on systemic exposure to DTBZ at the NOAEL, there were low safety margins for effects observed in males in the pivotal repeated dose toxicity study and juvenile animal studies; based on deuterated α-HTBZ and β-HTBZ, safety margins were low for all studies.

2.5.4.7. Local Tolerance

No local tolerance studies were conducted with DTBZ or TBZ.

2.5.4.8. Other toxicity studies

The collective DTBZ-related CNS effects *in vivo* are most likely associated with perturbations of monoamine neurotransmitters, as postulated by the Applicant. Data from post-marketing experience showed lack of abuse potential for DTBZ. When considering all available evidence, the non-clinical data, including primary and secondary pharmacology, function observation battery in rats, with the clinical experience of DTBZ, indicate no abuse potential for DTBZ.

M1 and M4 are minor and inactive circulating metabolites of DTBZ. Early in the DTBZ drug development process, before determined that M1 and M4 were minor metabolites in humans, safety assessment of these metabolites commenced, and the Applicant submitted relevant data characterizing the toxicity profile of these metabolites (namely M1). No specific concern was identified.

In terms of impurities, SD-996 is a diastereomer of DTBZ, and SD-990 is the analogous diastereomer of TBZ. The diastereomers are inevitable chemical conversions of DTBZ and TBZ through a pH-catalysed isomerization at the carbonyl α-carbon (Carbon 3) to which the iso-butyl side chain is attached. Acidic conditions accelerate isomerization to a steady state equilibrium ratio. Based on a maximum recommended human dose of 48 mg/day and the proposed specification in drug substance, the SD-996 diastereomer of DTBZ requires qualification under ICH Q3A(R2) and Q3B(R2) guidance. Certificate of analysis indicates that SD-996 was present in the DTBZ batch used in the pivotal GLP-compliant 3-month toxicology study of DTBZ in rats (study SD-809-NC-025) and the GLP mouse micronucleus study (study SD-809-NC-044). Due to the acidic dose formulations, the percentage of SD-996 used throughout study SD-809-NC-025 varied relative to the combined peak area of DTBZ and SD-996 as assessed in a supplemental analysis (Study SD-809-NC-050). For the purposes of dose qualification, the lowest concentration was selected as a conservative estimate for exposure in the GLP 3-month rat study and used as an estimate for the rat embryo-foetal toxicology, the GLP mouse micronucleus study, and the juvenile toxicology study (study SD-809-NC-055).

The highest dose of DTBZ intended for approval is 48 mg per day in adults. The highest amount of SD-996 that a 60 kg subject could receive from administration of DTBZ containing SD-996 at the proposed specification limit yielded greater than a 2-fold safety factor for SD-996 dose in adults relative to adult rat and mouse Human Equivalent Dose (HED) values.

The HED for SD-996 in rat and mouse provides dose multiples with respect to the highest proposed human dose of DTBZ with SD-996 at the upper limit in drug product. Studies with SD-996 as a formulation impurity revealed no genotoxicity findings under the tested conditions. Therefore, SD-996 is adequately qualified.

Another impurity is SD-997. This is a process impurity of DTBZ drug substance; it is also monitored in drug product as a specified degradant. SD-997 does not require qualification under ICH Q3B(R2) guidance. Early in the development, however, a proposed specification for of SD-997 was higher than the ICH threshold and hence a 14-day general toxicity study (study **SD-809-NC-076**) was conducted. In addition, per current recommendations (e.g., ICH M7 Guidance) genotoxicity studies were performed with SD-997 (studies **SD-809-NC-058** and **SD-809-NC-059**). Genotoxicity evaluation consisted of *in vitro* studies as well as QSAR assessments (study **DRK23-3092**).

SD-997 did not exaggerate toxicities associated with DTBZ or introduce novel findings. As suggested by the Applicant, there is a 17-fold or greater safety factor based on SD-997 as a drug formulation impurity. It is therefore agreed that this impurity is also adequately qualified.

DTBZ is likely non-phototoxic and photosafety does not represent a concern.

2.5.5. Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) provided by the Applicant followed the *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use* (EMEA/CHMP/SWP/4447/00, corr. 1, 2006) and the *Questions and Answers on 'Guideline on the environmental risk assessment of medicinal products for human use'* document (EMA/CHMP/SWP/44609/2010 Rev. 1, 2016).

An ERA Phase I study was conducted to consider the environmental risk arising from Austedo 12, 24, 30, 36, 42 and 48 mg prolonged-release tablets.

Relevant endpoints, methods used and results obtained were discussed by the applicant and summarised in the table below.

Table 1: Summary of main study results

Substance (INN): Deutetrabenazine			
CAS-number (if available): 0000605465			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	pH 4.0=1.4 pH 7.0 =3.0 pH 9.0 = 3.1	Potential PBT: **N**
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow} OECD 107	pH 4.0=1.4 pH 7.0 =3.0 pH 9.0 = 3.1	**not B**
PBT-statement:	Deutetrabenazine is considered to be not PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{sw\ refined}$	0.0007296	µg/L	< 0.01 threshold: **N**
Other concerns (e.g. chemical class)			**N**

PBT: ECHA's persistence, bioaccumulation and toxicity; PEC_{sw}: Environmental Concentration in surface water

As outlined in the table Log Dow values experimentally determined by the Shake Flask Method (Test OECD Guideline 107), at environmentally relevant pH values, were 1.4 at pH 4.0, 3.0 at pH 7.0, and 3.1 at pH 9.0.

Log Dow values are below the trigger value of 4.5. Therefore, DTBZ is not a persistent and bio accumulative substance. Therefore, no further screening of persistence, bioaccumulation and toxicity (PBT) assessment is required.

The Fpen refinement presented by the applicant was based on tardive dyskinesia prevalence data, published in a recent study of TD patients in Europe, according to the guideline EMA/CHMP/SWP/44609/2010, rev1, 2016.

Based on the low values obtained for Refined PECsurfacewater (0.00073 µg/L) and log Dow at 3 environmentally relevant pHs no Phase II assessment is required.

Therefore, it can be assumed that Austedo 12, 24, 30, 36, 42 and 48 mg PR tablets approval is unlikely to pose a risk to the environment following its prescribed usage in patients.

Nevertheless, precautionary and safety measures must be taken to minimise environmental risk and enhance environmental protection, according to the *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use* (EMEA/CHMP/SWP/4447/00, corr 1, 2006). Therefore, the statement "*Any unused medicinal product or waste material should be disposed of in accordance with local requirements*" was included in SmPC section 6.6.

2.5.6. Discussion on non-clinical aspects

Teva proposed DTBZ, a reversible inhibitor of the vesicular monoamine transporter type 2 (VMAT2), as once daily osmotic PR formulation for the treatment of moderate to severe TD in adults.

DTBZ is structurally related to the VMAT2 inhibitor TBZ.

Data from competitive binding assays indicate that deuterated and non-deuterated α-HTBZ and β-HTBZ metabolites have similar binding affinities for VMAT2, with Ki values showing minimal differences, which

were attributed to random variability. Further assays identified the [+] enantiomers of α-HTBZ and β-HTBZ as the active moieties with significantly lower Ki and IC50 values compared to the [−] enantiomers. Additionally, minor metabolites M1 and M4 were characterized and found to have 63-fold lower VMAT2 affinities, deeming them non-active. Overall, DTBZ efficacy is attributed to the [+] metabolites, despite DTBZ itself not being an active moiety, due to its rapid metabolism and low clinical exposure.

The applicant did not perform *in vivo* pharmacodynamic studies with DTBZ. Overall results from the pharmacological studies identified the deuterated metabolites [+]-α-HTBZ and [+]-β-HTBZ as the active moieties inhibiting VMAT2 and demonstrated that the substitution of hydrogen by deuterium does not change the primary or the secondary pharmacology of DTBZ relative to that of TBZ. TBZ demonstrated efficacy in several published pharmacological animal studies, particularly in the context of monoamine depletion.

The secondary pharmacology screen for deuterated forms of α-HTBZ and β-HTBZ showed no substantial activation of secondary targets, except for binding to Sigma and serotonin 5-HT7 receptors, which exhibited an antagonistic effect for deuterated [-]-HTBZ metabolites. DTBZ administered within the recommended clinical dose range resulted in clinical exposure levels of both deuterated α-HTBZ and β-HTBZ insufficient to significantly engage the sigma receptors. The IC_{50} values for binding of deuterated α-HTBZ and β--HTBZ metabolites to the sigma receptor exceed the clinical exposure by 25-fold and 4-fold, respectively, at the highest clinical dose (based on the C_{max} free fraction). The 5-HT7 receptor, a G-protein coupled serotonin receptor, plays roles in mood regulation, circadian rhythm, and cognition. While 5-HT7 antagonism showed antidepressant and anxiolytic effects in animal models, no approved drugs selectively target this receptor. However, the clinical implications of selective 5-HT7 inhibition remain uncertain, requiring further research. The off-target binding activities of the deuterated α-HTBZ and β-HTBZ did not differ systematically from their non-deuterated forms. The absence of unexpected toxicity in non-clinical safety studies with DTBZ further supports these findings. The minor human metabolites M1 and M4 do not contribute to VMAT2 efficacy and are unlikely to affect off-target activity.

Stand-alone *in vivo* central nervous system, respiratory and cardiovascular safety pharmacology studies were not performed with DTBZ. However, assessments were made during GLP-compliant 3-month repeated dose toxicity studies in rats and juvenile rats. In the 3-month study, rats received DTBZ or TBZ orally, with functional observational battery evaluations showing no significant differences in most parameters between test and control groups, except for increased grooming noted in the TBZ group. Catalepsy, a common reaction to dopamine-reducing drugs like TBZ, increased with TBZ dosage, reaching significance at 30 mg/kg/day. DTBZ, at the same dose, showed comparable catalepsy effects to TBZ, indicating similar pharmacological responses. The juvenile toxicity study identified DTBZ-related effects, such as higher rearing counts and resistance to handling, at doses ≥5 mg/kg/day, with no effects observed at 2.5 mg/kg/day. Despite these findings, no adverse effects on auditory startle response or learning and memory were noted at any dosage level.

In vitro studies on the cardiovascular system demonstrated significant inhibition of hERG potassium channel current by deuterated α-HTBZ and β-HTBZ, with IC50 concentrations well above predicted C_{max} values after DTBZ administration in humans. However, no *in vivo* cardiovascular or respiratory safety pharmacology studies were conducted for DTBZ.

Tetrabenazine safety pharmacology studies, compliant with ICH S7A guidelines, assessed CNS, respiratory, and cardiovascular effects. In rats, TBZ induced mild CNS effects, including increased grooming and catalepsy at high doses. Respiratory studies showed transient increases in tidal volume and respiratory rate, with no clinically significant impact. In dogs, cardiovascular effects were minimal, with transient heart rate increases and mild left ventricular pressure changes, mostly linked to individual variability. Overall, TBZ did not present significant adverse cardiovascular risks *in vivo*.

Drug interaction information in the product label for DTBZ related to non-clinical pharmacodynamic interactions are based on the product label for TBZ.

The non-clinical pharmacokinetic programme included studies conducted with DTBZ, deuterated α-HTBZ, deuterated β-HTBZ and other minor metabolites. Absorption of DTBZ was characterised *in vitro*, in stand-alone PK studies and toxicokinetic evaluations within toxicology studies. The whole-body distribution, excretion, and the blood-to-brain ratio of [^{14}C] DTBZ total drug related material (TDRM) was evaluated in rat. In addition, toxicokinetics of the minor human deuterated metabolites M1 and M4 were evaluated in rodents and in PK studies in dogs and rabbits.

Validated high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) methods were applied to measure the concentrations of various test analytes, including DTBZ and its deuterated and non-deuterated metabolites, in plasma and dose formulations from toxicology studies. These methods also quantified minor metabolites and impurities in formulations with CMC or DMSO. Additionally, radiochemical methods for [^{14}C]-DTBZ and [^{14}C]-TBZ were developed for rat distribution and excretion studies, and qualified HPLC-MS/MS methods were used for *in vitro* metabolism studies.

In vitro evaluations of DTBZ and its deuterated α-HTBZ and β-HTBZ metabolites demonstrated high permeability and indicated no interaction with MDR1 and BCRP transporters at clinically relevant concentrations. While in Phase 1 studies, deuterium substitution in DTBZ increased the half-lives and approximately doubled the AUC values of deuterated α-HTBZ and β-HTBZ compared to TBZ, rodents did not show the same consistent effects from deuteration as humans, likely due to species differences in CYP enzymes. Repeated-dose studies in rats and mice revealed comparable half-lives and AUC values for deuterated and non-deuterated metabolites, with no accumulation noted. Juvenile rats exhibited higher exposures than adults, and in a PK study in adult Beagle dogs, AUC and t½ values for DTBZ and α-HTBZ were similar after a 1 mg/kg oral dose of DTBZ and TBZ, but the AUC for β-HTBZ was 3.2- and 2.7-fold greater in males and females, respectively, after DTBZ compared to TBZ. After a single oral dose of DTBZ and TBZ to CD-1 and CF-1 mice and New Zealand White rabbits, the C_{max} and AUC values of DTBZ and the deuterated M1 and M4 minor metabolites were similar (in general no more than 2-fold different) compared with TBZ and the corresponding non-deuterated metabolites. No relevant gender differences were found.

In a radiolabelled tissue distribution study in Lister Hooded rats, [^{14}C]-DTBZ-related radioactivity was primarily found in the uveal tract, urinary bladder, small intestine, and liver, peaking at 1-hour post-dose and declining thereafter. By seven days, most radioactivity had been eliminated, with remaining concentrations in the uveal tract, kidney cortex, liver, pigmented fur, nasal mucosa, and thyroid gland, and by 21 and 35 days, it was only measurable in the uveal tract and pigmented fur. In Sprague Dawley rats, a single oral dose showed blood-to-brain partition ratios of 1 or higher between 1 to 8 hours post-dose, with faster decline in the brain than blood, indicating no accumulation in the brain. Human studies showed comparable distribution of radioactivity in blood and plasma with no preferential binding. DTBZ and its deuterated metabolites were not substrates for human MDR1, BCRP, OATP1B1, OATP1B3, or OCT1 transporters. The extent of plasma protein binding of deuterated α HTBZ for human, monkey, dog, rat, and mouse plasma proteins were in the range of 55% to 85%, which were comparable to deuterated β-HTBZ binding, ranging from 48% to 85%, with no concentration dependency. The extent of plasma protein binding of DTBZ and deuterated α-HTBZ and β-HTBZ was similar to TBZ and the non-deuterated α-HTBZ and β HTBZ, measured under the same concentrations.

The comprehensive non-clinical metabolism data of DTBZ are consistent with the metabolic profiles observed in humans, with no additional structurally-related metabolites of DTBZ relative to TBZ. Deuterated human circulating metabolites were either represented in rats treated with DTBZ or represented in humans, by non-deuterated human metabolites following administration of TBZ. Introduction of deuterium in DTBZ and the deuterated HTBZ metabolites attenuates O-linked

demethylation of the HTBZ metabolites by human CYP2D6, without affecting the absorption, distribution, or excretion. The prolonged half-lives of deuterated HTBZ metabolites observed in humans were not observed in rats. In rats, the absorption, distribution, metabolism and excretion of DTBZ are similar to TBZ, with no impact on the safety evaluation.

Data in healthy subjects who are poor CYP2D6 metabolizers showed that the exposure to deuterated α HTBZ and deuterated β HTBZ would be increased similarly to taking strong CYP2D6 inhibitors (maximum exposure increased 2-fold and total exposure approximately 4-fold). This information is documented accordingly in the SmPC.

A dedicated PK study in participants to assess the effect of hepatic impairment on the PK of DTBZ and its active metabolites was not conducted. In addition, patients with TD who had impaired hepatic function were excluded from pivotal clinical trials. Since DTBZ is extensively metabolised in the liver, and due to the potential increase in systemic exposure, the DTBZ use in patients with hepatic impairment is contraindicated (as outlined in SmPC section 4.3).

After administering [^{14}C]-DTBZ to rats, about 60% of the radioactivity was primarily excreted via faeces, with approximately 30% via urine up to 120 hours post-dose. Similarly, administering an equal oral dose of [^{14}C]-TBZ to rats resulted in recovery of radioactivity to the same degree and in equal proportions across various excreta compartments, suggesting that deuteration did not affect excretion mechanisms.

DTBZ and the deuterated α-HTBZ and β-HTBZ metabolites seem devoid of DDI potential at the maximal therapeutic exposures. On the other hand, concomitant use of strong CYP2D6 inhibitors (e.g., quinidine, antidepressants such as paroxetine, fluoxetine and bupropion) showed to increase the systemic exposure to the active dihydro-metabolites of deutetrabenazine by approximately 3-fold. This information is documented accordingly in the SmPC.

Findings after both single and repeated oral doses of DTBZ include reduced body weight gain in males, CNS-related clinical observations in males and females, changes in reproductive organ weights, oestrous cycle arrest, and mammary hyperplasia in females. Reduced body weight gain in male rats after DTBZ dosing was like that previously observed with TBZ and was considered adverse in the 14-day study and at the 1-month interim phase of the GLP-compliant 3-month repeat dose study at doses ≥30 mg/kg/day and at doses ≥10 mg/kg/day after 3 months. Clinical signs in the non-GLP and the GLP studies included partial eye closure, tremors, hypoactivity/lethargy, flattened body posture and rigid tone, all of which were noted in rats treated with TBZ in the presented studies and in those conducted in support of Xenazine® (TBZ) approval (US FDA 2008).

Partial eye closure is an expected pharmacological effect of VMAT2 inhibition due to reduced sympathetic tone in the autonomic ganglia controlling eyelid opening. Tremors (male only) were considered adverse in severity at 50 mg/kg/day in the 14-day study but not at 30 mg/kg/day in the 3-month repeated dose study. Clinical signs persisted for the duration of each study but showed clear intradose attenuation each day. By contrast, test article-related effects on body weight gain were most pronounced the first week of each repeat dose study with subsequent recovery. Mammary hyperplasia and oestrous cycle arrest at the proestrus phase in study SD-809-NC-025 were considered an expected physiological consequence of reduced CNS dopamine with attendant disinhibition of prolactin. Oestrous cycle effects in female rats were noted with TBZ in studies supporting Xenazine® approval (HSDB 2019).

Equal doses of DTBZ and TBZ had similar effects on body weight gain in pregnant rats and were both negative for foetal toxicities, similar to results described in Xenazine® USPI (HSDB 2019).

Adverse clinical observations after repeated oral doses of DTBZ in juvenile rats consisted of tremors and hyperactivity/changes in motor activity. Similar changes in motor findings were also observed in adult rats that were administered DTBZ or TBZ. Changes in motor behaviour and other CNS-related effects are likely related to the pharmacological action of the drug, with changes in central dopamine

neurotransmission. Pre-dose hyperactivity was observed with DTBZ and TBZ doses of 10 and 30 mg/kg/day after approximately 12 days of dosing in adults. Tremors were noted after 30 and 50 mg/kg/day DTBZ and TBZ in adult males in Study SD-809-NC-006, with the effects at 50 mg/kg/day considered adverse. In the 3-month GLP toxicology study (Study SD-809-NC-025), non-adverse tremors were observed in all males and approximately 50% of females at 30 mg/kg/day and sporadically in those dosed with 10 mg/kg/day. Thus, clinical observations were qualitatively the same in juveniles dosed with DTBZ and adults dosed with DTBZ and TBZ, although they were observed at lower doses. Similarly, adult humans and children experience qualitatively similar AEs after oral administration of TBZ.

Regarding the lack of studies in non-rodents, the applicant referred to the comparative dog PK study with DTBZ and TBZ (Study DP-2016-057) and to published data on a 9-months repeated dose toxicity study with tetrabenazine conducted in dogs. Considering the findings of these studies, but also the available evidence with rodents and the 3R's principles, this approach may be considered satisfactory.

Deutetrabenazine, its deuterated metabolites and impurities were well-tolerated, and the main toxicities across a range of studies were CNS-related clinical signs and occasional body weight decreases associated with decreased food consumption. Consistent with similar exposure and indistinguishable pharmacology, the toxicological profile of DTBZ was similar to that of TBZ in direct comparison at equal doses. The similar toxicity profiles of DTBZ and TBZ indicated that prior experience with TBZ can substantially contribute to the understanding of the toxicities of DTBZ across a broad range of toxicology studies, enabling a scientifically sound read-across opportunity.

There is no indication of genetic toxicological potential for DTBZ, the major circulating deuterated HTBZ metabolites or the minor metabolites, M1 and M4.

Carcinogenicity studies were not conducted with DTBZ. A weight of evidence approach, based on DTBZ pharmacology and the understanding of TBZ, suggested that DTBZ is not likely to be carcinogenic in humans.

The fertility and early embryonic development data for DTBZ, are similar to the fertility effects reported to TBZ, with the main effects being dose-related disruption of oestrus cyclicity, reported in the adult studies but not in the juvenile toxicology studies, with no effects on mating or fertility in both males and females.

Embryo-foetal assessment resulted in no embryo-foetal toxicities and similar maternal effects after DTBZ and TBZ exposure. It is expected that additional embryo-foetal development, fertility, and pre- and postnatal development results would likely mimic what has been documented for TBZ. Juvenile toxicity studies in rats showed that DTBZ was not associated with fertility effects. Based on the overall pharmacology, PK and toxicology similarities between DTBZ and TBZ (notably in the fertility and embryo-foetal developmental endpoints), it is anticipated that a pre-and postnatal developmental toxicity study with DTBZ would obtain results similar to those reported for TBZ. Given the lack of an identified NOEL in the TBZ pre- and post-natal developmental study (with a low dose below the MRHD on a mg/m^2 basis), the conduct of a dedicated pre- and postnatal developmental toxicity study with DTBZ appeared to be of very limited value.

The safety profile of deuterated β-HTBZ was further investigated in rats in a dedicated juvenile animal study with administration of deuterated β-HTBZ from PND 25 to PND 70 (study **DS-2017-035**). In this study there were no test item-related (deuterated β-HTBZ or DTBZ) adverse effects on clinical observations, body weights and body weight gains (deuterated β-HTBZ only), food consumption, ophthalmologic findings, behaviour (open field observations, motor activity, auditory startle and learning and memory), clinical pathology (haematology, clinical chemistry and coagulation), femur lengths, organ weights, sexual maturation, oestrus cycling, mating and fertility, Caesarean section parameters, sperm morphology, motility and counts, macroscopic (including counts of corpora lutea and implantations for

the reproductive females) and microscopic post-mortem evaluations. As noted in all previous toxicology studies of DTBZ, there were DTBZ-related reduced male body weights and body weight gains observed during the treatment and early post-treatment periods. Based on these data, the systemic and reproductive NOAEL for deuterated β-HTBZ was determined to be 7 mg/kg/day.

Moreover, concerning safety data for the deuterated β-HTBZ metabolite, since low exposure levels to this metabolite were also attained in the rat embryo-foetal development study (0.26- and 0.08-fold human exposure based on total and unbound AUC, respectively, at 30 mg/kg BID), the applicant justified the absence of a dedicated embryo-foetal development study with deuterated β-HTBZ and also discussed a potential impact of the metabolite deuterated β-HTBZ on embryo-foetal development.

Teva relied on the EFD study conducted in rabbits with TBZ wherein the developmental NOEL was determined at the high (materno-toxic) dose of 60 mg/kg/day. The exposure to non-deuterated β-HTBZ metabolite at this dose level was 1142 ng.h/mL, which is 4.5-fold higher than that of deuterated β-HTBZ in humans (255.1 ng/h/mL). This margin can be viewed as small but it is acceptable to consider that no additional EFD study is required with this metabolite.

It was also noted from XENAZINE US label[1] that EFD and PPND studies had been conducted in rats with 9-desmethyl-β-DHTBZ, the downstream metabolite of β-HTBZ, at doses of 8, 15, and 40 mg/kg/day. In the EFD study, increased embryofoetal mortality and reduced body weight were observed from 15 mg/kg/day and at 40 mg/kg/day, respectively. In the PPND study, increases in gestation duration, stillbirths, and offspring postnatal mortality (40 mg/kg/day); decreases in pup weights (40 mg/kg/day); and neurobehavioural (increased activity, learning and memory deficits) and reproductive (decreased litter size) impairment (15 and 40 mg/kg/day) were observed. The label indicates that exposure levels (AUC) to 9-desmethyl-β-DHTBZ at the NOAEL of 8 mg/kg/day are lower than those attained in patients treated with (non-deuterated) tetrabenazine. However, the Applicant considered that there is no need to include in (section 5.3 of) DTBZ SmPC information on the studies conducted with 9-desmethyl-β-DHTBZ as this is a minor metabolite in humans, representing less than 10% of the total drug-related radioactivity.

No local tolerance studies were conducted with DTBZ or TBZ.

The collective DTBZ-related CNS effects *in vivo* are most likely associated with perturbations of monoamine neurotransmitters. Data from post-marketing experience showed lack of abuse potential for DTBZ. When considering all available evidence, the non-clinical data, including primary and secondary pharmacology, function observation battery in rats, with the clinical experience of DTBZ indicated no abuse potential for DTBZ.

No dedicated toxicology studies are mandatory for excipients considering that no novel excipients are used in deutetrabenazine prolonged-release tablets, and materials meet compendial requirements or are comprised of compendial components.

Several impurities were subject to toxicological qualification as per ICHQ3 through HED calculation from GLP-repeat-dose toxicology studies. No concern was identified.

Deutetrabenazine is likely non-phototoxic and photosafety does not represent a concern.

An ERA was performed to evaluate the potential risk resulting from the use of Austedo 12, 24, 30, 36, 42 and 48 mg PR tablets, according to EMA´s Guidelines on the *Environmental Risk Assessment of Medicinal Products for Human Use* EMEA/CHMP/SWP/4447/00, June 2006 and EMA/CHMP/SWP/44609/2010 Rev. 1, 2016.

[1] NDA 021894 : label

Deutetrabenazine refined PECsurfacewater is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow is below 4.5.

Considering the above data DTBZ is not expected to pose a risk to the environment when used as prescribed.

2.5.7. Conclusion on the non-clinical aspects

Based on the established non-clinical safety profile of DTBZ (with scientifically sound comparability to VMAT2 inhibitor TBZ), the available clinical safety data, post-marketing experience (with more than 73000 patient-years in both TD and HD patients), and in line with 3R principles of animal research, additional animal studies are not expected to provide any additional meaningful information to assess the safety profile of DTBZ and, therefore, these are considered not necessary. The Applicant's view is that non-clinical studies of DTBZ and its active metabolites, deuterated α-HTBZ and deuterated β-HTBZ, produced indistinguishable pharmacology and comparable rodent pharmacokinetics, general toxicity, genotoxicity and embryo-foetal development profiles relative to TBZ and its corresponding non-deuterated metabolites. If this position may be admitted, when strictly comparing data generated with DTBZ *versus* TBZ, several deficiencies were identified from a non-clinical perspective for DTBZ and these deficiencies are also applicable to the reference compound TBZ.

While there are safety margins for DTBZ, there are no or very low safety margins for the active HTBZ metabolites, as animals (rats in the adult and juvenile repeat-dose toxicology studies) were insufficiently exposed to deuterated metabolites. In retrospect, it seems this failure for toxicological qualification at non clinical level was also for HTBZ metabolites within the development of TBZ. Then, it is difficult to reconcile the lack of sufficient exposure in the studies with the applicant's assumption that the non-clinical program supports the approval of DTBZ. This is not in line with ICHM3 requirement. The reason would be to consider that human hindsight on TBZ and clinical data with DTBZ may take precedence over these non-clinical failures.

Experimental demonstration of selectivity of deuterated both TBZ and HTBZ metabolites relative to non-deuterated analogs for VMAT2 *versus* VMAT1 was requested, as well as demonstration of reversibility of binding to VMAT2 and reversible depletion of monoamine. The applicant did not provide further experimental data to establish the comparative selectivity of deuterated *versus* non-deuterated species for VMAT isoforms. It is agreed that binding of DTBZ and its metabolites to VMAT2 did not differ from their non-deuterated counterparts based on studies provided at the time of initial submission. Teva submitted a literature review that justifies the higher selectivity for VMAT2 over VMAT1, as well as reversibility of binding for non-deuterated species. All of these data, combined with the publication showing the reconstruction by cryoelectron microscopy and the functional characterization of the vesicular complex of the monoamine transporter 2-tetrabenazine, render reasonable the extrapolation to deuterated species. In this context, no changes are deemed necessary in section 5.1. of DTBZ PI where stated that 'deuterated α-dihydrotetrabenazine [HTBZ] and deuterated β-HTBZ)', are reversible inhibitors of VMAT2'.

In summary, collective evidence demonstrated that DTBZ is, from a non-clinical perspective, a safe treatment for patients with moderate to severe TD.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by Teva.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.6.2. Clinical pharmacology

Deutetrabenazine (DTBZ) clinical development programme included both randomised fixed-dose and flexible titration regimens, supplemented by clinical pharmacology evaluations and population PK (PopPK) and PK/pharmacodynamics (PD) modelling to support efficacy and safety of the proposed dosing regimen to treat patients with tardive dyskinesia (TD).

The initial pharmaceutical development of DTBZ included comparing exposure of DTBZ with tetrabenazine (TBZ) to inform doses and initial dosing regimen (BID) to be evaluated in patients with TD.

Deutetrabenazine TD clinical development programme comprised three trials in patients with TD, and two in patients with HD-associated chorea providing supportive data, using a **matrix formulation BID**, as well as five Phase 1 trials in healthy participants using an **osmotic PR formulation QD**. The latter is the intended commercial formulation.

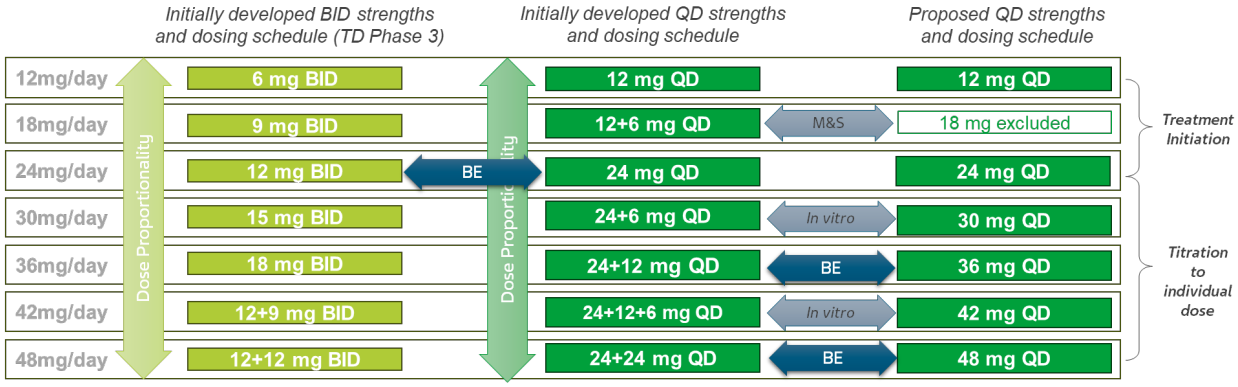
The overall aim of the subsequent pharmaceutical development of the DTBZ osmotic PR drug delivery formulation QD was to match PK exposures of DTBZ to that of the matrix formulation BID, and thereby generate an equivalent therapeutic effect in TD.

Therefore, data from biopharmaceutic studies supported by modelling and simulation formed the basis to bridge efficacy and safety from the clinical matrix formulation BID to the commercial osmotic PR formulation QD (see Figure below).

The approach was supported by Phase 1 PK trials with the proposed commercial osmotic PR formulation QD. The pivotal evidence for the bridging programme is a repeated dose bioequivalence (BE) trial conducted at a single dose strength (24 mg) that demonstrated bioequivalence between osmotic PR formulation QD (test) and matrix formulation BID (reference) (study **TV50717-BE-10179**). Based on the dose proportionality demonstrated for both the matrix formulation BID and the osmotic PR formulation QD (study **TV50717-PK-10175**), the BE findings obtained at 24 mg/day could be extrapolated to other strengths and over the entire dose range. The Phase 1 trials were supplemented by PopPK and PK/PD modelling and simulations, which allowed to predict outcomes of efficacy and safety following administration of the osmotic PR formulation QD.

In addition to these evaluations serving as the main bridging evidence, Teva conducted a trial which demonstrated that DTBZ osmotic PR formulation QD can be taken with or without food (study **TV50717-BE-10165**), and 2 BE trials supporting the registration of additional strengths of the osmotic PR formulation QD, studies **TV50717-BE-10201** and **TV50717-BE-10192**).

Figure 4: Overview of the development of and bridging strategy for the proposed commercial Osmotic PR Tablet QD strengths



BE=bioequivalence; BID=twice daily; M&S=modelling and simulation; PR=prolonged release; QD=once daily; TD=tardive dyskinesia.
Notes: BE of QD 1x24 mg (test) to BID 2×12 mg (reference) was evaluated in Trial TV50717-BE-10179.
BE of QD 1×36 mg (test) to QD 24 mg + 12 mg (reference) was evaluated in Trial TV50717-BE-10201.
BE of QD 1×48 mg (test) to QD 2×24 mg (reference) was evaluated in Trial TV50717-BE-10192.

2.6.2.1. Pharmacokinetics

Population Modelling

The PK data of 378 subjects, from studies **TV50717-PK-10175** and **TV50717-BE-10179,** who received the BID or QD formulation, comprising 25620 α-HTBZ, 25182 β-HTBZ and 25344 parent DTBZ observations, were used for the analysis. A summary of the continuous and categorical covariates characteristics of the data stratified by study is provided in the table below.

Table 2: Summary statistics of continuous and categorical information for subjects included in the analysis dataset

Characteristic	TV50717-BE-10179 [N=262]	TV50717-PK-10175 [N=116]	TOTAL [N=378]
Age (years)	38.6 (9.27) [18-55]	40.9 (10.4) [19-55]	39.3 (9.69) [18-55]
Body mass index (kg/m2)	26.7 (2.74) [18.8-30]	26.7 (2.71) [19.8-29.9]	26.7 (2.72) [18.8-30]
Body weight (kg)	76.4 (11.4) [50-100]	75.2 (10.8) [50.2-99]	76.1 (11.2) [50-100]

N: Number of subjects
Entries represent: Mean (Standard deviation) [Minimum-Maximum]

Characteristic	Category	TV50717-BE-10179 [N=262]	TV50717-PK-10175 [N=116]	TOTAL [N=378]
Indication	HV	262 (100%)	116 (100%)	378 (100%)
Female Gender	No	173 (66%)	65 (56%)	238 (63%)
	Yes	89 (34%)	51 (44%)	140 (37%)
Race	White	228 (87%)	99 (85.3%)	327 (86.5%)
	Black or African American	34 (13%)	17 (14.7%)	51 (13.5%)
Ethnicity	Not Hispanic or Latino	2 (0.763%)	1 (0.862%)	3 (0.794%)
	Hispanic or Latino	260 (99.2%)	115 (99.1%)	375 (99.2%)
CYP2D6 metabolizer status	UM	0 (0%)	0 (0%)	0 (0%)
	EM	248 (94.7%)	110 (94.8%)	358 (94.7%)
	IM	14 (5.34%)	6 (5.17%)	20 (5.29%)
	PM	0 (0%)	0 (0%)	0 (0%)

N: Number of subjects, EM: extensive metabolizers, HV: healthy volunteer, IM: intermediate metabolizers, PM: poor metabolizers, UM: ultra-metabolizers.
Values represent the number of subjects in each category and percentage within this category.

Sex categorical covariate was included in the final model for α-HTBZ. The Pop-PK dataset (PMX-21-14-Ver-01) included 238 males (63%) and 140 females (37%). Overall, the effect of sex was not identified to significantly impact the clearance (CL) parameter of DTBZ and its deuterated α- and β-HTBZ active metabolites, as outlined in SmPC section 5.2.

The subject race and ethnicity were highly unbalanced as most subjects falling under the white (86.5%) and "Hispanic or Latino" (99.2%) category. In the course of the procedure, the applicant provided new PK data and reports with regards to the effect of race (e.g., TV50717-PK-10198 CSR and Report PMXM-2024-07). As suggested by the aggregated data provided, it is agreed that race is unlikely to be an important covariate. This information is outlined in SmPC section 5.2.

The CYP2D6 metabolizer status was also imbalanced (i.e., 94.7% of extensive metabolizers vs. 5.3% of intermediate). The poor and ultra-rapid CYP2D6 metabolizer statuses were not included in studies TV50717-PK-10175 and TV50717-BE-10179. Therefore, the numbers of subjects in the CYP2D6 intermediate (n= 20, 5.3%), poor (n=0) and ultra-rapid (n=0) metabolisers were too low and not considered sufficient to detect a potential clinically relevant change in PKs. Therefore, no formal conclusion could initially be drawn for these subgroups of patients.

In the course of the procedure, the applicant addressed this concern. The drug-drug interaction potential of DTBZ co-administration with a strong CYP2D6 inhibitor, paroxetine, was studied in healthy participants in study **SD-809-C-08** and SmPC section 4.5 updated with results from the performed *in vivo* study with paroxetine pointing out that *"In the presence of a strong CYP2D6 inhibitor (paroxetine), systemic exposure of the individual active metabolites increased 1.9-fold for deuterated α-dihydrotetrabenazine [HTBZ] and 6.5-fold for deuterated β-HTBZ resulting in an overall 3-fold increase in the active metabolites, deuterated total (α + β)-HTBZ (see section 5.2)".* Furthermore, submitted data justified inclusion in SmPC section 4.2 that in patients who are poor CYP2D6 metabolisers, the daily dose of DTBZ should not exceed 36 mg. The reader should refer to sub-section 2.6.8.13 (Safety related to drug-drug interactions and other interactions - CYP2D6 inhibitors) of this AR for further details.

The PK of parent DTBZ, α-HTBZ, and β-HTBZ population was described by a two-compartment model with linear elimination. Models for HTBZ, α- and β-HTBZ metabolite appear to be developed separately for each compound which might not be optimal if all three entities contribute to pharmacological effect. Previously developed α-HTBZ, and β-HTBZ population PK models were predictive of the new BID data. The QD data was modelled by adding a parallel first- and zero-order absorption model with lag times to the previous BID model and only estimating QD-related absorption parameters. Model for β-HTBZ failed the qualification step and subsequently scaling factor indicating 23% decrease in clearance (CL) was applied so the model could be predictive of the data. This is not considered a good modelling practice. Moreover, Visual Predictive Check (VPC) plot for the parent indicates that the model overpredicts variability of both formulations.

Nevertheless, the population PK parameter estimates of the final model were overall precisely estimated. Model diagnostics for all analytes and VPCs of the final model for 24 mg QD stratified by studies did not reveal any major deficiencies. Overall, it was agreed that the PK models well described the PK data from the studies TV50717-PK-10175 and TV50717-BE-10179; although some under-prediction of 5th and 95th percentiles of the observed data was noted.

Based on model results, the $C_{avg,ss}$ (steady-state average concentration) exposures and AUC were overall comparable between BID and QD formulations: geometric mean of $C_{avg,ss}$ total metabolites was 17.8 ng/mL for QD compared to 19.5 ng/mL for the BID following 24 mg dose and 35.6 ng/mL for QD versus 39.01 for BID following 48 mg dose. However, the QD formulation was shown to provide approximately 25% lower C_{max} compared to the BID formulation: geometric mean of $C_{max,ss}$ total metabolites was 23.5 ng/mL for QD compared to 31.45 ng/mL for the BID following 24 mg and 46.9 ng/mL for QD versus 63.2 for BID following 48 mg dose.

The impact of this lower C_{max} on efficacy endpoint, namely the change from baseline in the total motor Abnormal Involuntary Movement Scale (AIMS) score, was evaluated at steady-state in TD patients using the previously linear E-R models under the alternative assumptions that C_{max} or C_{avg} (average concentration) of total (α + β)-HTBZ is the main predictor of efficacy.

Under the conservative assumption that $C_{max,ss}$ is the major driver of efficacy, E-R analyses suggested a maximum decrease in efficacy of -13.4% in patients with TD using the QD product at the 48 mg dose. Given that the approval of the proposed prolonged release tablets is based on a bridging strategy from the IR tablets (as the reference drug-product), approval of QD product depend on clinical efficacy demonstration and its extrapolation from the IR formulation.

The decrease in efficacy was less marked (below 10%) at lower doses: -5.1 and -8.7% for the 12 and 24 mg doses, respectively. The predicted absolute change in Abnormal Involuntary Movement Scale (AIMS) scores were ≤ 0.4 points (-2.94 versus -2.54 for the 48 mg dose) with 90th percentiles largely overlapping, when assessing the impact of C_{max} and C_{avg} following BID versus QD dosing. The table below summarises the change from baseline results in AIMS Score at steady state, using $C_{max,ss}$ as predictor.

Table 3: Overview of the change from baseline in AIMS Score at steady-state based on Cmax,ss as predictor in extensive CYP2D6 metabolizers between the BID and QD formulations

Total daily dose	CHGBL AIMS [BID Cmax,ss]	CHGBL AIMS [QD Cmax,ss]	QD-vs-BID CHGBL AIMS [%BID]
12 mg	-1.8 [-6.93, 3.34]	-1.71 [-6.84, 3.42]	-5.12%
24 mg	-2.17 [-7.31, 3.01]	-1.98 [-7.2, 3.22]	-8.69%
48 mg	-2.94 [-8.02, 2.21]	-2.54 [-7.74, 2.67]	-13.4%

Simulated values are reported as 'mean [5% quantile, 95% quantile]'. For the relative change comparison of the mean, the values represent the ratio of the reported QD and BID metrics (i.e., 100*([value QD]/[value BID] - 1)).

Absorption

Characterization of DTBZ absorption following oral administration was based on data from studies **SD-809-C-12** (mass balance study), **TV50717-SAD-10132, TV50717-BE-10165, TV50717-BE-10179, TV50717-BE-10192 and TV50717-BE-10201**. Moreover, data from *in vitro* studies evaluated the relevant absorption transporters involved in DTBZ absorption.

Following oral administration, DTBZ is rapidly metabolised in the liver by the enzyme carbonyl reductase to its active deuterated metabolites alpha-dihydrotetrabenazine (α-HTBZ) and beta-dihydrotetrabenazine (β-HTBZ), which are isomers. These metabolites are subsequently metabolised, primarily by CYP2D6 with minor contributions from CYP1A2 and CYP3A4/5.

DTBZ and its deuterated α-HTBZ and β-HTBZ metabolites were found not to be substrates of efflux transporters, including multidrug resistance protein 1 (MDR1, also called permeability glycoprotein [P-gp]) and breast cancer resistance protein (BCRP).

After administration of [^{14}C]-radiolabelled DTBZ in the mass balance study (SD-809-C-12) the extent of absorption was estimated as at least 80%, based on total recovered radioactivity in urine. Moreover, it was observed that plasma SD-809 exposure (AUC_{0-t}) represents approximately 0.04% of plasma d_6-(α+β)-HTBZ metabolites exposure.

Study TV50717-SAD-10132

In study TV50717-SAD-10132, single ascending doses of 24, 48 and 72 mg DTBZ were administered to CYP2D6 extensive/intermediate (EM) and poor metabolizers (PM).

For the CYP2D6 extensive/intermediate metabolizers, the geometric mean C_{max} values for parent (DTBZ) were 159, 224, and 540 pg/mL following the 24, 48, and 72 mg doses, respectively, and the corresponding median t_{max} values were 4.0 hours, generally ranging from 2.00 to 6.00 hours.

For the CYP2D6 poor metabolizers, the C_{max} value for parent (DTBZ) at the 72 mg dose level was similar to the extensive/intermediate metabolizers, with respective geometric mean C_{max} values of 568 pg/mL versus 540 pg/mL. For the 24 mg and 48 mg dose levels, an outlier subject was observed, increasing

C_{max} levels and inter-subject variability. The subject's C_{max} for parent (DTBZ) following the 24 and 48 mg doses (i.e. 5517.66 pg/mL and 11746.19 pg/mL) exceeded more than 33- to 37-times the geometric mean (without the outlier) C_{max} for the corresponding dose levels (i.e. 166.798 pg/mL and 320.383 pg/mL). However, the outlier subject's $AUC_{0-\infty}$ for DTBZ following the 24 and 48 mg doses (i.e. 25360.22 pg.h/mL and 77558.58 pg.h/mL) represented respectively 0.66% and 1.15% of subject's total [α+β]-HTBZ (i.e. 3819038.95 pg.h/mL for the 24 mg dose level and 6736664.5 pg.h/mL for the 48 mg dose level).

For the poor metabolizers, median t_{max} values (range) were 3.0 hours for the 24 mg dose, and 3.5 hours for both the 48 and 72 mg doses.

For the extensive/intermediate metabolizers, the geometric mean C_{max} values for (α+β)-HTBZ was 50410, 115418, and 153613 pg/mL following the 24, 48, and 72 mg doses, respectively. The corresponding median (range) t_{max} values were 4.0 hours for the 24 mg dose, and 6.0 hours for both the 48 and 72 mg doses.

For the poor metabolizers, the geometric mean C_{max} values for (α+β)-HTBZ was more than 1.5-times higher than in cohort 1EM at the same doses of 24, 48, and 72 mg, with respective geometric mean C_{max} values of 87586, 178699, and 252888 pg/mL. Peak concentrations appeared at comparable times for the PM and EM cohorts.

The maximum exposure to parent at all dose levels was less than 1% compared to exposure to the active metabolites (total [α+β]-HTBZ).

Study TV50717-BE-10165

The absorption of DTBZ (parent) was rapid on average following a single dose administration of the 24 mg QD osmotic tablet formulation on fasting condition, with a median t_{max} of 1.0 h (range 1.0 to 24h). On fed state conditions, absorption was delayed, with median t_{max} estimated as 4 h (range 1.0 to 18h).

Little to no lag time was observed (median t_{lag} as 0 h, range 0-2 h) after administration of the 24-mg QD osmotic tablet (test).

Regarding α-HTBZ, the median t_{max} was estimated as 6.0 h (range 1.0 to 18h) on fasting conditions and as 11.9 h (range 1.0 to 18h) on fed conditions. Regarding β-HTBZ, the median t_{max} as estimated as 1.5 h (range 1.0 to 18h) on fasting conditions and as 6.0 h (range 1.0 to 16h) on fed conditions.

The exposure ($AUC_{0-\infty}$) to DTBZ following administration of the 24-mg QD osmotic tablet on fed and fasting states represented 0.42% and 0.45% of the corresponding total [α+β]-HTBZ metabolite exposure, respectively.

Study TV50717-BE-10179

The absorption of DTBZ (parent) was rapid on average following multiple dose administration of the 24 mg QD osmotic tablet formulation on fed condition, with a median $t_{max, ss}$ (Time to maximum observed drug concentration during a dosing interval) of 3.0 h (range 0.0 to 24h). In comparison to the immediate BID formulation, in general, the PR QD formulation resulted in more controlled drug release over the 24h period and a relatively flatter PK curve.

For Day 7, in the period of 0 to 24h, subjects ID , and showed the highest concentration ($c_{max,ss}$) at pre-dose (corresponding to the 24 h post dose of Day 6). Therefore, for these subjects $t_{max,ss}$ was estimated as 0 h, being considered not to reliably estimate $c_{max,ss}$ following administration of the 24 mg QD osmotic tablet on Day 7. However, given the high number of subjects, this wrongly estimated values did not

affect the median $t_{max,ss}$. Nevertheless, the appropriate range to be considered should be the range determined for Day 6, i.e. [0.5 to 23.75]h.

It was observed for both Day 6 and 7 that some subjects showed a delayed absorption of DTBZ for the ER component of the formulation, with $t_{max,ss}$ estimated as ~24h.

For both α-HTBZ and β-HTBZ, the median t_{max} was estimated as 3.0 h (range 1.0 to 18h) on fed condition.

The steady state exposure ($AUC_{0-24,ss}$) to DTBZ following administration of the 24-mg QD osmotic tablet on fed state represented 0.45% of the corresponding total [α+β]-HTBZ metabolite steady state exposure.

Study TV50717-BE-10192

Following single dose administration of the 48 mg QD osmotic tablet (test) or 2x24 mg QD osmotic tablet (reference), on fasting condition, two distinctly peaks in mean plasma DTBZ (parent) concentration were observed, attributable to, respectively, the IR and ER components of the QD tablet formulation. Both treatments administered in the fasted state showed a median $t_{max, ss}$ of 8.0 h (range 0.5 to 36h). The geometric mean for C_{max} following the administration of 48 mg QD osmotic tablet or 2x24 mg QD osmotic tablet was approximately 280 pg/mL.

One participant (ID, female, extensive metabolizer) presented a pharmacokinetic profile showing a very high exposure to DTBZ. The observed C_{max} for this participant was approximately 10 times higher than the highest observed C_{max} value for all the other participants, for both test and reference products and the derived AUC_{0-t} was approximately 11 times and 5 times higher than the highest derived AUC_{0-t} value for all the other participants, for test and reference products, respectively. A similar pattern was seen for $AUC_{0-\infty}$ parameter.

The DTBZ elimination $t_{1/2}$ for the outlier participant no. showed estimates for test and reference within the range of $t_{1/2}$ values derived for all the other participants. Therefore, increased DTBZ exposure seems not to be related with the elimination of DTBZ.

Separate investigations at the clinical site and bioanalytical laboratory were performed and did not indicate that the high DTBZ plasma concentrations in this participant were due to sample processing, storage, or other protocol deviation/violations.

For both α-HTBZ and β-HTBZ, the median t_{max} was estimated as 2.0 h (range 0.5 to 24h) and 1.5 h (range 1.0 to 24h), on fasting condition. The geometric mean for C_{max} following the administration of 48 mg QD osmotic tablet or 2x24 mg QD osmotic tablet was 23.2 ng/mL for α-HTBZ and approximately 13.7 ng/mL for β-HTBZ.

For the outlier with high DTBZ (parent) plasma concentrations (Participant), for all post-dose PK timepoints, the α-HTBZ and β-HTBZ plasma concentrations for test and reference treatment fall within the minimum/maximum range reported for the other participants (i.e., with outlier data excluded).

The single participant with outlier DTBZ (parent) plasma concentrations did not experience any adverse events (AEs); none of the changes in their laboratory test results, vital signs, or physical examination measurements were considered clinically significant.

The exposure ($AUC_{0-\infty}$) to DTBZ following administration of the 1x48 mg QD tablet and the 2x24 mg QD tablets represented 0.45% and 0.44% of the corresponding total [α+β]-HTBZ metabolite exposure, respectively.

Study TV50717-BE-10201

Following single dose administration of the 36 mg QD tablet (test) or 1×12 mg + 1×24 mg DTBZ QD tablets (reference), on fasting condition, two distinct peaks in mean plasma DTBZ (parent) concentration were shown, attributable to the IR and ER components of the QD tablet formulation.

The absorption of DTBZ (parent) was rapid on average, with little to no lag time observed (median t_{lag} of 0.00 h) after administration of the 1×36 mg QD tablet (test) and 1×12 mg + 1×24 mg QD tablets (reference). The time to maximal concentration (t_{max}) for DTBZ (parent) differed between the test (median of 6.0 h, range 0.5-48.0h) and reference (median of 1.5 h, range 0.5-20.0h), but the median values still fell within each reported range. Similar results were obtained for all other PK parameters comparing the 1×36 mg QD tablet (test) and 1×12 mg + 1×24 mg QD tablets (reference). The geometric mean for C_{max} following the administration of 36 mg QD tablet (test) or 1×12 mg + 1×24 mg DTBZ QD tablets was 238 pg/mL.

One participant (ID, female, extensive metabolizer) presented a pharmacokinetic profile showing a very high exposure to DTBZ. The observed C_{max} for this participant was approximately 10 times higher than the highest observed C_{max} value for all the other participants, for both test and reference products and the derived AUC_{0-t} was approximately 10 times and 5 times higher than the highest derived AUC_{0-t} value for all the other participants, for test and reference products, respectively. A similar pattern was seen for $AUC_{0-\infty}$ parameter.

The DTBZ elimination $t_{1/2}$ for the outlier participant ID showed estimates for test and reference within the range of $t_{1/2}$ values derived for all the other participants. Therefore, increased DTBZ exposure seemed not to be related with the elimination of DTBZ.

Separate investigations at the clinical site and bioanalytical laboratory were performed and did not indicate that the high DTBZ plasma concentrations in this participant were due to sample processing, storage, or other protocol deviation/violations.

For both α-HTBZ and β-HTBZ, t_{max} (time to maximum observed drug concentration during a dosing interval) differed between the test (median = 1.5, range 1.0-18.0) and reference (median of 11.0, range 1.0-20.0h), but the median values still fell within the reported range. Therefore, there was an inversion on t_{max} values between DTBZ (parent) and its metabolites: for the fastest parent median t_{max} (i.e., 1.5h for the reference) corresponds to delayed t_{max} for metabolites (i.e., 11h), while for the delayed parent median t_{max} (6.0h for the test) corresponds the fastest t_{max} for metabolites (i.e., 1.5h).

For the outlier with high DTBZ (parent) plasma concentrations (Participant), for all post-dose PK timepoints, the α-HTBZ and β-HTBZ plasma concentrations for test and reference treatment fell within the minimum/maximum range reported for the other participants (i.e., with outlier data excluded).

The single participant with outlier DTBZ (parent) plasma concentrations did not experience any AEs. None of the changes in this participant's laboratory test results, vital signs, or physical examination measurements was considered clinically significant.

The exposure ($AUC_{0-\infty}$) to DTBZ following administration of the 1×36 mg QD tablet (test) and 1×12 mg + 1×24 mg QD tablets represents 0.42% and 0.56% of the corresponding total [α+β]-HTBZ metabolite exposure, respectively.

With regards to SmPC section 5.2 (absorption), as supported by the submitted clinical documentation, the text below was agreed by the CHMP:

"*Following oral administration of deutetrabenazine, the extent of absorption is at least 80%.*

Peak plasma concentrations of deutetrabenazine and its active metabolites (deuterated α HTBZ and deuterated β HTBZ) are reached within 3 hours after repeated dosing, followed by sustained plateaus for several hours allowing for a 24-hour dosing interval."

Bioavailability

The biopharmaceutical programme for DTBZ started by evaluating the impact of deuteration on the exposure to DTBZ compared to TBZ, in order to leverage the similar pharmacological effect and select the most appropriate dosing regimen. Results showed that the attenuated metabolism of DTBZ compared to TBZ allowed to achieve comparable exposure (i.e., AUC) with approximately half of the DTBZ drug load, and that the prolonged half-life supported a BID dosing schedule compared to the 3 times a day (TID) dosing schedule sometimes used for TBZ.

The absolute bioavailability (BA) of DTBZ was not determined due to the inability to formulate DTBZ as a solution for IV administration, given its low solubility. However, after administration of [^{14}C]-radiolabelled DTBZ in the mass balance study **SD-809-C-12** the extent of absorption was estimated as at least 80%, based on total recovered radioactivity in urine. Based on the extensive metabolism and on the very low relative exposure (AUC) of parent DTBZ in relation to metabolites (total (α+β)-HTBZ), a low absolute bioavailability is expected. Moreover, DTBZ solubility data and permeability data from mock transfected (control) and breast cancer resistance protein (BCRP) transfected MDCKII or multidrug resistance protein 1 (MDR1) transfected Abcb1KO-MDCKII cell monolayers, enable to classify DTBZ as BCS Class II (low solubility, high permeability), according to ICH M9 guideline.

The pharmacokinetics and relative bioavailability of DTBZ, in comparison to tetrabenazine (TBZ) and their respective α-HTBZ and β-HTBZ metabolites, following the same 25 mg single oral dose on the form of powder in gelatin capsules, was evaluated in study **AUS-SD-809-CTP-06**. Following this study results, a new study was performed (study **AUS-SD-809-CTP-07**) to evaluate safety and pharmacokinetics of two candidate formulations of DTBZ relative to TBZ and to select a DTBZ formulation for further use in other clinical trials.

Study AUS-SD-809-CTP-06

Plasma concentrations of both tetrabenazine (TBZ) and DTBZ were low and transient relative to the concentrations observed for their respective metabolites.

In the CYP2D6 extensive metabolizers, plasma concentrations for deuterated metabolites (d_6-α-HTBZ and d_6- β-HTBZ) were higher than the corresponding non-deuterated metabolites (α-HTBZ and β-HTBZ).

For extensive metabolizers, the mean elimination $t_{1/2}$ were nearly double for total d_6-(α+β)-HTBZ (7.61 hours) than for total (α+β)-HTBZ (4.05 hours). In addition, C_{max} values were slightly higher (mean 67.9 versus 60.1 ng/mL) and t_{max} slightly later (median 1.5 hours versus 1.0 hour) for total d_6-(α+β)-HTBZ compared to total (α+β)-HTBZ. Overall, exposure to total d_6-(α+β)-HTBZ as assessed by $AUC_{0-\infty}$ was more than double that calculated for total (α+β)-HTBZ (mean 414 versus 177 ng·h/mL). A similar effect of deuteration was observed looking at all evaluable subjects, however, as expected, mean exposure ($AUC_{0-\infty}$) and elimination $t_{1/2}$ for both α-HTBZ and d_6-α-HTBZ were higher when CYP2D6 IMs and PMs were included in the analysis.

Based on their similar median t_{max} and mean C_{max} values, deuteration did not appear to affect the apparent rate of conversion of DTBZ to its α-HTBZ and β-HTBZ metabolites compared with the apparent rate of conversion of TBZ to its α-HTBZ and β-HTBZ metabolites. The increased exposure (as assessed by AUC) to total (α+β)-HTBZ following administration of DTBZ arose from attenuated metabolism of the α-HTBZ and β-HTBZ metabolites to their respective O-demethylated metabolites, by CYP2D6, relative to the metabolism of the α-HTBZ and β-HTBZ metabolites of TBZ to their respective O-demethylated metabolites.

Study AUS-SD-809-CTP-07

In Part 1, two matrix-based SD-809 ER formulations as candidate formulations for the matrix tablet BID drug product were tested: Formulation A, containing 15 mg DTBZ, was a gastro-erosional tablet and Formulation B, containing 15 mg DTBZ, was a gastro-retentive tablet.

In Part 1, the relative bioavailability was compared between corresponding metabolites of SD-809 and tetrabenazine for each of the two test formulations in both the fasted and fed state. The C_{max} values of all HTBZ metabolites were significantly lower for both SD-809 ER formulations at a dose level of 15 mg than for tetrabenazine at a dose level of 25 mg. The t_{max} values were significantly later for the metabolites of both SD-809 ER formulations compared with tetrabenazine (2.5 to 6 hours compared with 1 hour). The apparent half-life was found to be significantly longer for the HTBZ metabolites of SD-809 compared with tetrabenazine. However, the AUC_{0-t} values for fasted dose administration were generally comparable between the products. In the fed state there was a moderate increase in AUC_{0-t} with the administration of DTBZ. Therefore, in comparison to tetrabenazine 25 mg on fasting conditions, administration of either ER formulation (A and B) preserved the systemic exposure to the active metabolites, while substantially reducing the C_{max}.

Following review of the pharmacokinetic and safety data from Part 1, formulation A (gastro-erosional tablet) was selected for dosing in Part 2.

Part 2 was an open-label, single ascending dose (7.5 mg, 15 mg and 22.5 mg) and multiple ascending dose (7.5 mg BID, 15 mg BID and 22.5 mg BID) investigation of SD-809 ER and tetrabenazine (25 mg) in healthy subjects.

In this Part 2, following single and multiple doses, the terminal elimination half-lives for d_6-α-HTBZ, d_6-β-HTBZ, and d_6-(α+β)-HTBZ for all SD-809 ER doses administered were longer than their non-deuterated counterparts in the tetrabenazine control. For SD-809 ER following both single doses and at steady state, both AUC and C_{max} of d_6-α-HTBZ, d_6-β-HTBZ, and d_6-(α+β)-HTBZ increased with increasing doses. The median t_{max} of HTBZ analytes was consistent at 3 to 4 hours post-dose for both single dose and steady state across the dose range of SD-809 ER, compared with approximately 1 hour for tetrabenazine. At steady state, the peak to trough fluctuation for the HTBZ analytes of SD-809 was much lower (3- to 6-fold) than those observed for the corresponding analytes of tetrabenazine (8- to 21-fold).

The relative bioavailability of each SD-809 ER dose was not calculated in comparison to tetrabenazine 25 mg, on both single dose and steady sate conditions. Nevertheless, on steady state, the AUC_{0-12} derived for d_6-(α+β)-HTBZ following administration of the SD-809 ER 15 mg BID regimen was similar to the AUC_{0-12} derived for (α+β)-HTBZ following administration of a tetrabenazine 25 mg BID regimen.

As determined from regression models using exposure data from single dose ($AUC_{0-\infty}$) and from steady-state (AUC_{0-12}), the dose of DTBZ that provided a comparable exposure derived for total (α+β)-HTBZ to that provided by TBZ 25 mg was estimated to be between 11.4 and 13.2 mg. Similar estimates were obtained using power model regression and linear model regression analyses.

For both parts, plasma concentrations of both tetrabenazine (TBZ) and DTBZ were low and transient relative to the concentrations observed for their respective metabolites.

Bioequivalence

Following approval of DTBZ as a matrix-based formulation for BID administration under the brand name AUSTEDO® in the United States (US) for treatment of TD on 30 August 2017, and subsequently in several other countries (China, Israel, South Korea, Australia, Brazil, and Chile), a once-daily (QD) tablet was developed to further improve ease of use, decrease pill burden, and potentially improve adherence. The osmotic drug delivery system was chosen for the osmotic PR formulation QD development programme based on the results of study **TV50717-BA-10150** (**using PR-only prototype**).

Characterization of bioequivalence using DTBZ QD osmotic tablet formulation is based on data from studies **TV50717-BE-10165, TV50717-BE-10179, TV50717-BE-10192** and **TV50717-BE-10201**.

Study TV50717-BE-10165

Following oral administration of a single 24 mg osmotic PR tablet QD, compared to a single 12 mg matrix tablet BID administered twice, 12 h apart under fed conditions in healthy participants, bioequivalence was demonstrated for AUC_{0-t} and $AUC_{0-\infty}$ for the α- and β-HTBZ metabolites (individually and as a sum), but not for the DTBZ (parent), where a higher exposure was observed. Regarding C_{max}, the 24 mg osmotic PR tablet QD showed a lower bioavailability for DTBZ (parent) and for the metabolites α- and β-HTBZ (individually and as a sum). Difference in C_{max} between the test and reference was to be expected considering the osmotic pump technology employed in the 24 mg osmotic tablet administered as a single dose.

Study TV50717-BE-10179

Following oral administration of 24 mg osmotic PR tablet QD, compared to 12 mg matrix tablet BID in healthy participants, in the fed state, for the steady state it was observed that bioequivalence criteria for $AUC_{0-24h,ss}$ were met for all analytes and also for $C_{max,ss}$ of DTBZ (parent). In addition, $C_{min,ss}$ (steady-state minimum observed plasma concentration) of α-HTBZ, β-HTBZ and total (α+ β)-HTBZ) met bioequivalence criteria. The release profile from the osmotic pump did slightly affect some PK parameters that did not meet BE criteria (lower bioavailability on $C_{max,ss}$ for the active metabolites and higher bioavailability for DTBZ $C_{min,ss}$). The clinical relevance of $C_{max,ss}$ difference of the active HTBZ metabolites as well as the PK shape difference was further evaluated by the E-R analyses.

Study TV50717-BE-10192

Following oral administration of a single dose of a DTBZ 1x48 mg QD tablet (test), compared with a single dose of DTBZ 2x24 mg QD tablet (reference) under fasted conditions, bioequivalence was concluded for the parent and α- and β-HTBZ metabolites (individually and as a sum) on C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

Study TV50717-BE-10201

Following oral administration of a single dose of a DTBZ 1×36 mg QD tablet (test), compared with a single dose of DTBZ 1×12 mg + 1×24 mg QD tablet (reference), under fasted conditions, bioequivalence was concluded for the parent and α- and β-HTBZ metabolites (individually and as a sum) on C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

Regarding the 12 mg strength, data on dose proportionality of DTBZ after single dose can be derived from trial TV50717-PK-10175 (using the osmotic PR tablets) and from Trial SD-809-C-11 (using the DTBZ matrix BID tablets). As per provided results, the systemic exposure [in terms of parent DTBZ and (α+β)-HTBZ active metabolites], of a PR 24 mg tablet is twice than that of a PR 12 mg tablet (assuming PK linearity). Therefore, the 12 mg strength can be considered for approval, although noted that a formal comparison 2*12 mg *vs* 1*24 mg would have been more relevant.

Influence of Food

The influence of food on the pharmacokinetics of DTBZ and its α- and β-HTBZ active metabolites (individually and as a sum) was assessed in study **TV50717-BE-10165** following administration of DTBZ 24 mg QD osmotic tablet formulation.

A high calorie, high-fat breakfast had no effect on the pharmacokinetics of DTBZ (parent) and its active metabolites (deuterated α-HTBZ and β-HTBZ). Consequently, osmotic PR tablets QD may be

administered with or without food. Therefore, with regard to the SmPC, as supported accordingly by clinical documentation, the following wording was agreed for section 4.2 and 5.2:

Section 4.2 (Method of Administration)

"The prolonged-release tablets can be taken with or without food."

Section 5.2 (Absorption)

"Absorption is not influenced by food intake."

Distribution

The concentration range tested (0.1 µM and 10 µM) for the different analytes (DTBZ, α-HTBZ and β-HTBZ) was considered appropriate, covering the geometric mean C_{max} values at steady state for each analyte, observed in study TV5017-BE-10179, following multiple dose administration of DTBZ 24 mg osmotic PR tablet (i.e., 0.183 ng/mL for DTBZ, 18.20 ng/mL for α-HTBZ and 8.68 ng/mL for β-HTBZ), by 1768 fold for DTBZ, by 18 fold for α-HTBZ and by 37 fold for β-HTBZ.

The apparent volume of distribution (V/F) was estimated from the different phase 1 studies performed with the osmotic PR formulation QD. The geometric means for V/F estimates ranged between 261908 L to 334547 L and were similar between studies. An overall mean can be calculated as 299188 L. Based on PopPK modelling (report PMX-21-14-Ver-01) the volume of distribution for the central compartment (Vc/F) and for the peripheral compartment (Vp/F) for DTBZ = deuterated α-HTBZ and deuterated β-HTBZ, were estimated and the wording below agreed for inclusion in SmPC section 5.2:

"The protein binding of deutetrabenazine, deuterated α-HTBZ and deuterated β-HTBZ in human plasma is 82%, 57%, and 49% respectively, with no preferential binding of total radioactivity to the cellular components of human blood after ^{14}C-deutetrabenazine administration.

Single oral dose of either ^{14}C-deutetrabenazine or ^{14}C-tetrabenazine to rats in a quantitative whole-body autoradiography study resulted in similar blood to brain ratios. Results of PET scan studies in humans showed that following intravenous injection of ^{11}C-tetrabenazine or α-HTBZ, radioactivity is rapidly distributed to the brain, with the highest binding in the striatum and lowest binding in the cortex. No human PET scan studies have been performed with deutetrabenazine.

Based on population pharmacokinetic modelling, after oral administration, the apparent volumes of distribution (Vc/F) for deutetrabenazine, deuterated α HTBZ, and deuterated β HTBZ is 13 700 L, 490 L, and 860 L, respectively".

Elimination

In the mass balance study **SD-809-C-12**, a single oral dose of 25 mg [^{14}C]-SD-809 was administered in the fasted state, in the form of powder in capsule. Therefore, it is not expected any deviation on the observed study results due to the formulation. Urine samples were collected from pre-dose to the morning of Day 8 (168 h post-dose); faecal samples were collected from admission until discharge (up to 216h).

A mean total radioactivity of 82.90% (range 75% to 86%) and of 9.32% (range 8% to 10%) from the administered dose was recovered in urine and faeces, respectively.

A mean total radioactivity of 92.2% from the administered dose was recovered (range 84% to 97%, with 5 subjects showing more than 90% recovered and one subject with 84% recovered).

This shows an asymptotic cumulative radioactivity curve (urine and faeces).

In conclusion, the total recovery in the mass balance study is considered as sufficient.

Given that the majority (>80%) of radioactivity was recovered in the urine, renal clearance is the main pathway of elimination for all radiolabelled drug-derived materials. Urinary excretion of the deuterated α-HTBZ and β-HTBZ metabolites accounted for <10% of the administered dose.

In urine samples it was noted a mean of 65.7% of sample radioactivity regarding metabolites U1 to U5, and 27.2% regarding additional minor metabolites. Therefore, a total mean of 92.9% of sample radioactivity has been characterized in the urine.

Based on the different phase 1 studies performed with the osmotic PR formulation QD, the elimination $t_{1/2}$ of DTBZ, and deuterated α-HTBZ, β-HTBZ, and total (α+β)-HTBZ metabolites were estimated as approximately 17 hours, 12 hours, 9 hours, and 11 hours, respectively. These estimates are in agreement with popPK model estimates of 11.4 hours for DTBZ, 11 hours for α-HTBZ, and 8.2 hours for β-HTBZ.

Based on the different phase 1 studies performed with the osmotic PR formulation QD, the geometric means for the apparent clearance (CL/F) of DTBZ ranged between 11601 L/h to 13001 L/h and showed to be similar between studies. An overall mean of 12103 L/F can be calculated. Based on PopPK modelling, CL/F for DTBZ, α-HTBZ, and β-HTBZ were estimated as 11750 L/h, 67 L/h, and 260 L/h, respectively. Estimates from non-compartmental analysis and PopPK analysis are concordant.

With regard to SmPC, the following wording, supported accordingly by clinical documentation, was agreed for Section 5.2 (Elimination):

"In a mass balance study in six healthy subjects, 75% to 86% of the deutetrabenazine dose was excreted in the urine, and faecal recovery accounted for 8% to 11% of the dose. Urinary excretion of deuterated α-HTBZ and deuterated β-HTBZ each accounted for less than 10% of the administered dose. Sulphate and glucuronide conjugates of deuterated α-HTBZ and deuterated β-HTBZ, as well as products of oxidative metabolism, accounted for the majority of metabolites in the urine.

Based on population pharmacokinetic modelling, after oral administration, for deutetrabenazine, deuterated α-HTBZ and deuterated β-HTBZ, the apparent clearance values (CL/F) are 11,750 L/h, 67 L/h, and 260 L/h; the half-lives are 11.4 h, 11 h, and 8.2 h".

Deutetrabenazine and its active metabolites are not substrates or inhibitors of the human transporters, predominantly located in the liver, intestines, central nervous system (CNS) and kidney, that were studied in vitro at clinically relevant concentrations.

Metabolism

The metabolites of DTBZ in human circulation were determined from an open-label, 2-period Phase 1 ADME study that compared the mass balance, metabolite profile, and metabolite identification after a single 25-mg oral dose of [^{14}C]-DTBZ with a single 25 mg oral dose of [^{14}C]-TBZ. As a complement to the clinical ADME trial, the metabolism of DTBZ, deuterated α-HTBZ and β-HTBZ was investigated in *in vitro* systems and compared to the corresponding non-deuterated compounds.

The main metabolic pathway for both DTBZ and TBZ starts with their rapid reduction to the active metabolites α-HTBZ and β-HTBZ by carbonyl reductase. DTBZ and TBZ were found to be present at similarly low levels in plasma. Plasma exposure to deuterated HTBZ metabolites was greater than exposure to the corresponding nondeuterated HTBZ metabolites, as predicted from *in vitro* results that had demonstrated the operation of a kinetic deuterium isotope in the O-demethylation reactions mediated by CYP2D6. The increased elimination $t_{1/2}$ of deuterated HTBZ was accompanied by a concomitant decrease in exposure to both free and conjugated O-desmethyl metabolites.

In addition to metabolites resulting from CYP2D6 activity, minor metabolites of DTBZ include metabolites formed by oxidation and direct glucuronidation.

Phase 1 ADME study using [^{14}C]-radiolabelled DTBZ and TBZ, administered as a powder-in-capsule, confirmed that the deuterium substitutions in DTBZ did not alter its metabolic pathway, and all deuterated metabolites that were formed from DTBZ were also formed as nondeuterated from TBZ. A total of 24 metabolites of TBZ and 22 metabolites of DTBZ, respectively, were detected in time-proportionally pooled plasma or cohort urine samples collected. All 22 metabolites of DTBZ were among the 24 metabolites of TBZ. From these, 6 metabolites accounted for approximately 10% or more of the total sample radioactivity in at least 1 subject during the course of the metabolite profiling study. These metabolites were assigned as M1 to M6 and identified as follows:

- M1: 2-methylpropanoic acid metabolite of β-HTBZ (originally identified as a carboxylic acid)
- M2: sulphate conjugate of O-desmethyl β-HTBZ
- M3: sulphate conjugates of O-desmethyl α-HTBZ
- M4: mono-hydroxy metabolite of parent (tetrabenazine or SD-809)
- M5: β-HTBZ
- M6: α-HTBZ

The geometric mean for deuterated metabolites M1 and M4 exposure (AUC_{0-t}) represents 10.6% (range 8.5% to 11.8%, with 5 subjects showing >10% and one subject showing 8.5%) and 6.5% (range 5.3% to 9.7%) of the exposure derived from total radioactivity, respectively. In the case of M1, if ratio is based on $AUC_{0-\infty}$, it represents 9.0% (range 7.3% to 10.2%, with 2 subjects showing ≥10%) of the exposure derived from total radioactivity.

Deuterated metabolites M1 and M4 exposure (AUC_{0-t}) represents 74% and 45% of deuterated α-HTBZ exposure, respectively.

The profile of the major metabolites in the urine confirmed the attenuation of the O-demethylation of deuterated α- and β-HTBZ. Urinary levels of the deuterated metabolites of HTBZ (carboxylic acid and monohydroxy derivatives) and conjugates of HTBZ were increased in parallel with a reduction in conjugates of deuterated-O-desmethyl HTBZ metabolites relative to their nondeuterated counterparts.

Results derived from the phase 1 ADME study were consistent with observations on the HTBZ and O-desmethyl metabolites in comparative *in vitro* metabolism studies conducted in human liver microsomes, human liver S9 fractions, and in the presence of recombinant CYP2D6 isozymes. The proposed metabolism pathways are therefore considered plausible.

Human exposure to the metabolites of TBZ was used to qualify the DTBZ metabolites. Furthermore, the exposures to the active deuterated α-HTBZ and β-HTBZ metabolites and the non-active deuterated M1 and M4 metabolites were evaluated *in vivo* in rats, mice, rabbits and dogs in comparison to the non-deuterated forms.

With regard to SmPC section 5.2, the following wording, supported accordingly by clinical documentation included in the submitted dossier, was agreed by CHMP:

"In vitro studies using human liver microsomes demonstrate that deutetrabenazine is extensively biotransformed, mainly by carbonyl reductase, to its major active metabolites, deuterated α-HTBZ and

deuterated β-HTBZ, which are subsequently metabolized primarily by CYP2D6, with minor contributions of CYP1A2 and CYP3A4/5, to form several minor metabolites.

Deutetrabenazine and its active metabolites did not inhibit or induce any CYP enzymes that were studied in vitro at clinically relevant concentrations."

Inter-Conversion

In the submitted dossier DTBZ was described as a racemic mixture of R,R and S,S enantiomers that, following oral administration, is rapidly metabolised in the liver by the enzyme carbonyl reductase to its active deuterated metabolites alpha-dihydrotetrabenazine (α-HTBZ) and beta-dihydrotetrabenazine (β-HTBZ), which are isomers.

In a recent literature publication (Clinical Pharmacology in Drug Development 2023, 12(4); DOI: 10.1002/cpdd.1205), it is described that DTBZ is reduced to form four deuterated dihydrotetrabenazine (deuHTBZ) stereoisomers: [+]-α-deuHTBZ, [+]-β-deuHTBZ, [−]-α-deuHTBZ, and [−]-β-deuHTBZ.

In vitro VMAT2 inhibition assays were conducted by the authors in human platelet homogenates to determine the ability of the four deuHTBZ metabolites to inhibit the binding of HTBZ to the VMAT2 transporter.

Moreover, the pharmacokinetics of each of the four deuHTBZ metabolites were assessed in a single-center, phase 1, open-label, crossover study (NBI-98854-1723) following single-dose administration of deutetrabenazine (24 mg) to 18 healthy males subjects. Blood samples were collected until 144 hours post dose.

[+]-α-deuHTBZ has shown to present the highest pharmacological activity, followed by [+]-β-deuHTBZ enantiomers. However, [+]-α-deuHTBZ presented the lowest exposure, representing only 5% of [+]-β-deuHTBZ exposure.

Nevertheless, there are no data suggesting that PK assessments of the individual enantiomers for an individual drug are essential to the assessment of safety and efficacy of the individual drug. It was not explored a possible chiral inter-conversion because the plasma levels of each enantiomer will reach a steady state, and each patient will be exposed to all 4 enantiomeric metabolites at a stable ratio. Therefore, the extensive wealth of safety data collected in the DTBZ clinical programme can be attributed to the 4 enantiomeric metabolites as a sum.

The demonstration of interconversion between isomers would require administering each enantiomer separately to subjects.

Pharmacokinetics of Metabolites

The pharmacokinetics of deuterated metabolites d_6-α-HTBZ, d_6-β-HTBZ, d_3-9-O-desmethyl-α-HTBZ, d_3-9-O-desmethyl-β-HTBZ, M1 and M4 were investigated in the mass balance **study SD-809-C-12**, following a single oral dose administration of [^{14}C]]-SD-809 under the form of powder in capsule. Additionally, the pharmacokinetics of deuterated d_6-α-HTB and, d_6-β-HTBZ were characterised in phase 1 clinical trials performed with different strengths/dose of the osmotic PR tablet QD formulations.

It was considered as low relevance the characterization of the pharmacokinetics of each of the four enantiomers formed from absorbed deutetrabenazine by hepatic metabolism, mainly by carbonyl reductase, i.e. [+]-α-deuHTBZ, [+]-β-deuHTBZ, [−]-α-deuHTBZ, and [−]-β-deuHTBZ, as described in the literature (Brar S et al, 2023 - DOI: 10.1002/cpdd.1205).

Consequences of possible genetic polymorphism

Study **TV50717-SAD-10132** assessed exposures after single doses of 24, 48, and 72 mg of DTBZ (matrix formulation BID) in CYP2D6 poor and extensive metabolizers. Maximum and total exposure (C_{max}

and AUC) to DTBZ, α-HTBZ and β-HTBZ metabolites was higher in CYP2D6 PM compared to CYP2D6 EM. However, C_{max} occurred at a comparable median t_{max}.

For DTBZ, C_{max} was approximately 1.5-times higher for CYP2D6 PM compared to CYP2D6 EM, at each dose level, and for $AUC_{0-\infty}$ increased 4- to 5-fold.

For α-HTBZ, C_{max} was approximately 1.2-times higher for CYP2D6 PM compared to CYP2D6 EM, at each dose level, and for $AUC_{0-\infty}$ increased 2-fold.

For β-HTBZ, C_{max} was approximately 2-times higher for CYP2D6 PM compared to CYP2D6 EM, at each dose level, and for $AUC_{0-\infty}$ increased 10-fold.

The higher maximum and total exposure to the metabolites was a result of a longer elimination $t_{1/2}$. The prolongation of geometric mean $t_{½}$ was more pronounced for β-HTBZ (23.3 to 25.1 hours) than for α-HTBZ (16.9 to 18.1 hours), resulting in relatively higher exposure levels for β-HTBZ relative to α-HTBZ.

With regards to SmPC section 5.2 (Special Populations), the following wording, supported accordingly by the submitted clinical documentation was agreed:

Poor CYP2D6 Metabolisers

"Although the pharmacokinetics of deutetrabenazine and its metabolites have not been systematically evaluated in patients who do not express the drug-metabolizing enzyme CYP2D6, data in healthy subjects who are poor CYP2D6 metabolizers shows that the exposure to deuterated α-HTBZ and deuterated β-HTBZ would be increased similarly to taking strong CYP2D6 inhibitors (maximum exposure increased 2-fold and total exposure approximately 4-fold) (see sections 4.2 and 4.5)."

Section 4.2 (Posology)

"In patients receiving strong CYP2D6 inhibitors or who are poor CYP2D6 metabolisers, the daily dose of deutetrabenazine *should not exceed 36 mg (see sections 4.5 and 5.2)."*

Dose proportionality and time dependencies

Based on results from study **TV50717-PK-10175**, the applicant concluded that dose proportionality was demonstrated across the full clinical dose range (6 mg, 12 mg, 24 mg, and 48 mg) for C_{max}, AUC_{0-36h}, $AUC_{0-\infty}$ of all analytes (DTBZ [parent], deuterated α-HTBZ, deuterated β-HTBZ, and deuterated total [α+β] HTBZ), following administration of 2×6 mg, 1×12 mg, 1×24 mg, and 2×24 mg osmotic PR tablets QD under fed conditions. Of note, the 6 mg osmotic PR tablet dosage strength was not included in this MAA.

Overall, the applicant's claim of dose proportionality of DTBZ in the dose range of 12 mg to 48 mg is endorsed. The wording below was agreed for inclusion in SmPC section 5.2 (Pharmacokinetic Properties - Linearity/non-linearity), as supported accordingly by submitted clinical documentation:

"Dose proportionality was observed in the dose range of 12 mg to 48 mg."

Regarding time dependency, study **AUS-SD-809-CTP-07** was designed to evaluate accumulation and time dependency of DTBZ following repeated doses administration in the form of gastro-erosional ER tablets (7.5 mg, 15 mg and 7.5 mg + 15 mg) in a BID regimen.

Study results indicated a slight time dependency in the pharmacokinetics of deuterated α-HTBZ and β-HTBZ metabolites, compatible with a slight increase (10 – 20%) in the observed half-life for deuterated HTBZ analytes at steady state, compared with single dose.

Special populations

Impaired Renal Function

No clinical trials were conducted to assess the effect of renal impairment on the pharmacokinetics of DTBZ and its active metabolites. However, given that the major route of elimination of the active moieties is non-renal (with <10% active moieties excreted in urine) and the dosing instructions, based on up-titration guided by tolerability and efficacy responses, potential risks are considered minimised. Limited data in patients with mild to moderate renal impairment from the Phase 3 trials did not indicate safety concerns.

Information on the levels of systemic exposures of total (α+β)-HTBZ active metabolites were presented by renal function group (normal, mild, moderate and severe, according to eGFR).

With regard to the SmPC section 4.2 and 5.2, the following wording, supported accordingly by submitted clinical documentation was agreed:

Section 4.2

Renal impairment
"No dose adjustment is necessary in patients with renal impairment (see section 5.2)."

Section 5.2

Renal Impairment

"No clinical studies have been conducted to assess the effect of renal impairment on the pharmacokinetics of deuterated α-HTBZ and deuterated β-HTBZ. Based on population pharmacokinetic analyses, the effect of renal impairment on the pharmacokinetic exposures of deuterated total (α+β)-HTBZ is negligible. As the major route of elimination of the active metabolites is non-renal, it is unlikely that patients with any degree of renal impairment will be exposed to excessive concentrations of deutetrabenazine and its active metabolites."

Impaired Hepatic Function

The effect of hepatic impairment on the pharmacokinetics of DTBZ and its active metabolites has not been studied. Patients with TD who had impaired hepatic function were excluded from clinical trials. Hepatic impairment was agreed as a contraindication for DTBZ and the following text agreed for inclusion in SmPC section 4.2, 4.3 and 5.2.

Section 4.2

Hepatic impairment
"The use of deutetrabenazine in patients with hepatic impairment is contraindicated (see sections 4.3 and 5.2)."

Section 4.3

"Hepatic impairment (see section 4.2)."

Section 5.2

Hepatic Impairment

"The effect of hepatic impairment on the pharmacokinetics of deutetrabenazine and its active metabolites has not been studied. Since deutetrabenazine is extensively metabolised in the liver and due to the potential increase in systemic exposure the use of deutetrabenazine in patients with hepatic impairment is contraindicated (see section 4.3)."

Gender, Race / Ethnicity and Body Weight

Sex categorical covariate was included in the final model for α-HTBZ. The Pop-PK dataset (study **PMX-21-14-Ver-01**) included 238 males (63%) and 140 females (37%). Overall, the effect of sex was not identified to significantly impact the clearance (CL) parameter of DTBZ and its deuterated α and β-HTBZ active metabolites.

It was also agreed that, as suggested by aggregated data, race is unlikely to be an important covariate. on the PK exposures of DTBZ.

Body weight (BW) continuous covariate was included in the final model for α-HTBZ and β-HTBZ. BW was identified as a statistically significant covariate on the clearances (CL and Q) and volumes of distribution (V_c and V_p) of deuterated α-HTBZ with exponent effects (allometric scaling) of 1.11, 1.1 1.12 and 1.31 respectively (both higher than the classical values of 0.75 and 1) and on Q and V_p parameters of deuterated β-HTBZ with exponent effects of 1.46 and 1.45, respectively.

Despite BW being identified as a significant covariate in the PopPK model, with higher body weights resulting in lower exposures α and β HTBZ active metabolites, particularly for the extreme weight groups, the correlation with individual response (change from baseline for AIMS scores at week 12) to DTBZ treatment was not established. Consequently, it is believed that most patients would not experience clinically relevant differences in exposure due to weight differences.

In summary, the text below was included in SmPC section 5.2 (Special Populations):

"Based on population pharmacokinetic analyses there is no apparent effect of gender, race, and age (18-64 years) on the pharmacokinetics of deuterated α-HTBZ and deuterated β-HTBZ."

"The majority of patients had a body weight of 50 kg to <120 kg, and only a limited number of patients with a body weight of <50 kg or ≥120 kg was included in clinical trials. Population pharmacokinetic analyses predict higher exposures of deuterated α-HTBZ and deuterated β-HTBZ in patients with lower body weights and lower exposures in patients with higher body weights, however, body weight was not correlated to individual response as measured by change in AIMS total score at week 12 of treatment."

Elderly

The pharmacokinetics of DTBZ and its α-HTBZ and β-HTBZ metabolites was studied in healthy subjects following administration of the osmotic PR tablets QD formulation and in TD patients following administration of the matrix tablets BID formulation.

Across all studies performed with healthy subjects, all participants were in the range of 18 to 55 years. Across all studies performed with TD patients, all participants were in the range of 21 to 81 years.

Population PK modelling tested age at baseline as a covariate in each model developed for DTBZ, α-HTBZ and β-HTBZ. This covariate was not included in any of the final models.

In the population dataset, the majority of patients (89.3%= 598/669) were adults aged between [18-64 years]; 62 patients (9.2% 62/669) were in the age group [65-74 years], 9 (<1%) in the group [75-84 years] and no patient was > 85 years.

As per the provided Pop-PK modelling outputs, the effect of age on the PKs of DTBZ was investigated within the Pop-PK analyses and, overall, it was found not to significantly affect the systemic exposures of α- and β-HTBZ active metabolites. However, and despite the agreed conclusion, the numbers of patients included in both groups of age [75-84 y] and >85 years is too low and not considered sufficient to detect a potential clinically relevant change in PK parameters. Therefore, no formal conclusion could be drawn for these two subgroups of age.

The following text was agreed for inclusion in SmPC section 5.2:

"Based on population pharmacokinetic analyses there is no apparent effect of gender, race, and age (18-64 years) on the pharmacokinetics of deuterated α-HTBZ and deuterated β-HTBZ.

Limited pharmacokinetic data are available for patients 65-74 years of age (approx. 9% of the patients) and 75-84 years of age (approx. 1% of the patients). No data are available for those over 85 years of age. Therefore, no definitive pharmacokinetic conclusions can be made for patients over 65 years of age."

Paediatric Population

As previously outlined in this AR (and in SmPC section 5.1), a product specific Paediatric Investigation Plan (PIP) waiver was granted for DTBZ. The waiver applies to all subsets of the paediatric population from birth to less than 18 years of age. Therefore, in SmPC section 4.2 the following text is included:

"*There is no relevant use of Austedo in the paediatric population for the indication of tardive dyskinesia*".

Pharmacokinetic interaction studies

In Vitro

DTBZ and both deuterated α-HTBZ and β-HTBZ were evaluated in a series of *in vitro* studies to determine enzyme induction and inhibition as well as the substrate potential of DTBZ and its deuterated metabolites with transporter proteins.

The CYP interaction evaluations were performed with clinically relevant concentrations, estimated based on the exposures at a maximal therapeutic dose, 48 mg of DTBZ osmotic PR tablet QD, at steady state (study **TV50717-BE-10179**, using $C_{max,ss}$ multiplied by 2).

For CYP interactions, DTBZ, deuterated α-HTBZ and deuterated β-HTBZ were evaluated for inhibition of human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 enzymes (at concentrations from 0.1 to 100 µM for DTBZ, and at 1 and 10 µM for α- and β-HTBZ) and induction of CYP1A2, CYP2B6, and CYP3A4 (at DTBZ concentrations from 0.12 to 30 µM).

It was concluded that DTBZ and its deuterated active metabolites did not inhibit any CYPs in human liver microsomes at clinically relevant concentrations. In addition, DTBZ, incubated with human hepatocytes for 48 hours, to evaluate the induction potential of CYP1A2, CYP2B6 and CYP3A4 (that DTBZ metabolised to the active deuterated α-HTBZ and β-HTBZ metabolites), did not induce these CYPs (<2-fold increase in mRNA, <20% CYP activity of the positive controls) at clinically relevant concentrations.

The drug interaction potential of DTBZ, deuterated α-HTBZ, and deuterated β-HTBZ on transporters was also evaluated *in vitro*. Substrate potential was assessed for the human transporters MDR1 (P-gp), BCRP, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, and organic cation transporter (OCT) 1. The inhibition potential of DTBZ, deuterated α-HTBZ, and deuterated β-HTBZ was assessed for the following transporters: BCRP, MDR1, BSEP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2, as well as human P-gp. It was concluded that DTBZ, deuterated α-HTBZ, and deuterated β-HTBZ were not substrates and did not inhibit any of the human transporters at clinically relevant concentrations.

In Vivo

The drug-drug interaction potential of DTBZ co-administration with a strong CYP2D6 inhibitor, paroxetine, was studied in healthy participants. When co administered with paroxetine, systemic exposure ($AUC_{0-\infty}$) of α-HTBZ was 1.9-fold higher and β-HTBZ was 6.5-fold higher, resulting in an approximately 3-fold increase in $AUC_{0-\infty}$ for total (α+β)-HTBZ. With paroxetine, C_{max} of α-HTBZ and β-HTBZ were 1.2-fold and 2.2-fold higher, respectively, and the $t_{1/2}$ values of the metabolites were

prolonged (total [α+β]-HTBZ $t_{1/2}$ increased from 9.75 hours to 16.0 hours). Based on these results, a maximal dose of 36 mg was selected for patients who are poor CYP2D6 metabolisers or receiving concomitant therapy with strong CYP2D6 inhibitors (as fluoxetine and bupropion).

SmPC Section 4.5 detailed the results from the performed *in vivo* study with paroxetine, as outlined below:

"Concomitant use of strong CYP2D6 inhibitors, such as quinidine (antiarrhythmic and antimalarial medicinal product), and paroxetine, fluoxetine, and bupropion (antidepressants), has been shown to increase the systemic exposure to the active dihydro-metabolites of deutetrabenazine. In the presence of a strong CYP2D6 inhibitor (paroxetine), systemic exposure of the individual active metabolites increased 1.9-fold for deuterated α-dihydrotetrabenazine [HTBZ] and 6.5-fold for deuterated β-HTBZ resulting in an overall 3-fold increase in the active metabolites, deuterated total (α + β)-HTBZ (see section 5.2). A reduction in the dose of deutetrabenazine may be necessary when adding a strong CYP2D6 inhibitor in patients maintained on a stable dose of deutetrabenazine. The daily dose of deutetrabenazine should not exceed 36 mg in patients taking strong CYP2D6 inhibitors (see section 4.2)."

Moreover, the wording below was agreed for SmPC section 4.2:

"In patients receiving strong CYP2D6 inhibitors or who are poor CYP2D6 metabolisers, the daily dose of deutetrabenazine should not exceed 36 mg (see section 4.5 and 5.2)."

2.6.2.2. Pharmacodynamics

Mechanism of action

DTBZ and the major circulating metabolites (deuterated α-dihydrotetrabenazine [HTBZ] and deuterated β-HTBZ) of DTBZ, are reversible inhibitors of VMAT2, resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores. While the precise mechanism of action by which DTBZ exerts its effects in the treatment of TD is unknown, it is believed to be related to its effect as a depletor of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals.

DTBZ is structurally related to TBZ. DTBZ incorporates two trideuteromethoxy groups (-OCD3) at the 9- and 10-positions, while two trihydromethoxy groups (-OCH3) exist at the corresponding positions in TBZ. The -OCD3 groups confer a greater resistance to enzymatic modification, resulting in a slower metabolism and a profound improvement of the pharmacokinetic (PK) properties of DTBZ compared to TBZ. While the incorporation of the -OCD3 groups improves the PK properties, the substitution of hydrogen by deuterium does not change the primary and secondary pharmacology.

In vitro binding and functional studies have shown high binding affinity and functional effect of DTBZ and its deuterated metabolites α-HTBZ and β-HTBZ to the primary target VMAT2.

The non-clinical results demonstrated that DTBZ and the deuterated α-HTBZ and β-HTBZ metabolites are reversible inhibitors of VMAT2, resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores. A series of *in vitro* studies were conducted to establish the binding and functional effect of DTBZ, deuterated α-HTBZ and β-HTBZ, where TBZ and its nondeuterated active metabolites were included as a comparison. All comparative pharmacology evaluations of the major circulating metabolites deuterated α-HTBZ and deuterated β-HTBZ were shown to be similar to their nondeuterated forms. The separate deuterated enantiomeric metabolites were also evaluated with regard to the primary target VMAT2.

Primary and Secondary pharmacology

Primary Pharmacology

The Abnormal Involuntary Movement Scale (AIMS) is a 12-item clinician-rated scale to assess severity of dyskinesias (specifically, orofacial movements and extremity and truncal movements) in patients. This scale is widely used in clinical trials to detect and follow the severity of TD over time. A 2-point decrease from baseline in the AIMS total score is considered clinically important (minimally clinically important change). The TD trials included in the DTBZ TD efficacy programme used AIMS descriptors, which are consistent with those utilised in large trials in schizophrenia, and were developed based on the work of Munetz and Benjamin. These descriptors have been shown to be valid in describing the severity of abnormal movements in TD and have been accepted by scientific experts in movement disorders and psychiatry, who uniformly agreed that they are appropriate for providing guidance to Investigators in grading the severity of TD in clinical trials. To enable the systematic evaluation of the primary endpoint, AIMS was digitally video-recorded using a standard protocol for both Trials C-18 and C-23. AIMS assessment was performed by the site investigator and confirmed by an independent movement disorder expert via central video rating. This process allowed for a systematic assessment of dyskinesia that was not influenced by participant reports of tolerability or efficacy. Assessment of the AIMS by site personnel was performed in all 3 TD trials.

DTBZ demonstrated a statistically significant and clinically meaningful improvement in TD motor symptoms as measured by the AIMS total score from baseline to week 12 in both Trial C-18 (3.0 point mean reduction from baseline, for a mean treatment effect difference from placebo of −1.4 points [p=0.0188]) and Trial C-23 (3.3 point mean reduction from baseline with DTBZ 36 mg/day, for a mean treatment effect difference from placebo of −1.9 points [p=0.001]). The effect occurred from as early as week 2 and was sustained over the 12-week treatment period.

A statistically significant and clinically meaningful improvement in the AIMS total score from baseline at week 12 was also demonstrated when similar analysis was conducted in the ITTPB population of Trial C-23. This is further supported by the pooled analysis of efficacy data from Trial C-18 and Trial C-23 (24 mg/day and 36 mg/day), which demonstrated a clinically meaningful improvement in AIMS total score at the end of treatment for DTBZ compared with placebo (3.3 point mean reduction from baseline to week 12 in the DTBZ group; mean treatment effect difference of −1.8 points; p<0.001).

Table 4: Abnormal Involuntary Movement Scale (AIMS): change in AIMS total score from baseline to week 12 in trial C-18 (flexible dose trial; mITT population

Statistic	Change in AIMS Total Score		
	Placebo	DTBZ	Treatment Effect[a] (SE)
Baseline			
n	57	56	--
Mean (SD) score	9.6 (3.78)	9.7 (4.14)	--
Week 12			
n	51	52	--
Least squares mean (SE)	–1.6 (0.46)	-3.0 (0.45)	–1.4 (0.60)
Minimum, maximum	-9, 5	-16, 3	--
95% CI for mean	–2.5, -0.7	–3.9, -2.1	-2.6, -0.2
p-value	--	--	0.0188

Source: SD-809-C-18 Clinical Study Report, Table 7, Table 10.
[a] Treatment effect is defined as difference in means between DTBZ and placebo.
AIMS=Abnormal Involuntary Movement Scale; CI=confidence interval; mITT=modified intent-to-treat; n=total number of participants at timepoint; SD=standard deviation; SE=standard error.
Notes: p-value is from a mixed model repeated measures analysis with change from baseline in AIMS total score (sum of items 1 to 7) as dependent variable.
The analysis population in this table includes participants who received trial drug, had at least 1 post-baseline assessment, and had any baseline AIMS total score (defined as the mITT populaiton in the protocol).

Table 5: Abnormal Involuntary Movement Scale (AIMS): change in AIMS Score from baseline to week 12 in trial C-23 (Fixed-dose trial; mITT population)

Statistic	Placebo	DTBZ 12 mg/day	DTBZ 24 mg/day	DTBZ 36 mg/day
Baseline				
n	58	60	49	55
Mean (SD) score	9.5 (2.71)	9.6 (2.40)	9.4 (2.93)	10.1 (3.21)
Week 12				
n	56	53	45	52
LS mean (SE)	–1.4 (0.41)	–2.1 (0.42)	–3.2 (0.45)	–3.3 (0.42)

Statistic	Placebo	DTBZ 12 mg/day	DTBZ 24 mg/day	DTBZ 36 mg/day
Treatment effect: LS mean difference (DTBZ – placebo)	--	-0.7	–1.8	–1.9
95% CI	--	–1.84, 0.42	–3.00, –0.63	–3.09, –0.79
p-value	--	0.217[a]	0.003[a]	0.001

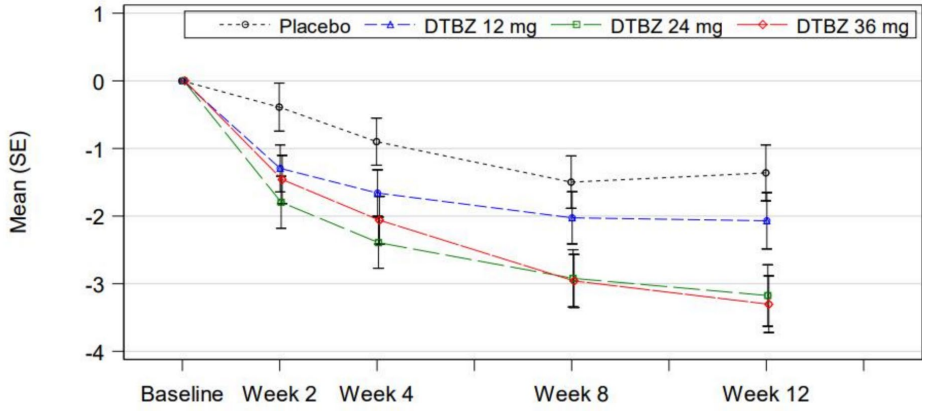
Source: TDISE19, Summary 5.1.
[a] Nominal p-value due to hierarchical method of analysis for primary and key secondary endpoints.
AIMS=Abnormal Involuntary Movement Scale; CI=confidence interval; LS=least squares; mITT=modified intent-to-treat; n=number of participants at timepoint; SD= standard deviation; SE=standard error.
Notes: AIMS total score (sum of items 1 through 7) was assessed by blinded central video rating. The statistical model was a mixed model for repeated measures with treatment group, visit, treatment group-by-visit interaction, and baseline use of dopamine receptor antagonist as fixed effects and the baseline value as a covariate. The model was fit using an unstructured covariance structure. The analysis population in this table is the mITT population as defined in the protocol, and included all participants in the ITT population who had a baseline AIMS total score ≥6 as assessed by central video rating, were randomised to treatment, received trial drug, and had at least 1 post-baseline AIMS total score assessment. For the relevant analysis results in the ITTPB population refer to Table 4.

Table 6: Abnormal involuntary movement scale (AIMS): change in AIMS score from baseline to week 12 in trial C-23 (Fixed-dose trial; ITTPB population)

Statistic	Placebo	DTBZ 12 mg/day	DTBZ 24 mg/day	DTBZ 36 mg/day
Baseline				
n	71	73	72	72
Mean (SD) score	8.5 (3.26)	8.6 (3.15)	7.7 (3.54)	8.6 (3.87)
Week 12				
n	68	66	64	65
LS mean (SE)	–1.0 (0.36)	–1.5 (0.36)	–2.4 (0.36)	–2.9 (0.36)
Treatment effect: LS mean difference (DTBZ – placebo)	--	-0.5	–1.3	–1.8
95% CI	--	–1.46, 0.48	–2.32, –0.35	–2.83, –0.87
p-value	--	0.324[a]	0.008[a]	<0.001

Source: TDISE19, Summary 5.2.
[a] Nominal p-value due to hierarchical method of analysis for primary and key secondary endpoints.
AIMS=Abnormal Involuntary Movement Scale; CI=confidence interval; ITTPB=intent-to-treat postbaseline; LS=least squares; n=number of participants at timepoint; SD=standard deviation; SE=standard error.
Notes: AIMS total score (sum of items 1 through 7) was assessed by blinded central video rating. The statistical model was a mixed model for repeated measures with treatment group, visit, treatment group-by-visit interaction, and baseline use of dopamine receptor antagonist as fixed effects and the baseline value as a covariate. The model was fit using an unstructured covariance structure. The analysis population in this table is the ITTPB population as defined in the protocol, and participants who received trial drug, had at least 1 postbaseline assessment, regardless of their centrally based baseline AIMS total score.

Figure 5: Least squares mean (+/- SE) AIMS total score changes from baseline to each visit by treatment group (blinded central video rating) in trial C-23 (Fixed-dose trial; mITT population)



Sample Size					
Placebo	58	58	57	57	56
DTBZ 12 mg	60	60	58	56	53
DTBZ 24 mg	49	49	47	46	45
DTBZ 36 mg	55	55	52	53	52

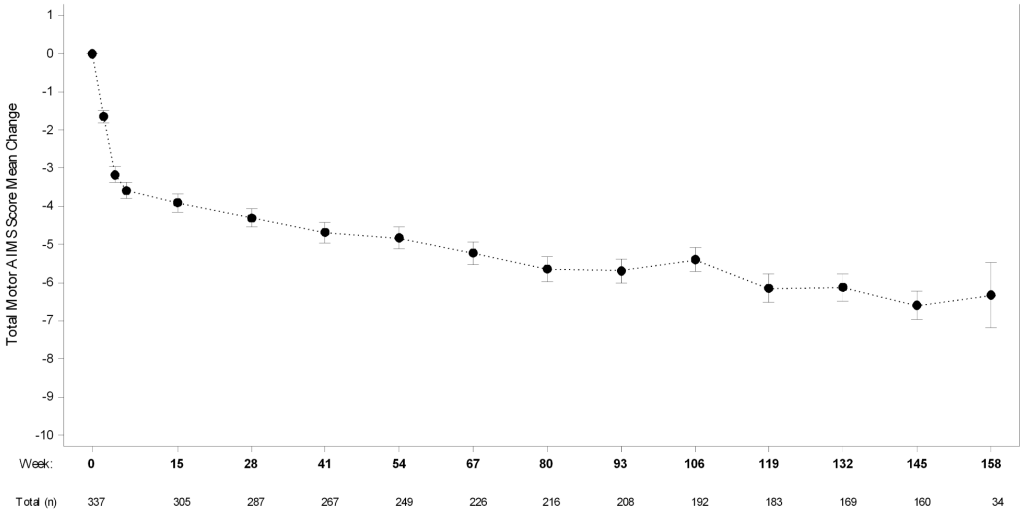
Source: SD-809-C-23, Post Hoc Figure 3.
AIMS=Abnormal Involuntary Movement Scale; mITT=modified intent-to-treat; SE=standard error.

The long-term Phase 3 open-label Trial C-20 affirmed the long-term benefit and tolerability of DTBZ at relatively high doses (up to 48 mg/day as per inclusion criteria; average of 38.3 mg/day at week 15 and 39.4 mg/day at week 145) and supported persistence of efficacy for up to approximately 3 years. In this trial, TD patients received daily doses of DTBZ, starting at 12 mg/day and increasing in 6 mg/day increments at weekly intervals until adequate dyskinesia control was achieved, a clinically significant adverse event occurred, or the maximum daily dose of 48 mg DTBZ per day was reached. There was a

sustained long-term improvement from baseline in AIMS total score, Clinical Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC) over the treatment period. The mean daily dose of DTBZ at the end of titration (week 6) was 35.7 mg/day and remained stable throughout the rest of the trial.

A 6.6 point improvement (decrease) from baseline in AIMS total score for up to approximately 3 years (week 145) was observed (Figure 4). Decreases in the AIMS total score from baseline were observed as early as week 2 of DTBZ titration, after which there was a sustained reduction in the AIMS total score. Efficacy was maintained through week 158 of therapy with minimal changes in dose over time (35.7 mg/day at the end of titration [week 6], 38.3 mg/day at week 15 and 39.4 mg/day at week 145), indicative of clinically meaningful long-term benefit.

Figure 6: Mean (+/- SE) AIMS total score changes from baseline to each visit in trial C-20 part A (Site rating; ITT population)



Source: SD-809-C-20 Clinical Study Report, Figure 4.
AIMS=Abnormal Involuntary Movement Scale; ITT=intent-to-treat; n=number of participants; SE=standard error.

Secondary Pharmacology

The *in vitro* effects of deuterated α-HTBZ and deuterated β-HTBZ on the human ether-à-go-go-related gene (hERG) potassium channel current were evaluated in voltage-clamped human embryonic kidney cells (HEK-293) that stably express hERG (Study DS-2018-00707). Deuterated α-HTBZ and deuterated β-HTBZ inhibited hERG potassium channel current with IC50 values of 12.9 and 7.8 μM, respectively. These concentrations are approximately 144- and 116-fold higher than the calculated at steady state unbound C_{max} for α-HTBZ and β-HTBZ metabolites, respectively, after DTBZ administration of 22.5 mg BID in humans (Study AUS-SD-809-CTP-07).

In addition, as part of the secondary pharmacology screening assay, deuterated α-HTBZ and deuterated β-HTBZ, as well as their non-deuterated forms, at 10 μM did not displace a selective [3H] radioligand from hERG channels expressed in Chinese Hamster Ovary (CHO) cells (Study **SD-809-NC-009**).

No *in vivo* cardiovascular safety pharmacology studies have been performed with DTBZ. In a crossover study of 4 conscious Beagle dogs, single doses of TBZ (5, 10, or 20 mg/kg with a 7-day washout between doses) did not produce changes in corrected QT (QTc) or dose-related, statistically significant changes in heart rate or blood pressure as compared to vehicle control.

Trial **SD-809-C-21** was a randomized, double-blind, placebo- and positive-(moxifloxacin)-controlled, 6-period crossover trial to evaluate the effects of DTBZ (administered as DTBZ matrix tablets BID) and TBZ on cardiac repolarization in healthy adult participants who were CYP2D6 EM or IM. Trial drug (single doses of 12 mg DTBZ, 24 mg DTBZ, 50 mg TBZ, 400 mg moxifloxacin, or placebo) was administered to participants in either the fasted or fed state. Electrocardiograms (ECGs) were collected continuously via a Holter monitor and triplicate 12-lead digital ECGs were recorded; data were extracted at 3 predose time points starting at 1.25 hours prior to dosing and at 12 time points over the first 24 hours following dosing. Assessment of all ECG measurements were performed at a central ECG laboratory. A total of 48 participants were enrolled and 42 received trial drug; 41 participants were included in the PK analysis population.

Key Pharmacodynamic Results

- Assay sensitivity was verified with the positive control moxifloxacin, which produced placebo-corrected change from baseline in QTcF (ΔΔQTcF) increases that met pre-specified criteria and produced a maximal effect on ΔΔQTcF of 14.0 (11.94, 15.98, 2-sided 90% confidence interval [CI]) ms at hour 8.
- The maximum time-matched ΔΔQTcF increases (least squares mean [90% confidence interval (CI)]) with DTBZ 12 mg and 24 mg were 2.8 (0.7, 4.8) ms and 4.5 (2.4, 6.5) ms, respectively. The maximum mean ΔΔQTcF and the upper bound of the 90% 2-sided CI (95% 1-sided CI) for this maximum change were below the threshold of regulatory concern (5 ms and 10 ms, respectively) at all time points tested.
- The maximum mean ΔΔQTcF increase with TBZ exceeded 5 ms at hour 2 through hour 4. The maximum mean (90% CI) ΔΔQTcF increase with TBZ was 7.6 (5.6, 9.5) ms.
- Analysis of the corrected QT with Bazett's method yielded similar results as compared with Fridericia's method. The increases were all <5 ms and the upper bounds of the 2-sided 90% CIs were below 10 ms at all time points.

An additional trial (TV50717-SAD-10132) was conducted to evaluate the effect of therapeutic and supra-therapeutic exposures to DTBZ and its metabolites on cardiac repolarization, both in CYP2D6 poor metabolisers (PM) and CYP2D6 extensive metabolisers (EM) or intermediate metabolisers (IM) healthy participants. This was a double-blind, placebo-controlled trial to evaluate the concentration-QT (C-QT) correlation using the Fridericia's corrected QT (QTcF) interval.

In this trial, exposures exceeding the anticipated maximum concentrations at steady state in both CYP2D6 PM and CYP2D6 EM or IM were achieved by administration of high single doses (24, 48, and 72 mg) of DTBZ matrix tablets BID. C-QTc modelling was used to evaluate the relationship between plasma concentrations of DTBZ and its active (α- and β-HTBZ) metabolites, and ΔQTcF.

- Based on the C-QTc analysis with the primary model, which includes individual concentrations of α-HTBZ and β-HTBZ, a clinically significant QT prolongation was excluded at the observed exposures following single doses of 24, 48, and 72 mg in CYP2D6 EM and PM. Predictions for steady state confirmed that the upper bound of the 90% CI of QT prolongation would not exceed 10 ms at the maximum recommended doses in both populations. This was also true for a CYP2D6 PM taking a daily dose of 48 mg instead of the recommended dose of 36 mg.
- The comparable effects of α-HTBZ and β-HTBZ on cardiac repolarization observed *in vivo* were in agreement with the comparable *in vitro* effects of multiple concentrations of α-HTBZ and β-HTBZ on the human hERG channel current (Study DS-2018-00707). Deuterated α-HTBZ and β-HTBZ inhibited hERG potassium channel current with IC50 values of 12.9 and 7.8 μM, respectively. The corresponding safety margins, calculated as ratio of 50% inhibitory effect and the predicted unbound

$C_{max,ss}$ (PMX-20-13) of deuterated α-HTBZ and β-HTBZ at the maximum recommended doses were 216- and 242-fold, respectively, in EM and 172- and 52-fold, respectively, in PM.

- The PK comparison of the DTBZ matrix BID and osmotic PR QD formulations (Trial TV50717-BE-10179) showed that the conclusions from Trial TV50717-SAD-10132 apply also for the DTBZ osmotic PR formulation QD because neither maximum nor total exposure were higher compared to the DTBZ matrix formulation BID.

Concentration-QTc analysis was performed using TV50717-SAD-10132 trial data for PM and EM participants. Linear mixed-effects modelling was applied to assess the effect of DTBZ matrix tablet BID and its active metabolite concentrations on change-from-baseline QTcF (ΔQTcF). A model with both α -HTBZ and β-HTBZ was selected as primary. The estimated slopes of α-HTBZ and β-HTBZ plasma concentrations in the C-QTc relationship showed a small treatment effect on the intercept and positive slope. Both were not statistically significant. The effect on ΔΔQTcF was predicted to be 6.04 ms (90% CI: 3.13 to 8.95) and 6.11 ms (90% CI: 3.14 to 9.08) at the t_{max} of α-HTBZ and β-HTBZ, respectively, for the PM cohort for the TEV-50717 72 mg dose. Similarly, the effect on ΔΔQTcF was predicted to be 3.08 ms (90% CI: -0.08 to 6.25) at t_{max} of α-HTBZ or at t_{max} of β-HTBZ for the EM cohort for the 72 mg DTBZ matrix tablet BID dose. In summary, TEV-50717 (DTBZ) at the studied doses did not have a clinically relevant effect on HR or the PR and QRS interval. Prolongation of QTcF was seen, in particular with the highest dose (72 mg) in both PMs and EMs. Based on the models in the concentration-QTc analysis, an effect of TEV-50717 (DTBZ) on ΔΔQTcF can be excluded within the observed range of TEV-50717 (DTBZ), α-HTBZ, and β-HTBZ plasma concentration up to ~11700 pg/mL, ~150000 pg/mL, and 140000 pg/mL, respectively.

Figure 7: Scatter plot of observed plasma concentrations for α-HTBZ and estimated placebo-adjusted ΔQTcF (Model with α-HTBZ, and β-HTBZ) (Model F) (Concentration-QTc analysis set).

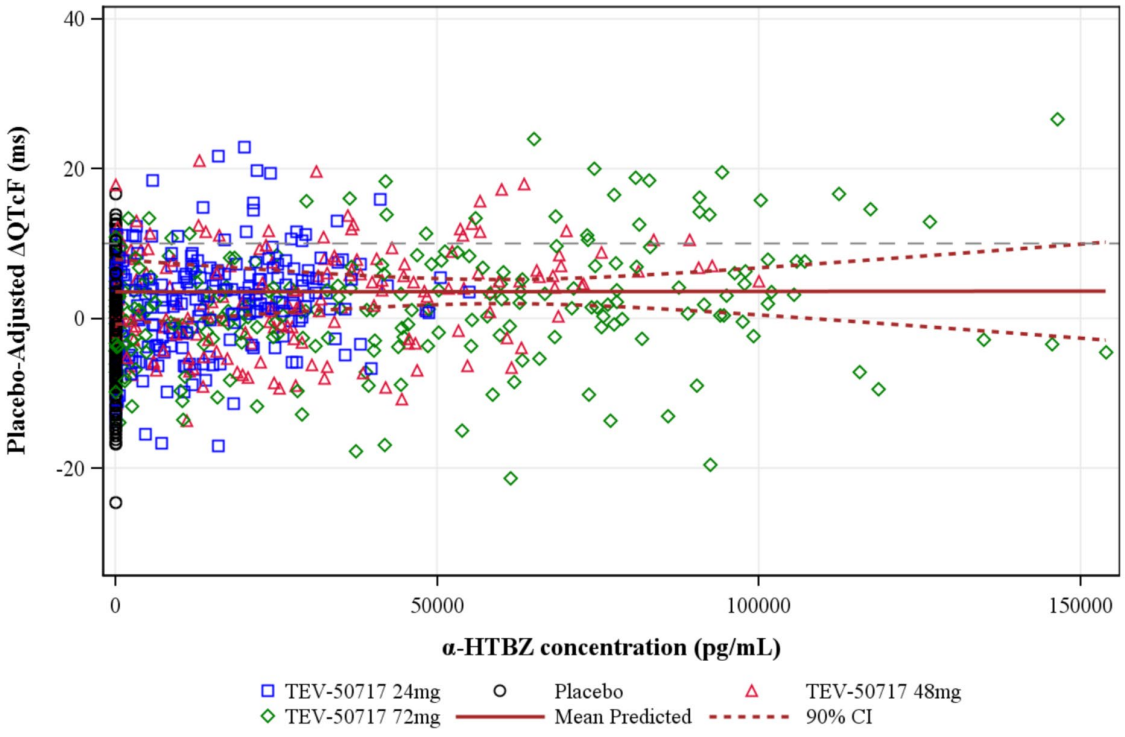
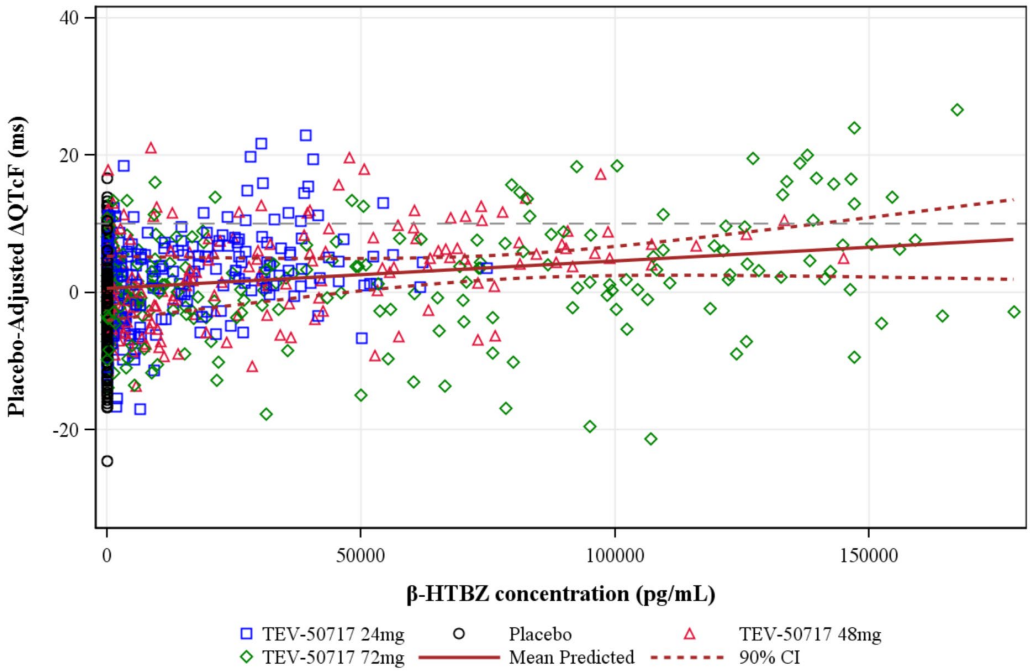


Figure 8: Scatter plot of observed plasma concentrations for β-HTBZ and estimated placebo-adjusted ΔQTcF (Model with α-HTBZ, and β-HTBZ) (Model F) (Concentration-QTc analysis set).



2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Absorption

Characterization of DTBZ absorption following oral administration is based on data from studies **SD-809-C-12** (mass balance study), **TV50717-SAD-10132, TV50717-BE-10165, TV50717-BE-10179, TV50717-BE-10192 and TV50717-BE-10201**. Moreover, data from *in vitro* studies evaluated the relevant absorption transporters involved in DTBZ absorption.

Following oral administration, DTBZ is rapidly metabolised in the liver by the enzyme carbonyl reductase to its active deuterated metabolites alpha-dihydrotetrabenazine (α-HTBZ) and beta-dihydrotetrabenazine (β-HTBZ), which are isomers. These metabolites are subsequently metabolised, primarily by CYP2D6 with minor contributions from CYP1A2 and CYP3A4/5.

The C_{max} of DTBZ, deuterated α-HTBZ, and deuterated β-HTBZ was reached within approximately 3 hours after osmotic PR tablet QD repeated dose administration. After administration of the osmotic PR tablet QD, C_{max} was followed by sustained plateaus for several hours.

DTBZ and its deuterated α-HTBZ and β-HTBZ metabolites were found not to be substrates of efflux transporters, including multidrug resistance protein 1 (MDR1, also called permeability glycoprotein [P-gp]) and breast cancer resistance protein (BCRP).

The absolute BA of DTBZ was not determined due to the inability to formulate the DTBZ as a solution for IV administration, given its low solubility. However, after administration of [^{14}C]-radiolabelled DTBZ in the mass balance study (SD-809-C-12) the extent of absorption was estimated as at least 80%, based on total recovered radioactivity in urine. Moreover, based on the extensive metabolism and on the very low relative exposure (AUC) of parent DTBZ in relation to metabolites (total (α+β)-HTBZ), a low absolute bioavailability was estimated.

Bioavailability

The pharmacokinetics and relative bioavailability of SD-809 - deutetrabenazine (DTBZ) in comparison to tetrabenazine (TBZ) and their respective α-HTBZ and β-HTBZ metabolites, following the same 25 mg single oral dose in the form of powder in gelatin capsules, were evaluated in study **AUS-SD-809-CTP-06**. Following these study results, a new study was performed, study **AUS-SD-809-CTP-07**, to evaluate the safety and pharmacokinetics of two candidate formulations of DTBZ relative to TBZ, and to select a DTBZ formulation for further use in other clinical trials.

Bioequivalence

Following approval of DTBZ as a matrix-based formulation for BID administration under the brand name AUSTEDO® in the US, for the treatment of TD, on 30 August 2017, and subsequently in several other countries (China, Israel, South Korea, Australia, Brazil, and Chile), a once-daily (QD) tablet was developed to further improve ease of use, decrease pill burden, and potentially improve adherence. The osmotic drug delivery system was chosen for the osmotic PR formulation QD development programme based on the results of study **TV50717-BA-10150,** using a **PR-only prototype**.

Characterization of bioequivalence using DTBZ QD osmotic tablet formulation is based on data from studies **TV50717-BE-10165**, **TV50717-BE-10179, TV50717-BE-10192** and **TV50717-BE-10201**.

However, only the 24 mg strength was characterised and compared to the IR formulation (study **TV50717-BE-10165**). Hence, and based on the Guideline on modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1), it is expected that the remaining strengths (12, 30, 36, 42 and 48 mg) should prove similar biopharmaceutical performances in comparison to the 24 mg PR tablet. For this purpose, the applicant provided one BE study (**TV50717-BE-10192**), comparing the systemic exposures after single administration of 1×48 mg vs 2×24 mg, that supported the proportionality of the biopharmaceutical performances of the two strengths. Despite evidence of dose proportionality within all QD strengths was not obtained in a single dedicated PK trial, this can be concluded from the totality of evidence collected in multiple biopharmaceutical trials.

Food Effect

The influence of food on the pharmacokinetics of DTBZ and its α- and β-HTBZ active metabolites (individually and as a sum) was assessed in study **TV50717-BE-10165** following administration of DTBZ 24 mg QD osmotic tablet formulation.

A high calorie, high-fat breakfast had no effect on the pharmacokinetics of DTBZ (parent) and its active metabolites (deuterated α-HTBZ and β-HTBZ). Consequently, osmotic PR tablets QD may be administered with or without food. This information is reflected accordingly in the PI (e.g. SmPC section 4.2, 5.2 and PL).

Distribution

In vitro assessments were performed to determine the plasma protein binding. Plasma protein binding in human plasma for DTBZ, deuterated α-HTBZ, and deuterated β-HTBZ was 81.7% to 82.2% for DTBZ, 55.2% to 57.2% for α-HTBZ, and 48.1% to 48.6% for β-HTBZ.

Based on PopPK modelling, after oral administration, the apparent volume of distribution (Vc/F) values for DTBZ, deuterated α-HTBZ, and deuterated β-HTBZ were 13700 L, 490 L, and 860 L, respectively, following osmotic PR tablet QD administration.

Biotransformation

Based on *in vitro* studies in human liver microsomes, DTBZ is extensively bio-transformed, mainly by carbonyl reductase, to its major active metabolites deuterated α-HTBZ and deuterated β-HTBZ, which are subsequently metabolised, primarily by CYP2D6, with minor contributions of CYP1A2 and CYP3A4/5, to form several minor metabolites. These minor metabolites include demethylated metabolites, their sulphate conjugates, and direct glucuronide conjugates of deuterated α-HTBZ and deuterated β-HTBZ as well as products of oxidative metabolism, as identified following administration of [^{14}C]-labelled DTBZ to healthy participants. As expected, the rapid and extensive metabolism of the parent drug resulted in low plasma concentrations of DTBZ as compared to the active deuterated metabolites after oral dose administration in clinical trials.

DTBZ is as a racemic mixture of R,R and S,S enantiomers that, following oral administration is rapidly metabolized in the liver by the enzyme carbonyl reductase to its active deuterated metabolites alpha-dihydrotetrabenazine (α-HTBZ) and beta-dihydrotetrabenazine (β-HTBZ), which are isomers.

In a recent literature publication (Brar S et al, 2023 - Clinical Pharmacology in Drug Development 2023, 12(4); DOI: 10.1002/cpdd.1205), it is described that DTBZ is reduced to form four deuterated dihydrotetrabenazine (deuHTBZ) stereoisomers: [+]-α-deuHTBZ, [+]-β-deuHTBZ, [−]-α-deuHTBZ, and [−]-β-deuHTBZ.

In vitro VMAT2 inhibition assays were conducted by the authors in human platelet homogenates to determine the ability of the four deuHTBZ metabolites to inhibit the binding of HTBZ to the VMAT2 transporter. Moreover, the pharmacokinetics of each of the four deuHTBZ metabolites were assessed in a single-center, phase 1, open-label, crossover study (NBI-98854-1723) following single-dose administration of deutetrabenazine (24 mg) to 18 healthy males subjects.

[+]-α-deuHTBZ has shown to present the highest pharmacological activity, followed by [+]-β-deuHTBZ enantiomers. However, [+]-α-deuHTBZ presents the lowest exposure, representing only 5% of [+]-β-deuHTBZ exposure.

Nevertheless, there are no data suggesting that PK assessments of the individual enantiomers for an individual drug are essential to the assessment of safety and efficacy of the individual drug. It was not explored a possible chiral inter-conversion because the plasma levels of each enantiomer will reach a steady state, and each patient will be exposed to all 4 enantiomeric metabolites at a stable ratio. Therefore, the extensive wealth of safety data collected in the DTBZ clinical programme can be attributed to the 4 enantiomeric metabolites as a sum. The effect of CYP2D6 polymorphism on the metabolism of deuterated α-HTBZ and β-HTBZ was assessed in study TV50717-SAD-10132. Simulations were performed predicting exposure parameters $C_{max,ss}$ or $C_{avg,ss}$ for total (α+β)-HTBZ based on the maximum daily dose of 36 mg of osmotic PR tablet QD formulation. As expected, a 2.5-fold and 3-fold increase on $C_{max,ss}$ or $C_{avg,ss}$ was observed for the PM in comparison to the EM. However, given the proposed dose titration scheme for the DTBZ, no safety concerns are raised.

Elimination

In a mass-balance trial in 6 healthy participants, 75% to 86% of the [^{14}C]-radiolabelled DTBZ dose was excreted in the urine, and faecal recovery accounted for 8% to 11% of the dose. Urinary excretion of deuterated α-HTBZ and deuterated β-HTBZ each accounted for less than 10% of the administered dose. Sulphate and glucuronide conjugates of the α-HTBZ and β-HTBZ metabolites of DTBZ, as well as products of oxidative metabolism, accounted for the majority of metabolites in the urine.

A mean total radioactivity of 92.2% from the administered dose was recovered.

Given that the majority (>80%) of radioactivity was recovered in the urine, renal clearance is the main pathway of elimination for all radiolabelled drug-derived materials. Urinary excretion of the deuterated α-HTBZ and β-HTBZ metabolites accounted for <10% of the administered dose.

Based on the different phase 1 studies performed with the osmotic PR formulation QD, the elimination $t_{1/2}$ of DTBZ, and deuterated α-HTBZ, β-HTBZ, and total (α+β)-HTBZ metabolites were estimated as approximately 17 hours, 12 hours, 9 hours, and 11 hours, respectively, being in agreement with PopPK model estimates.

In light of the different phase 1 studies performed with the osmotic PR formulation QD, the geometric means for the apparent clearance (CL/F) of DTBZ ranged between 11601 L/h to 13001 L/h and showed to be similar between studies. An overall mean of 12103 L/F can be calculated. Estimates from non-compartmental analysis and PopPK analysis are concordant.

Lack of effect of disease, age, gender, and body weight

The PK of DTBZ and its deuterated active metabolites was similar between healthy participants and patients with TD, as well as between age groups and gender. Based on PopPK analyses, although body weight was a numerically significant covariate, it is not considered to be clinically meaningful.

Lack of effect of renal impairment

Although PK in patients with renal impairment has not been evaluated in a dedicated study, and the impact of renal impairment on PK has not been investigated within the PopPK approach, as no subject with any degree of renal impaired function appear to be included in PopPK analysis (PMX-21-14-Ver-01), the applicant concluded that dose adjustment based on renal function is not considered necessary since the majority of DTBZ and its deuterated active metabolites are extensively metabolized. Urinary excretion of the deuterated active metabolites from DTBZ each accounted for less than 10% of an orally administered dose. This was further supported by a pooled analysis from participants in the phase 3 trials, which indicated that adverse events were similar in participants with mild to moderate renal impairment compared with participants with normal renal function. In addition, as DTBZ is a titrated medicinal product, it is unlikely that patients with any degree of renal impairment will be exposed to excessive concentrations of DTBZ and its deuterated active metabolites.

In summary, the limited data in patients with mild to moderate renal impairment from the Phase 3 trials did not indicate safety concerns.

The applicant estimated for each participant in Trials C-18 and C-23 the exposure (C_{avg}, C_{max}, and C_{min}) for (α+β)-HTBZ, through the final PopPK model, assuming the same representative dose of 36 mg/day and using individual post-hoc PK parameters. Previously, it was shown that C_{avg} was the main driver of efficacy.

Summary statistics was calculated per the renal function group (normal, mild, moderate and severe, according to eGFR). A slight increase on C_{avg}, C_{max}, and C_{min} means is observed from normal to mild and to moderate impairment, supported by an appropriate number of participants. This increase in exposure was seen as not clinically relevant and no dose adjustment is required for renal impairment patients.

Effect of hepatic impairment

The PK in patients with hepatic impairment was not evaluated and, since the major route of elimination of the active drug moieties is by hepatic metabolism, DTBZ should not be administered to patients with hepatic impairment. This contraindication was outlined accordingly in the PI.

Race, Ethnicity and/ Body weight

Based on population pharmacokinetic analyses there is no apparent effect of gender, race, and age (18-64 years) on the pharmacokinetics of deuterated α-HTBZ and deuterated β-HTBZ.

Limited pharmacokinetic data are available for patients 65-74 years of age (approx. 9% of the patients) and 75-84 years of age (approx. 1% of the patients). No data are available for those over 85 years of age. Therefore, no definitive pharmacokinetic conclusions can be made for patients over 65 years of age.

Drug-Drug Interactions

At clinically relevant concentrations, DTBZ, deuterated α-HTBZ, and deuterated β-HTBZ did not inhibit any CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) in human liver microsomes, and did not induce the tested CYP enzymes (CYP1A2, CYP2B6, and CYP3A4) after a 48-hour incubation in human hepatocytes.

Moreover, DTBZ and its deuterated metabolites (α-HTBZ and β-HTBZ) did not inhibit human transporters multidrug resistance protein 1 (MDR1, P-gp), BCRP, bile salt export pump, multidrug and toxin extrusion transporter (MATE)1, MATE2-K, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, organic anion-transporting polypeptide (OATP)1B1 and OATP1B3.

DTBZ and its deuterated metabolites (α-HTBZ and β-HTBZ) were also not found to be substrates for efflux MDR1 and BCRP and uptake OATP1B1, OATP1B3, and OCT1 human transporters.

The drug-drug interaction potential of DTBZ co-administration with a strong CYP2D6 inhibitor, paroxetine, was studied in healthy participants. When co-administered with paroxetine, systemic exposure ($AUC_{0-\infty}$) of α-HTBZ was 1.9-fold higher and β-HTBZ was 6.5-fold higher, resulting in an approximately 3-fold increase in $AUC_{0-\infty}$ for total (α+β)-HTBZ. With paroxetine, C_{max} of α-HTBZ and β-HTBZ were 1.2-fold and 2.2-fold higher, respectively, and the $t_{½}$ values of the metabolites were prolonged (total [α+β]-HTBZ $t_{½}$ increased from 9.75 hours to 16.0 hours). Based on these results, a maximal dose of 36 mg is agreed for patients who are poor CYP2D6 metabolisers or are receiving concomitant therapy with strong CYP2D6 inhibitors.

Exposure-Response

The difference in the PK exposures as well as the difference in the shapes of the PK curves of the total (α+β)-HTBZ from the DTBZ matrix tablet BID versus osmotic PR tablet QD formulations was shown to be not significant with regard to efficacy.

Bioequivalence Trial TV50717-BE-10179 showed that the GMRs of C_{max} for the HTBZ- metabolites were slightly below 80%. The impact of this non-BE C_{max} between the DTBZ matrix tablet BID and the osmotic PR tablet QD formulations was evaluated in the exposure-efficacy analysis. The difference in the efficacy outcomes were shown to be not clinically meaningful.

Nevertheless, the clinical efficacy and safety data of deutetrabenazine in target patients with TD are available only with the BID immediate release (IR) formulation, which is not approved in EU and not claimed in the current submission. A range of new prolonged release (PR) formulations (osmotic tablets 12, 24, 30, 36, 42 and 48 mg) to be administered once a day (QD) is claimed. Therefore, a bridging strategy followed. The efficacy Exposure-Response (E-R) analyses indicate that the approximately 25% decrease in C_{max} observed with QD formulation would result on a mean decrease of approximately -13.4% in clinical efficacy at steady state (from -2.94 to 2.54 on the change from baseline in AIMS score) in comparison to the BID formulation. Such decrease should be taken into account in the assessment of the benefit-risk balance for the proposed PR QD formulation.

Pharmacodynamics

α-HTBZ and β-HTBZ are reversible inhibitors of VMAT2, resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores. A series of in-vitro studies were conducted in order to establish the binding and functional effect of deuterated α-HTBZ and β-HTBZ, as well as the separate deuterated metabolites [+ or −]- α-HTBZ and [+ or −]-β-HTBZ to the primary target VMAT2. These studies identified the [+] metabolites as the active moieties inhibiting VMAT2 with a 50% inhibitory concentration (IC50) values in the range of ~10 nM compared to >1000 nM for the [−] metabolites.

The non-clinical results demonstrated that DTBZ and the deuterated α-HTBZ and β-HTBZ metabolites are reversible inhibitors of VMAT2, resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores. A series of *in vitro* studies were conducted to establish the binding and functional effect of DTBZ, deuterated α-HTBZ and β-HTBZ, where TBZ and its non-deuterated active metabolites were included as a comparison. Comparative pharmacology evaluations of the major circulating metabolites deuterated α-HTBZ and deuterated β-HTBZ showed similarity to their nondeuterated forms. The separate deuterated enantiomeric metabolites were also evaluated with regard to the primary target VMAT2.

Clinical efficacy in participants with TD confirmed the expected pharmacological effects of VMAT2 inhibition following DTBZ administration. Exposure-efficacy response evaluation of changes in AIMS scores, a measure assessing the severity of dyskinesias, following DTBZ treatments showed that the DTBZ (administered BID, as the matrix formulation) resulted in clinically and statistically significant improvement over placebo. A detailed comparison of C_{max} and AUC effect on AIMS total scores indicated similarity between the osmotic PR formulation QD and the matrix formulation BID. However, lower C_{max} values were observed for the active metabolites in the BE trials, although it did not appear to impact VMAT2 inhibition in a clinically relevant manner.

The applicant also presented data to support long-term DTBZ treatment, with clinically meaningful efficacy (in terms of sustained reduction in AIMS total score and achievement of treatment success based on CGIC) both in participants with psychotic disorders and those with mood and other disorders regardless of baseline DRA use (post-hoc analyses).

The effect of DTBZ on cardiac repolarization in CYP2D6 extensive metabolisers (EM) or intermediate metabolisers (IM) healthy participants was initially investigated in the placebo- and positive-controlled QT Trial SD-809-C-21 in comparison to TBZ. The highest tested dose of DTBZ in this trial (24 mg) provided a comparable total exposure (AUC) of total active metabolites ([α+β]-HTBZ) to the highest tested dose of TBZ (50 mg). In contrast to TBZ, DTBZ did not increase the time-matched placebo-adjusted QTcF interval or exceed the 90% 2-sided CI above the thresholds of regulatory concern regarding proarrhythmic potential (5 ms and 10 ms, respectively).

A double-blind, placebo-controlled trial (TV50717-SAD-10132) was conducted to evaluate the concentration-QT (C-QT) correlation using the Fridericia's corrected QT (QTcF) interval. In that trial, exposures exceeding the anticipated maximum concentrations at steady state in both CYP2D6 poor metabolisers (PM) and CYP2D6 extensive metabolisers (EM) or intermediate metabolisers (IM) were achieved by administration of high single doses (24, 48, and 72 mg) of DTBZ matrix tablets BID. Based on the established C-QT model, the expected QT prolongation for patients in both populations receiving the maximum recommended doses at steady state will not exceed 10 msec. This is also true for a CYP2D6 PM taking a daily dose of 48 mg instead of their recommended dose of 36 mg.

Trials evaluating QT interval prolongation showed that DTBZ may prolong QT interval, but the degree of such QT prolongation is not significant at clinically relevant exposures.

The applicant included in SmPC section 4.4 information that DTBZ may prolong the QTc interval; therefore, it should be used with caution in combination with other medicinal products that prolong the

QTc interval and in patients with congenital long QT syndrome, a history of cardiac arrhythmias, bradycardia, hypokalaemia or hypomagnesaemia. Additionally, a cross-reference to SmPC section 4.5 (where additional information on examples of concomitant QT prolonging medicines that should be used with caution) was included.

Pharmacodynamic drug-drug interactions is a possibility with deutetrabenazine, through primary pharmacodynamics if co-administration with other VMAT2 inhibitors were to be performed. However, co-administration of deutetrabenazine with reserpine or the newer and selective VMAT2 inhibitors is unlikely to be considered and additionally the applicant has included information regarding this possible interaction in SmPC section 4.5. Information on possible PD interaction with MAO inhibitors was also added in this section.

The applicant reported minor effects of deutetrabenazine on 5-HT receptors from non-clinical development, claiming that secondary PD interactions are unlikely to occur due to reduced off-target effects. Several publications show evidence of clinically used medicines to be able to modulate VMAT2, namely SSRI antidepressants, beta-2 adrenergic agonists/antagonists and anti-psychotics, some by different mechanisms without directly interacting with the active site of VMAT2.

Teva stated that, since DTBZ is a titrated medicinal product with dosing being determined individually for each patient, based on adequate reduction of TD symptoms and tolerability, this should minimize the risk of potential additive effects. Additionally, given the warning regarding close monitoring of patients with depression and the inclusion of anti-psychotics in section 4.4, this lessens the concern regarding the unknown PD effects of SSRIs and anti-psychotics on VMAT2 receptors. Furthermore, the clinical relevance of these potential PD interactions is yet to be fully established.

Deutetrabenazine inhibits VMAT2 which leads to monoamine concentration reduction such as dopamine, serotonine, or noradrenaline. Dopamine concentration depletion may lead to neuroleptic malignant syndrome (detailed in SmPC section 4.4), or to other extrapyramidal symptoms such as acute dyskinesias and dystonic reactions, tardive dyskinesia, Parkinsonism and others. The risk of encountering such events can be potentiated by co-administration with other neuroleptic or antipsychotic medicinal products such as, but not limited to sultopride, chlorpromazine, clozapine risperidone and others.

Concomitant use of monoamine inhibitors (MAO-I) with DTBZ can lead to large amounts of accumulated noradrenaline which can be released systemically. In the brain, serotonin is also released. The release of these substances results in marked central excitation and hypertension.

Since DTBZ can lead to monoamine depletion, concurrent use with levodopa or other dopaminergic medicinal products could lead to antagonising effects; this information has been included in SmPC section 4.5.

Recent publications on transport and inhibition mechanisms of human VMAT2 suggests that several VMAT2 mutations can impair tetrabenazine inhibitory effect on VMAT2. However, due to the limited information on these mutations a clinically relevant problem does not seem foreseeable at the moment, particularly given the potential mitigation of risks with the gradual dose escalation of DTBZ.

The difference in the PK exposures as well as the difference in the shapes of the PK curves of the total (α+β)-HTBZ from the DTBZ matrix tablet BID versus osmotic PR tablet QD formulations with regard to efficacy were evaluated in BE Trial TV50717-BE-10179 and showed that the GMRs of C_{max} for the HTBZ-metabolites were slightly below 80%. The impact of this non-BE C_{max} between the DTBZ matrix tablet BID and the osmotic PR tablet QD formulations was evaluated in the exposure-efficacy analysis. The difference in the efficacy outcomes was considered by the applicant as not clinically meaningful.

There were no particular safety concerns with DTBZ matrix tablet BID exposures in the HD and TD development program. DTBZ matrix tablet BID did not show an exposure-safety relationship in

participants with TD who received doses ranging from 12 mg/day to 48 mg/day in Trials SD-809-C-18 and SD-809-C-23. In the SD-809-C-15 trial, DTBZ matrix tablet BID was generally well tolerated, with rates of AEs similar to those following treatment with placebo. In the SD-809-C-16 open-label extension trial, DTBZ BID was well tolerated, and its safety was consistent with the known safety profile of the drug and results of the parent trial (SD-809-C-15).

Population pharmacokinetics/PD (PopPK/PD) modelling and simulation evaluations were performed to further support the dosing regimen by bridging results from trials utilizing different formulations and in different patient populations, with a focus on osmotic PR tablets QD.

In the comparison of the predicted change from baseline in the total motor AIMS score to support dose proportionality, the applicant stated that C_{avg} was used as the predictor of efficacy instead of AUC or C_{max}. However, on the trials that aimed to support the PK bridging of formulations the applicant has focused the results on C_{max} and AUC. The applicant has provided a comparison of the predicted change from baseline in the total motor AIMS score in both scenarios (C_{max} or C_{avg} as predictors), demonstrating similarity.

Dose selection for the Phase 3 programme in TD using the DTBZ clinical matrix formulation BID was based on targeting similar exposure (AUC) for the deuterated active metabolites as for the nondeuterated active metabolites of TBZ following TBZ administration.

Data obtained with the fixed-dose regimen in the Phase 3 trial C-23 justify the proposed titration schedule: the initial titration to 24 mg/day can be achieved within 1 week by increasing the dose from the initial 12 mg/day to 24 mg/day in the second week, i.e. the 12 mg/day to 24 mg/day titration step is favourable to bring patients to their individual efficacious dose range (24 to 48 mg/day) faster. This is justified by a low adverse event rate based on an exposure safety analysis of the Phase 3 data. DTBZ dosing should be determined individually for each patient, based on adequate reduction of TD symptoms and tolerability. Therapy should be initiated at 12 mg QD for 1 week. The dose should then be increased to 24 mg QD for another week. After this second week, the dose should then be titrated at weekly intervals in increments of 6 mg QD, based on reduction of TD symptoms and tolerability. The efficacious dose range is considered to be 24 mg to 48 mg.

The maximum recommended daily dose is 48 mg. The rate and extent of exposure, based on C_{max} and C_{avg}, as well as ER modelling, are similar between the DTBZ matrix tablet BID and osmotic PR tablet QD, thereby allowing a QD- instead of a BID-dosing schedule. As higher exposures are observed in patients receiving strong CYP2D6 inhibitors or who are poor CYP2D6 metabolisers, the total daily dose of DTBZ should not exceed 36 mg in these patients. In the Phase 3 trials (Trials C-18 and C-23) the maximum dose was 36 mg for participants that were also receiving treatment with strong CYP2D6 inhibitors.

The TD efficacy trials indicate that an efficacious dose is typically reached in a range between 24 mg and 48 mg per day.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacokinetic section of this initial MAA was based on data from the Phase 1 and Phase 2/3 studies. Generally, the characterization of the pharmacokinetics of DTBZ and its deuterated metabolites is appropriate. However, the clinical pharmacology program, including pivotal studies for B/R demonstration, was mostly conducted using an immediate release BID formulation (not approved in EU and not claimed in this MAA submission) and not the to-be marketed prolonged release QD formulation. Therefore, a bridging strategy supported by a pivotal multi-dose relative bioavailability study in healthy volunteers and exposure-responses (E-R) analyses was applied. Despite evidence of

dose proportionality within all QD strengths was not obtained in a single dedicated PK trial, this can be concluded from the totality of evidence collected in multiple biopharmaceutical trials.

The clinical pharmacodynamic section of this application, was based on data from the Phase 1 and Phase 2/3 studies. Generally, also the characterization of the pharmacodynamics of deutetrabenazine was considered appropriate.

2.6.5. Clinical efficacy

The tardive dyskinesia (TD) clinical development programme included 2 randomised, double-blind, placebo-controlled trials, the Phase 2/3 Trial **SD-809-C-18** (flexible dose; hereafter referred to as **C-18**) and the Phase 3 Trial **SD-809-C-23** (fixed dose; hereafter referred to as **C-23**). In addition, the results of a Phase 3 one open label, flexible dose, long-term extension safety study in TD, **SD-809-C-20** (hereafter referred to as **C-20**), and other supportive studies in Huntington's disease (HD) were included in the dossier for this initial MAA.

The Phase 3 trials in TD were conducted using a matrix formulation BID. Subsequently, Teva developed an osmotic PR formulation QD, which is the intended commercial formulation. Thus, safety and efficacy of the intended commercial PR formulation QD was supported by data from biopharmaceutic Phase 1 trials that demonstrated bioequivalence (BE) and dose proportionality, and evaluated relative bioavailability (BA), together with extensive PK/pharmacodynamic (PD) modelling and simulation. Dose proportionality of DTBZ matrix formulation BID was demonstrated in Trials AUS-**SD-809-CPT07** and **SD-809-C-11**. Collectively, these results bridged between the matrix formulation BID and the osmotic PR formulation QD. The osmotic PR tablets QD demonstrated similar exposure and are expected to have a similar clinical response to the DTBZ matrix tablets BID.

The HD-associated chorea efficacy programme included 2 Phase 3 trials, the randomised, double-blind, placebo-controlled Trial **SD-809-C-15** (hereafter referred to as **C-15**) and the open-label single-arm, 2-cohort Trial **SD-809-C-16** (hereafter referred to as **C-16**). The C-15 trial data do not provide support for the efficacy of DTBZ in the sought indication of TD whereas trial C-16 provided important data related to the impact of the dosing regimen and exposure parameters driving therapeutic effect and was therefore considered supportive of this application in TD by the applicant. Of note, Teva outlined in its dossier that the HD indication will not be registered in the EU.

Table 7: Overview of clinical trials in the TD clinical development programme

Trial Number	Trial Title (Formulation)
Phase 3 trials in adults with TD	
SD-809-C-18 (flexible-dose trial)	A Randomized, Double-Blind, Placebo-Controlled Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia (matrix formulation BID)
SD-809-C-23 (fixed-dose trial)	A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia (matrix formulation BID)
SD-809-C-20 (long-term trial)	An Open-label, Long-term Safety Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia (matrix formulation BID)
	Part A: 6-week titration to effect and up to 158 weeks open-label treatment
	Part B: 1-week randomised withdrawal period and 12 weeks of open-label treatment
	Part C: 52-week open-label treatment (Europe only)

Trial Number	Trial Title (Formulation)
Supportive Phase 3 trials in adults with HD	
SD-809-C-15 (First-HD)	A Randomized, Double-Blind, Placebo-Controlled Study of SD-809 Extended Release for the Treatment of Chorea Associated with Huntington Disease (matrix formulation BID)
SD-809-C-16 (ARC-HD)	An Open-Label, Long-Term Safety Study of SD-809 ER in Subjects with Chorea Associated with Huntington Disease (matrix formulation BID)
Phase 1 trials in healthy adult participants	
TV50717-BE-10179	An Open-label, Randomized, Repeated Dose, 2-Treatment, 2-Period, 2-Sequence Crossover Study with Full Replicate Design in Healthy Subjects to Assess the Bioequivalence and Relative Bioavailability at Steady State Between Once Daily Administration of a 24-mg Extended Release Tablet of TEV-50717 and Twice Daily Administration of a 12-mg AUSTEDO® Tablet (osmotic PR formulation QD and matrix formulation BID)
TV50717-PK-10175	An Open-label, Randomized, Single Dose, 4-way, 4-sequence, Crossover Study in Healthy Subjects to Assess the Dose Proportionality of 6 mg, 12 mg, and 24 mg Extended Release Tablets of TEV-50717 in the Fed State Over the Clinical Dose Range (6-48 mg) (osmotic PR formulation QD)

Table 8: Overview of clinical trials in the TD clinical development programme (continued)

Trial Number	Trial Title (Formulation)
TV50717-BE-10165	An Open-label, Randomized, 3-Period, 3-Treatment, 6-Sequence Study in Healthy Subjects to Compare the Bioavailability of TEV-50717 and its Active Metabolites Between a Single Dose of a TEV-50717 24-mg Tablet and a Single AUSTEDO® 12-mg Tablet Administered Twice 12 Hours Apart and to Evaluate the Effect of Food on the Pharmacokinetics Following a Single TEV-50717 24-mg Osmotic Tablet (osmotic PR formulation QD and matrix formulation BID)
TV50717-BE-10192	An Open-Label, Randomized, 2-Sequence, 2-Period, 2-Treatment, Crossover Study in Healthy Subjects to Assess the Bioequivalence of TEV-50717 and Its Active Metabolites After Single Doses of 1×48 mg (Test) vs 2×24 mg (Reference) TEV-50717 QD Tablets (osmotic PR formulation QD)
TV50717-BE-10201	An Open-Label, Randomized, 2-Sequence, 2-Period, 2-Treatment, Crossover Study in Healthy Subjects to Assess the Bioequivalence of TEV-50717 and Its Active Metabolites After Single 36 mg Doses of Test and Reference TEV-50717 QD Tablets (osmotic PR formulation QD)

AUSTEDO®=deutetrabenazine matrix tablet administered twice daily; BID=twice daily; ER=extended release; PR=prolonged release; QD=once daily; SD-809=deutetrabenazine; TEV-50717=deutetrabenazine.

Further details about DTBZ clinical trials are provided in the table below.

Table 9: DTBZ clinical trials

Study Number/Title	Participant Population	Participant Characteristics	Treatment (Dose, Dosage Form, Route) [Batch Number]	Number of Participants
AUS-SD-809-CTP-06 A Phase 1, Randomized, Double-Blind, Single-Dose Crossover Study to Compare the Pharmacokinetics, Safety and Tolerability of SD-809 (Deutetrabenazine) with	Healthy adults	Age range 18-39 years 48% male	DTBZ (25 mg, unformulated-powder-in-capsule, p.o.) [AUS01-050] TBZ (25 mg, unformulated-powder-in-capsule, p.o.) [AUS01-049]	DTBZ: 11 TBZ: 10 Total: 21 Included in the PK analysis: PM: 4

Study Number/Title	Participant Population	Participant Characteristics	Treatment (Dose, Dosage Form, Route) [Batch Number]	Number of Participants
Tetrabenazine in Healthy Volunteers				IM: 3 EM: 13
SD-809-C-12 An Open-Label, Two-Period Study Designed to Evaluate and Compare the Mass Balance Recovery, Metabolite Profile and Metabolite Identification of Oral Doses of Both [^{14}C]-SD-809 and [^{14}C]-Tetrabenazine in Healthy Male Subjects	Healthy adults	Age range 37-62 years 100% male Excludes CYP2D6 PM or ultra-rapid metabolizers	[^{14}C]-DTBZ (25 mg, unformulated-powder-in-capsule, p.o.) [113049/C/01] [^{14}C]-TBZ (25 mg, unformulated-powder-in-capsule, p.o.) [113049/C/02]	[^{14}C]-DTBZ: 6 [^{14}C]-TBZ: 6 Total: 12
SD-809-C-21 A Randomized, Double-Blind, Placebo- and Positive-Controlled Crossover Study to Evaluate the Effects of Single **Doses of SD-809** (Deutetrabenazine) and Tetrabenazine on the Corrected QT Interval	Healthy adults	Age range 18-49 years 75% male Excludes CYP2D6 PM phenotype, ultra-rapid metabolizer phenotype, or allelic duplication	DTBZ (12 or 24 mg, matrix tablets BID, p.o.) TBZ (25 mg, p.o.) Moxifloxacin (400 mg, p.o.) Placebo equivalents (p.o.) [Batch numbers: See SD-809-C-21 CSR, Appendix 16.1.6]	DTBZ 12 mg: 45 DTBZ 24 mg: 44 DTBZ placebo: 43 TBZ 50 mg: 46 TBZ placebo: 45 Moxifloxacin: 47 Total: 48
TV50717-SAD-10132 A Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Electrocardiographic Effects, Pharmacokinetics, Safety, and Tolerability of TEV-50717 (Deutetrabenazine)	Healthy adults	CYP2D6 PM: Age range 23-55 years 29% male CYP2D6 EM (note cohort included IM): Age range 32-52 years 33% male	DTBZ: placebo ratio=9:3 PM: (24 mg; 48 mg; 72 mg, matrix tablets BID, p.o.) [N465571] EM: (24 mg; 48 mg; 72 mg, matrix tablets BID, p.o.) [N465571] Placebo (p.o.) [N471471]	PM: 24 EM: 12 Total: 36
TV50717-PK-10175 An Open-label, Randomized, Single Dose, 4-way, 4-sequence, Crossover Study in Healthy Subjects to Assess the Dose Proportionality of 6 mg, 12 mg, and 24 mg Extended-Release Tablets of TEV-50717 in the Fed State Over the Clinical Dose Range (6-48 mg)	Healthy adults	Age range 19-55 years 56% male CYP2D6 EM or CYP2D6 IM or combination of the 2	DTBZ (A, 2×6 mg; B, 1×12 mg; C, 1×24 mg; D, 2×24 mg, osmotic PR tablets QD, p.o.) [batch numbers available on request] Single dose; washout minimum of 6 days apart	Sequence ABDC: 29 Sequence BCAD: 29 Sequence CDBA: 29 Sequence DACB: 29 Total: 116
AUS-SD-809-CTP-07 Part 2 A Phase 1 Study to Evaluate the Pharmacokinetics of Two Extended Release (ER) Formulations of SD-809 with and without Food, Compared to Tetrabenazine Tablets and	Healthy adults	Age range 18-42 years 71% male	DTBZ (7.5 mg, 15 mg, and/or 22.5 mg, matrix tablets BID, p.o.) [7.5 mg, 3459-34; 15 mg, 3441-23]	Total: 24

Study Number/Title	Participant Population	Participant Characteristics	Treatment (Dose, Dosage Form, Route) [Batch Number]	Number of Participants
the Pharmacokinetics and Dose Proportionality of the Selected Formulation Following Single and Multiple Doses		Includes CYP2D6 EM or IM	Single dose; repeated doses TBZ (25 mg, BID dosing, p.o.) [15404] Single dose; repeated doses	
SD-809-C-08 A Drug Interaction Study of SD-809 ER and Repeated Doses of Paroxetine	Healthy adults	Age range 19-49 years 67% male Includes CYP2D6 EM or IM	DTBZ (22.5 mg [1×7.5 mg+1×15 mg], osmotic PR tablet QD, p.o.) [3459-34R, 3441-23R] Single dose on day 1 and day 11 Paroxetine (20 mg, tablet, p.o.) [MM1153] Repeated QD doses on days 4 through 12	Total: 24
SD-809-C-18 (ARM-TD) A Randomized, Double-Blind, Placebo-Controlled Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia	Adult participants with TD	Age range 25-75 years 48% male	DTBZ (starting 12 mg/day, 2×6 mg BID, adjusted weekly at increments of 6 mg/day; up to 48 mg/day unless the participant was receiving a strong CYP2D6 inhibitor, in which case the maximum total daily dose was limited to 36 mg/day, matrix tablets BID, p.o.) [batch numbers available on request] Placebo (BID, p.o.) [batch numbers available on request]	DTBZ: 58 Placebo: 59 Total: 117
SD-809-C-23 (AIM-TD) A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia	Adult participants with TD	Age range 21-81 years 45% male	DTBZ (12, 24, and 36 mg/day, 2×6, 2×12, and 2×18 mg BID over 12 weeks; the 24- and 36-mg/day doses were titrated during a 4-week dose escalation phase, ahead of an 8-week maintenance phase, matrix tablets BID, p.o.) [batch	DTBZ 12 mg/day: 75 DTBZ 24 mg/day: 74 DTBZ 36 mg/day: 75 Placebo: 74 Total: 298

Study Number/Title	Participant Population	Participant Characteristics	Treatment (Dose, Dosage Form, Route) [Batch Number]	Number of Participants
			numbers available on request] Placebo (BID, p.o.) [batch numbers available on request]	
SD-809-C-15 (First-HD) A Randomized, Double-Blind, Placebo-Controlled Study of SD-809 Extended Release for the Treatment of Chorea Associated with Huntington Disease	Adults with manifest HD and chorea	Age range 23-74 years 56% male	DTBZ (6 mg/day to 48 mg/day, titrated based on chorea control and tolerability, matrix tablets BID, p.o.) [6 mg: N451173; 9 mg: N451737; 12 mg: N451174] Placebo (BID, p.o.) [N450607]	DTBZ: 45 Placebo: 45 Total: 90
SD-809-C-16 (ARC-HD), ARC-Rollover Cohort An Open-Label, Long-Term Safety Study of SD-809 ER in Subjects with Chorea Associated with Huntington Disease	Adults with HD and chorea who completed First-HD	Age range 23-75 years 55% male	DTBZ (6 mg/day to 72 mg/day, titrated based on chorea control and tolerability, matrix tablets BID, p.o.) [see SD-809-C-16 CSR, Appendix 16.1.6]	Total: 82
SD-809-C-16 (ARC-HD), ARC-Switch Cohort An Open-Label, Long-Term Safety Study of SD-809 ER in Subjects with Chorea Associated with Huntington Disease	Adults with HD and chorea currently receiving TBZ	Age range 32-75 years 60% male	DTBZ (starting regimen based on algorithm for achieving AUC of deuterated total (α+β)-HTBZ comparable to that of TBZ; titrated after 1 week based on chorea control and tolerability to maximum of 72 mg/day, matrix tablets BID, p.o.) [see SD-809-C-16 CSR, Appendix 16.1.6]	Total: 37

2.6.5.1. Dose-response studies

No dose response studies were conducted. The applicant relied on published clinical experience with tetrabenazine (TBZ), a VMAT2 inhibitor structurally similar to deutetrabenazine (DTBZ) that has also been used in the treatment of TD. Therefore, doses of DTBZ in the phase 3 studies were based on population pharmacokinetic modelling to provide exposure comparable to the total (α+β)-HTBZ achieved with TBZ.

As above anticipated, the phase 3 trials used a clinical matrix-based gastro erosional formulation for twice daily dosing, different from the osmotic PR formulation QD intended to be commercialised. The reader should refer to the PK section of this assessment report (AR) for further details e.g., on the bioequivalence (BE) studies between the two formulations. In the initial PK trials, BE was achieved with

approximately 50% lower DTBZ doses compared to TBZ. The therapeutic benefit of these doses was observed in the phase 3 efficacy trials in participants with TD (Trials C-18 and C-23).

The Phase 2/3 SD-809-C-18 study could be partly considered a dose-finding study, since it was a phase 2, flexible dose with doses up to 48 mg per day. This study is discussed as a confirmatory efficacy study thereafter.

The proposed initiation and titration scheme for DTBZ in this MAA submission differs from that used in the phase 3 clinical trials in TD. Specifically, titration to an efficacious dose range is being shortened by 1 week by increasing the dose from 12 to 24 mg/day in the second week, excluding the 18 mg dosing step in between (of note, the applicant did not seek approval for DTBZ 18 mg). Post-marketing/real-world experience from the US, where DTBZ has been on the market since 2017, has been used to justify accordingly this change. Exclusion of the 18 mg dosing step from the initiation and titration scheme was further supported by an integrated safety data analysis from the Phase 3 trials in TD (C-18 and C-23), HD-associated chorea (C-15 and C-16) trials and an exposure-safety modelling analysis (the reader could also refer to sub-section 2.6.5.2.2). the AE profiles of 12 mg, 18 mg and 24 mg/day doses indicated that excluding the 18 mg dosing step is expected to be safe.

2.6.5.2. Main studies

2.6.5.2.1. SD-809-C-18: A randomised, double blind, placebo-controlled study of SD-809 (DTBZ) for the treatment of moderate to severe tardive dyskinesia.

Methods

This was a Phase 2/3, randomised, double-blind, placebo-controlled, parallel-group trial in participants with TD. Participants initiated DTBZ at a low dose (12 mg per day) and then escalated to a dose ranging from 24 to 48 mg per day at which maximum benefit was observed while side effects were minimised.

Participants were randomised in a 1:1 ratio to receive either DTBZ matrix formulation BID (initiated at 12 mg with titration up to a maximum daily dose of 48 mg) or placebo. The trial included a screening period of up to 4 weeks, a 6-week titration period, a 6-week maintenance period, and a 1-week washout period. During the 6-week titration period, investigators titrated the dose of trial drug (DTBZ or placebo) on a weekly basis to a dose at which adequate dyskinesia control was achieved and the participant tolerated the treatment regimen, or until the maximum permitted dose, ranging from 24 to 48 mg per day, was reached.

Study Participants

The study was conducted at a total of 41 centres; 29 sites in the United States, 7 sites in Poland, 3 sites in Slovakia, and 2 sites in the Czech Republic.

92 patients were planned to be enrolled; data from 117 patients were analysed for efficacy and safety.

Key inclusion criteria (full criteria provided in the clinical study report) were:

a. Patient is between 18 and 75 years of age, inclusive.

b. Patient has a history of using a dopamine receptor antagonist (DRA) for at least 3 months (or 1 month in patients 60 years of age and older).

c. Patient has a clinical diagnosis of TD and has had symptoms for at least 3 months prior to screening.

d. The patient's TD symptoms are bothersome to the patient or cause functional impairment.

e. At the screening and baseline visits, the patient has:

- Moderate or severe abnormal movements as judged by the Investigator based on Item 8 of the Abnormal Involuntary Movement Scale (AIMS), AND
- A total motor AIMS score of ≥6 (based on Items 1 through 7) as assessed by the investigator. Note: A video recording of the AIMS at screening was also reviewed by a blinded central rater to confirm eligibility prior to randomization.

f. For patients with underlying psychiatric illness:

- Patient is psychiatrically stable and has had no change in psychoactive medications (including, but not limited to, neuroleptics, benzodiazepines, anticonvulsants, and mood stabilizers) for ≥30 days before screening (45 days for antidepressants).
- Patients on long-acting (depot) medications been on stable therapy (dose, frequency) for ≥3 months before screening.
- Patient has a mental health provider who is aware of the patient's participation in the trial and does not anticipate any changes to the patient's treatment regimen (drug, dose, frequency) in the next 3 months.

Key exclusion criteria (full criteria provided in the clinical study report):

a. Patient has received any of the following medications within 30 days of screening or baseline:

- Tetrabenazine, reserpine, α-methyl-p-tyrosine (AMPT), botulinum toxin (within 3 months of screening), and medications with strong anticholinergic activity (trihexyphenidyl, benztropine, orphenadrine, procyclidine, and biperiden)
- Metoclopramide, promethazine, and prochlorperazine
- Stimulants (ie, methylphenidate, amphetamine/dextroamphetamine, lisdexamphetamine, etc), or monoamine oxidase inhibitors (MAOIs)
- Levodopa or dopamine agonists

b. Patient has participated in any previous study of SD-809 in which they received SD-809.

c. Patient has a neurological condition other than TD that may interfere with assessing the severity of dyskinesias.

d. Patient has a serious untreated or undertreated psychiatric illness at screening or baseline.

e. Patient has active suicidal ideation at screening or baseline.

f. Patient has a history of any of the following within the last 6 months of screening:

- Previous intent to act on suicidal ideation with a specific plan (positive answer to question 5 on the Columbia-Suicide Severity Rating Scale [C-SSRS]), irrespective of level of ambivalence at the time of suicidal thought
- Previous preparatory acts to commit suicide or suicidal behaviour
- A previous actual, interrupted, or aborted suicide attempt

g. Patient has a score ≥11 on the depression subscale of the Hospital Anxiety and Depression Scale (HADS) at screening or baseline.

h. Patient is developmentally disabled or has evidence of dementia.

i. Patient has an unstable or serious medical illness at screening or baseline.

Treatments

Patients were centrally randomized in a 1:1 ratio to receive either SD-809 or placebo. SD-809 oral tablets at strengths of 6, 9, 12, 15, and 18 mg were used. The starting dose of 12 mg/day was titrated to obtain adequate control of dyskinesias that was well tolerated up to a maximum of 48 mg/day (36 mg/day for patients receiving a strong cytochrome P450-2D6 [CYP2D6] inhibitor) administered in 2 divided doses. Duration of Treatment: Twelve weeks, including a 6-week titration phase followed by a 6-week maintenance phase.

There was no rescue medication.

Objectives

This was a superiority study against placebo.

Objectives:

- To evaluate the efficacy of SD-809 to reduce the severity of abnormal involuntary movements of tardive dyskinesia (TD);
- To evaluate the safety and tolerability of titration and maintenance therapy with SD-809 in patients with drug-induced TD.

Outcomes/endpoints

Primary Efficacy Measure and Endpoint:

The change in AIMS score (Items 1 through 7) from baseline to week 12, as assessed by blinded central video rating. The baseline AIMS score is defined for each patient as the day 0 assessment.

Secondary Efficacy Measures and Endpoints:

The secondary efficacy variables and endpoints are as follows:

Key Secondary Endpoints:

- The proportion of patients who are a treatment success (defined as Much Improved or Very Much Improved) at week 12 based on the CGIC
- The proportion of patients who are a treatment success (defined as Much Improved or Very Much Improved) at week 12 based on the PGIC.
- The change in the modified CDQ-24 (Craniocervical Dystonia Questionnaire) from baseline to week 12.

Sample size

92 patients were planned to be enrolled; data from 117 patients were analysed for efficacy and safety.

Randomisation and blinding (masking)

Participants were centrally randomised in a 1:1 ratio to receive either DTBZ or placebo. Randomisation was stratified by use of DRA at baseline (currently taking versus not taking a DRA). The screening AIMS examination was reviewed by a blinded central rater to confirm eligibility prior to randomisation; however, for logistical reasons, the baseline examinations could not be centrally reviewed prior to randomisation. As a result, 16 participants (14.1%) were randomised with baseline centrally-read AIMS total scores <6, indicating TD that was less severe than specified by the protocol inclusion criteria. Therefore, post hoc sensitivity analyses were conducted in the subgroup of participants with a baseline AIMS total score of ≥6, restricting the population to what was intended in the protocol.

Blinding: An Interactive Technology Response System (ITRS, including web and voice) was used to stratify patients by baseline use of DRAs (currently taking versus not currently taking a DRA) and to provide the treatment assignment for each patient.

Statistical methods

Analysis Populations: The Intent-to-Treat (ITT) Population was defined as all randomized patients. The Modified ITT (mITT) Population was defined as all patients in the ITT Population who received study drug and had at least 1 centrally read postbaseline assessment of the AIMS from at least 1 scheduled postbaseline time point. The mITT Population was the primary analysis population for all efficacy endpoints. The Per-Protocol Population was defined as all patients in the mITT Population who were compliant (80% to 105%) with randomized study drug, had measurable levels of active metabolites at the time of the week 12 AIMS assessment (SD-809 arm only), and had no major protocol deviations. The Safety Population was defined as all patients who were administered any study drug.

Primary Analysis: The primary analysis was carried out in the mITT Population using a linear mixed model for repeated measurements (MMRM) with the change from baseline in AIMS score as the dependent variable. The model included fixed effects for treatment, each scheduled time point (5 levels: weeks 2, 4, 6, 9, and 12), the treatment-by-time point interaction, and the DRA status. The baseline AIMS score was included as a covariate. The unstructured covariance model was used, and the primary analysis compared the SD-809 and placebo groups at week 12 using a 2-sided test at the 5% level of significance. This was based on the F-test using the Satterthwaite method to compute the denominator degrees of freedom. The primary analysis of the primary endpoint was repeated in the Per-Protocol Population. Sensitivity analyses were performed in the mITT and ITT Populations using analysis of covariance (ANCOVA) models with missing data imputed as the least favourable change from baseline and imputed as the last observation carried forward (LOCF).

Analyses of Secondary Endpoints:

The secondary efficacy endpoints were analysed using a hierarchical testing procedure. If the primary analysis was statistically significant ($p<0.05$), then the first key secondary endpoint was to be analysed, also at the 5% level of significance (2-sided). If the first key secondary endpoint was statistically significant, then the second key secondary endpoint was to be similarly analysed, and so forth. For any analysis that was not statistically significant, all subsequent analyses of key secondary endpoints were exploratory rather than confirmatory. For the PGIC and CGIC endpoints, the proportions of patients who were a treatment success were compared between treatments using Pearson's chi-square test. Treatment success according to these scales was defined as a rating of "much improved" or "very much improved" at week 12. Patients who did not provide a response at week 12 were assumed to be treatment failures. The analysis of the CDQ-24 total score was performed using an ANCOVA model with change from baseline to week 12 in CDQ-24 score as the dependent variable, treatment and the DRA status as factors, and the baseline CDQ-24 score as a covariate. Missing data for individual items were imputed

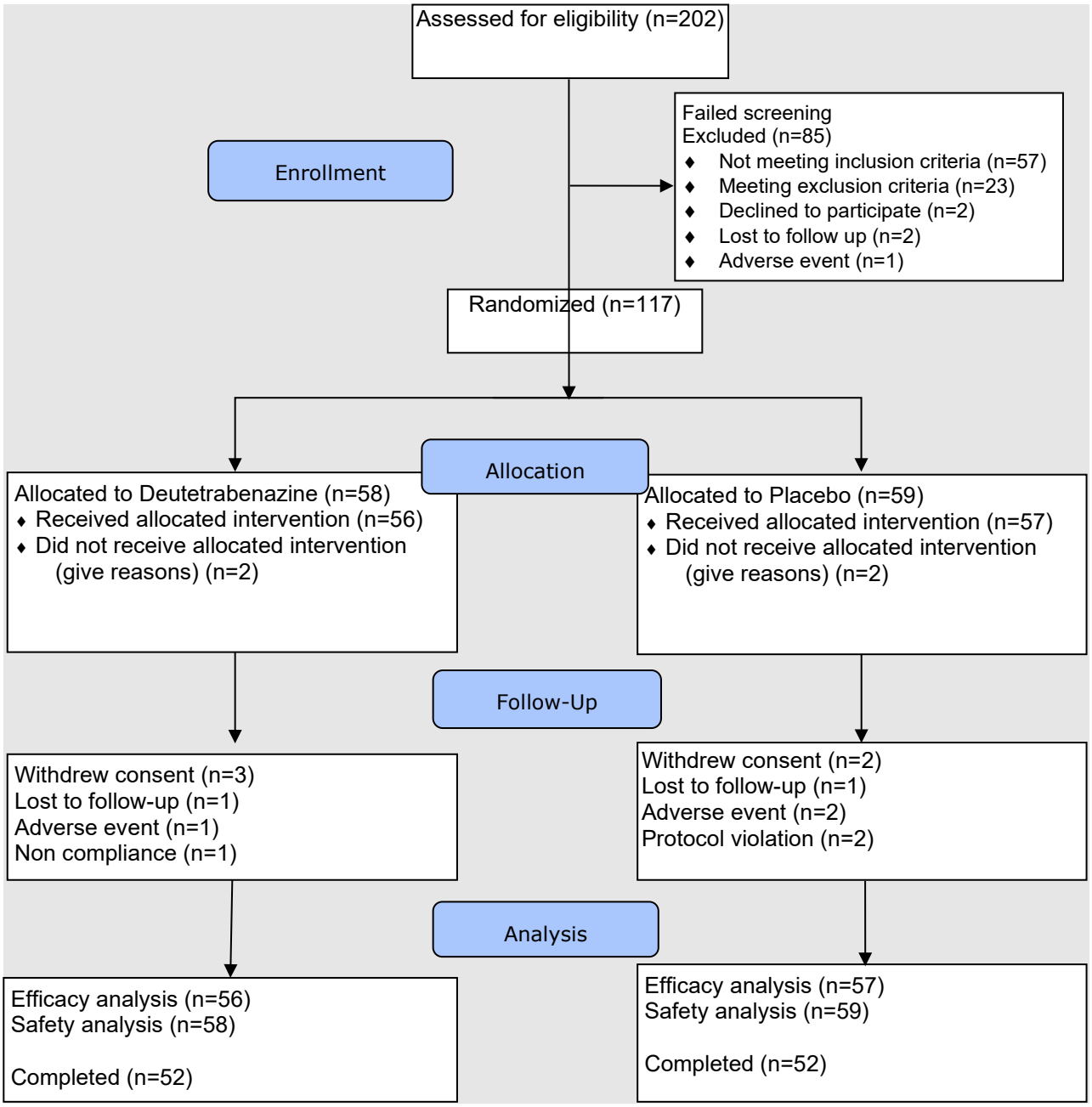
using the LCOF. The p-value for the difference between the SD-809 and placebo groups at week 12 is based on the F-test. Analyses of the key secondary endpoints were repeated in the ITT Population and in the Per-Protocol Population. Sensitivity analyses of the key secondary endpoints in the mITT Population excluded missing data instead of imputing missing results.

Analyses of Additional Efficacy Endpoints:

The percentage change in AIMS score from baseline to week 12, as assessed by blinded central video rating, was analysed using methods similar to those used for the primary endpoint. The cumulative proportion of responders at week 12 for response levels ranging from a 10% improvement from baseline to a 90% improvement from baseline was summarized and reported in steps of 10 percentage points. Patients with a missing AIMS score were considered to be AIMS non-responders. The analysis tested for a higher response rate in the active arm *versus* placebo at week 12 using Pearson's chi-square test. The change in AIMS from baseline to week 12 based on the local rater score was analysed using the MMRM method as described for the primary endpoint.

Results

Figure 9: Participant flow



Conduct of the study

The original protocol (dated 24 March 2014) was amended twice, and 1 country-specific amendment was prepared. A summary of the protocol amendments is provided in the table below.

Table 10: Summary of protocol amendments

Amendment	Date	Major changes (other changes administrative or clarification)
01	20 May 2014	• Addition of video recording of AIMS assessment at week 2 (an outcome of discussion with FDA) • Addition of CGIC at week 2 • CDQ-24 endpoint reclassified as an additional secondary endpoint (an outcome of discussion with FDA) • Addition of sensitivity analyses • Addition of procedures for handling missing data
02	08 July 2014	• Title amended to provide a better description of the study • Expansion of the role of the independent monitoring committee to include monitoring of all data, including safety data • Modified excluded medications to better reflect medications likely to have significant interactions with SD-809 and/or directly oppose the effects of SD-809 based on known mechanism of action • Added additional guidance on specific excluded anticholinergics and stimulants • Removed exclusion of patients who previously did not respond to tetrabenazine or who discontinued tetrabenazine due to an AE that was considered related to tetrabenazine and was either moderate/severe in severity, or met criteria for an SAE • Added exclusion for participation in any previous study of SD-809 in which patients received SD-809 • Revised time frame for prior suicidality from 5 years to 6 months • Brief physical examination moved from screening visit to baseline visit • Specified that UPDRS III (motor), BARS, and ESS were to be performed at the investigator's discretion at unscheduled visits
02.1 (Czech Republic)	10 October 2014	• Added urine pregnancy tests for women of childbearing potential at weeks 4, 9, 12, and 13 visits and at unscheduled visits (at the investigator's discretion) • Specified that the caregiver must be in contact with the patient a minimum of 4 times per week and must oversee any complications the patient may experience during the course of the study

AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; CDQ-24=Craniocervical Dystonia Questionnaire; CGIC=Clinical Global Impression of Change; ESS=Epworth Sleepiness Scale; SAE=serious adverse event; UPDRS=Unified Parkinson's Disease Rating Scale.

Baseline data

The mITT Population was 52.2% female, 69.9% white, and had a mean age of 54.9 years. In the mITT Population, the mean duration of TD was 75 months, the mean AIMS score was 9.6, 80.5% of patients were using a DRA, and 15.0% were using a strong CYP2D6 inhibitor. Almost all patients had comorbid psychiatric disorders (111 patients [98.2%]).

Table 11: Summary of demographic and baseline characteristics (mITT population; N=113)

Parameter	SD-809 (N=56)	Placebo (N=57)	Total (N=113)
Age, years			
Mean (SD)	56.9 (8.52)	53.0 (10.67)	54.9 (9.81)
Minimum, maximum	40, 75	25, 70	25, 75
Gender, n (%)			
Female	28 (50.0)	31 (54.4)	59 (52.2)
Male	28 (50.0)	26 (45.6)	54 (47.8)
Race, n (%)			
White	37 (66.1)	42 (73.7)	79 (69.9)
Black or African American	17 (30.4)	14 (24.6)	31 (27.4)
Asian	2 (3.6)	1 (1.8)	3 (2.7)
Ethnicity, n (%)			
Hispanic or Latino	4 (7.1)	10 (17.5)	14 (12.4)
Not Hispanic or Latino	51 (91.1)	46 (80.7)	97 (85.8)
Not reported	1 (1.8)	1 (1.8)	2 (1.8)
Weight, kg			
Mean (SD)	87.31 (24.421)	85.55 (20.883)	86.42 (22.621)
Minimum, maximum	47.3, 182.1	45.1, 166.6	45.1, 182.1
BMI, kg/m^2			
Mean (SD)	30.50 (8.025)	29.63 (6.957)	30.06 (7.484)
Minimum, maximum	16.2, 66.8	18.1, 59.3	16.2, 66.8
Duration of tardive dyskinesia, months			
Mean (SD)	75.0 (82.08)	75.0 (82.52)	75.0 (81.93)
Minimum, maximum	3, 326	3, 436	3, 436
AIMS (Items 1 to 7), centrally read			
Mean	9.7 (4.14)	9.6 (3.78)	9.6 (3.94)
Minimum, maximum	1, 20	3, 18	1, 20
Using a DRA, n (%)	43 (76.8)	48 (84.2)	91 (80.5)
Using a strong CYP2D6 inhibitor, n (%)	9 (16.1)	8 (14.0)	17 (15.0)

Parameter	SD-809 (N=56)	Placebo (N=57)	Total (N=113)
CYP2D6 genotype, n (%)			
Poor metabolizer	5 (8.9)	1 (1.8)	6 (5.3)
Not poor metabolizer[a]	51 (91.1)	56 (98.2)	107 (94.7)
Background comorbid illness, n (%)			
Psychiatric disorders	55 (98.2)	56 (98.2)[b]	111 (98.2)
Schizophrenia	30 (54)	32 (56)	62 (55)
Schizoaffective disorder	9 (16)	8 (14)	17 (15)
Bipolar/Depression	13 (23)	15 (26)	28 (25)
Other	4 (7)[c]	1 (2)	5 (4)
Gastrointestinal disorders	2 (3.6)	0	2 (1.8)

Source: Tables 14.1.2.1.2, 14.1.2.2.2, 14.1.2.3.2, and Ad hoc Table 38.
[a] Includes patients who are intermediate, extensive, and ultrarapid CYP2D6 metabolizers and patients whose specific non-poor CYP2D6 genotype could not be distinguished.
[b] One patient had missing information for subtype of psychiatric illness.
[c] One patient had a nonpsychiatric background comorbid illness.
BMI=body mass index; CYP2D6=cytochrome P450 2D6; DRA=dopamine receptor antagonist; mITT=modified Intent-to-Treat; N=total number of patients; n=number of patients in subgroup; SD=standard deviation.

Concomitant medication at baseline

Fifty-eight patients (100.0%) in the SD-809 group and 57 patients (96.6%) in the placebo group were receiving at least 1 concomitant medication at baseline. Use of ATC classes of CNS-active concomitant medications at baseline was generally balanced between groups, including antipsychotics (SD-809 group: 46 patients [79.3%] versus placebo: 51 [86.4%]), antidepressants (SD-809 group: 33 [56.9%] versus placebo: 29 [49.2%]), antiepileptics (SD-809 group: 17 [29.3%] versus placebo: 15 [25.4%]), and anxiolytics (SD-809 group: 12 [20.7%] versus placebo: 12 [20.3%]).

The most commonly used antipsychotics at baseline were quetiapine (SD-809 group: 13 [22.4%] versus placebo: 18 [30.5%]) and risperidone (SD-809 group: 9 [15.5%] versus placebo: 7 [11.9%]).

Table 12: Summary of CNS-active and other common (>20% of patients) concomitant medications used at baseline (Safety Population; N=117)

Therapeutic pharmacological subgroup Preferred term	SD-809 (N=58) n (%)	Placebo (N=59) n (%)	Total (N=117) n (%)
Any concomitant medication	58 (100)	57 (96.6)	115 (98.3)
Antipsychotics	46 (79.3)	51 (86.4)	97 (82.9)
Antidepressants	33 (56.9)	29 (49.2)	62 (53.0)
Antiepileptics	17 (29.3)	15 (25.4)	32 (27.4)
Anxiolytics	12 (20.7)	12 (20.3)	24 (20.5)
Hypnotics and sedatives	11 (19.0)	11 (18.6)	22 (18.8)
Opioids	10 (17.2)	10 (16.9)	20 (17.1)

Source: Table 14.1.3.1.2 and Listing 16.2.4.7.2.
ADHD=attention deficit hyperactivity disorder; CNS=central nervous system; N=total number of patients; n=number of patients in subgroup.
Notes: Includes concomitant medications in use at time of patient's baseline visit. Patients are counted at most once for an ATC class or a Preferred Term.

Numbers analysed

Study Initiation Date (first patient enrolled): 11 June 2014.

Study Completion Date (last patient completed): 21 May 2015.

Statistical analyses were conducted according to the statistical analysis plan, dated 28 April 2015.

A total of 117 participants with TD were randomised to DTBZ (N=58) or placebo (N=59) treatment and received at least 1 dose of trial drug. Six participants in the DTBZ group withdrew from the trial, including 1 participant due to an adverse event. Seven participants in the placebo group withdrew from the trial, including 2 participants due to an adverse event.

A total of 52 patients (89.7%) in the SD-809 group and 52 patients (88.1%) in the placebo group completed the study. Of the 117 patients in the ITT Population, 4 patients without at least 1 centrally read postbaseline assessment of the AIMS were excluded from the mITT Population (N=113).

The mean total duration of trial drug exposure was similar between the 2 treatment groups (77.39 days for DTBZ, 77.64 days for placebo).

Outcomes and estimation

Primary endpoint (AIMS score)

There was a reduction in TD motor symptoms as measured by AIMS total score from baseline to week 12 in this trial.

DTBZ treatment provided a statistically significant reduction in the AIMS total score (indicating improvement) from baseline to week 12, based on central reading (a 3.0-point mean reduction compared to a 1.6-unit mean reduction in the placebo group, for a mean treatment effect difference of –1.4 points; p=0.0188).

Table 13: Abnormal involuntary movement scale: change in AIMS score from baseline to week 12 (mITT population; N=113)

Statistic	Change in AIMS score		
	SD-809 (N=56)	Placebo (N=57)	Difference in means (SD-809 - placebo) and SE
n	52	51	--
Least squares mean[a] (SE)	-3.0 (0.45)	-1.6 (0.46)	-1.4 (0.60)
Minimum, maximum	-16, 3	-9, 5	--
95% CI for mean	-3.9, -2.1	-2.5, -0.7	-2.6, -0.2
p-value[a]	--	--	0.0188

Source: Table 14.2.1.1.1 and Table 14.2.1.2.1 and Listing 16.2.6.1.2.

[a] p-value is from an MMRM analysis with change from baseline in AIMS score as dependent variable. The model includes fixed effects for treatment, time point (weeks 2, 4, 6, 9, and 12), treatment-by-time point interaction, DRA status, and baseline AIMS as a covariate. An unstructured covariance model is used. The Satterthwaite method is used to compute the denominator degrees of freedom for the F-test and LS means estimates. The p-value is based on the F-test.

AIMS=Abnormal Involuntary Movement Scale; DRA=dopamine receptor antagonist; CI=confidence interval; mITT=modified Intent-to-Treat; MMRM=mixed model repeated measures; N=total number of patients; SE=standard error.

Note: Based on centrally read AIMS score (sum of Items 1 to 7).

As a supportive analysis, change from baseline to week 12 in AIMS was analysed for the Per-Protocol Population. Similar results were observed in the Per-Protocol Population compared with the mITT Population with a slightly larger treatment effect (difference of LS means: -1.6 [p=0.0427; 95% CI: -3.1, -0.1]) in the Per-Protocol Population.

First Key Secondary Endpoint (Clinical Global Impression of Change CGIC)

DTBZ treatment resulted in a numerically higher proportion of participants who achieved treatment success at week 12, based on CGIC ("much improved" or "very much improved": 48.2% versus 40.4% in the placebo group), however, the results were not statistically significant at the p<0.05 level (p=0.4001).

Table 14: Treatment success at week 12 as determined by the CGIC (mITT population; N=113)

	SD-809 (N=56) n (%)	Placebo (N=57) n (%)	Difference in treatment success SD-809 - placebo (95% CI)[a]
Treatment success at week 12[b]	27 (48.2)	23 (40.4)	7.9 (-10.2, 25.2)
p-value[c]	--	--	0.4001

Source: Table 14.2.2.1.1 and Listing 16.2.6.2.

[a] Newcombe interval for the difference in binomial proportions.

[b] A treatment success was defined as "much improved" or "very much improved" at the week 12 visit. Patients whose status at week 12 was not known, as well as patients who were not "much improved" or "very much improved" at the week 12 visit, were considered treatment failures.

[c] p-value is from Pearson's chi-square test.

CI=confidence interval; mITT=modified Intent-to-Treat; N=total number of patients; n=number of patients in subgroup.

A prespecified supportive analysis assessing CGIC treatment success by baseline disease severity as measured by baseline Abnormal Involuntary Movement Scale (AIMS) score subgroup (<median value, ≥ median value) was planned. There was no statistically significant difference between DTBZ and placebo (PLB), among the different groups also. The median AIMS score at baseline was 9.0. A higher percentage

of patients in the SD-809 group experienced CGIC treatment success in the subgroup with baseline AIMS ≥9 (SD-809, 55.9%; placebo, 36.4%) than with the subgroup with baseline AIMS <9 (SD-809, 36.4%; placebo, 45.8%).

Other Key Secondary Endpoints

Patient Global Impression of Change (PGIC)

DTBZ treatment resulted in a numerically higher proportion of participants who achieved treatment success at week 12, based on PGIC ("much improved" or "very much improved": 42.9% versus 29.8% in the placebo group; nominal p=0.1497).

mCDQ-24

DTBZ treatment resulted in a numerically better response on the modified mCDQ-24 scale compared to the placebo group at week 12 (least squares [LS] mean: −11.1 versus −8.3, respectively; nominal p=0.3200).

Additional Secondary Endpoints

DTBZ treatment resulted in a numerically larger percentage reduction in AIMS total score from baseline to week 12 (LS mean percentage change: −26.7% versus −15.5% in the placebo group; nominal p=0.0193 [for ranked changes]).

DTBZ treatment resulted in a numerically higher proportion of participants who were considered AIMS responders (based on percent reduction in AIMS total score) for all the defined response reduction thresholds from baseline to week 12.

DTBZ treatment resulted in a numerically higher change in AIMS total score from baseline to week 12, based on the local rater evaluations (LS mean change: −4.9 points versus −3.7 points in the placebo group; nominal p=0.1508)

Table 15: MCIC of mean total motor AIMS scores at week 12 based on PGIC as Anchor (Hauser Method)

Impression of Change	DTBZ (pooled)[a]		Placebo (pooled)	
	N	Mean (SE)	N	Mean (SE)
"Very much improved"	23	-5.0 (0.46)	9	-3.8 (1.43)
"Much improved"	43	-4.4 (0.54)	23	-3.2 (0.67)
"Minimally improved"	46	-2.4 (0.47)	34	-1.4 (0.43)
"Not changed"	26	-1.5 (0.58)	25	0.4 (0.46)
"Minimally worse"	4	-2.8 (2.78)	7	-0.4 (1.15)
"Much worse"	1	-3.0 (-)	0	-
MCIC[b]		-2.4		-

Source: Hauser 2022a, Table 1
[a] DTBZ 12 mg was excluded from the analysis by the pooled treatment group.
[b] MCIC was defined as the mean change in total motor AIMS score from baseline in the pooled DTBZ-treated group who were rated minimally improved on the PGIC at Week 12.
AIMS=Abnormal Involuntary Movement Scale; MCIC=minimal clinically important change; N=total number of participants; PGIC=Patient Global Impression of Change; SE=standard error

Table 16: MCIC of mean total motor AIMS scores at week 12 based on CGIC as anchor (Hauser Method)

Impression Score	DTBZ (pooled)[a]		Placebo (pooled)	
	N	Mean (SE)	N	Mean (SE)
"Very much improved"	22	-5.3 (0.70)	9	-5.6 (0.82)
"Much improved"	51	-4.5 (0.46)	23	-2.5 (0.75)
"Minimally improved"	42	-2.1 (0.46)	35	-1.5 (0.45)
"Not changed"	25	-1.3 (0.54)	25	0.5 (0.42)
"Minimally worse"	1	-1.0 (-)	7	-0.4 (0.78)
"Much worse"	2	-3.0 (0)	0	-
MCIC[b]		-2.1		-

Source: Hauser 2022a, Table 2
[a] DTBZ 12 mg was excluded from the analysis by the pooled treatment group.
[b] MCIC was defined as the mean change in total motor AIMS score from baseline in the pooled DTBZ-treated group who were rated minimally improved on the CGIC at Week 12.
AIMS=Abnormal Involuntary Movement Scale; CGIC=Clinician Global Impression of Change; MCIC=minimal clinically important change; N=total number of participants; SE=standard error

Table 17: MCID of mean total motor AIMS score at week 12 based on PGIC as Anchor (Stacy Method) (both DTBZ and placebo)

PGIC response	Treatment Improvement[a]		Treatment Success[b]	
	Yes	No	Yes	No
n (%)	220 (75)	75 (25)	112 (38)	183 (62)
LS mean (SE)	-3.1 (0.22)	-0.3 (0.37)	-4.0 (0.30)	-1.4 (0.25)
MCID	-2.8		-2.6	

Source: Barkay 2020
AIMS=Abnormal Involuntary Movement Scale; LS=least squares; MCID=minimal clinically important difference; n=number of participants in subgroup; PGIC=Patient Global Impression of Change; SE=standard error.
a.Treatment improvement was defined as "very much improved," "much improved," or "minimally improved" on the PGIC.

Table 18: MCID of mean total motor AIMS score at week 12 based on CGIC as Anchor (Stacy Method) (both DTBZ and placebo)

CGIC response	Treatment Improvement[a]		Treatment Success[b]	
	Yes	No	Yes	No
n (%)	224 (76)	71 (24)	122 (41)	173 (59)
LS mean (SE)	-3.1 (0.23)	-0.3 (0.37)	-4.1 (0.27)	-1.1 (0.25)
MCID	-2.8		-3.0	

Source: Barkay 2020
AIMS=Abnormal Involuntary Movement Scale; CGIC=Clinical Global Impression of Change; LS=least squares; MCID=minimal clinically important difference; n=number of participants in subgroup; SE=standard error.
[a.]Treatment improvement was defined as "very much improved," "much improved," or "minimally improved" on the CGIC.
[b.]Treatment success was defined as "very much improved" or "much improved" on the CGIC
Note: These data are a pooled analyses from Trials C-18 and C-23.

Table 19: Treatment success at week 12 as determined by CGIC, Trial C-18 (mITT population; N=113)

	DTBZ (N=56) n (%)	Placebo (N=57) n (%)	Difference in treatment success DTBZ - placebo (95% CI)a
Treatment success at week 12[b]	27 (48.2)	23 (40.4)	7.9 (-10.2, 25.2)
p-value[c]	--	--	0.4001

Source: SD-809-C-18 CSR Table 15, Table 14.2.2.1.1 and Listing 16.2.6.2.
[a]Newcombe interval for the difference in binomial proportions.
[b]A treatment success was defined as "much improved" or "very much improved" at the week 12 visit. Participants whose status at week 12 was not known, as well as participants who were not "much improved" or "very much improved" at the week 12 visit, were considered treatment failures.
[c]p-value is from Pearson's chi-square test.
CGIC=Clinical Global Impression of Change; CI=confidence interval; DTBZ = deutetrabenazine; mITT=modified Intent-to-Treat; N=total number of participants; n=number of participants in subgroup.

Table 20: Treatment success at week 12 as determined by the PGIC, trial C-18 (mITT population; N=113)

	DTBZ (N=56) n (%)	Placebo (N=57) n (%)	Difference in percentages for treatment success (DTBZ - placebo) and 95% CIa
Treatment success at week 12[b]	24 (42.9)	17 (29.8)	13.0 (-4.6, 29.6)
p-value[c]	--	--	0.1497

Source: SD-809-C-18 CSR Table 19, Table 14.2.3.1.1 and Listing 16.2.6.2.

[a]Newcombe interval for the difference in binomial proportions.
[b]A treatment success was defined as "much improved" or "very much improved" at the week 12 visit. Participants whose status at week 12 was not known, as well as participants who were not "much improved" or "very much improved" at the week 12 visit, were considered treatment failures.
[c]p-value is from Pearson's chi-square test.

CI=confidence interval; DTBZ = deutetrabenazine; mITT=modified Intent-to-Treat; N=total number of participants; n=number of participants in subgroup; PGIC=Patient Global Impression of Change.

Table 21: Multiple comparisons and multiplicity for trial C-18

Testing Order	Endpoint	Comparison
1	Change from baseline to week 12 in total motor AIMS score, **p = 0.0188**	DTBZ versus placebo
2	The proportion of participants who were a treatment success at week 12, based on the CGIC, p = 0.4001	DTBZ versus placebo
3	The proportion of participants who were a treatment success at week 12, based on the PGIC, nominal p = 0.1497	DTBZ versus placebo
4	Change from baseline to week 12 in mCDQ-24 score, nominal p = 0.3200	DTBZ versus placebo

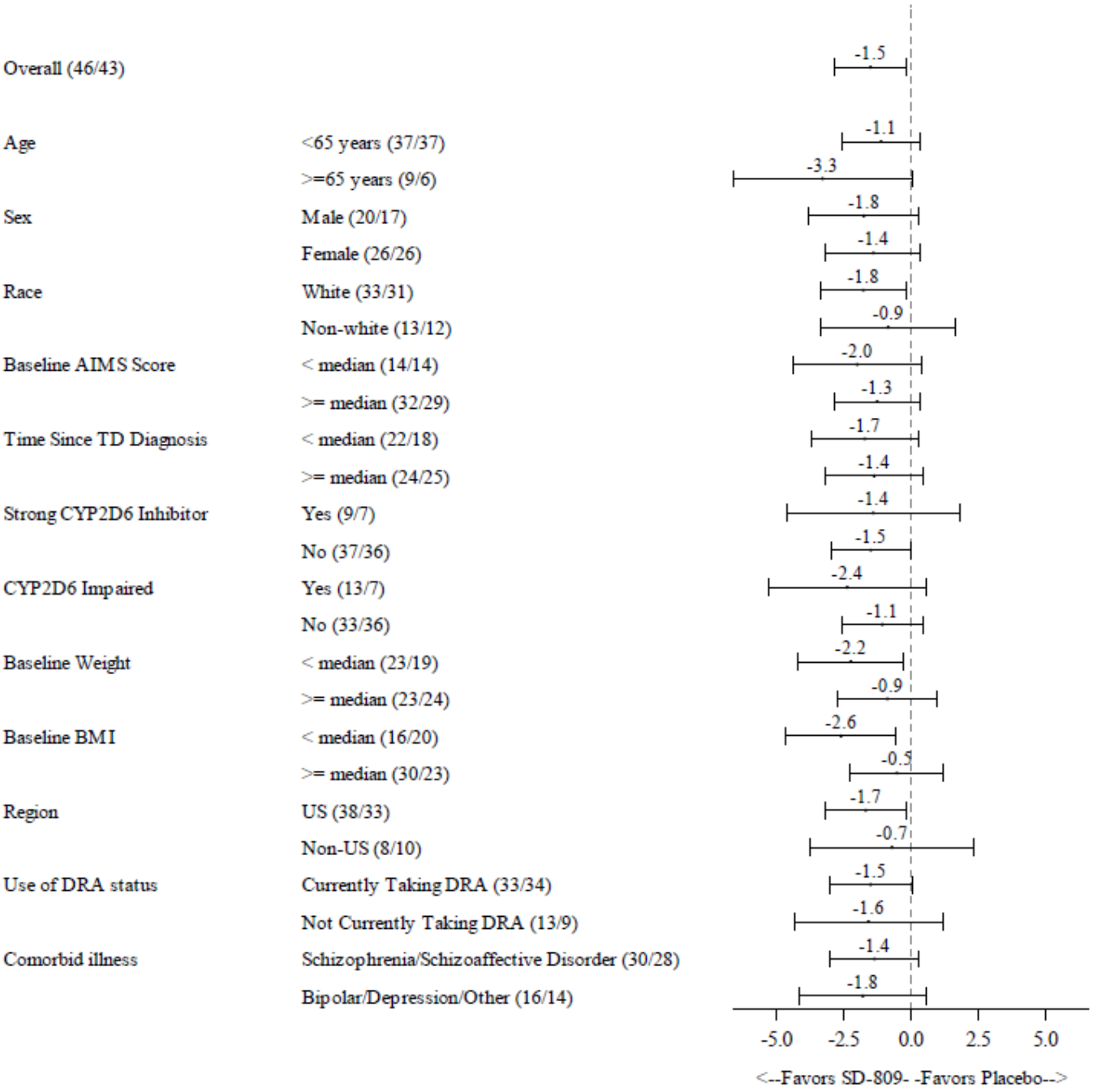
Source: SD-809-C-18 Statistical Analysis Plan; SD-809-C-18 CSR Summary 14.2.1.1.1, Summary 14.2.2.1.1, Summary 14.2.3.1.1, and Summary 14.2.4.1.1.1

AIMS=Abnormal Involuntary Movement Scale; CGIC=Clinical Global Impression of Change; DTBZ = deutetrabenazine; mCDQ-24=modified Craniocervical Dystonia Questionnaire 24; PGIC=Participant Global Impression of Change.

Underlined and bolded p-value indicates statistically significant p <0.05.

Ancillary analyses

Figure 10: Trial C-18: subgroup analysis of AIMS total score treatment effect from baseline to week 12 (blinded central video rating; mITT population)



AIMS=Abnormal Involuntary Movement Scale; BMI=body mass index; CI=confidence interval; CYP2D6=cytochrome P450 2D6; DRA=dopamine receptor antagonist; LS=least squares; mITT=modified intent-to-treat; TDISE=integrated summary of efficacy for tardive dyskinesia; US=United States.

Note: Forest plot is the LS mean treatment difference and 95% CI. Numbers in parentheses are sample size respective to the 2 compared treatment groups (SD-809=DTBZ BID/Placebo). Non-US participants were enrolled from the following countries of the EU: Germany, Poland, Slovakia, Czech Republic, and Hungary.

Post hoc analysis - Participants with a Centrally-read Baseline AIMS ≥6

Participants with more severe disease at baseline experienced greater efficacy with DTBZ treatment. Post hoc analysis performed for these participants (N=97) improved upon the primary (reduction in the AIMS total score) and key secondary (treatment success based on CGIC) efficacy signals.

Table 22: Primary efficacy endpoint: change from baseline in AIMS score by treatment and study visit; mITT population – subject with baseline AIMS score ≥6

Visit	SD-809 (N=48)	Placebo (N=49)	Total (N=97)	p-value (1)
Week 12				
n	46	43	89	
Mean (SD)	7.3 (4.17)	8.8 (3.96)	8.0 (4.11)	
Median	7.0	8.0	7.0	
Q1, Q3	5.0, 9.0	6.0, 12.0	5.0, 11.0	
Min - Max	1, 17	2, 17	1, 17	
Change from Baseline				
n	46	43	89	
Mean (SD)	-3.3 (3.39)	-1.8 (3.23)	-2.6 (3.38)	
Median	-3.0	-1.0	-2.0	
Q1, Q3	-6.0, -1.0	-4.0, 0.0	-5.0, 0.0	
Min - Max	-16, 3	-9, 5	-16, 5	
Mixed Model for Repeated Measurements (MMRM) [1]				
LSMean (SE)	-3.4 (0.48)	-1.9 (0.51)	-2.7 (0.38)	
LSMean 95% CI	(-4.3, -2.4)	(-2.9, -0.9)	(-3.4, -1.9)	
Treatment Differences (SD-809 minus Placebo)				
LSMean Difference (SE)	-1.5 (0.67)			0.0267
LSMean Difference 95% CI	(-2.8, -0.2)			

Table 23: Key secondary endpoint: treatment success based on clinical global impression f change by visit missing – treatment failure mITT population – subjects with baseline AIMS score change <6

	SD-809 (N=8)	Placebo (N=8)	Total (N=16)	p-value [1,2]
Week 12				
N	8	8	16	
Number (%) of Treatment Successes [3]	2 (25.0%)	6 (75.0%)	8 (50.0%)	
95% Confidence Interval [1,4]	3.2%, 65.1% *	34.9%, 96.8% *	24.7%, 75.3% *	
Number of Treatment Failures due to imputation	2	0	2	
Number of Treatment Failures not due to imputation	4	2	6	
Difference in Success Rates (SD-809 minus Placebo)	-50.0%			0.1319*
95% Confidence Interval [1,5]	-85.5%, 4.8%*			

2.6.5.2.2. Trial SD-809-C-23: A randomized, double-blind, placebo-controlled, fixed-dose study of SD-809 (DTBZ) for the Treatment of Moderate to Severe tardive dyskinesia

Methods

This was a Phase 3, double-blind, placebo-controlled, parallel-group trial in participants with TD in which all participants started at a low initial dose and then escalated to a prespecified target dose.

Participants were randomly assigned (1:1:1:1) to receive 1 of 3 fixed target dose regimens of DTBZ matrix formulation BID (12 mg, 24 mg, or 36 mg) or placebo. Participants underwent dose escalation (i.e. forced titration) over the initial 4 weeks of treatment to reach their target dose, followed by 8 weeks of maintenance therapy at that dose.

Study Period: 29 October 2014 to 19 August 2016 (last patient last visit).

Study Participants

Patients with bothersome tardive dyskinesia (due to a DRA) for over 3 months were enrolled. Two hundred eighty eight (288) patients were planned to be enrolled; 298 patients were randomized, and

data from 293 patients were analysed for safety, and data from 288 patients were analysed for efficacy and safety.

The study was conducted at a total of 75 centres: 38 sites in the United States (US), 19 in Poland, 7 in Hungary, 6 in the Czech Republic, 3 in Slovakia, and 2 in Germany. A complete list of investigators and their affiliations is included in the clinical study report.

The mean duration of exposure to DTBZ was 79.0, 77.5, and 75.8 days for participants in the DTBZ 12 mg/day, 24 mg/day, and 36 mg/day groups, respectively, and 80.5 days in the placebo group. The median number of days of treatment was 84.0 days for participants in each treatment group.

Key inclusion criteria

a. The patient was between 18 and 80 years of age, inclusive.

b. The patient had a history of using a dopamine receptor antagonist (DRA) for at least 3 months (or 1 month in patients 60 years of age and older).

c. The patient had a clinical diagnosis of TD and had symptoms for at least 3 months prior to screening.

d. The patient's TD symptoms were bothersome to the patient or caused functional impairment.

e. At the screening and baseline visits, the patient had:

- Moderate or severe abnormal movements as judged by the investigator based on Item 8 of the Abnormal Involuntary Movement Scale (AIMS), AND
- A total motor AIMS score of ≥6 (based on items 1 through 7) as assessed by the investigator.

  Note: A video recording of the AIMS assessment at screening was also reviewed by a blinded central rater to confirm eligibility based on items 1 through 7 of the AIMS prior to randomization.

f. For patients with underlying psychiatric illness:

- The patient was psychiatrically stable and had no change in psychoactive medications (including, but not limited to, neuroleptics, benzodiazepines, anticonvulsants, and mood stabilizers) for ≥30 days before screening (45 days for antidepressants).
- Patients on long-acting (depot) medications had been on stable therapy (dose, frequency) for ≥ 3 months before screening.
- The patient had a health care provider who was aware of the patient's participation in the trial and did not anticipate any changes to the patient's treatment regimen (drug, dose, frequency) in the following 3 months.

Key exclusion criteria

a. The patient had received any of the following medications within 30 days of screening or baseline:

- Tetrabenazine, reserpine, α-methyl-p-tyrosine, botulinum toxin (within 3 months of screening), medications with strong anticholinergic activity (trihexyphenidyl, benztropine, orphenadrine, procyclidine, and biperiden).
- Metoclopramide, prochlorperazine, or promethazine.
- Stimulants (i.e., methylphenidate, amphetamine/dextroamphetamine, lisdexamphetamine), or monoamine oxidase inhibitors.
- Levodopa or dopamine agonists.

b. The patient had previously participated in a study with SD-809.

c. The patient had a neurological condition other than TD that may have interfered with assessing the severity of dyskinesias.

d. The patient had a serious untreated or undertreated psychiatric illness at screening or baseline.

e. The patient had active suicidal ideation at screening or baseline.

f. The patient had a history of any of the following within 6 months of screening:

- Previous intent to act on suicidal ideation with a specific plan.
- Previous preparatory acts to commit suicide or suicidal behaviour.
- A previous actual, interrupted or aborted suicide attempt.

g. The patient had a score ≥11 on the Hospital Anxiety and Depression Scale - Depression Subscale at screening or baseline.

h. The patient had dementia.

i. The patient had an unstable or serious medical illness at screening or baseline.

Treatments

This was a 12-week study, including a 4-week dose-escalation period to reach their randomized dose (12, 24, or 36 mg/day), followed by an 8-week maintenance period, and a 1-week washout period. Patients who successfully completed the study and were tolerating SD-809 had the option to rollover into an open-label extension study (Study SD-809-C-20). For those patients who did not enter the open label study, there was an additional 3-week posttreatment safety follow-up period. For patients who completed the study, overall study participation was up to 20 weeks. During maintenance, a one-time dose reduction of 6 mg/day (managed in a blinded fashion through the IRT) was permitted for patients who experienced a clinically significant adverse event.

Allowed and non-allowed medication is discussed in the inclusion / exclusion criteria.

Objectives

A superiority study against placebo, to evaluate the efficacy of fixed doses of SD-809 to reduce the severity of abnormal involuntary movements of tardive dyskinesia (TD), and to evaluate the safety and tolerability of fixed doses of SD-809 in patients with TD.

Outcomes/endpoints

Primary Efficacy Measure and Endpoint

- The primary efficacy endpoint was the change in AIMS (items 1 through 7) as assessed by blinded central video rating from baseline (defined for each patient as the value from the day 0 visit) to week 12.

Secondary Efficacy Measures and Endpoints

Key Secondary Endpoint

- The proportion of patients who were a treatment success (Much or Very Much Improved) at week 12, based on the CGIC.

Additional Secondary Endpoints

- The proportion of patients who were a treatment success (Much or Very Much Improved) at week 12, based on the PGIC.
- The change in the mCDQ-24 score from baseline to week 12.
- The proportion of patients who had a 50% or greater reduction in AIMS score from baseline to week 12.
- The percent change in AIMS score from baseline to week 12.
- The cumulative proportion of responders based on the change in AIMS score from baseline to week 12, ranging from a 10% improvement from baseline to a 90% improvement from baseline in steps of 10 percentage points.

Safety Endpoints

- Incidence of adverse events; serious adverse events; severe adverse events; treatment-related adverse events; and adverse events leading to dose reduction, dose suspension, or withdrawal for the overall treatment period, as well as all adverse events assessed separately for the dose-escalation, maintenance, and follow-up periods.
- Observed values and changes in clinical laboratory parameters (haematology, chemistry, and urinalysis).
- Observed values and changes in vital signs.
- Observed values in ECG parameters and abnormal findings.
- Number of patients with postbaseline Fridericia's heart rate-corrected QT interval values >450, >480, and >500 ms; PR interval values >200 ms, QRS duration values >100 ms, and QT interval values >500 ms.
- Observed values and changes in UPDRS motor, BARS, HADS, C-SSRS, ESS, and MoCA©.

Sample size

Given a 1:1:1:1 randomization ratio (SD-809 12 mg:SD-809 24 mg:SD-809 36 mg:placebo) and the use of a 2-sided test at the alpha=0.05 level of significance, and assuming that the SD of the AIMS score change from baseline to maintenance therapy is equal to 3.4, a sample size of 228 patients (57 patients per group) was needed to provide at least 80% power to detect a treatment difference of 1.8 units in the AIMS score. To account for the fact that approximately 20% of randomized patients may be excluded from the primary analysis population due to a baseline AIMS score <6, the planned enrolment was approximately 288 patients. However, study enrolment continued until it was estimated that 228 patients with a baseline AIMS score ≥6 had been randomized.

Randomisation and blinding (masking)

Participants and investigators were blind to the randomised treatment assignment during the trial.

An Interactive Response Technology (IRT) was used to stratify patients by baseline use of DRAs (currently taking versus not currently taking a DRA) and to provide the treatment assignment for each patient. Participants were randomly assigned (1:1:1:1) to receive 1 of 3 fixed target dose regimens of DTBZ matrix formulation BID (12 mg, 24 mg, or 36 mg) or placebo.

Statistical methods

Analysis Populations:

- Intent-to-Treat (ITT) Population: all randomized patients.
- Modified Intent-to-Treat (mITT) Population: all patients in the ITT Population who met the inclusion criterion of a baseline AIMS score ≥6 as assessed by central video rating, were randomized to treatment, received study drug, and had at least 1 postbaseline AIMS assessment. The primary analysis of efficacy was completed in the mITT Population.
- ITT Population with postbaseline assessment (ITTPB): a subset of the ITT Population and defined as all patients in the ITT Population who received study drug and had a postbaseline assessment of the AIMS, regardless of their baseline total motor AIMS score.
- mITT Population for First 200 Patients Randomized (mITT200) Population: a subset of the mITT Population and included the first 200 patients randomized in the mITT Population.
- Per-Protocol (PP) Population: a subset of the mITT Population and included patients in the mITT who had no major protocol deviations and who had a non-missing total motor AIMS score at week 8 or week 12. SD-809-treated patients also were required to have measurable active metabolites at the same visit as the non-missing AIMS score at week 8 or 12.
- Safety Population: all patients who were administered any study drug. Patients who were assigned a subject number but withdrew prior to dosing were not included in the Safety Population.

Primary Analysis

The primary analysis was conducted in the mITT Population using a linear mixed model for repeated measures (MMRM) with the change in the total motor AIMS score as the dependent variable. The model included fixed effects for treatment group, visit (four levels: weeks 2, 4, 8, and 12), the treatment group-by-visit interaction, baseline total motor AIMS score, and the baseline use of DRAs. The unstructured covariance model was used. The Kenward-Roger method was used to calculate the denominator degrees of freedom. The primary analysis compared the change in the AIMS score from baseline to week 12 between the 36-mg/day group and the placebo group using a 2-sided test at the alpha=0.05 level of significance. Analysis of the primary endpoint was repeated in the ITTPB, mITT200, and PP Populations. Sensitivity analyses were performed to analyse missing data (using the MMRM and an analysis of covariance [ANCOVA] model), data from other time points (weeks 2, 4, and 8), and treatment comparisons by region.

Key Secondary Analyses

Analyses were performed using a hierarchical testing procedure. If the primary analysis was statistically significant ($p<0.05$), then the first key secondary analysis was conducted, also at the 5% level of significance (2-sided). If the first key secondary analysis was statistically significant, then the second key secondary analysis was to be similarly conducted, and so forth. For any analysis that was not statistically significant, all subsequent key secondary analyses were exploratory rather than confirmatory.

A Cochran-Mantel-Haenszel (CMH) test stratified by baseline use of DRAs was used to analyse the proportion of patients who were considered a treatment success at week 12, based on the CGIC, and comparisons of SD-809 with placebo were performed and presented at weeks 2, 4, and 8. The same model used for the primary analysis, a linear MMRM, was used to analyse the change in total motor AIMS score from baseline at week 12 for SD-809 compared with placebo. Analyses were conducted according to the hierarchical testing procedure as follows:

1. The proportion of patients who were considered a treatment success at week 12, based on the CGIC: comparison of 36 mg/day and placebo
2. The change in total motor AIMS score from baseline at week 12: comparison of 24 mg/day and placebo
3. The proportion of patients who were considered a treatment success at week 12, based on the CGIC: comparison of 24 mg/day and placebo
4. The change in total motor AIMS score from baseline at week 12: comparison of 12 mg/day and placebo
5. The proportion of patients who were considered a treatment success at week 12, based on the CGIC: comparison of 12 mg/day and placebo

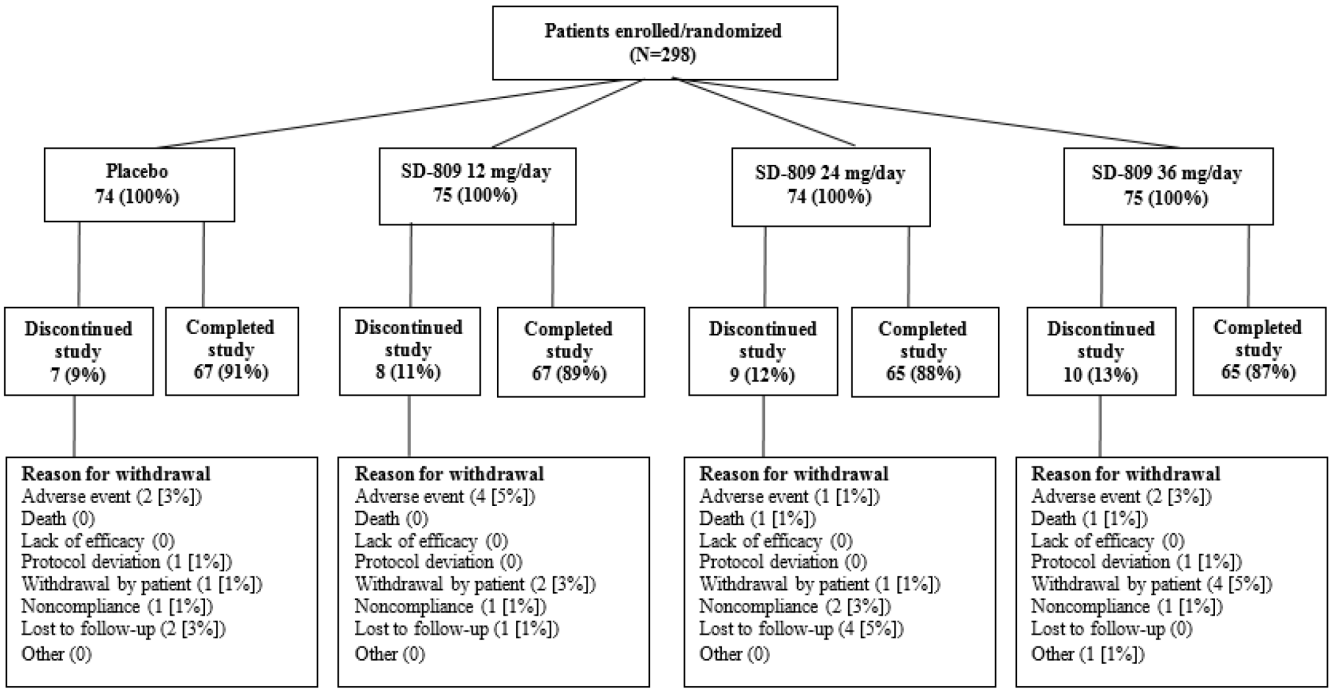
Analyses of the key secondary endpoints were repeated in the ITTPB and mITT200 Populations. Sensitivity analyses of the key secondary endpoints in the mITT Population were performed to account for missing data. The CGIC ratings were summarized as continuous data using descriptive statistics for all treatment groups. An exploratory shift analysis of CGIC was performed using a CMH test stratified by baseline use of DRAs.

Additional Secondary Analyses

The mCDQ-24 total score change from baseline to week 12 was analysed using an ANCOVA model with treatment group and baseline DRA use as factors and the baseline value as a covariate. Additional secondary endpoints that were defined as proportions were analysed using a CMH test stratified by baseline DRA use. In addition, the PGIC ratings at each visit were summarized using descriptive statistics for all treatment groups. The percent change in total motor AIMS score from baseline to week 12 was analysed using a linear MMRM.

Results

Figure 11: Participant flow



Recruitment

Study Period: 29 October 2014 to 19 August 2016 (last patient last visit)

Conduct of the study

There were 3 amendments to the protocol for this study.

Amendment 1 (Dated 28 August 2014)

Was issued before the enrolment period began; no patients were enrolled into the study while this amendment was in effect.

Amendment 2 (Dated 15 September 2014)

Also issued before any patients were enrolled into the study; all patients enrolled while this amendment was in effect.

Amendment 3 (Dated 29 October 2015)

102 patients enrolled into the study while this amendment was in effect. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study at that time.

The following major procedural changes (not all-inclusive) were made to the protocol:

- Increase in the number of study sites from approximately 60 to approximately 75 and the number of patients from approximately 200 to approximately 288.
- Increase in the upper limit of age for 8inclusion in the study to 80 years of age.

- Clarification that patients with a positive UDS were not excluded if they had a valid corresponding prescription for a medical condition.
- Removal of blinded interim analysis of variability.
- Change from coprimary analyses to a single primary analysis using a 2-sided test at the alpha=0.05 level.

Based on an analysis of Study SD-809-C-18, which also was designed to evaluate the safety and efficacy of SD-809 for the treatment of TD, the current study was amended prior to completion of enrolment and randomization to increase the sample size and modify the analysis of the primary endpoint. In Study SD-809-C-18, it was determined that 16 of 113 (14.1%) of the randomized patients had a centrally read baseline AIMS score <6. Thus, these patients did not meet the intended inclusion criteria. The protocol amendment for Study SD-809-C-23 clarified the definition of the primary analysis population to include patients with a centrally read baseline AIMS score ≥6. As the video recording of the baseline AIMS was collected prior to randomization and the study remained blinded, this approach did not introduce bias into the analysis of the study. Because it was not technically feasible to have the video recording centrally read prior to enrolment, site ratings were utilized for enrolment purposes.

Additionally, based on the treatment effect observed in Study SD-809-C-18, which was associated with a mean SD-809 dose of 38 mg/day, the statistical analysis strategy for the analysis of the primary endpoint was changed from a coprimary analysis of the 24- and 36-mg/day groups to a hierarchical analysis evaluating AIMS for the 36-mg/day group first, followed by testing of CGIC for the 36-mg/day group. This was followed by evaluation of AIMS for the 24-mg/day group, CGIC for the 24-mg/day group, AIMS for the 12-mg/day group, and then CGIC for the 12-mg/day group.

Baseline data

A total of 298 patients were randomized between the SD-809 12-, 24-, and 36-mg/day (N=75, 74, and 75, respectively) and placebo (N=74) groups. A total of 67 (89%), 65 (88%), and 65 (87%) patients in the SD-809 12-, 24-, and 36-mg/day groups, respectively, and 67 (91%) patients in the placebo group completed the study. The primary analysis population was the mITT Population (N=222), which included patients with a centrally read baseline AIMS score ≥6. The ITTPB Population (N=288) included randomized, treated patients with at least 1 postbaseline AIMS assessment irrespective of baseline AIMS score.

The mITT Population was 52% female, 79% white, and had a mean age of 57.0 years. The mean duration of TD was 5.57 years and the mean AIMS score was 9.6; 73% of patients were using a DRA and 18% had impaired cytochrome P450 2D6 (CYP2D6) function. In the mITT Population, underlying psychiatric illness was present in the majority of patients, including 104 (47%) patients with schizophrenia, 24 (11%) patients with schizoaffective disorder, 39 (18%) patients with bipolar disorder, 45 (20%) patients with depression, and 10 (5%) with other psychiatric disorders.

Outcomes and estimation

Primary Efficacy Endpoint

DTBZ 36 mg/day treatment provided a statistically significant reduction in the AIMS total score from baseline to week 12, based on central reading (a 3.3-point mean reduction, compared to a 1.4-point mean reduction in the placebo group, for a mean treatment effect difference of −1.9 points; p=0.001)

Table 24: Abnormal involuntary movement scale: change in total motor AIMS score from baseline to week 12 (mITT population; N=222)

Statistic	Placebo (N=58)	SD-809 12 mg/day (N=60)	SD-809 24 mg/day (N=49)	SD-809 36 mg/day (N=55)
n	56	53	45	52
LS mean (SE)	-1.4 (0.41)	-2.1 (0.42)	-3.2 (0.45)	-3.3 (0.42)
LS mean difference (SD-809 – placebo)	--	-0.7	-1.8	-1.9
95% CI	--	-1.84, 0.42	-3.00, -0.63	-3.09, -0.79
p-value	--	0.217	0.003	0.001

Source: Summary 15.11.1 and Listing 16.2.6.01.
AIMS=Abnormal Involuntary Movement Scale; CI=confidence interval; DRA=dopamine receptor antagonist; LS=least squares; max=maximum; min=minimum; mITT=modified Intent-to-Treat; MMRM=mixed model for repeated measures; N=total number of patients; n=number of patients in subgroup; SE=standard error.
Notes: Total motor AIMS score (sum of items 1 through 7) was assessed by blinded central video rating. The statistical model was an MMRM with treatment group, visit, treatment group-by-visit interaction, and baseline use of DRAs as fixed effects and the baseline value as a covariate. The model was fit using an unstructured covariance structure.

First Key Secondary Efficacy Endpoint

DTBZ 36 mg/day treatment resulted in a not statistically significant at the p<0.05 level (p=0.059) higher number of participants who achieved treatment success at week 12, based on CGIC ("much improved" or "very much improved": 44% versus 26% in the placebo group).

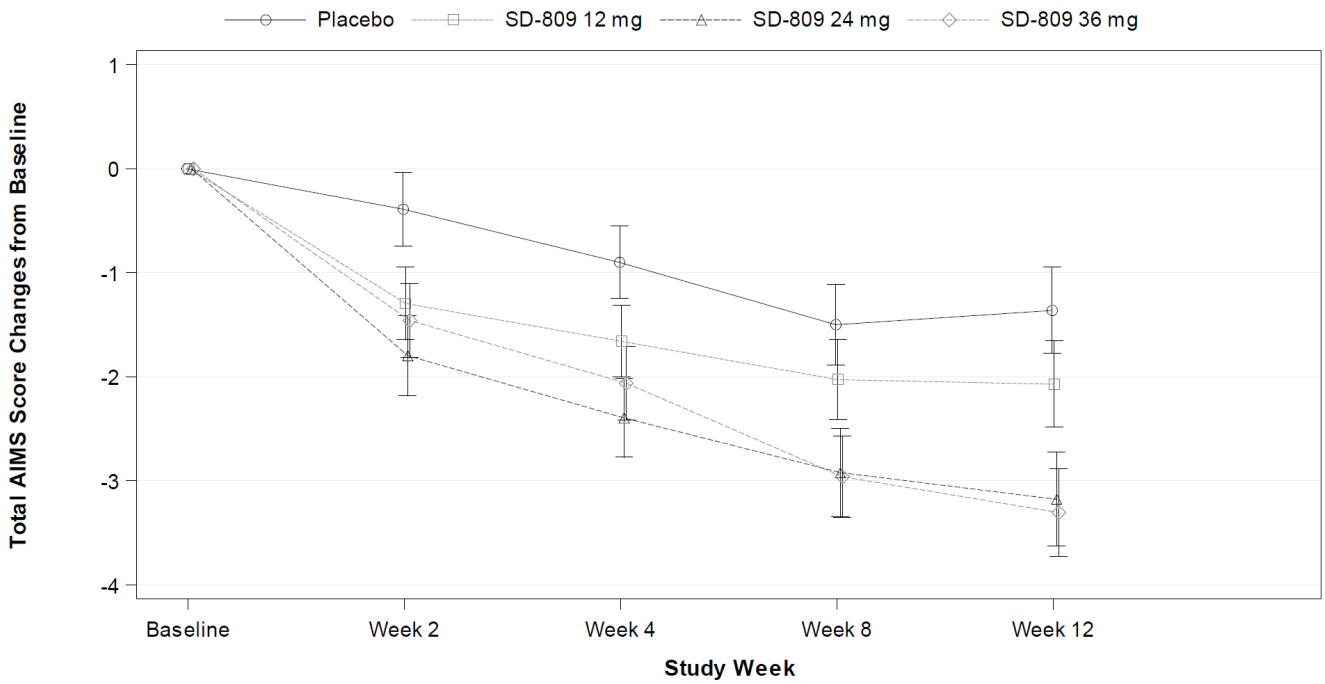
Table 25: Clinical global impression of change: proportion of patients considered a treatment success based on the CGIC at week 12 for SD-809 compared with placebo (mITT population; N=222)

Variable	Placebo (N=58)	SD-809 12 mg/day (N=60)	SD-809 24 mg/day (N=49)	SD-809 36 mg/day (N=55)
n	58 (100)	60	49	55 (100)
Treatment success, n (%)	15 (26)	17 (28)	24 (49)	24 (44)
Success 95% CI	16.3, 38.4	18.5, 40.8	35.6, 62.5	31.4, 56.7
Odds ratio (SD-809/placebo)	--	1.15	2.71	2.11
OR 95% CI	--	0.509, 2.610	1.211, 6.052	0.960, 4.645
p-value	--	0.734	0.014	0.059

Source: Summary 15.12.1 and Listing 16.2.6.02.
CGIC=Clinical Global Impression of Change; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; DRA=dopamine receptor antagonist; mITT=modified Intent-to-Treat; N=total number of patients; n=number of patients in subgroup; OR=odds ratio.
Notes: The statistical test was a CMH test stratified by baseline use of DRAs. The success 95% CI was calculated with the Wilson (score) confidence limits. The odds ratio was the Mantel-Haenszel estimate of the common odds ratio. Patients with missing data at a visit were classified as a treatment failure at that visit.

Other analyses (exploratory)

Figure 12: Least squares mean (SE) of total motor AIMS score changes from baseline to each visit by treatment group (mITT population; N=222)



Sample Size

Placebo	58	58	57	57	56
SD-809 12 mg	60	60	58	56	53
SD-809 24 mg	49	49	47	46	45
SD-809 36 mg	55	55	52	53	52

Source: Figure 17.1.
AIMS=Abnormal Involuntary Movement Scale; mITT=modified Intent-to-Treat; SE=standard error.
Total motor AIMS score (sum of items 1 through 7) was assessed by blinded central video rating.

ITTPB population (required by FDA)

Table 26: Abnormal involuntary movement scale: change in total motor AIMS score from baseline to week 12 for SD-809 compared with placebo (ITTPB population; N=288)

Statistic	Placebo (N=71)	SD-809 12 mg/day (N=73)	SD-809 24 mg/day (N=72)	SD-809 36 mg/day (N=72)
n	68	66	64	65
LS mean change (SE)	-1.0 (0.36)	-1.5 (0.36)	-2.4 (0.36)	-2.9 (0.36)
LS mean difference (SD-809 – placebo)	--	-0.5	-1.3	-1.8
95% CI	--	-1.46, 0.48	-2.32, -0.35	-2.83, -0.87
p-value	--	0.324	0.008	<0.001

Source: Summary 15.11.4 and Listing 16.2.6.01.
AIMS=Abnormal Involuntary Movement Scale; DRA=dopamine receptor antagonist; CI=confidence interval; ITTPB=Intent-to-Treat Population with postbaseline assessment; LS=least squares; max=maximum; min=minimum; MMRM=mixed model for repeated measures; N=total number of patients; n=number of patients in subgroup; SE=standard error.
Notes: Total motor AIMS score was assessed by blinded central video rating. The statistical model was an MMRM with treatment group, visit, treatment group-by-visit interaction, and baseline use of DRAs as fixed effects and the baseline value as a covariate. The model was fit using an unstructured covariance structure.

PP population

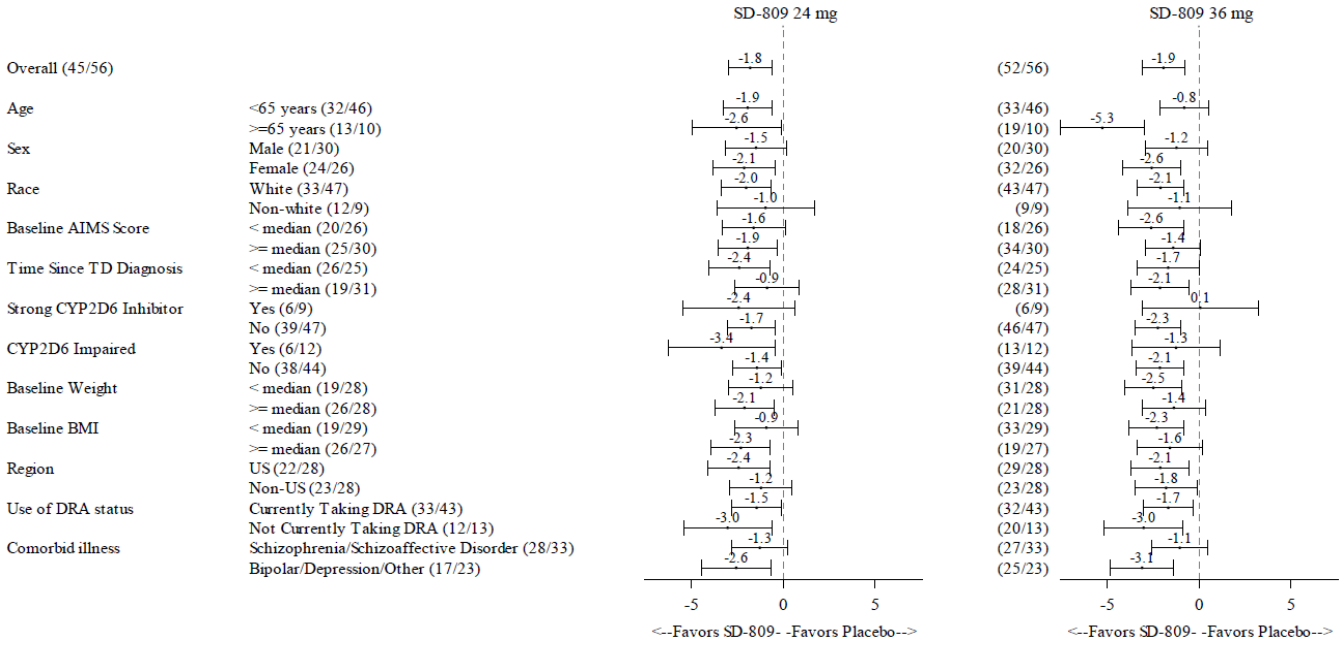
Table 27: Abnormal involuntary movement scale: change in total motor AIMS score from baseline to week 12 for SD-809 compared with placebo (PP population; N=180)

Statistic	Placebo (N=51)	SD-809 12 mg/day (N=49)	SD-809 24 mg/day (N=36)	SD-809 36 mg/day (N=44)
n	51	48	36	44
LS mean change (SE)	-1.3 (0.44)	-2.0 (0.44)	-3.5 (0.51)	-3.0 (0.46)
LS mean difference (SD-809 – placebo)	--	-0.7	-2.2	-1.7
95% CI	--	-1.89, 0.52	-3.49, -0.88	-2.94, -0.46
p-value	--	0.263	0.001	0.008

Source: Summary 15.11.5 and Listing 16.2.6.01.
AIMS=Abnormal Involuntary Movement Scale; CI=confidence interval; DRA=dopamine receptor antagonist; LS=least squares; max=maximum; min=minimum; MMRM=mixed model for repeated measures; N=total number of patients; n=number of patients in subgroup; PP=Per-Protocol; SE=standard error.
Notes: Total motor AIMS score was assessed by blinded central video rating. The statistical model was an MMRM with treatment group, visit, treatment group-by-visit interaction, and baseline use of DRAs as fixed effects and the baseline value as a covariate. The model was fit using an unstructured covariance structure.

Ancillary analyses

Figure 13: Trial C-23: Subgroup analysis of AIMS total score treatment effect from baseline to week 12 for DTBZ 24 mg/day and 36 mg/day (Blinded Central Video Rating; mITT population)



AIMS=Abnormal Involuntary Movement Scale; BMI=body mass index; CI=confidence interval; CYP2D6=cytochrome P450 2D6; DRA=dopamine receptor antagonist; LS=least squares; mITT=modified intent-to-treat; TDISE=integrated summary of efficacy for tardive dyskinesia; US=United States.

Note: Forest plot is the LS mean treatment difference and 95% CI. Numbers in parentheses are sample size respective to the 2 compared treatment groups (SD-809=DTBZ BID/Placebo). Non-US participants were enrolled from the following countries of the EU: Germany, Poland, Slovakia, Czech Republic, and Hungary.

Special subgroup analyses

Concomitant DRA medication

Table 28: Abnormal involuntary movement scale: LS mean change in total motor AIMS score from baseline to week 12 by baseline DRA use (mITT population; N=222)

Statistic	DRA use: yes				DRA use: no			
	Placebo (N=45)	SD-809 12 mg/day (N=45)	SD-809 24 mg/day (N=37)	SD-809 36 mg/day (N=35)	Placebo (N=13)	SD-809 12 mg/day (N=15)	SD-809 24 mg/day (N=12)	SD-809 36 mg/day (N=20)
n	43	41	33	32	13	12	12	20
LS mean change	-1.7	-2.0	-3.2	-3.4	0.0	-2.4	-3.1	-3.1
SE of LS mean	0.46	0.46	0.52	0.53	0.84	0.84	0.88	0.68
LS mean difference (SD-809 – placebo)	--	-0.2	-1.5	-1.7	--	-2.4	-3.0	-3.0
95% CI	--	-1.50, 1.07	-2.82, -0.10	-3.06, -0.31	--	-4.71, -0.02	-5.44, -0.64	-5.16, -0.89
p-value	--	0.745	0.036	0.017	--	0.048	0.013	0.006

Source: Summary 15.20 and Listing 16.2.6.01.
AIMS=Abnormal Involuntary Movement Scale; CI=confidence interval; DRA=dopamine receptor antagonist; LS=least squares; mITT=modified Intent-to-Treat; MMRM=mixed model for repeated measures; N=total number of patients; n=number of patients in subgroup; SE=standard error.
Notes: Total motor AIMS score was assessed by blinded central video rating. The statistical model was an MMRM with treatment group, visit, DRA status, treatment group-by-visit interaction, treatment group vs DRA status interaction, visit by DRA status interaction, and treatment group-by-visit-by-DRA status interaction and the baseline value as a covariate. The model was fit using an unstructured covariance structure.

Analysis by Region

Table 29: Abnormal involuntary movement scale: total motor AIMS score changes from baseline to week 12 by region and treatment group for SD- 809 36 mg/day compared with placebo (mITT population; N=222)

Statistic	US				EU			
	Placebo (N=30)	SD-809 12 mg/day (N=37)	SD-809 24 mg/day (N=24)	SD-809 36 mg/day (N=32)	Placebo (N=28)	SD-809 12 mg/day (N=23)	SD-809 24 mg/day (N=25)	SD-809 36 mg/day (N=23)
n	28	32	22	29	28	21	23	23
LS mean change (SE of LS mean)	-1.2 (0.57)	-2.2 (0.53)	-3.6 (0.65)	-3.3 (0.56)	-1.5 (0.59)	-1.9 (0.65)	-2.7 (0.63)	-3.3 (0.64)
LS mean difference (SD-809 – placebo)	--	-1.0	-2.4	-2.1	--	-0.4	-1.2	-1.8
95% CI	--	-2.50, 0.55	-4.13, -0.75	-3.69, -0.55	--	-2.10, 1.34	-2.91, 0.47	-3.51, -0.10
p-value	--	0.208	0.005	0.008	--	0.664	0.156	0.038

Source: Summary 15.11.8 and Listing 16.2.6.01.
AIMS=Abnormal Involuntary Movement Scale; CI=confidence interval; DRA=dopamine receptor antagonist; EU=European Union; LS=least squares; max=maximum; min=minimum; mITT=modified Intent-to-Treat; MMRM=mixed model for repeated measures; N=total number of patients; n=number of patients in subgroup; SE=standard error; US=United States.
Notes: The statistical model was an MMRM with treatment group, visit, region, treatment group-by-visit interaction, treatment group vs region interaction, visit-by-region interaction, treatment group-by-visit-by-region interaction, and baseline use of DRAs as fixed effects and the baseline value as a covariate. The model was fit using an unstructured covariance structure. Total motor AIMS score was assessed by blinded central video rating.

Modelling and simulation for the proposed different up-titration scheme

As above anticipated, the proposed initiation and titration scheme for DTBZ differs from the one used in the Phase 3 clinical trials in TD. Specifically, titration to an efficacious dose range was shortened by 1 week by increasing the dose from 12 to 24 mg/day in the second week, excluding the 18 mg dosing step in between. Post-marketing/real-world experience from the US, where DTBZ has been on the market since 2017, showed that, for a significant proportion of patients, the approved treatment initiation scheme, i.e., weekly dose increases in 6 mg/day increments, was not followed. Patients often remained on starting or low doses (≤18 mg/day) for many weeks with poor adherence and, in some cases, even DTBZ discontinuation. Keeping patients on DTBZ doses ≤18 mg/day for longer periods appeared to make challenging to arrive to the efficacious dose range of 24 to 48 mg/day in a timely manner. Exclusion of the 18 mg dosing step from the initiation and titration scheme was further supported by an integrated safety data analysis from the Phase 3 trials in TD (C-18 and C-23) and HD-associated chorea (C-15 and C-16) trials and an exposure-safety modelling analysis. Those results showed similar AE profiles of 12 mg, 18 mg and 24 mg/day doses indicating that excluding the 18 mg dosing step is expected to be safe. Modelling analyses of DTBZ exposure and safety data provided additional support for the exclusion of the 18 mg/day step.

Use in mild TD patients

The Phase 3 trials in TD included participants with moderate to severe TD defined as having a baseline AIMS total score ≥6 per site rater. However, to evaluate the efficacy of DTBZ in patients with mild TD, a post-hoc analysis was performed in participants from the efficacy Trials C-18 and C-23 who had a*n Abnormal Involuntary Movement Scale (AIMS) total score <6 based on blinded central video rating. The applicant considered that these results could support the benefit of TD patients from DTBZ treatment in the full range of disease severity and therefore initially applied for a broad indication: treatment of tardive dyskinesia in adults.*

Table 30: Proportion of participants considered a treatment success based on the CGIC at week 12 for DTBZ compared with placebo, trial C-23 (mITT population; N=222)

Statistics	Placebo (N=58)	DTBZ 12 mg/day (N=60)	DTBZ 24 mg/day (N=49)	DTBZ 36 mg/day (N=55)
Treatment success, n (%)	15 (26)	17 (28)	24 (49)	24 (44)
Treatment success 95% CI	16.3, 38.4	18.5, 40.8	35.6, 62.5	31.4, 56.7
Odds ratio (DTBZ/placebo)	--	1.15	2.71	2.11
OR 95% CI	--	0.509, 2.610	1.211, 6.052	0.960, 4.645
p-value	--	0.734	0.014	0.059

Source: SD-809-C-23 CSR Table 15, Summary 15.12.1 and Listing 16.2.6.02.

CGIC=Clinical Global Impression of Change; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; DRA=dopamine receptor antagonist; DTBZ = deutetrabenazine; mITT=modified Intent-to-Treat; N=total number of participants; n=number of participants in subgroup; OR=odds ratio.

Notes: The statistical test was a CMH test stratified by baseline use of DRAs. The treatment success 95% CI was calculated with the Wilson (score) confidence limits. The odds ratio was the Mantel-Haenszel estimate of the common odds ratio.

Participants with missing data at a visit were classified as a treatment failure at that visit.

Table 31: Multiple comparisons and multiplicity for trial C-23

Testing Order	Endpoint	Comparison
1	Change from baseline to week 12 in total motor AIMS score, p = 0.001	36 mg/day DTBZ versus placebo
2	The proportion of participants who were a treatment success at week 12, based on the CGIC, p = 0.059	36 mg/day DTBZ versus placebo
3	Change from baseline to week 12 in total motor AIMS score, nominal p = 0.003	24 mg/day DTBZ versus placebo
4	The proportion of participants who were a treatment success at week 12, based on the CGIC, nominal p = 0.014	24 mg/day DTBZ versus placebo
5	Change from baseline to week 12 in total motor AIMS score, nominal p = 0.217	12 mg/day DTBZ versus placebo
6	The proportion of participants who were a treatment success at week 12, based on the CGIC, nominal p = 0.734	12 mg/day DTBZ versus placebo

Source: Trial C-23 Statistical Analysis Plan; SD-809-C-23 CSR Summary 15.11.1 and Summary 15.12.1.

AIMS=Abnormal Involuntary Movement Scale; CGIC=Clinical Global Impression of Change; DTBZ=deutetrabenazine
Underlined and bolded p-value indicates statistically significant p <0.05.

Only bolded nominal p-values indicate p <0.05.

The CHMP objected Teva's proposed broad indication: the target population is broader than the trial(s) population, it includes all patients regardless of disease severity and without mentioning that symptoms are bothersome to the patient and/or cause functional impairment. Only functionally impaired moderate to severely affected patients should be treated with DTBZ, given the lower response in the least severe and the risks of the treatment.

The expansion of the indication to cover the milder forms could not be acceptable as not supported by the presented data. The post-hoc analysis in participants which scored centrally as having a possible milder form of TD was challenged, since the central assessment did not substitute the investigator rating, which considered the total impact (temporal and systemic) whereas the central assessment was only partial.

Furthermore, patients with lower AIMS had an even lower magnitude of effect.

Subgroup analyses in the more severe population treated with higher doses and those not taking concomitantly dopamine receptor antagonists (DRAs) had more favourable results as measured by AIMS, but the number of non DRA treated patients was very small and its relevance and external validity uncertain.

The applicant justified that the C18 and C23 trials included population was representative of the real world potentially benefitting patients: in fact, it covered TD patient characteristics such as age, genders, socioeconomic backgrounds and geographic locations. The (meagre) efficacy results did not seem to depend upon biases from these characteristics, and refining the population did not seem to improve the efficacy response. However, TD patients enrolled into the study were assessed by the investigator as being stable on concomitant psychiatric illness and psychiatric medication, and having moderate to severe symptoms, and these aspects cannot be demeanoured, as well as the functional impairment that patients had to present to be included into the study.

In summary, the results of the post-hoc analysis in mild TD subjects of trials C-18 and C-23 (n=38 for DTBZ treated with the 24 mg/day and 36 mg/day doses and n=20 for placebo) were considered by CHMP as exploratory, not clinically and statistically confirmatory (p=0.079, treatment effect -0.92).

Furthermore, the magnitude of effect was even lower with the milder patients (C18: 0.8 AIMS score; C23: 24 mg: 0.8; 36 mg: 1.6 AIMS score) than with those more severe (C18: 1.5; C23: 24 mg: 1.8; 36 mg: 1.9).

Therefore, the applicant made an alternative proposal in the course of the procedure: to align the intended DTBZ therapeutic indication with the trial population in TD pivotal clinical trials, as requested by the CHMP. Ultimately, the wording in SmPC Section 4.1 was revised to reflect a restriction to moderate to severe TD as following: "*Austedo is indicated for the treatment of moderate to severe tardive dyskinesia in adults*", thus also conveying that DTBZ *should only be used in adult patients with tardive dyskinesia presenting with symptoms that were bothersome to the patient or caused functional impairment.*

2.6.5.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present initial MAA. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 32: Summary of efficacy for trial SD-809-C-18

<table>
<tr><td colspan="4">Title: A Randomized, Double-Blind, Placebo-Controlled Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia</td></tr>
<tr><td>Study identifier</td><td colspan="3">SD-809-C-18</td></tr>
<tr><td rowspan="2">Design</td><td colspan="3">A randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy, safety, and tolerability of deutetrabenazine (DTBZ, also referred to as SD-809) for the treatment of patients with tardive dyskinesia (TD). The study included a 4-week screening period, 6-week titration period, 6-week maintenance period, and a 1-week washout. Patients who successfully completed the study and were tolerating the study drug had the option to rollover into an open-label extension study. For those patients who did not enter the open-label study, there was an additional 3-week posttreatment safety follow-up period. For patients who completed the main study phase, overall study participation was up to 20 weeks.</td></tr>
<tr><td colspan="2">Duration of main phase:
Duration of Run-in phase:
Duration of Extension phase:</td><td>12 weeks (84 days)
Not applicable
Not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Superiority</td></tr>
<tr><td rowspan="2">Treatments groups (randomized)</td><td colspan="2">DTBZ
Flexible dosing of 12mg/day up to 48mg/day (or up to 36mg/day for participants receiving a strong CYP2D6 inhibitor), administered twice daily (BID)</td><td>N = 58</td></tr>
<tr><td colspan="2">Placebo</td><td>N = 59</td></tr>
<tr><td rowspan="2">Endpoints and definitions</td><td>Primary endpoint</td><td>Abnormal Involuntary Movement Scale (AIMS) total score</td><td>Change in total AIMS score (Items 1 through 7) during the 12-week treatment period</td></tr>
<tr><td>Secondary endpoint</td><td>Clinical Global Impression of Change (CGIC) scale</td><td>Proportion of patients who achieved treatment success based on the CGIC scale at week 12</td></tr>
</table>

	Secondary endpoint	Patient Global Impression of Change (PGIC) scale	Proportion of patients who achieved treatment success based on the PGIC scale at week 12
	Secondary endpoint	Craniocervical Dystonia Questionnaire (CDQ-24) score	Change in the modified CDQ-24 during the 12-week treatment period
Database lock	Undisclosed		
Results and Analysis			
Primary Endpoint			
Analysis population and time point description	Modified Intent-to-Treat (mITT) population The mITT population (N=113) is defined as all randomized patients who received the study drug and had at least 1 centrally read post-baseline assessment of the AIMS total score from at least 1 scheduled post-baseline timepoint. The primary and secondary endpoints were completed at 12 weeks.		
Change in total AIMS score (Items 1 through 7) during the 12-week treatment period	**Treatment group**	**DTBZ**	**Placebo**
	Number of Subjects (N)	56	57
	LS mean (SE)	-3.0 (0.45)	-1.6 (0.46)
	95% confidence interval	-3.9, -2.1	-2.5, -0.7
	Difference in means (SE)	-1.4 (0.60)	
	p-value vs placebo	0.0188	
Key secondary endpoints			
Proportion of patients who achieved treatment success based on the CGIC scale at week 12	**Treatment group**	**DTBZ**	**Placebo**
	Number of patients with treatment success at week 12	27 (48.2%)	23 (40.4%)
	Difference in treatment success (SE)	7.9 (-10.2, 25.2)	
	p-value vs placebo	0.4001	
Proportion of patients who achieved treatment success based on the PGIC scale at week 12			
	Treatment group	**DTBZ**	**Placebo**
	Number of patients with treatment success at week 12	24 (42.9%)	17 (29.8%)
	Difference in treatment success (SE)	13.0 (-4.6, 29.6)	
	p-value vs placebo	0.1497	

Change in the modified CDQ-24 during the 12-week treatment period			
	Treatment group	**DTBZ**	**Placebo**
	LS mean (SE)	-11.1 (2.14)	-8.3 (2.31)
	Difference in means (SE)	-2.7 (2.74)	
	p-value vs placebo	0.3200	
Notes	The secondary efficacy endpoints were analysed using a hierarchical testing procedure. As the primary analysis was statistically significant ($p<0.05$), the first key secondary endpoint was analysed at the 5% level of significance (2-sided). As the first key secondary endpoint was not statistically significant, all subsequent analyses of key secondary endpoints were exploratory rather than confirmatory.		

Table 33: Summary of efficacy for trial SD-809-C-23

Title: A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia			
Study identifier	SD-809-C-23		
Design	A randomized, double-blind, placebo-controlled, fixed-dose, parallel-group study designed to evaluate the efficacy, safety, and tolerability of DTBZ (SD-809) for the treatment of patients with TD. The study included a up to 4-week screening period, 4-week dose-escalation period, 8-week maintenance period, and a 1-week washout period. Patients who successfully completed the study and were tolerating DTBZ had the option to rollover into an open-label extension study (SD-809-C-20). For those patients who did not enter the open-label study, there was an additional 3-week posttreatment safety follow-up period. For patients who completed the main study phase, overall study participation was up to 20 weeks.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks (84 days) Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups (randomized)	DTBZ 12mg/day administered BID		N = 75
	DTBZ 24mg/day administered BID		N = 74
	DTBZ 36mg/day administered BID		N = 75
	Placebo		N = 74
Endpoints and definitions	Primary endpoint	Abnormal Involuntary Movement Scale (AIMS) score	Change in total AIMS score (Items 1 through 7) during the 12-week treatment period
	Secondary endpoint	Clinical Global Impression of Change (CGIC) scale	Proportion of patients who achieved treatment success based on the CGIC scale at week 12
Database lock	Undisclosed		
Results and Analysis			
Primary Endpoint			

Analysis population and time point description	Modified Intent-to-Treat (mITT) population The mITT population (N=222) included patients with a centrally read baseline AIMS total score ≥ 6 who were randomized, received at least 1 dose of study drug, and had at least 1 postbaseline AIMS total score assessment. The primary endpoint and key secondary endpoints were completed at 12 weeks.				
Change in total AIMS score (Items 1 through 7) during the 12-week treatment period	**Treatment group**	**DTBZ 12mg/day**	**DTBZ 24mg/day**	**DTBZ 36mg/day**	**Placebo**
	Number of Subjects (N)	60	49	55	58
	LS mean (SE)	-2.1 (0.42)	-3.2 (0.45)	-3.3 (0.42)	-1.4 (0.41)
	95% confidence interval	-1.84, 0.42	-3.00, -0.63	-3.09, -0.79	-
	Difference in means	-0.7	-1.8	-1.9	--
	p-value vs placebo	0.217	0.003	0.001	--
Key secondary endpoints					
Proportion of patients who achieved treatment success based on the CGIC scale at week 12	**Treatment group**	**DTBZ 12mg/day**	**DTBZ 24mg/day**	**DTBZ 36mg/day**	**Placebo**
	Number of patients with treatment success at week 12	17 (28%)	24 (49%)	24 (44%)	15 (26%)
	95% confidence interval	18.5, 40.8	35.6, 62.5	31.4, 56.7	16.3, 38.4
	p-value vs placebo	0.734	0.014	0.059	--

Table 34: Statistical analysis plan approval and database lock dates – trials C-18, C-23, and C-20

Trial	SAP Approval Date	Database Lock Date
C-18	29 April 2015	29 May 2015
C-23	01 Sept 2016	07 Sept 2016
C-20	23 Sept 2020	26 Jan 2021

Note: SAP approval dates are based on the dates of the last signature in the SAP PDF document.

2.6.5.4. Clinical studies in special populations

The applicant did not present specific studies in subpopulations, apart from the report regarding mild forms of TD.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Pooled efficacy data from the two Phase 3 confirmatory studies

The TD efficacy programme included 2 randomised, double-blind, placebo-controlled trials, the Phase 2/3 Trial C-18 and C-23.

Trial population

The participants in DTBZ Phase 3 development programme for the treatment of tardive dyskinesia were generally representative of the population of patients with moderate to severe TD in the real world. Most of the trial participants had comorbid psychiatric illnesses, such as schizophrenia, schizoaffective disorder or mood disorders (depression, bipolar disorder) and were treated with concomitant medications, such as antipsychotics and / or other psychiatric medications.

The clinical trial participants were at least 18 years of age, with a clinical diagnosis of TD and a history of dopamine receptor antagonists (DRAs) use for at least 3 months (or 1 month in participants 60 years of age and older). Participants with underlying psychiatric illness were required to be psychiatrically stable and on a stable dose of antipsychotics.

Efficacy Endpoints

Treatments for TD aim to reduce the involuntary movements and improve the patients' quality of life. The efficacy endpoints in this development programme were representative of each of these goals and included assessments of severity of TD, global impressions of change, quality of life using validated disease-specific and more generic outcomes and reflect the perspectives of both the clinician and patient. Specifically, improvement of dyskinesias, including improvement of motor symptoms was measured by the abnormal involuntary movement scale (AIMS) total score. In addition, overall improvement of TD symptoms was evaluated by a clinician (clinical global impression of Change -CGIC) and a patient (patient global impression of change - PGIC) rated scale, and improvement of quality of life was evaluated by a modified version of the Craniocervical Dystonia Patient-Reported Questionnaire (mCDQ-24). Specifically, the primary efficacy endpoint for trials C-18 (flexible-dose trial) and C-23 (fixed-dose trial; DTBZ 36 mg/day dose) was the change from baseline to week 12 in the AIMS total score (sum of Items 1 through 7 – the reader should refer below for further details) as assessed by blinded central video rating. The key secondary endpoint for trials C-18 and C-23 (DTBZ 36 mg/day dose) was the proportion of participants who achieved treatment success at week 12, based on the CGIC. Trial C-20 included the same efficacy measures as the two randomised trials (Trials C-18 and C-23).

<u>Primary Endpoint</u>

The AIMS is a 12-item clinician-rated scale to assess severity of dyskinesias (specifically, orofacial movements and extremity and truncal movements) in patients. This scale is widely used in clinical trials to detect and follow the severity of TD over time. A 2-point decrease from baseline in the AIMS total score is considered clinically important (minimally clinically important change). The TD trials included in the DTBZ TD efficacy programme used AIMS descriptors, which are consistent with those utilised in large trials in schizophrenia, and were developed based on the work of Munetz and Benjamin in 1988. These descriptors showed to be valid in describing the severity of abnormal movements in TD and are accepted by scientific experts in movement disorders and psychiatry, who uniformly agreed they are appropriate to provide guidance to investigators in grading the severity of TD in clinical trials. To enable the systematic evaluation of the primary endpoint, AIMS was digitally video-recorded using a standard protocol for both C-18 and C-23 trials. AIMS assessment was performed by the site investigator and confirmed by an independent movement disorder expert via central video rating. This process allowed for a systematic assessment of dyskinesia not influenced by participant reports of tolerability or efficacy. Assessment of the AIMS by site personnel was performed in all 3 TD trials.

Key Secondary Endpoints

The key secondary endpoints included a clinician-rated (CGIC) and patient-rated (PGIC) tool for assessing overall improvement of TD symptoms after initiating therapy (i.e., treatment success), as well as a measure of disease-specific quality of life (mCDQ-24).

Tools such as CGIC and PGIC are commonly used in trials where the main objective is to evaluate treatment success in terms of reduction (improvement) of the severity of symptoms for the condition examined. These clinician and patient-rated global measures of change are validated and readily understood practical measures that correlate with disability in several chronic conditions.

The Craniocervical Dystonia Questionnaire (CDQ-24) is a validated disease-specific quality of life questionnaire developed for use in patients with craniocervical dystonia, including both cervical dystonia and blepharospasm. The CDQ-24 was selected and adjusted for use in the DTBZ TD trials to focus directly on the impact of TD on patient's quality of life. Specifically, eleven of the 24 items in the CDQ-24 were modified (mCDQ-24) so that they were more appropriate for TD participants. The mCDQ-24 assessment includes stigma, emotional well-being, pain, activities of daily living, and social/family life domains.

The primary and key secondary endpoints in Trials C-18 and C-23 were tested in a hierarchical manner. As a result, results of secondary hypotheses analysed after the last endpoint reached statistical significance at the $p<0.05$ level were considered exploratory and nominal p-values are displayed.

Choice of Control Groups

The Phase 3 randomised efficacy trials (Trials C-18 and C-23) used a placebo-controlled design. The use of placebo is justified to characterise efficacy and safety of an investigational medicinal product in a new trial population, for trials with short-term exposure and where safety is carefully monitored.

Analysis Sets

The intent-to-treat (ITT) population included all participants randomised, regardless of whether or not a participant received a dose of trial drug.

In Trial C-18 the primary analysis population included all participants in the ITT population who received the trial drug and had at least 1 centrally read post-baseline assessment of AIMS total score, irrespective of their baseline AIMS total score (defined as the modified intent-to-treat [mITT] population in the clinical study report - CSR).

For Trial C-23 the primary analysis population included all participants in the ITT population with a centrally-read baseline AIMS total score ≥6 who received trial drug and had at least 1 centrally read post-baseline assessment of AIMS total score (defined as the mITT population in the CSR). Because it was not technically feasible to have the video recording centrally read prior to enrolment, site ratings were utilised for enrolment purposes.

Pooling Strategy

Individual trial results are presented for Trials C-18, C-23 and C-20. In addition, the primary and key secondary efficacy endpoints from Trials C-18 and C-23 were analysed as a pooled group to inform efficacy across DTBZ doses. In order to more precisely estimate the treatment effect of dose levels expected to be efficacious, the pooled DTBZ group included all participants in the DTBZ group from Trial C-18 and those from Trial C-23 treated with doses of 24 mg/day and 36 mg/day, i.e., doses within the efficacious dose range of 24 mg/day to 48 mg/day. The pooled DTBZ group was compared to the pooled placebo group from Trials C-18 and C-23.

Participant Subgroup Analyses

For Trials C-18 and C-23, the change from baseline in AIMS total scores and the proportion of participants who achieved treatment success based on CGIC were analysed for 13 subgroup categories based on intrinsic and extrinsic factors, including age, sex, race, AIMS total score at baseline, time since TD diagnosis, CYP2D6 inhibition and impairment, weight, body mass index, region, DRA use, and background comorbid illness. The analyses were performed as part of the integrated summary of efficacy (TDISE19 SAP).

Participant Disposition and Demographics

A total of 117 participants were randomised to treatment with DTBZ or placebo (58 and 59 participants, respectively) in Trial C-18. A total of 293 participants were randomised and received DTBZ 12 mg/day, 24 mg/day, and 36 mg/day, or placebo (74, 73, 74, and 72 participants, respectively) in Trial C-23. A total of 337 participants were enrolled and received DTBZ (227 participants on DTBZ and 110 participants on placebo in the parent trials [C-18 and C-23]) in Trial C-20.

Trial discontinuation rates in the DTBZ groups were similar across the two randomised trials (approximately 10% in Trial C-18, and 11% to 13% in Trial C-23), and similar to placebo (12% and 9%, in the respective trials). Rates of discontinuation due to AEs were low and comparable across trials and DTBZ groups (up to 5%), and similar to the rates in the placebo groups (up to 3%). As expected, due to the long-term participation (3 years) in Part A of Trial C-20, the overall trial discontinuation rate in Trial C-20 was higher (48%) than in the Trials C-18 and C-23; however, withdrawal due to AE was low (10%).

Demographic characteristics were well balanced between treatment groups in the mITT population in Trials C-18 and C-23. In both trials, the population was predominantly female, White, and non-Hispanic. The demographics in both trials were consistent with a typical TD patient population. In the C-18 (flexible-dose) trial, participants of the mITT population had a mean age of 55 years (range: 25 to 73 years), 55% were male, and 75% were Caucasian). In the C-23 (fixed-dose) trial, participants of the mITT population had a mean age of 57 years (range: 21 to 81 years), 48% were male, and 79% were Caucasian.

Concurrent diagnoses included schizophrenia/schizoaffective disorder (62%) and mood disorder (33%) (SD-809-C-18 CSR: participants enrolled, from 18 years of age, had a history of using a DRA for at least 3 months, or 1 month in patients 60 years of age and older). The randomisation schemes were stratified by baseline use of DRA (currently taking versus not currently taking). Of the participants, 75.5% were on a stable DRA dose, while 24.5% not receiving a DRA. Moreover, participants from EU countries were enrolled in both trials and comprised approximately 37% of the mITT population. Thus, Teva considered that participants from EU countries were well represented.

Baseline disease characteristics were generally similar between treatment groups in the mITT population in Trials C-18 and C-23. The mean AIMS total score at baseline was similar across the protocol-defined mITT treatment groups within each trial; 9.7 and 9.6 in the DTBZ and placebo groups of Trial C-18), and between 9.4 to 10.1 in the DTBZ groups and 9.5 in the placebo group for Trial C-23.

Overview of Efficacy Results

In the applicant’s view, their totality, the results of the primary and secondary endpoints of the 2 Phase 3 confirmatory efficacy trials in TD (C-18, C-23) demonstrated that VMAT2 inhibition by DTBZ and its deuterated active metabolites led to a statistical improvement of TD symptoms.

Table 35: Trials C-18 and C-23: AIMS total score change from baseline to week 12 by treatment group (Blinded Central Video Rating; mITT and ITTPB populations)

Statistic	C-18 (flexible dose)		C-23 (fixed dose)			
	Placebo	**DTBZ BID**	**Placebo**	**DTBZ BID 12 mg**	**DTBZ BID 24 mg**	**DTBZ BID 36 mg**
mITT Population[a]						
Baseline						
n	49	48	58	60	49	55
Mean (SE) AIMS total score	10.5 (0.47)	10.7 (0.50)	9.5 (0.36)	9.6 (0.31)	9.4 (0.42)	10.1 (0.43)
Week 12						
n	43	46	56	53	45	52
LS mean (SE)	-1.9 (0.51)	-3.4 (0.49)	-1.4 (0.41)	-2.1 (0.42)	-3.2 (0.45)	-3.3 (0.42)
LS mean difference (DTBZ - placebo)	--	-1.5	--	-0.7	-1.8	-1.9
95% CI	--	-2.84, -0.18	--	-1.84, 0.42	-3.00, -0.63	-3.09, -0.79
p-value	--	0.027	--	0.217[b]	0.003[b]	0.001
ITTPB Population[c]						
Baseline						
n	57	56	71	73	72	72
Mean (SE) AIMS total score	9.6 (0.50)	9.7 (0.55)	8.5 (0.39)	8.6 (0.37)	7.7 (0.42)	8.6 (0.46)
Week 12	51	52	68	66	64	65
LS mean (SE)	-1.6 (0.47)	-3.0 (0.45)	-1.0 (0.36)	-1.5 (0.36)	-2.4 (0.36)	-2.9 (0.36)
mITT Population[a]						
LS mean difference (DTBZ - placebo)	--	-1.4	--	-0.5	-1.3	-1.8
95% CI	--	-2.62, -0.24	--	-1.46, 0.48	-2.32, -0.35	-2.83, -0.87
p-value	--	0.019	--	0.324[b]	0.008[b]	<0.001

[a] The mITT population in this table is the population defined for the SCE that includes participants who received trial drug, had at least 1 postbaseline assessment, and had baseline AIMS total scores ≥6.

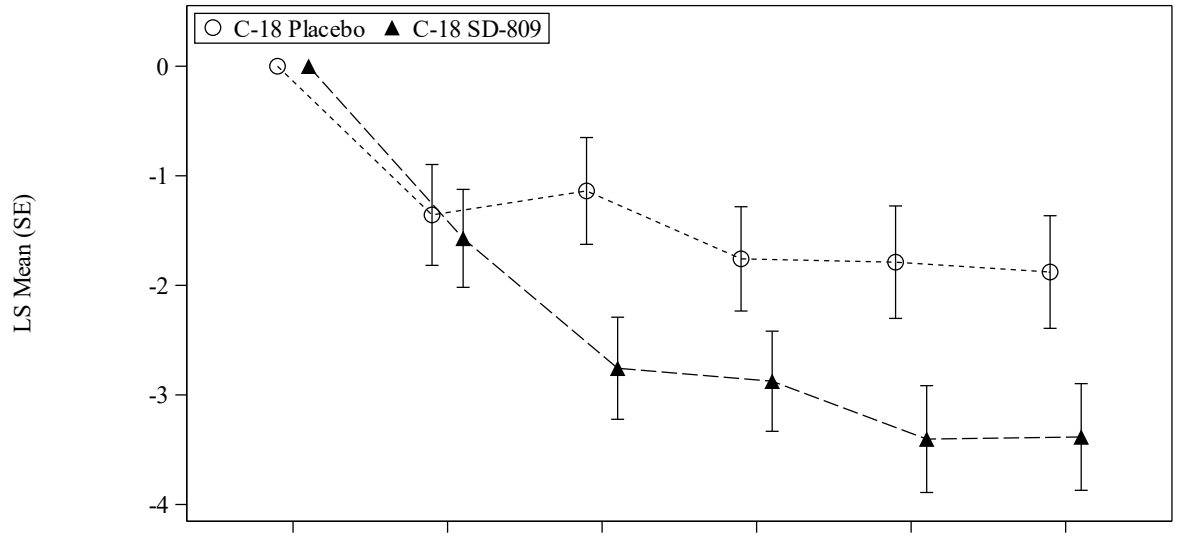
[b] Nominal p-value due to hierarchical method of analysis for primary and secondary key endpoints.

[c] The ITTPB population in this table is the population defined for the SCE that includes participants who received trial drug, had at least 1 postbaseline assessment, and had any baseline AIMS total score. This is the mITT population in the C-18 CSR.

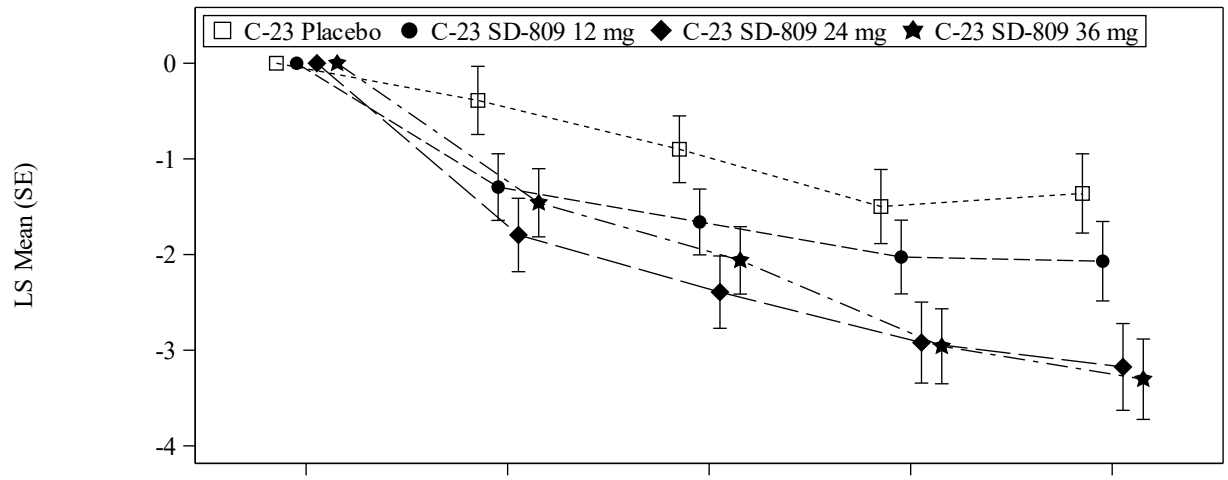
AIMS=Abnormal Involuntary Movement Scale; BID=twice a day; CI=confidence interval; CSR=clinical study report; ITTPB=intent-to-treat postbaseline; LS=least squares; mITT=modified intent-to-treat; MMRM=mixed model for repeated measures; n=number of participants per subset; SCE=summary of clinical efficacy; SE=standard error; TDISE=integrated summary of efficacy for tardive dyskinesia.

In Teva's view the analysis of the AIMS total score treatment effect using pooled data from Trial C-18 and the efficacious doses from Trial C-23, a reduction in AIMS total score from baseline to week 12 was observed for the pooled DTBZ group compared with the pooled placebo group (LS mean treatment difference of −1.8 points; $p<0.001$), supporting the consistency of the AIMS treatment effect observed in the individual trials for the DTBZ group of Trial C-18 and the DTBZ 36 mg/day and 24 mg/day groups of Trial C-23.

Figure 14: Trials C-18 (Flexible Dose) and C-23 (Fixed Dose): least squares mean (±SE) of AIMS total score changes from baseline to each visit by treatment group (Blinded Central Video Rating; mITT population)



Visit:	Baseline	Week 2	Week 4	Week 6	Week 8/9	Week 12
C-18 SD-809 (n)	48	47	47	47	47	46
C-18 Placebo (n)	49	48	45	46	43	43



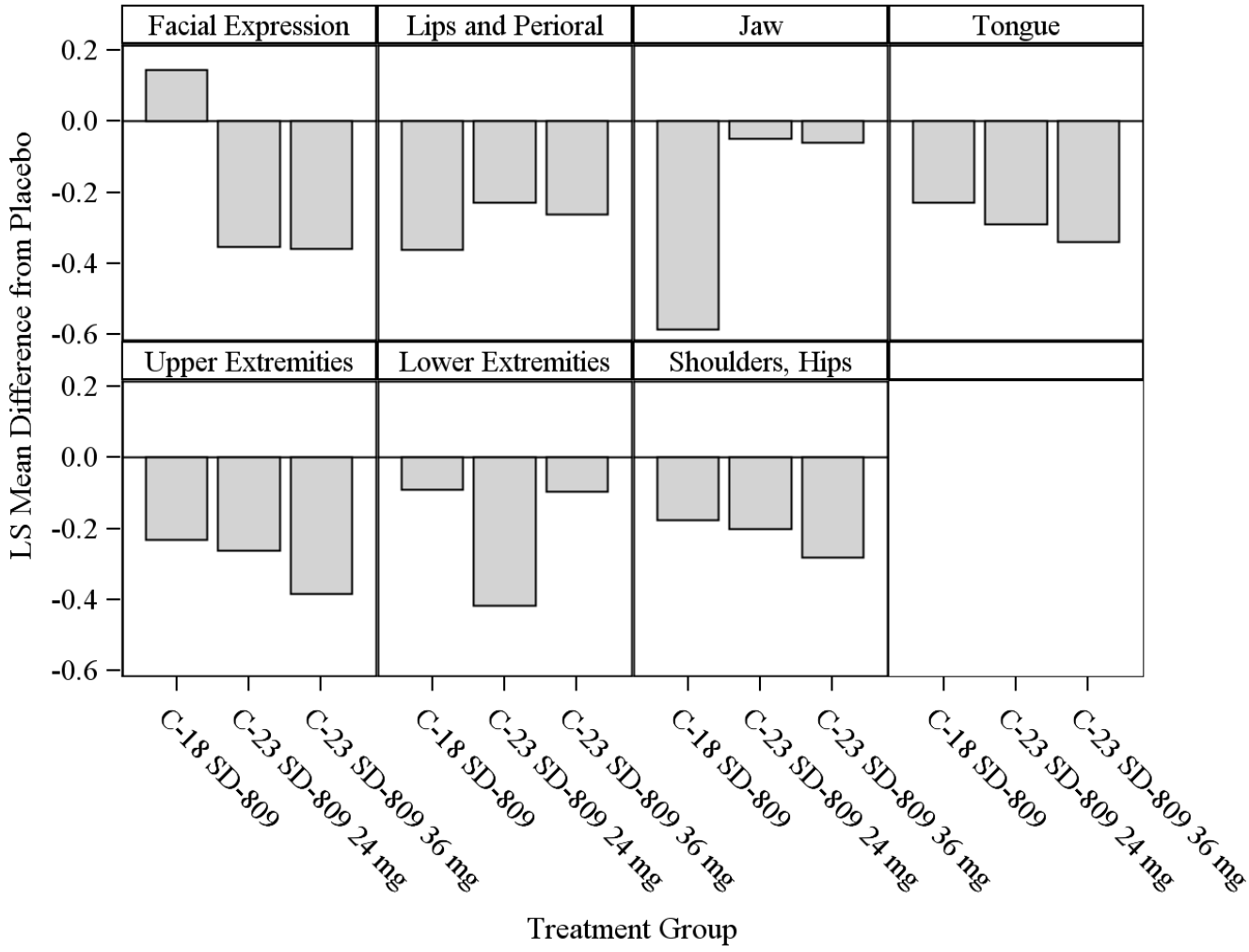
Visit:	Baseline	Week 2	Week 4	Week 8/9	Week 12
C-23 36 mg (n)	55	55	52	53	52
C-23 24 mg (n)	49	49	47	46	45
C-23 12 mg (n)	60	60	58	56	53
C-23 Placebo (n)	58	58	57	57	56

Source: TDISE19, Ad Hoc Graph 9.1 and Ad Hoc Graph 9.2.

AIMS=Abnormal Involuntary Movement Scale; LS=least squares; mITT=modified intent-to-treat; n=number of participants; SD-809=DTBZ; SE=standard error; TDISE=integrated summary of efficacy for tardive dyskinesia.

In Teva's view, results for the change from baseline at week 12 for individual items of the AIMS total score (Items 1 through 7) showed that efficacy was observed for all body areas, although there was variation in the effect seen in the individual items across trials.

Figure 15: Trials C-18 and C-23: least squares mean difference in AIMS item scores at week 12 by treatment group (mITT population)



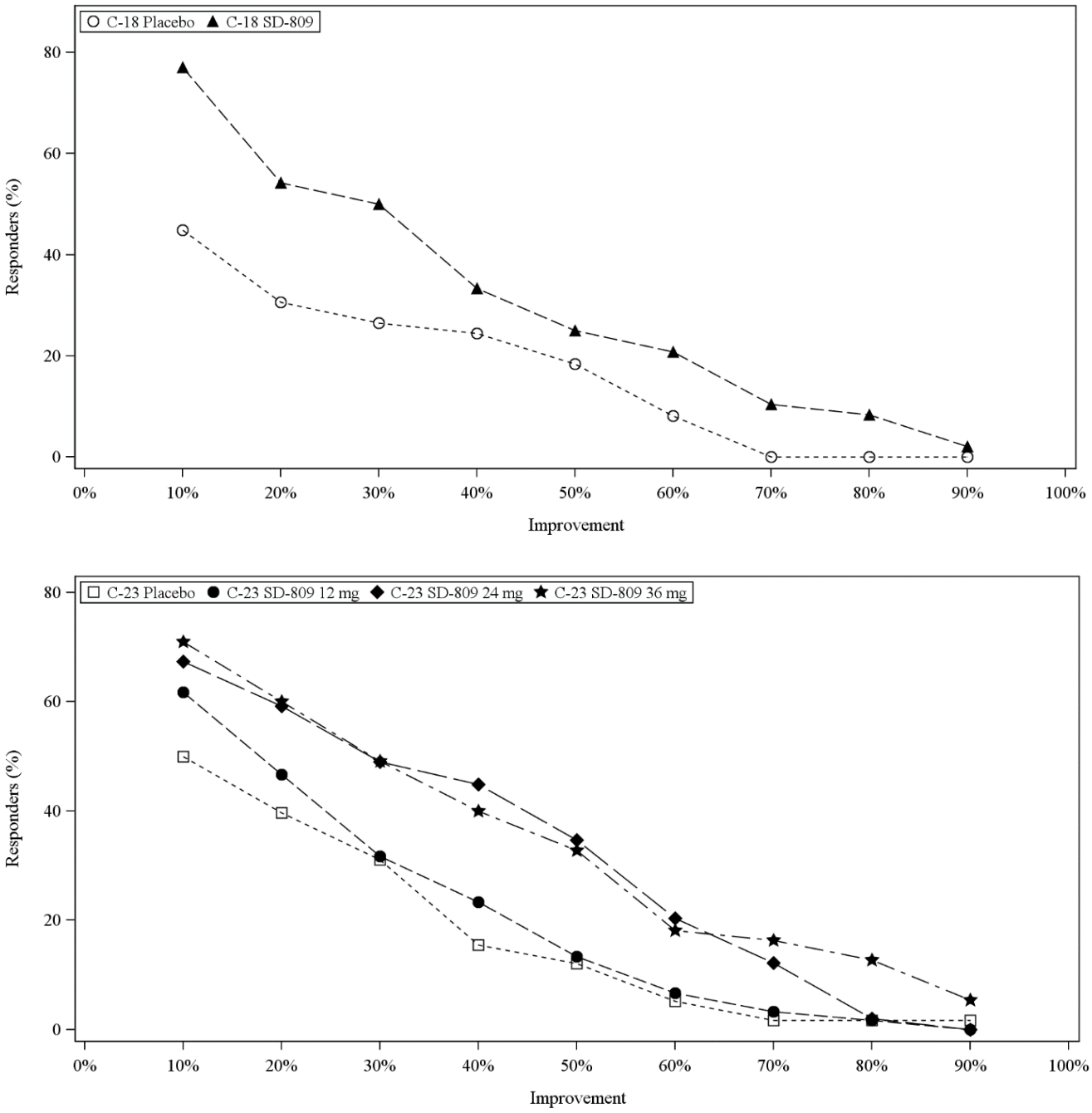
Source: TDISE19, Ad Hoc Graph 5.

AIMS=Abnormal Involuntary Movement Scale; LS=least squares; mITT=modified intent-to-treat; SD-809=DTBZ; TDISE=integrated summary of efficacy for tardive dyskinesia.

Responder Analysis by Reduction of AIMS Total Score

The cumulative proportion of responders at week 12, when analysed by a range of response thresholds, from 10% to 90% reduction (i.e., improvement) in AIMS total score, is shown below for the mITT populations in Trial C-18 (flexible dose – top panel) and Trial C-23 (fixed dose – bottom panel).

Figure 16: Trials C-18 and C-23: proportion of responders based on the reduction (ie, improvement) in AIMS total score at week 12 by treatment group (Blinded Central Video Rating; mITT population)



Source: TDISE19, Ad Hoc Graph 10.1 and Ad Hoc Graph 10.2.

AIMS=Abnormal Involuntary Movement Scale; mITT=modified intent-to-treat; SD-809=DTBZ; TDISE=integrated summary of efficacy for tardive dyskinesia.

At the 50% reduction in AIMS threshold, a greater proportion of participants in the mITT population achieved a response at week 12 in the DTBZ 36 mg/day and 24 mg/day groups in Trial C-23 compared with the placebo group (ORs of 3.80 [p=0.007] and 3.96 [p=0.005], respectively).

Treatment Success Rates Based on the CGIC

Main analysis

In both Trials C-18 and C-23, a higher proportion of participants in the DTBZ treatment group achieved treatment success compared to the placebo treatment group, as assessed by the investigators ("much improved" or "very much improved" on the CGIC scale) at week 12; however, the results were not statistically significant across all doses at the p<0.05 level.

Table 36: Trials C-18 and C-23: analyses of CGIC ratings at week 12 by treatment group (mITT population)

Outcome	**C-18**		**C-23**			
	Placebo (N=49)	**DTBZ BID (N=48)**	**Placebo (N=58)**	**DTBZ BID 12 mg (N=60)**	**DTBZ BID 24 mg (N=49)**	**DTBZ BID 36 mg (N=55)**
Treatment success based on CGIC at week 12[a]						
Treatment success, % (n/N)	35 (17/49)	52 (25/48)	26 (15/58)	28 (17/60)	49 (24/49)	44 (24/55)
OR (DTBZ/placebo)	--	1.97	--	1.15	2.71	2.11
OR 95% CI	--	0.875, 4.443	--	0.509, 2.610	1.211, 6.052	0.960, 4.645
p-value	--	0.099	--	0.734[c]	0.014[c]	0.059
Continuous data analysis of CGIC ratings[b]						
LS mean (SE)	2.8 (0.17)	2.6 (0.16)	3.2 (0.13)	2.9 (0.14)	2.6 (0.l5)	2.7 (0.14)
LS mean difference (DTBZ - placebo)	--	-0.2	--	-0.3	-0.6	-0.5
p-value	--	0.326	--	0.146	0.002	0.011

Source: TDISE19, Ad Hoc Summary 4, and Ad Hoc Summary 5.

[a] For each trial, the statistical test is a CMH test stratified by baseline use of DRAs. The odds ratio is the Mantel-Haenszel estimate of the common odds ratio. Participants with missing data at a visit were classified as a treatment failure at that visit. The denominator at each visit is the number of participants with an outcome at that visit.

[b] For each trial, the statistical model is an MMRM with treatment group, visit, treatment group by visit interaction, and baseline use of DRAs as fixed effects. The model is fit using an unstructured covariance structure.

[c] p-values are nominal.

BID=twice a day; CGIC=Clinical Global Impression of Change; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; DRA=dopamine receptor antagonist; MAR=missing at random; mITT=modified intent-to-treat; MMRM=mixed model for repeated measures; N=number of participants; n=number of participants per subset; OR=odds ratio; SE=standard error; TDISE=integrated summary of efficacy for tardive dyskinesia.

Treatment Success Rates Based on the PGIC

In both Trials C-18 and C-23, a higher proportion of participants in the DTBZ treatment group achieved treatment success compared to the placebo group, as assessed by participants who reported "much improved" or "very much improved" on the PGIC at week 12; however, the results were not statistically significant at the p<0.05 level.

Table 37: Trials C-18 and C-23: treatment success based on PGIC at week 12 by treatment group (mITT population)

Outcome	C-18		C-23			
	Placebo	**DTBZ BID**	**Placebo**	**DTBZ BID 12 mg**	**DTBZ BID 24 mg**	**DTBZ BID 36 mg**
Overall population						
n	49	48	58	60	49	55
Treatment success, % (n/N)	29 (14/49)	46 (22/48)	31 (18/58)	23 (14/60)	45 (22/49)	40 (22/55)
OR (DTBZ/placebo)	--	2.13	--	0.69	1.82	1.51
OR 95% CI	--	0.916, 4.939	--	0.302, 1.563	0.826, 3.994	0.694, 3.285
p-value	--	0.079	--	0.372	0.134	0.296

Source: TDISE19, Summary 7.1.

CI=confidence interval; CMH=Cochran-Mantel-Haenszel; DRA=dopamine receptor antagonist; mITT=modified intent-to-treat; N=number of participants; n=number of participants per subset; OR=odds ratio; PGIC=Patient Global Impression of Change; TDISE=integrated summary of efficacy for tardive dyskinesia.

Notes: For each trial, the statistical test is a CMH test stratified by baseline use of DRAs. If any of the expected cell counts are <5, exact Clopper Pearson limits are presented. The odds ratio is the Mantel-Haenszel estimate of the common odds ratio.

Participants with missing data at a visit were classified as a treatment failure at that visit.

The denominator at each visit is the number of participants with an outcome at that visit.

Modified CDQ-24 Change from Baseline

Improvements in total mCDQ-24 scores were greater for the DTBZ group compared with placebo in Trial C-18 (treatment effect of −4.4) and in the DTBZ 36 mg/day and 24 mg/day groups compared with placebo in Trial C-23 (treatment effects of −3.6 and −3.1, respectively).

Analysis of Treatment Effect Based on Dopamine Receptor Antagonist Use

Table 38: Change in total motor AIMS score from baseline to week 12 by baseline DRA use, trial C-18 (mITT population; N=113)

Statistics	DRA Use: YES		DRA Use: NO	
	DTBZ (N=43)	Placebo (N=48)	DTBZ (N=13)	Placebo (N=9)
LS mean	-3.0	-1.6	-3.0	-1.5
SE of LS mean	0.49	0.47	0.87	1.04
LS mean difference	-1.4	--	-1.6	--
95% CI	-2.75, -0.06	--	-4.24, 1.09	--

Source: SD-809-C-18 CSR Table 13
AIMS=Abnormal Involuntary Movement Scale; CI=confidence interval; DRA=dopamine receptor antagonist; DTBZ = deutetrabenazine; LS=least squares; mITT=modified intent-to-treat; N=total number of participants; SE=standard error.

Note: Total motor AIMS score (sum of Items 1 through 7) was assessed by blinded central video rating.

Table 39: LS mean change in total motor AIMS score from baseline to week 12 by baseline DRA use, trial C-23 (mITT population; N=222)

Statistic	DRA Use: YES				DRA Use: NO			
	Placebo (N=45)	DTBZ 12 mg/day (N=45)	DTBZ 24 mg/day (N=37)	DTBZ 36 mg/day (N=35)	Placebo (N=13)	DTBZ 12 mg/day (N=15)	DTBZ 24 mg/day (N=12)	DTBZ 36 mg/day (N=20)
LS mean change	-1.7	-2.0	-3.2	-3.4	0.0	-2.4	-3.1	-3.1
SE of LS mean	0.46	0.46	0.52	0.53	0.84	0.84	0.88	0.68
LS mean difference (DTBZ – placebo)	--	-0.2	-1.5	-1.7	--	-2.4	-3.0	-3.0
95% CI	--	-1.50, 1.07	-2.82, -0.10	-3.06, -0.31	--	-4.71, -0.02	-5.44, -0.64	-5.16, -0.89
p-value	--	0.745	0.036	0.017	--	0.048	0.013	0.006

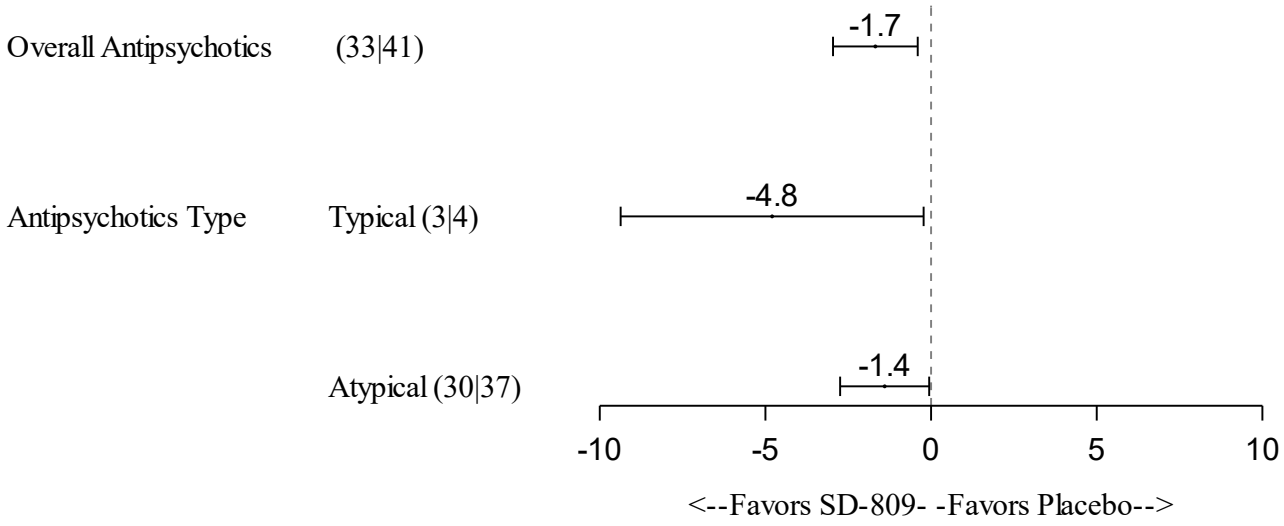
Source: SD-809-C-23 CSR, Table 20.

AIMS=Abnormal Involuntary Movement Scale; CI=confidence interval; DRA=dopamine receptor antagonist; DTBZ=deutetrabenazine; LS=least squares; mITT=modified Intent-to-Treat; MMRM=mixed model for repeated measures; N=total number of participants; SE=standard error.

Notes: Total motor AIMS score was assessed by blinded central video rating. The statistical model was an MMRM with treatment group, visit, DRA status, treatment group-by-visit interaction, treatment group vs. DRA status interaction, visit by DRA status interaction, and treatment group-by-visit-by-DRA status interaction and the baseline value as a covariate. The model was fit using an unstructured covariance structure.

Analysis of Treatment Effect Based on Typical Versus Atypical Antipsychotic Use

Figure 17: Forest plot of total motor AIMS score (Central Rating) mean change from baseline in week 12 - treatment effect analysis by antipsychotics type - comparison of DTBZ with placebo – trial C-18 (mITT population)



Source: SD-809-EU MAA Day 120, Graph 2.1.1.1

Note: Forest plot is the LS mean treatment difference and 95% CI. The numbers in parentheses represent the sample sizes for the treatment and placebo groups, respectively.

AIMS = Abnormal Involuntary Movement Scale; CI = confidence interval; DTBZ = deutetrabenazine; mITT = modified intent-to-treat; SD-809 = deutetrabenazine

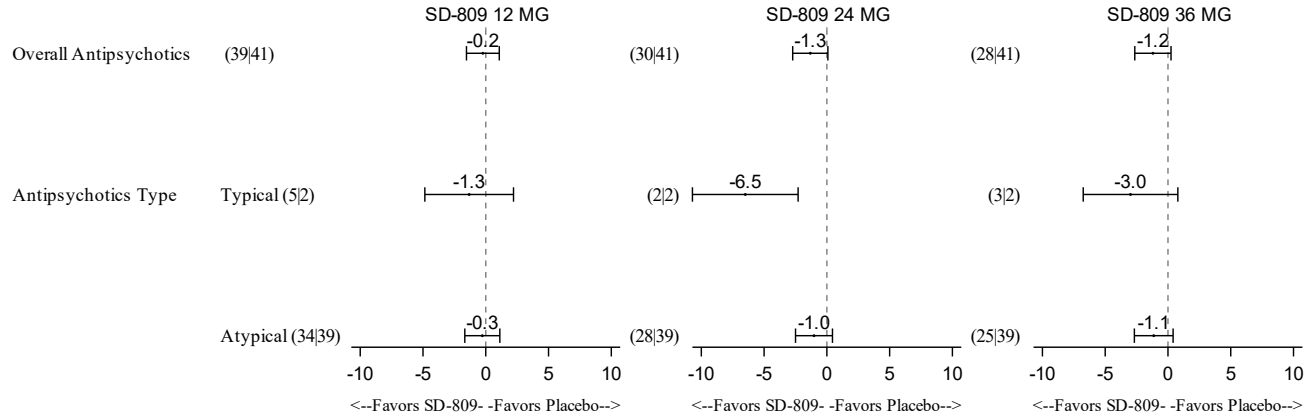
Table 40: Total motor AIMS scores (Central Rating) by antipsychotics type and treatment group in trial C-18 (mITT population)

Statistics	Typical Antipsychotics		Atypical Antipsychotics	
	Placebo (n=4)	DTBZ (n=3)	Placebo (n=41)	DTBZ (n=34)
Baseline (SE)	10.5 (2.25)	7.3 (1.67)	9.1 (0.61)	8.6 (0.67)
LS mean change from baseline to week 12 (SE)	-1.5 (1.32)	-4.7 (2.4)	-1.3 (0.55)	-2.5 (0.53)
LS mean difference DTBZ – Placebo (SE)	---	-4.8 (1.93)	---	-1.4 (0.68)

Source: SD-809-EU MAA D120 Summary 11

AIMS = Abnormal Involuntary Movement Scale; DTBZ= deutetrabenazine; LS=least square; mITT = modified intent-to-treat; n=number of participants in a subgroup; SE=standard error

Figure 18: Forest plot of total motor AIMS score (Central Rating) mean change from baseline to week 12 - treatment effect analysis by antipsychotic type - comparison of DTBZ with placebo - trial C-23 (mITT population)

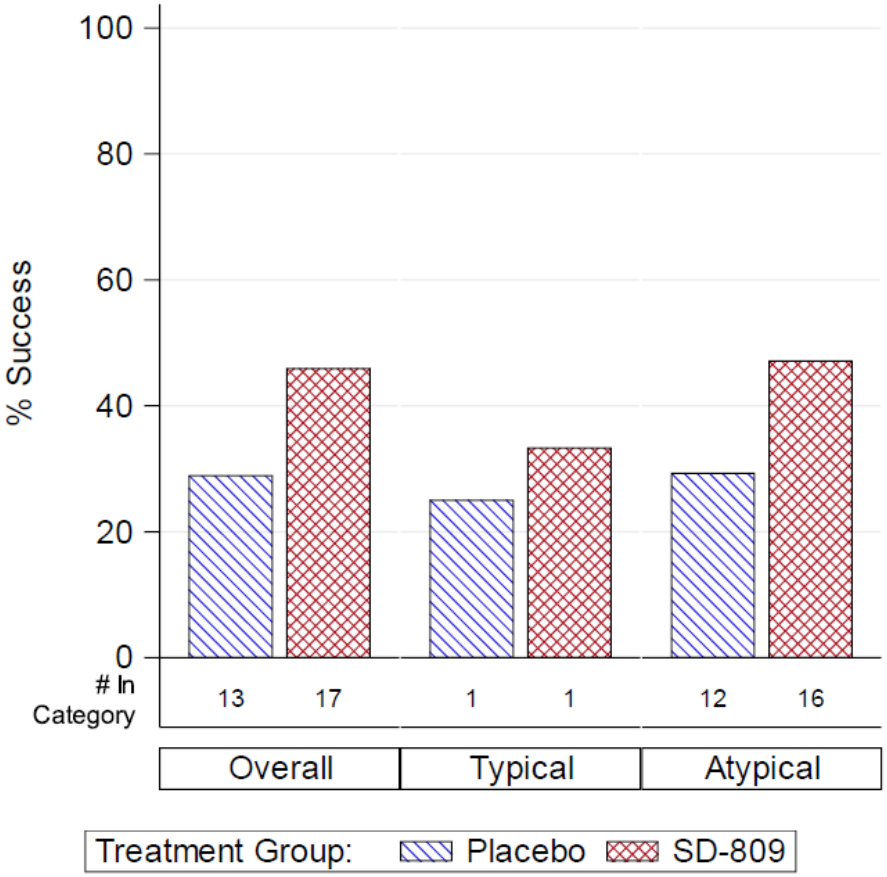


Source: SD-809-EU MAA Day 120, Graph 2.1.2.1

Note: Forest plot is the LS mean treatment difference and 95% CI. The numbers in parentheses represent the sample sizes for the treatment and placebo groups, respectively.

AIMS = Abnormal Involuntary Movement Scale; DTBZ = deutetrabenazine; mITT = modified intent-to-treat; SD-809 = deutetrabenazine

Figure 19: Proportion of participants who Achieved treatment success based on the PGIC week 12 by antipsychotics type and treatment group in trial C-18 (Missing=Treatment Failure) (mITT population)

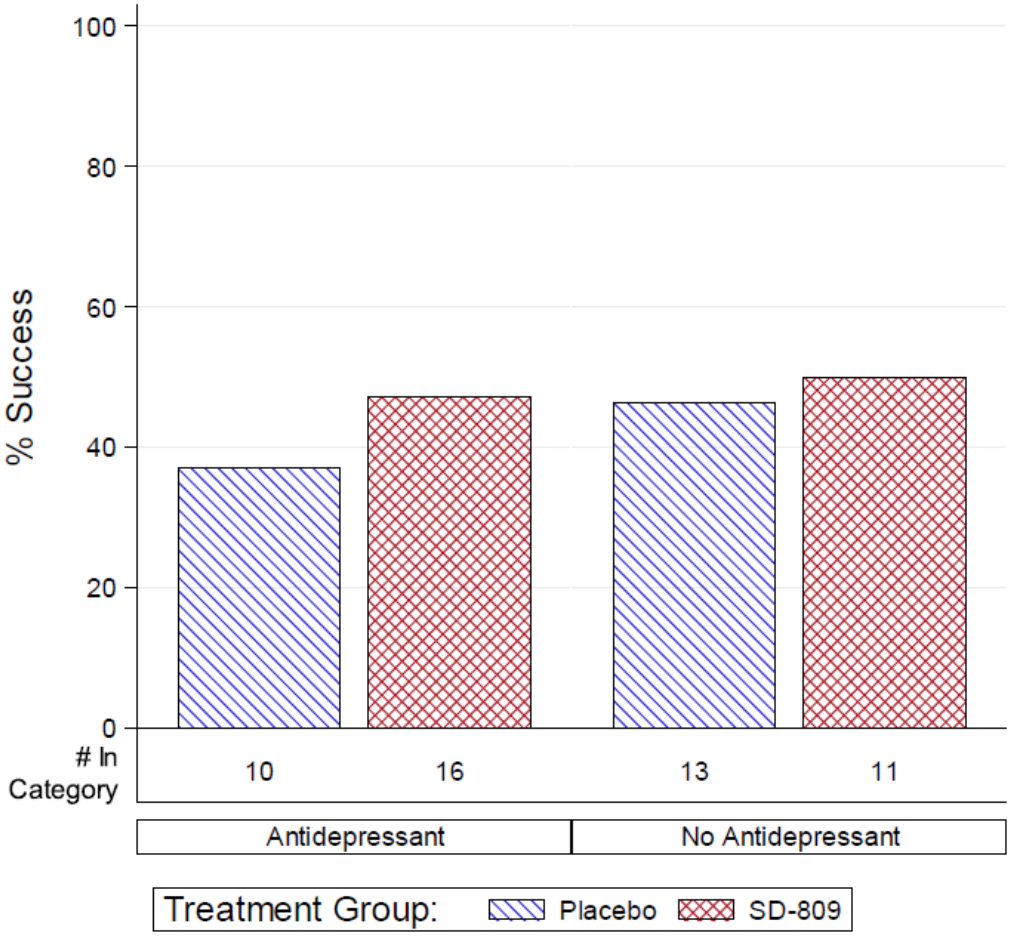


Source: SD-809-EU MAA Day 120, Graph 2.3.1

Note: % Success=percentage of participants who achieved treatment success

mITT = modified intent-to-treat; PGIC = Patient Global Impression of Change; SD-809 = deutetrabenazine

Figure 20: Proportion of participants who achieved treatment success based on the CGIC at week 12 by concomitant use of antidepressants versus no antidepressants and treatment group in trial C-18 (Missing=Treatment Failure) (mITT population)

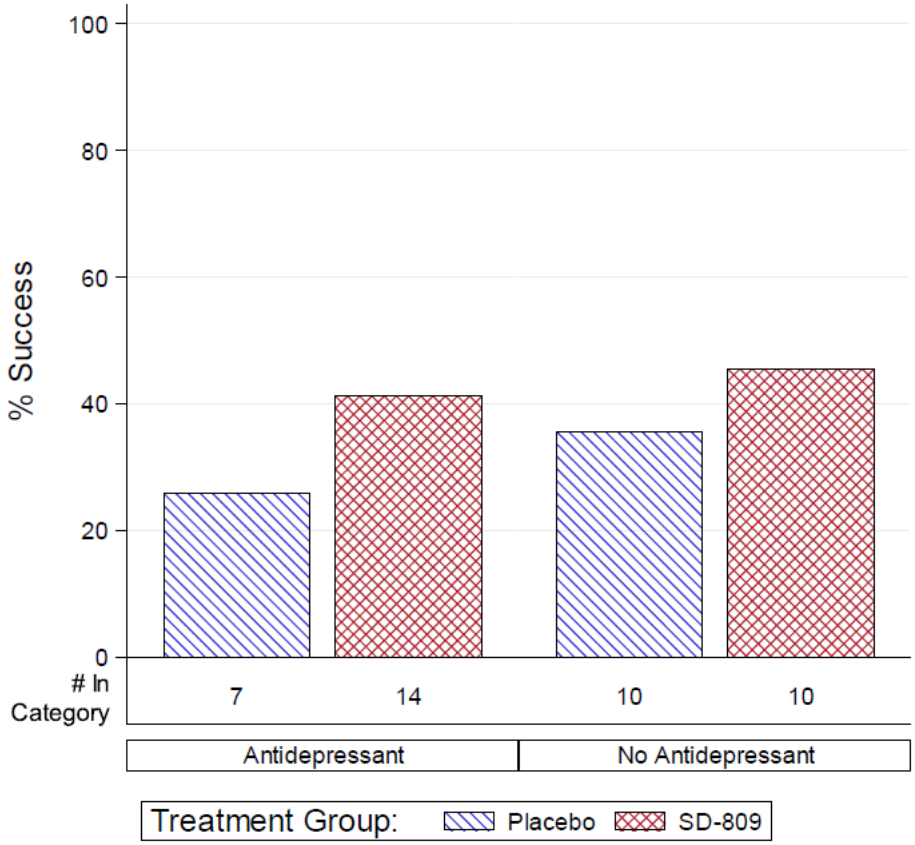


Source: SD-809-EU MAA Day 120, Graph 2.2.3

Note: % Success=percentage of participants who achieved treatment success

CGIC = Clinical Global Impression of Change; mITT = modified intent-to-treat; SD-809 = deutetrabenazine

Figure 21: Proportion of participants who achieved treatment success based on the PGIC at week 12 by concomitant use of antidepressants versus no antidepressants and treatment group in trial C-18 (Missing=Treatment Failure) (mITT population)



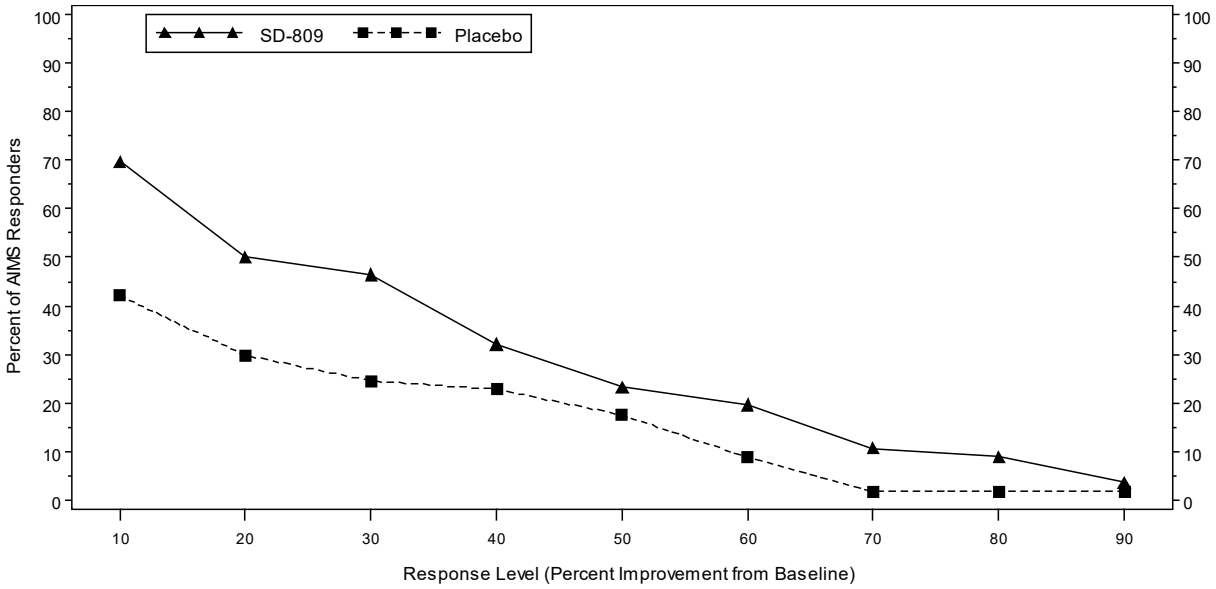
Source: SD-809-EU MAA Day 120, Graph 2.3.3

Note: % Success=percentage of participants who achieved treatment success

mITT = modified intent-to-treat; PGIC = Patient Global Impression of Change; SD-809 = deutetrabenazine

Responder Analysis by Reduction in Total Motor AIMS Score

Figure 22: Proportion of responders (Ranging from 10% to 90% Improvement) based on the change from baseline in total motor AIMS score at week 12 by treatment group, trial C-18 (mITT population, N=113)



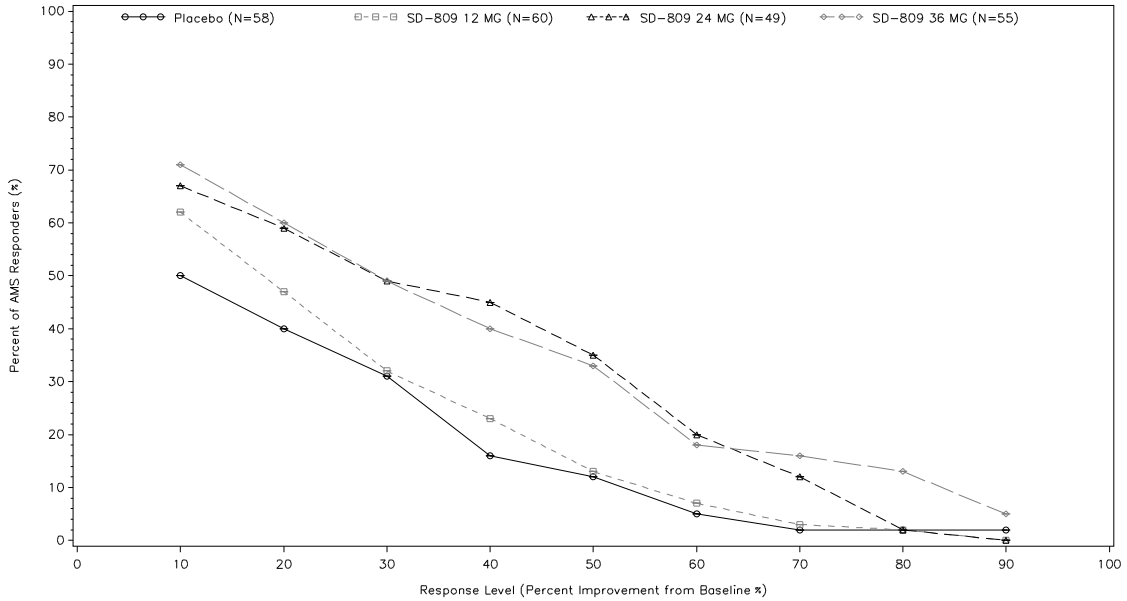
	Number of Subjects	Number of missing imputed as a non-responder
SD-809 (n):	56	4
Placebo (n):	57	6

Source: SD-809-C-18 CSR, Figure 3

Note: Participants who dropped out from the trial at week 12 and did not have an AIMS score, were considered non-responders

AIMS = Abnormal Involuntary Movement Scale; mITT = modified intent-to-treat; N = total number of participants; SD-809 = deutetrabenazine

Figure 23: Proportion of responders (Ranging from 10% to 90% Improvement) based on the change from baseline in total motor AIMS score at week 12 by treatment group, trial C-23 (mITT population, N=222)

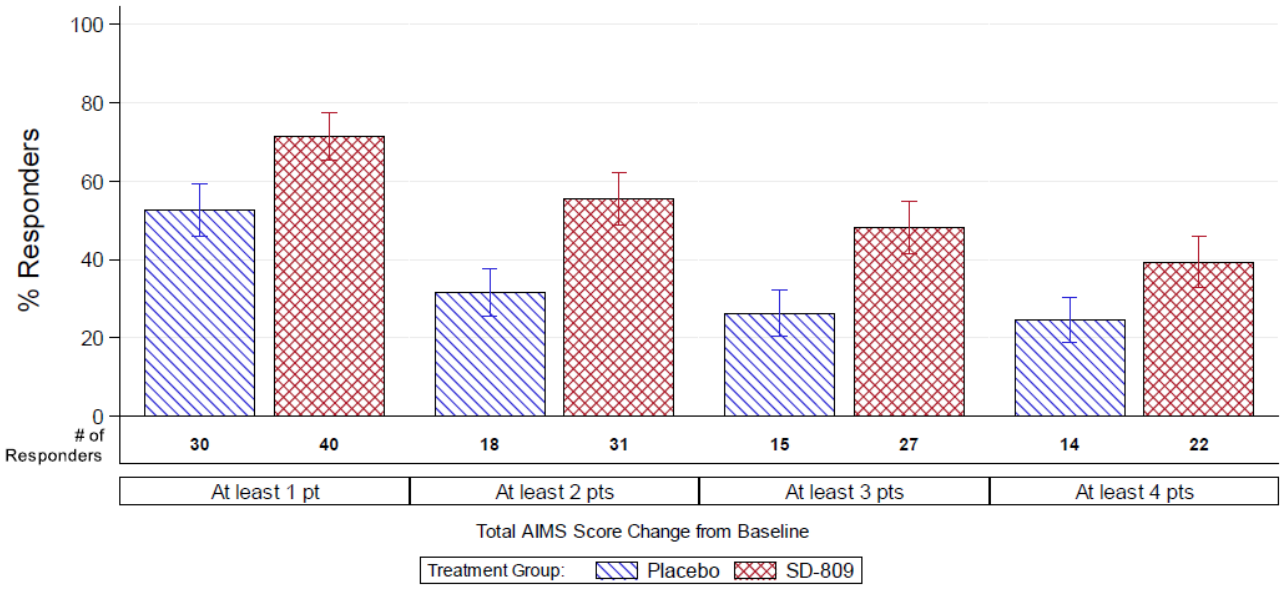


Source: SD-809-C-23 CSR, Figure 4

Note: Participants who dropped out from the trial at week 12 and did not have an AIMS score, were considered non-responders

AIMS = Abnormal Involuntary Movement Scale; mITT = modified intent-to-treat; N = total number of participants; SD-809 = deutetrabenazine

Figure 24: Proportion (SE) of participants reaching improvements on total motor AIMS score (Central Rating) of at least 1, 2, 3 or 4 points at week 12 by treatment for trial C-18 (Missing = Non-Responder) (mITT population)



Source: SD-809-EU MAA Day 120, Graph 7.1.2

Note: Proportion (SE)

AIMS = Abnormal Involuntary Movement Scale; mITT = modified intent-to-treat; SD-809 = deutetrabenazine; SE = standard error

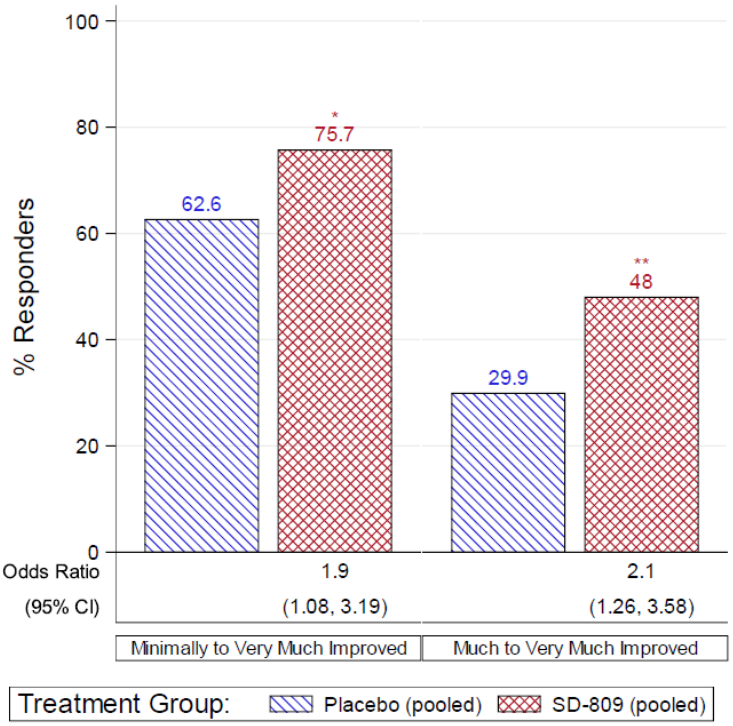
The applicant provided responder analyses based on the change from baseline in total motor AIMS score at week 12 as an aid to further interpret the clinical relevance of the efficacy results. As mentioned by Teva, this is in accordance with the CHMP guidance points to consider on multiplicity issues in clinical trials (CPMP/EWP/908/99; 2002). In Trial C-18, mIIT population with missing data were imputed as non-responders: 55% (31/56) of the patients treated with DTBZ had an improvement statistically significant in the total motor AIMS score of at least 2 points (clinical relevance threshold), compared to 32% (18/57) in the placebo group (nominal p=0.015). An improvement of at least 3 points from baseline was observed in 48% (27 /56) vs 26 % (15/57) of patients treated with DTBZ versus placebo, respectively (nominal p=0.020). An improvement of at least 4 points was observed in 39% (22/56) % versus 25% (14/57) (nominal p=0.113) of patients treated with DTBZ versus placebo, respectively. 71% (40/56) of the patients treated with DTBZ had an improvement in the total motor AIMS score of at least 1 point (not clinically relevant) compared to 52% (30/57) in the placebo group.

In Trial C-23, miTT population with missing data were imputed as non-responders: an improvement statistically significant in the total motor AIMS score of at least 2 points from baseline was observed in 53% (32/60) (nominal p=0.191), 61 % (30/49) (nominal p=0.038) and 65% (36/55) (nominal p=0.011) of patients treated with DTBZ 12, 24, and 36 mg/day, respectively versus placebo (24/58) (41%).

The applicant was requested to present responder analyses for all patients with different cut-off points for the primary endpoint (MCID >1 and <2, >=2 and <3, >= 3 and <4, >= 4). This analysis was not provided. The request was reiterated by CHMP e.g., in the D180 LoOI. Further details are provided thereafter in this AR.

Responder Analysis for CGIC and PGIC Using Different Cut-Offs

Figure 25: Proportion of responders based on CGIC score ≤3 ("Minimally" to "Very Much Improved") or CGIC score ≤2 "(Much" to "Very Much Improved") at week 12 by treatment (Missing=Treatment Failure) (mITT population)

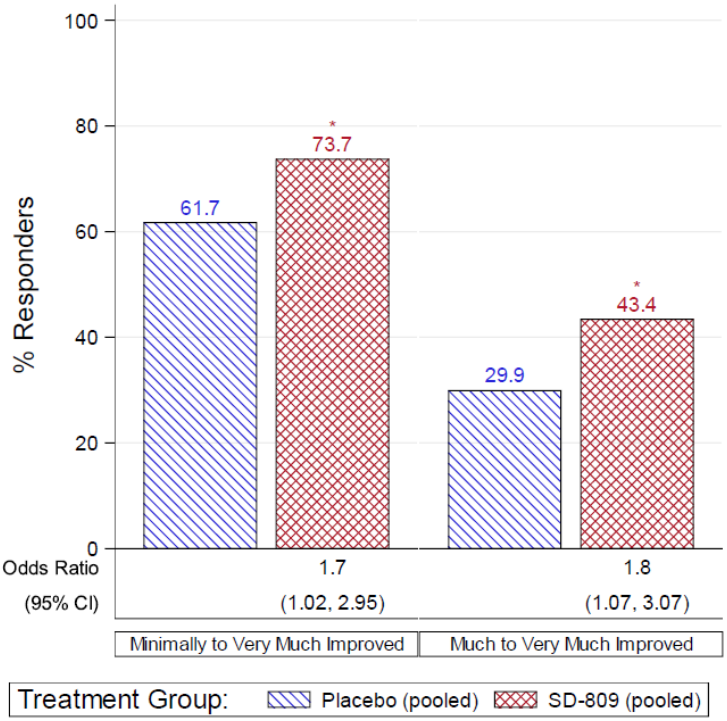


Source: SD-809-EU MAA Day 120, Graph 10

Note: Placebo (pooled) included placebo participants from trials C-18 and C-23.

SD-809 (pooled) included Deutetrabenazine participants from trials C-18 and C-23, 24 mg and 36 mg. Deutetrabenazine 12 mg was excluded from the analysis by the pooled.
The odds ratio is the Mantel-Haenszel estimate of the common odds ratio.
*P < 0.05; **P < 0.01; ***P < 0.001 versus placebo. CI, confidence interval.
CGIC = Clinical Global Impression of Change; mITT = modified intent-to-treat; SD-809 = deutetrabenazine

Figure 26: Proportion of responders based on PGIC Score ≤3 "(Minimally" to "Very Much" Improved) or PGIC score ≤2 ("Much" to "Very Much" Improved) at week 12 by treatment (Missing=Treatment Failure) (mITT population)

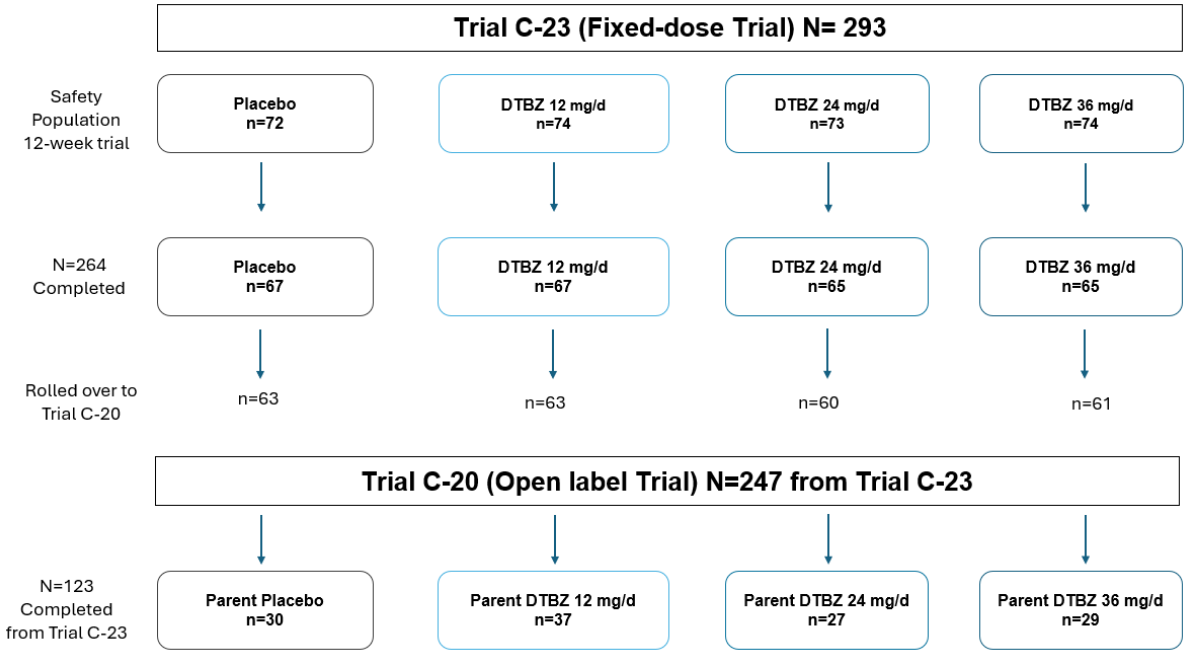


Source: SD-809-EU MAA Day120, Graph 9

Note: Placebo (pooled) included placebo participants from trials C-18 and C-23.

SD-809 (pooled) included Deutetrabenazine participants from trials C-18 and C-23, 24 mg and 36 mg. Deutetrabenazine 12 mg was excluded from the analysis by the pooled.
The odds ratio is the Mantel-Haenszel estimate of the common odds ratio.
*P < 0.05; **P < 0.01; ***P < 0.001 versus placebo. CI, confidence interval.
mITT = modified intent-to-treat; PGIC = Patient Global Impression of Change; SD-809 = deutetrabenazine

Figure 27: Patient disposition in trial C-23 and trial C-20 for participants rolling over from trial C-23



Source: SD-809-C-23 CSR, Summary 15.1; SD-809-EU MAA D120 Summary 2, Summary 4

DTBZ = deutetrabenazine; mg/d = milligrams per day; N = Number of participants; n = number of participants in a subgroup

Reasons for Discontinuations in Trial C-23

264 participants completed the trial and 29 discontinued the treatment (5 participants in the placebo arm, and 7, 8, 9 in the 12 mg/day, 24 mg/day, and 36 mg/day DTBZ arms, respectively). The most common reason for discontinuation was AEs (2 participants in the placebo arm, and 4, 1, 2 participants in the 12 mg/day, 24 mg/day, and 36 mg/day DTBZ arms, respectively).

Table 41: Adverse events among dropouts and trial completers by treatment group in trial C-23 (Safety Population)

Adverse Event Category	Dropouts[1](N=29)				Completed Trial[2](N=264)			
	Placebo (n=5)	DTBZ 12 mg (n=7)	DTBZ 24 mg (n=8)	DTBZ 36 mg (n=9)	Placebo (n=67)	DTBZ 12 mg (n=67)	DTBZ 24 mg (n=65)	DTBZ 36 mg (n=65)
Participants with any AE	3 (60.0%)	6 (85.7%)	5 (62.5%)	3 (33.3%)	31 (46.3%)	30 (44.8%)	27 (41.5%)	35 (53.8%)
Participants with any severe AE	0 (0.0%)	2 (28.6%)	3 (37.5%)	1 (11.1%)	2 (3.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)
Participants with any treatment-related AE	3 (60.0%)	2 (28.6%)	2 (25.0%)	1 (11.1%)	16 (23.9%)	11 (16.4%)	9 (13.8%)	17 (26.2%)
Participants with any serious AE	0 (0.0%)	2 (28.6%)	4 (50.0%)	2 (22.2%)	4 (6.0%)	0 (0.0%)	2 (3.1%)	2 (3.1%)
Participants with AE leading to dose suspension	1 (20.0%)	1 (14.3%)	1 (12.5%)	0 (0.0%)	1 (1.5%)	2 (3.0%)	0 (0.0%)	1 (1.5%)
Participants with AE leading to dose reduction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	3 (4.6%)

Source: SD-809-EU MAA Day 120, Summary 65.1
[1]Participants who dropped out of the trial at any time post enrollment.
[2]Participants who completed the primary endpoint assessment and the final study visit.
Participants are counted only once for each category.
AE = adverse events; DTBZ = deutetrabenazine; N = total number of participants; n = number of participants within each treatment arm.

Reasons for Discontinuations in Trial C-20

Table 42: Adverse events among dropouts and trial completers for parts A and B in trial C-20 (Safety Population)

	Dropouts [1]	**Completed Trial [2]**
Adverse Event Category	**(N=171)**	**(N=166) [3]**
Participants with any AE	128 (74.9%)	141 (84.9%)
Participants with any severe AE	33 (19.3%)	24 (14.5%)
Participants with any treatment-related AE	72 (42.1%)	82 (49.4%)
Participants with any serious AE	38 (22.2%)	30 (18.1%)
Participants with AE leading to dose suspension	19 (11.1%)	15 (9.0%)
Participants with AE leading to dose reduction	15 (8.8%)	38 (22.9%)

Source: SD-809-EU MAA D120, Summary 64.1

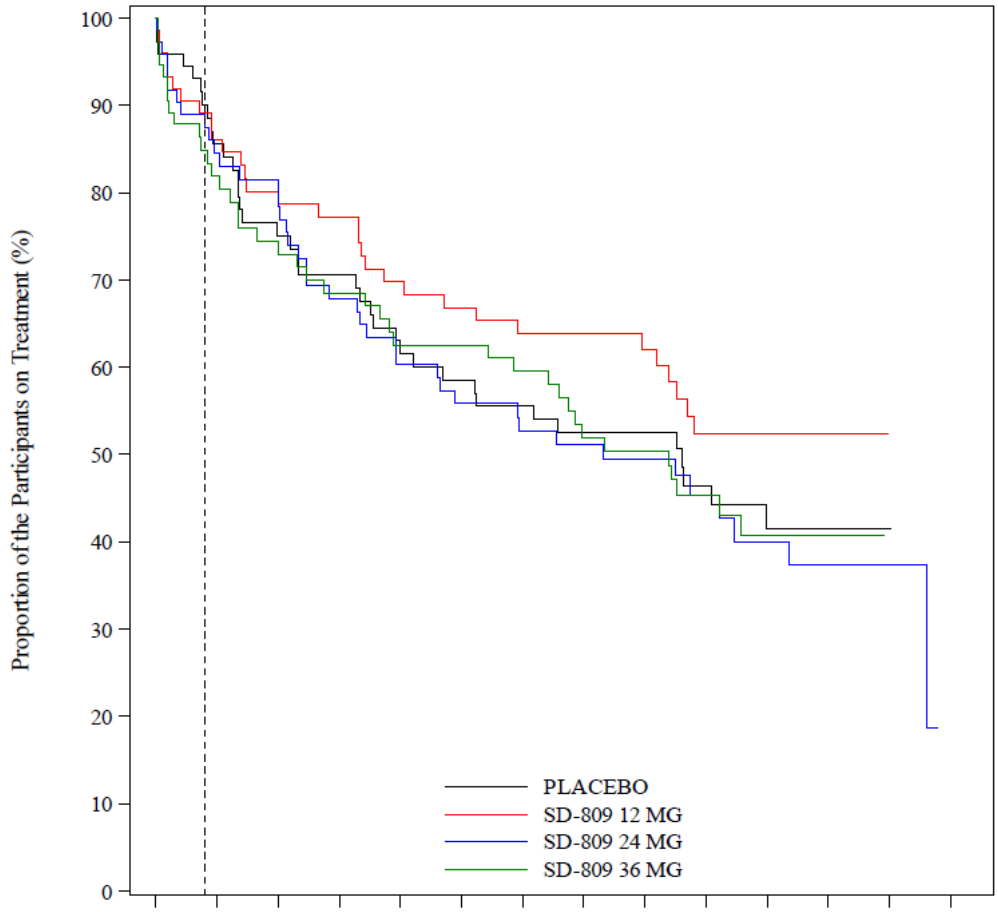
[1]Participants who dropped of the trial at any time post enrollment.
[2]Participants who completed the primary endpoint assessment and the final study visit.
[3]There were 39 participants who completed treatment in the parent Trial C-18, and there are 127 participants who completed treatment in the parent Trial C-23.

Note: Participants are counted only once for each category.

AE = adverse events; N = Number of participants

Time to Discontinuation of Participants from Start of Trial C-23 to End-of-Study in Trial C-20

Figure 28: Kaplan-Meier plot for time to discontinuation - all cause discontinuations for trials C-23 and C-20 parts A, B, and C (Safety Population)



SD-809 36 MG	74	55	50	46	42	42	39	34	31	22	18	18	0
SD-809 24 MG	73	56	54	45	40	37	34	32	28	18	15	14	2
SD-809 12 MG	74	58	54	52	47	45	42	39	34	25	19	19	0
PLACEBO	72	57	50	47	41	39	37	31	29	21	15	15	1

Number of participants

Individual Trajectories of All Participants from Start of Trial C-23 until the End-of-Study in Trial C-20

Figure 29: Individual trajectories of participants from trial C-23 entering into trial C-20: change from baseline in total motor AIMS score (Central Rating) -trial C-23 placebo group (ITT population)

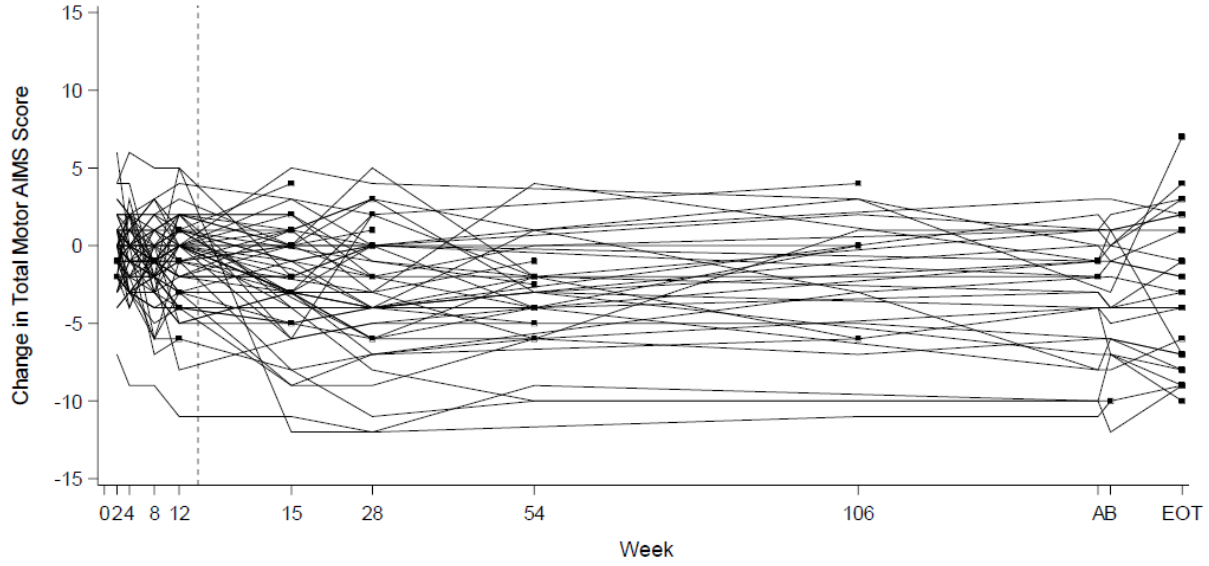


Figure 30: Individual trajectories of participants from trial C-23 entering into trial C-20: change from baseline in total motor AIMS score (Central Rating) - trial C-23 DTBZ 12 mg/day group (ITT population)

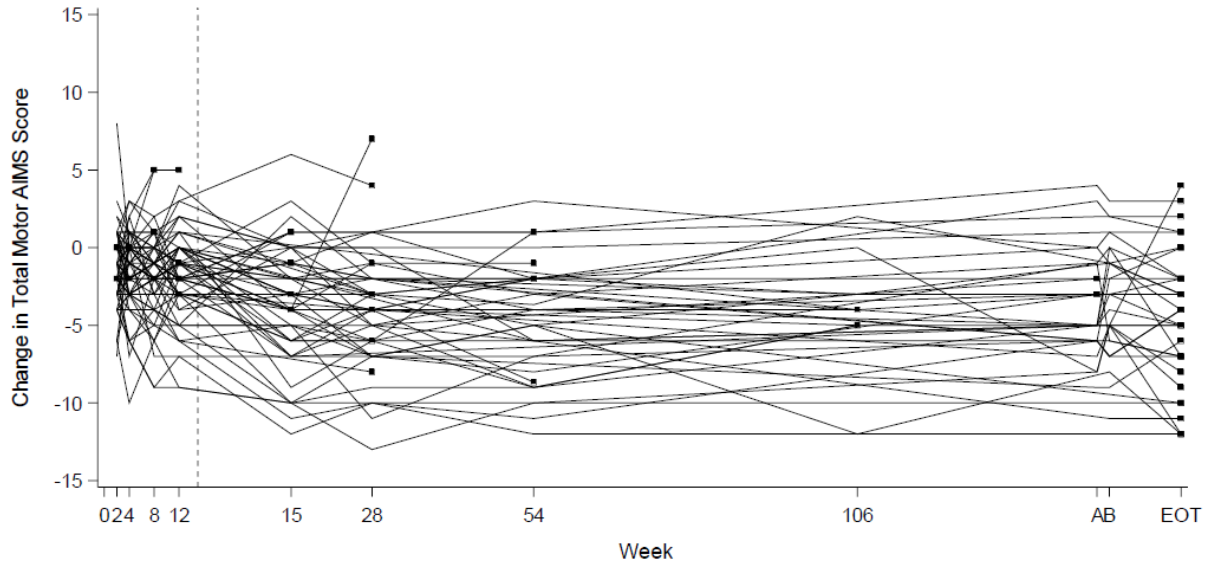


Figure 31: Individual trajectories of participants from trial C-23 entering into trial C-20: change from baseline in total motor AIMS score (Central Rating) - trial C-23 DTBZ 24 mg/day group (ITT population)

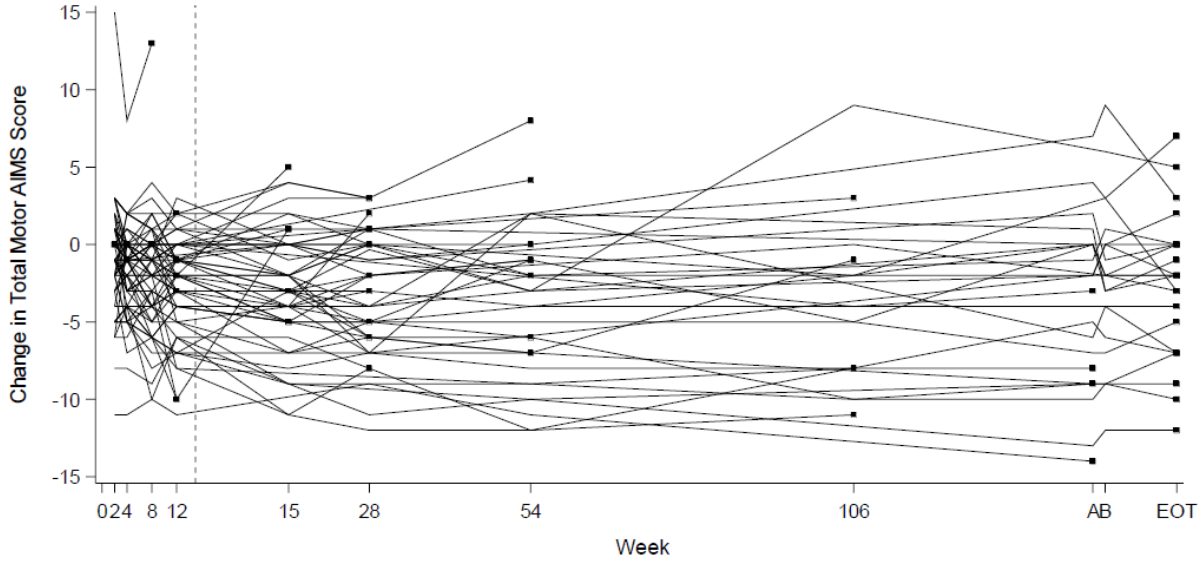
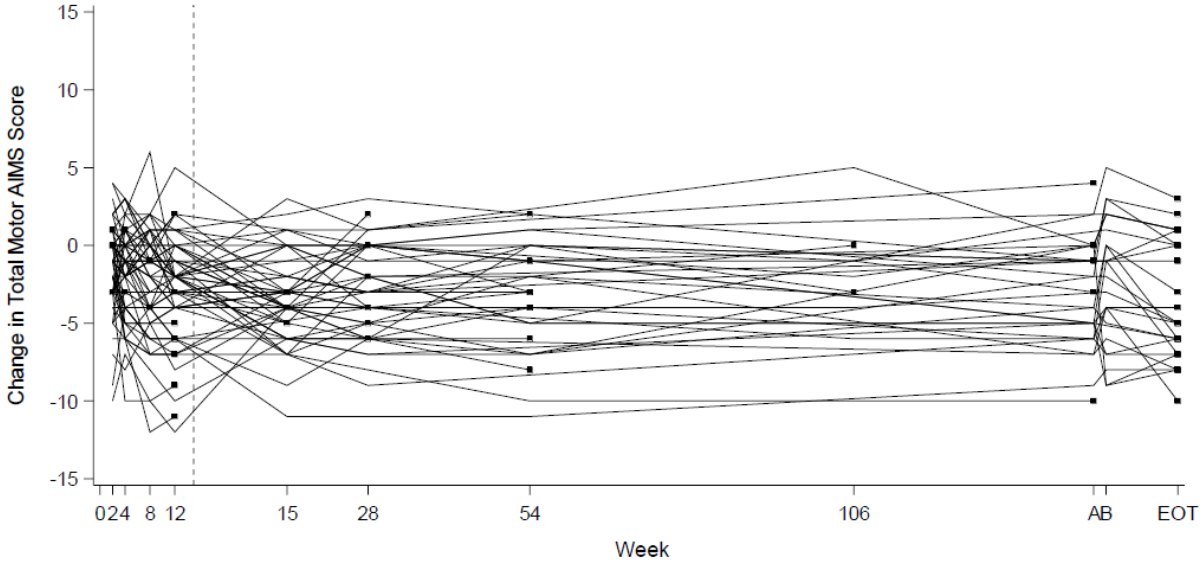
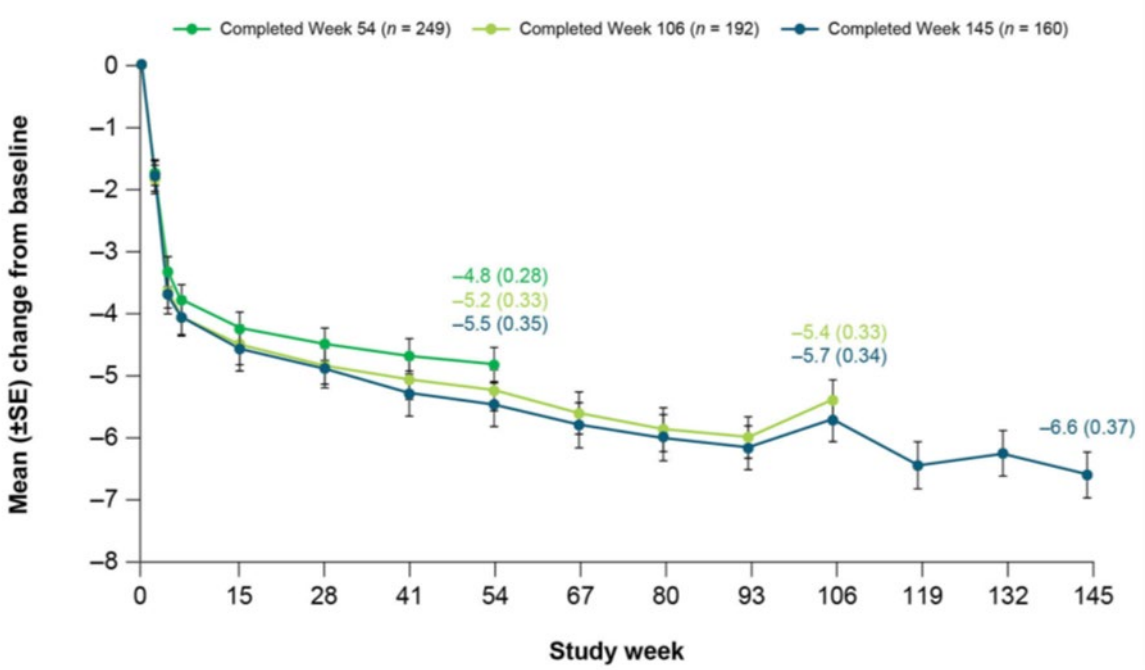


Figure 32: Individual trajectories of participants from trial entering into trial C-20: change from baseline in total motor AIMS score (Central Rating) - trial C-23 DTBZ 36 mg/day group (ITT population)



Efficacy in Participants who Completed Trial C-20 Versus Participants who Discontinued Trial C-20

Figure 33: Mean change from baseline to each visit (±SE) in total motor AIMS score among participants who completed 54, 106, and 145 weeks of treatment (Site Rating; ITT Population) – trial C-20 part A



Real-World Utilization of DTBZ Initiated by a 4-week Patient Titration Kit (TV50717-CNS-40189, START Trial, US)

Similarly to what was observed in Trials C-18 and C-23, this RWE trial showed a steady increase in the percentage of participants determined as a treatment success (defined by CGIC) in the TD cohort at week 4 (29%), week 8 (34%), week 12 (48%) and week 24/End of Study (EOS) (49%). In addition, at week 12, participants in the TD cohort had a mean (%) improvement in total motor AIMS score of -4.7 (-34.92%) from baseline, decreasing from a mean total motor AIMS score of 13.6 (standard deviation [SD 4.69]) at baseline to 9.1 (SD 4.89) at week 12.

RWE of Patient Experience with AUSTEDO® XR (DTBZ) Extended-Release Tablets (Osmotic PR Formulation QD) in the US (TV50717-NPC-40256, Patient Survey, US) Interim Results

This interim analysis (cut off date: 02 August 2024), explored patient-reported ease of use, effectiveness and satisfaction with QD DTBZ tablets. This non-interventional, prospective, cross-sectional survey included adults with TD or HD-associated chorea taking DTBZ QD tablets. Participants who completed or were due for their 12-week nurse outreach phone call (US shared solutions patient support programme) were eligible for screening.

Among 240 respondents who reported taking DTBZ QD, 209 were treated for TD and 31 for HD-associated chorea (TV50717-NPC-40256 [data on file]). Mean age for TD participants was 59.7 years (19, 90, 61, min, max, median, respectively). Specifically for the TD population, 95% of the participants felt that it was "very"/"somewhat" easy to include DTBZ QD tablets in their daily routine, and 99% reported it was "very"/"somewhat" easy to take DTBZ QD tablets. A total of 76% participants reported that their extra movements were "very much"/"much" improved with DTBZ QD tablets.

Generalisability of Phase 3 Trial Results

Post-Hoc Analysis in Participants with Milder TD

Figure 34: Change from baseline in total motor AIMS scores (Central Rating) at week 12 - treatment effect analysis by baseline total motor AIMS score of <6 vs ≥6 – comparison of DTBZ with placebo – trial C-18 (mITT population)

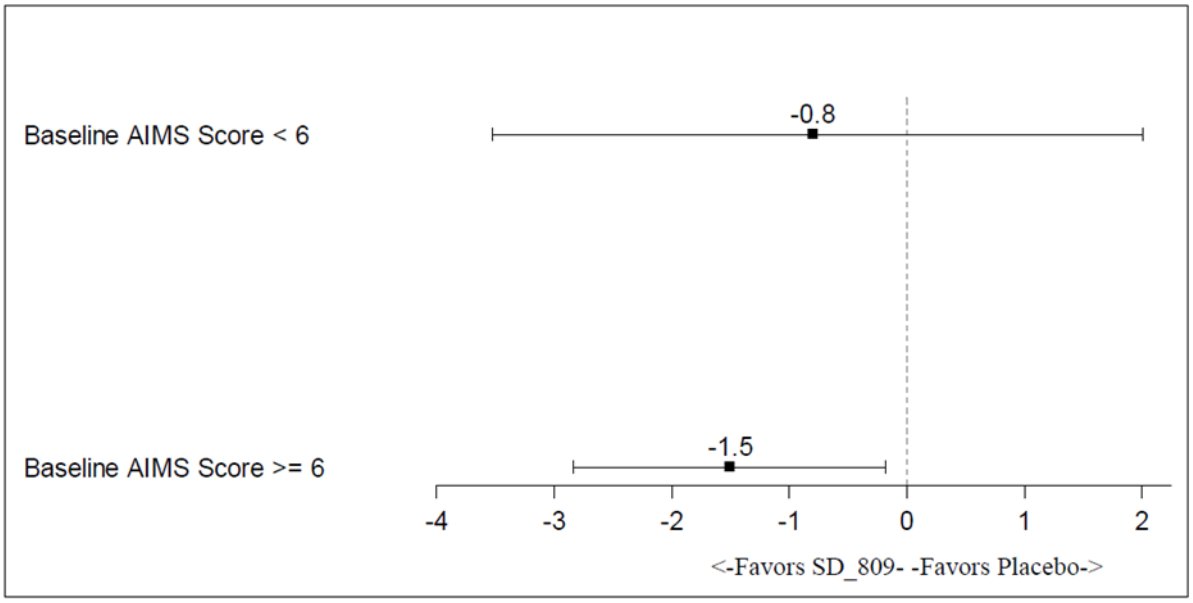
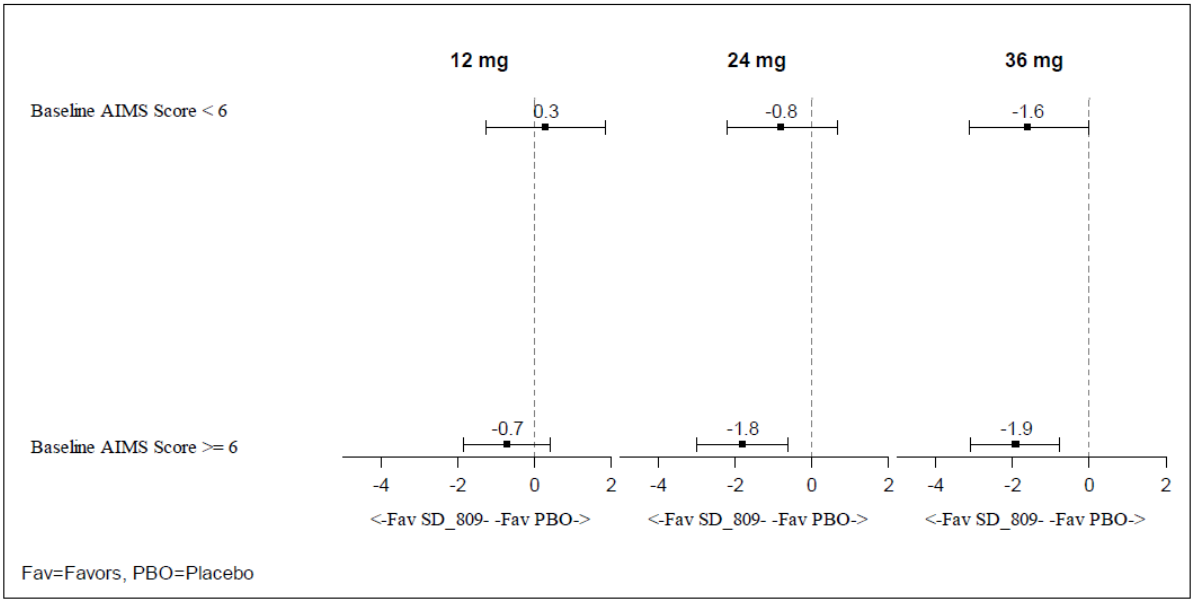
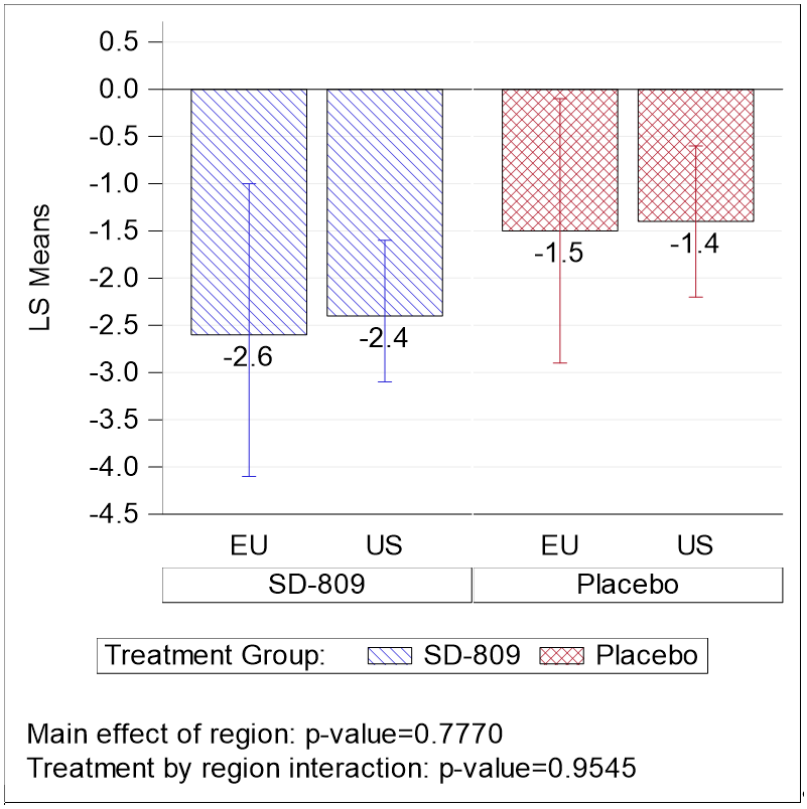


Figure 35: Change from baseline in total motor AIMS scores (Central Rating) at week 12 - treatment effect analysis by baseline total motor AIMS score of <6 vs ≥6 – comparison of DTBZ with placebo – trial C-23 (ITTPB population)



Potential interaction between geographical region and treatment effect

Figure 36: Change in total motor AIMS score from baseline at week 12 (Central Rating) by region and treatment group - trial C-18 (mITT population)



There was no difference in the magnitude of effect between EU and US regions. EU had higher responses but also higher placebo effects, and the net effect was similar.

Following the uncertainty regarding the value of improvement with DTBZ, which sustained the clinical efficacy major objection (MO), the applicant provided further data to support its position

The CHMP required Teva to further justify the clinical relevance of the primary endpoint results, also considering the lack of strong support from the secondary endpoints. The committee highlighted that such justification should include submission of:

a) Previously requested (and yet not provided) responder analyses for all patients with different cut-off points for the primary endpoint (MCID >1 and =2 and =3 and =4);

b) AIMS response anchored to PRO such as PGIC.

In addition, justification was awaited that the modest response observed outweighs the main safety concerns (e.g., anxiety, depression, or down titration of DRAs and risk of psychotic flare ups) identified by the CHMP.

To address the clinical relevance, Teva conducted responder analyses of the reduction in the total motor Abnormal Involuntary Movement Scale (AIMS) score from baseline using 3 approaches. The first utilised the conventional responder cut-offs, and the additional 2 non-overlapping categories and anchoring to the Patient Global Impression of Change (PGIC).

Responder Analyses Using Overlapping Categories of Reduction in Total Motor AIMS Score

Teva reiterated that, in both (flexible dose) C-18 and (fixed dose) C-23 trial, DTBZ demonstrated a statistically significant and clinically meaningful reduction in tardive dyskinesia (TD) motor symptoms, compared to placebo, as measured by the primary endpoint, the change in total motor AIMS score (central reading) from baseline to week 12:

- Trial C-18: DTBZ group showed a 3.0-point mean reduction versus 1.6 points in the placebo group, with a mean treatment effect difference of −1.4 points (p=0.0188; 95% confidence interval [CI]: -2.6, -0.2).
- Trial C-23: DTBZ 36 mg/day group showed a 3.3-point mean reduction versus 1.4 points in the placebo group, with a mean treatment effect difference of −1.9 points; (p=0.001; 95% CI: −3.09, −0.79).

The majority of participants on DTBZ experienced at least a 2-point reduction from baseline in the total motor AIMS score, an improvement considered clinically meaningful, based on the minimal clinically important change (MCIC) and the minimal clinically important difference (MCID).

Teva initially conducted responder analyses by reduction of total motor AIMS score from baseline to week 12 using cut-offs of percentages and absolute point changes.

The applicant flagged that:

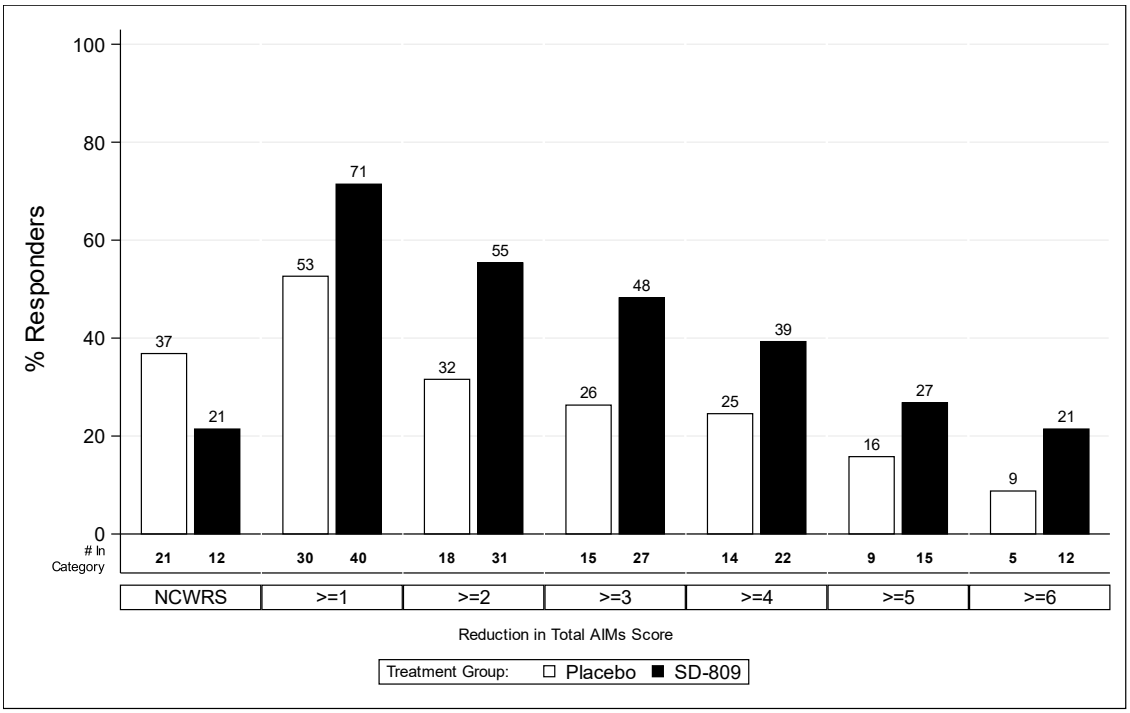
- At the ≥10% through ≥70% total motor AIMS score reduction thresholds, the proportions of AIMS responders in Trial C-18 and DTBZ 36 mg/day and 24 mg/day groups in Trial C-23 were greater than in the placebo group.
- In Trial C-18 a reduction in total motor AIMS score of ≥2 points was observed in 55% of the participants treated with DTBZ compared to 32% in the placebo group (nominal p=0.015). Similarly, in Trial C-23, a reduction in total motor AIMS score of ≥2 points was observed in 53% (nominal p=0.191), 61% (nominal p=0.038), and 65% (nominal p=0.011) participants treated with DTBZ 12, 24, and 36 mg/day, respectively, compared to 41% in the placebo group. Of note, Trial C-23 indicated that the 24 and 36 mg DTBZ doses were efficacious compared to placebo.

Stated the above, to justify the clinical relevance of the primary efficacy results, Teva performed additional responder analyses, in line with the Points to Consider on Multiplicity Issues in Clinical Trials (CPMP/EWP/908/99;2002).

Responders were defined as trial participants with an absolute reduction of ≥1, ≥2, ≥3, ≥4, ≥5, ≥6 points in total motor AIMS scores from baseline to week 12. This included the established MCIC/MCID threshold of 2 points reduction (Figure 40 and 41 below).

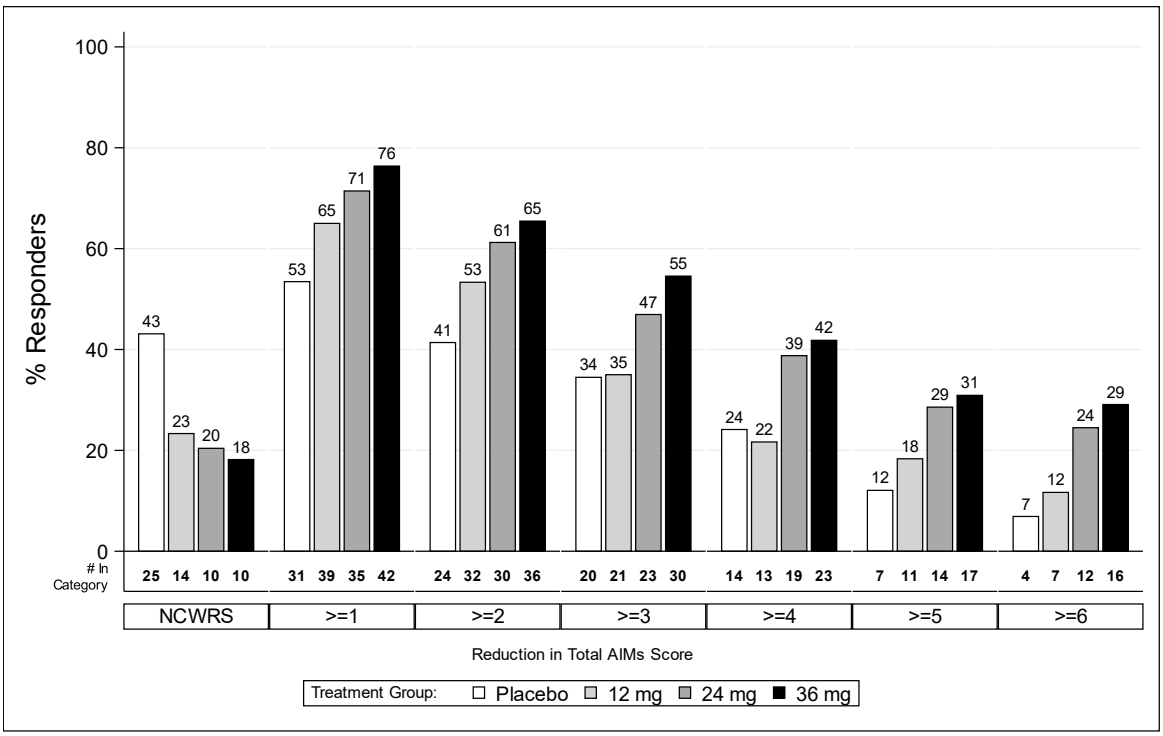
These analyses included additional cut-off values (≥5, ≥6) and the category "AIMS score unchanged or worsened (increased) (NCWRS)", thereby, in Teva's view, providing a more comprehensive evaluation of the clinical relevance of the primary endpoint results.

Figure 37: Proportion of participants reaching various cut-offs of change from baseline in total motor AIMS score (Central) at week 12 by treatment - trial C-18 (mITT population)



Source: EU MAA D180, Summary 3.2

Figure 38: Proportion of participants reaching various cut-offs of change from baseline in total motor AIMS score (Central) at week 12 by treatment - trial C-23 (mITT population)



Source: EU MAA D180, Summary 3.2

AIMS=Abnormal Involuntary Movement Scale; mITT=modified intent to treat; NCWRS=AIMS Score unchanged or worsened (increased).

Missing data are classified as non-responders.

In Teva's view, taken together, these responder analyses based on total motor AIMS score reduction demonstrated a clear separation in responder rates between DTBZ treatment and placebo independent of the exact definition of a clinically relevant effect or MCID. Importantly, the observed separation was reversed in the category of participants with no change or worsening in total motor AIMS score.

Responder Analyses Using Non-Overlapping Categories of Reduction in Total Motor AIMS Score

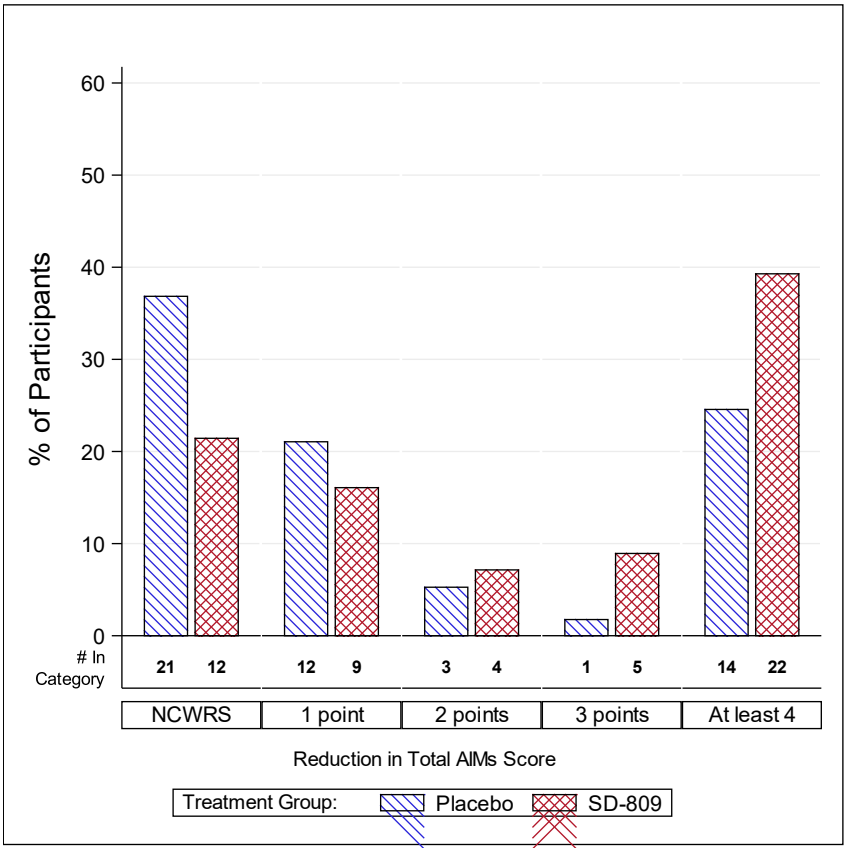
Additionally, the applicant provided a plot showing the distributions by treatment group using non-overlapping categories of reduction in total motor AIMS score:

Figure 42 shows a histogram (truncated at 0 and 4) of the distribution of total motor AIMS score reduction for each treatment group of Trial C-18. The overall distribution of total motor AIMS score reduction values for the DTBZ group is substantially (in Teva's view) shifted to the right compared to the distribution for the placebo group.

Figure 43 shows a histogram (truncated at 0 and 4) of the distribution of total motor AIMS score reduction for each treatment group of Trial C-23. The overall distribution of total motor AIMS score reduction values for the 24 mg and 36 mg DTBZ groups is substantially shifted to the right compared to the distribution for the placebo group.

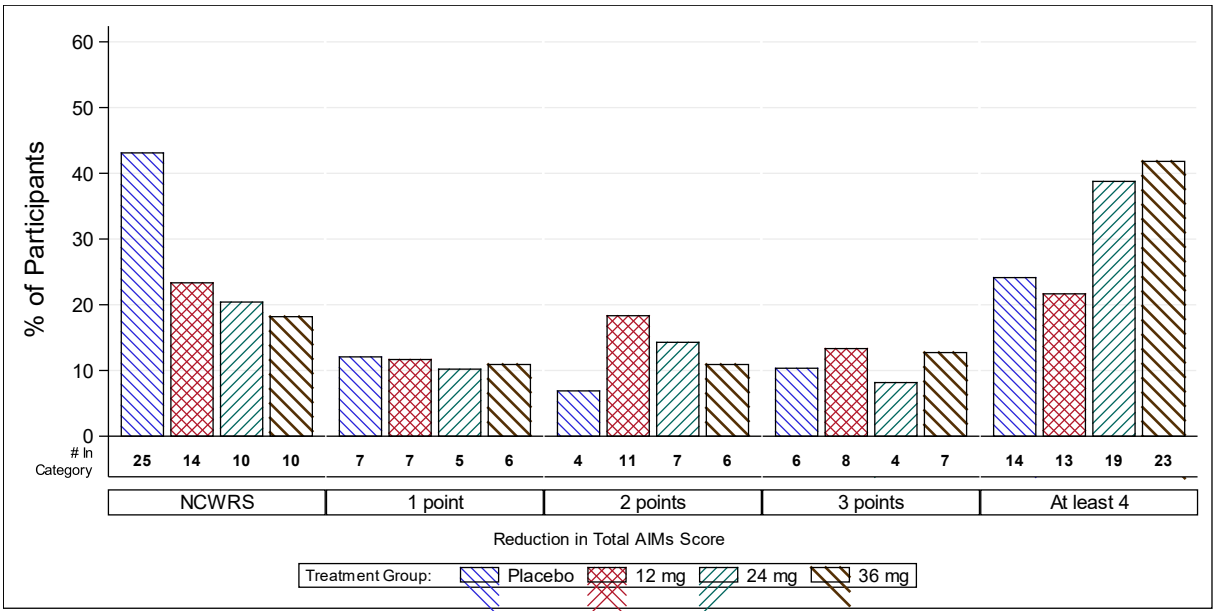
In Teva's view, in participants treated with DTBZ, shifts in the distribution of total motor AIMS score reduction are aligned with the responder analysis results above summarised, indicating clinical meaningfulness across various responder cut-offs.

Figure 39: Proportion of participants with specific categories of change from baseline in total motor AIMS score (Central) at week 12 by treatment - trial C-18 (mITT population)



Source: EU MAA D180, Summary 51.1.

Figure 40: Proportion of participants with specific categories of change from baseline in total motor AIMS score (Central) at week 12 by treatment - trial C-23 (mITT population)



Source: EU MAA D180, Summary 51.1.

AIMS=Abnormal Involuntary Movement Scale; mITT=modified intent to treat; NCWRS=AIMS Score unchanged or worsened (increased).

Missing data are not included in the analysis.

Responder Analyses Using Categories of Total Motor AIMS Score Response Anchored to PGIC

Teva presented a tabulation of total motor AIMS score reduction by treatment group anchored on categories of PGIC in the tables below. The applicant pointed out that, in general, the level of participants' reported improvement on PGIC tracks well with the level of total motor AIMS score reduction. Additionally, more participants reported improvements in TD symptoms in DTBZ treatment group compared to placebo.

The table below shows the mean change in total motor AIMS score from baseline at week 12 anchored to categories of PGIC for the DTBZ dose groups and placebo dose groups pooled across Trials C-18 and C-23. Specifically, the pooled DTBZ group included all dose groups from the C-18 flexible-dose trial and the 24 mg and 36 mg dose groups from the C-23 fixed-dose trial. Data from the C-23 12 mg dose group were excluded because efficacy was not established for this dose.

In general, the proportion of participants who reported "very much improved" or "much improved" on PGIC was greater in DTBZ compared to placebo. Additionally, the participants who reported "very much improved" or "much improved" on PGIC had a higher mean reduction (improvement) in total motor AIMS score on DTBZ compared to placebo. Conversely, the proportion of participants who reported "no change or worsening" on PGIC was greater on placebo compared to DTBZ.

Overall, in Teva's view, these findings supported that the clinician's perception of the patient's improved dyskinesias on the total motor AIMS score reflected the patient's experience of improved dyskinesias.

A similar analysis of the mean change in total motor AIMS score from baseline at week 12 anchored to categories of PGIC was performed separately for Trial C-23, pooling the DTBZ doses within the efficacious dose range, i.e., 24 mg and 36 mg, compared with placebo. In general, the proportion of participants who were "very much improved" or "much improved" on PGIC and the mean reductions in total motor

AIMS score were higher in the pooled DTBZ 24 mg and 36 mg group than in the placebo group. The proportions of participants who were "minimally improved" were similar in the DTBZ and placebo groups, although the mean reduction in total motor AIMS score was greater in the DTBZ group. A higher proportion of participants in the placebo group reported "no change or worsening", as outlined below.

Table 43: Total motor AIMS (Central) score change from baseline to week 12 versus PGIG by pooled treatment group in trials C-18 all doses and in C-23 24 mg and 36 mg doses (mITT population)

	DTBZ (N=141)		Placebo (N=97)	
	AIMS Change from BL		AIMS Change from BL	
PGIC	n (%)	Mean (SE)	n (%)	Mean (SE)
Very much improved	23 (16.3)	-5.0 (0.46)	9 (9.3)	-3.8 (1.43)
Much improved	43 (30.5)	-4.4 (0.54)	23 (23.7)	-3.2 (0.67)
Minimally improved	44 (31.2)	-2.4 (0.48)	34 (35.1)	-1.4 (0.43)
No change or worsening	31 (22.0)	-1.7 (0.58)	31 (32.0)	0.1 (0.44)

Source: SD-809-C-18 Listing 16.2.6.1.1 and 16.2.6.2. SD-809-C-23 Listing 16.2.6.01 and 16.2.6.02.
AIMS=Abnormal Involuntary Movement Scale; BL=baseline; DTBZ=deutetrabenazine; mITT=modified intent to treat; PGIC=Patient Global Impression of Change; SE=standar error.
Note: Pooled analysis includes Trials C-18 and C-23. Data from the 12 mg/day treatment group in Trial C-23 were excluded and patients from site 167 were also excluded.
The combined PGIC category for no change or worsening includes not changed, minimally worse, and much worse.

Table 44: Total motor AIMS (Central) score change from baseline to week 12 versus PGIG for DTBZ (24 and 36 mg) versus placebo (mITT population)

	DTBZ (N=97)		Placebo (N=55)	
	AIMS Change from BL		AIMS Change from BL	
PGIC	n (%)	Mean (SE)	n (%)	Mean (SE)
Very much improved	15 (15.5)	-5.2 (0.60)	5 (9.1)	-4.8 (2.03)
Much improved	29 (29.9)	-4.3 (0.62)	13 (23.6)	-2.5 (0.69)
Minimally improved	34 (35.1)	-2.5 (0.55)	19 (34.5)	-0.9 (0.60)
No change or worsening	19 (19.6)	-1.6 (0.85)	18 (32.7)	0.2 (0.65)

Source: SD-809-C-18 Listing 16.2.6.1.1 and 16.2.6.2. SD-809-C-23 Listing 16.2.6.01 and 16.2.6.02.
AIMS=Abnormal Involuntary Movement Scale; BL=baseline; DTBZ=deutetrabenazine; mITT=modified intent to treat; PGIC = Patient Global Impression of Change; SE=standard error.
Note: Data from the 12 mg/day treatment group in Trial C-23 were excluded.
The combined PGIC category for no change or worsening includes not changed, minimally worse, and much worse.

According to Teva, an additional analysis of the DTBZ 12 mg and placebo groups in Trial C-23 showed that the mean change in total motor AIMS score from baseline at week 12 was similar for both DTBZ 12 mg and placebo groups, with comparable proportions of participants reporting being "very much improved" or "much improved" on the PGIC scale. However, slightly more participants in the DTBZ 12 mg group reported being "minimally improved" compared to the placebo group.

The applicant considered the DTBZ's effective dose range to be 24 to 48 mg daily, so the 12 mg dose is just a starting dose and does not provide significant clinical benefit. When pooling data from the Trial C-23 DTBZ 12 mg, 24 mg, and 36 mg groups, the improvement rates for DTBZ were closer to placebo, indicating that the 12 mg dose reduced the overall reported improvement in TD, aligning with the Teva's view that 12 mg is below the efficacious dose range.

Table 45: Total motor AIMS (Central) score change from baseline to week 12 vs PGIC for DTBZ 12 mg and placebo mITT population – trial C-23

	DTBZ 12 mg (N=53)		Placebo (N=55)	
	AIMS Change from BL		AIMS Change from BL	
PGIC	n (%)	Mean (SE)	n (%)	Mean (SE)
Very much improved	3 (5.7)	-2.3 (1.86)	5 (9.1)	-4.8 (2.03)
Much improved	11 (20.8)	-2.4 (0.77)	13 (23.6)	-2.5 (0.69)
Minimally improved	28 (52.8)	-3.0 (0.50)	19 (34.5)	-0.9 (0.60)
No change or worsening	11 (20.8)	-0.1 (0.59)	18 (32.7)	0.2 (0.65)

Source: SD-809-C-18 Listing 16.2.6.1.1 and 16.2.6.2. SD-809-C-23 Listing 16.2.6.01 and 16.2.6.02.
AIMS=Abnormal Involuntary Movement Scale; BL=baseline; DTBZ=deutetrabenazine; mITT=modified intent to treat; PGIC = Patient Global Impression of Change; SE=stand error.
The combined PGIC category for no change or worsening includes not changed, minimally worse, and much worse.

Table 46: Total motor AIMS (Central) score change from baseline to week 12 vs PGIC for DTBZ by pooled treatment group mITT population – trial C-23

	DTBZ (N=150)		Placebo (N=55)	
	AIMS Change from BL		AIMS Change from BL	
PGIC	n (%)	Mean (SE)	n (%)	Mean (SE)
Very much improved	18 (12.0)	-4.7 (0.61)	5 (9.1)	-4.8 (2.03)
Much improved	40 (26.7)	-3.8 (0.51)	13 (23.6)	-2.5 (0.69)
Minimally improved	62 (41.3)	-2.8 (0.38)	19 (34.5)	-0.9 (0.60)
No change or worsening	30 (20.0)	-1.1 (0.59)	18 (32.7)	0.2 (0.65)

Source: SD-809-C-18 Listing 16.2.6.1.1 and 16.2.6.2. SD-809-C-23 Listing 16.2.6.01 and 16.2.6.02.
AIMS=Abnormal Involuntary Movement Scale; BL=baseline; DTBZ=deutetrabenazine; mITT=modified intent to treat; PGIC = Patient Global Impression of Change; SE=standard error.
Note: Pooled analysis for C-23 includes data from DTBZ 12, 24, and 36 mg doses
The combined PGIC category for no change or worsening includes not changed, minimally worse, and much worse.

The CHMP agreed that the additional analysis of the DTBZ 12 mg and placebo groups in Trial C-23 showed that the mean change in the total motor AIMS score from baseline at week 12 was similar for both the DTBZ 12 mg and placebo groups, with comparable proportions of participants reporting being "very much improved" or "much improved" on the PGIC scale. However, slightly more participants in the DTBZ 12 mg group reported being "minimally improved" compared to the placebo group. The applicant considered the DTBZ's effective dose range to be 24 to 48 mg daily, so the 12 mg dose was admitted as just a starting dose and mostly not provided significant clinical benefit. CHMP also noted that, when pooling data from trial C-23 DTBZ 12 mg, 24 mg, and 36 mg groups, the improvement rates for DTBZ were closer to placebo, indicating indeed that the 12 mg dose reduced the overall reported improvement in TD, aligning with the applicant's view that the 12 mg is below the efficacious dose range.

The applicant also analysed DTBZ data based on the Minimal Clinically Important Difference (MCID) method by Stacy 2019, using a Patient Global Impression of Change (PGIC) score ≤3 (named treatment improvement) and a PGIC score ≤2 (named treatment success) as anchors and the change in total motor Abnormal Involuntary Movement Scale (AIMS) score from baseline to week 12 in the pooled Trials C-18 and C-23 data: as detailed in the table below, 75% of participants on DTBZ had “treatment improvement” and 38% had “treatment success” based on PGIC.

Table 47: MCID of mean total motor AIMS score at week 12 based on PGIC as anchor (Stacy Method)

PGIC response	Treatment Improvement[a]		Treatment Success[b]	
	Yes	**No**	**Yes**	**No**
n (%)	220 (75)	75 (25)	112 (38)	183 (62)
LS mean (SE)	-3.1 (0.22)	-0.3 (0.37)	-4.0 (0.30)	-1.4 (0.25)
MCID	-2.8		-2.6	

Source: Barkay 2020; Response to Question 88a of the D120 LoQ, Table 4

[a.]Treatment improvement was defined as "very much improved," "much improved," or "minimally improved" on the PGIC.

[b.]Treatment success was defined as "very much improved" or "much improved" on the PGIC

AIMS=Abnormal Involuntary Movement Scale; LS=least squares; MCID=minimal clinically important difference; n=number of participants in subgroup; PGIC=Patient Global Impression of Change; SE=standard error.

Note: These data are a pooled analyses from Trials C-18 and C-23.

Taken together, these responder analyses using categories of total motor AIMS score response anchored to PGIC supported that:

- The level of participant reported improvement on PGIC tracks well with the level of total motor AIMS score reduction.
- The proportion of participants who reported "very much improved" or "much improved" on PGIC was greater on DTBZ than on placebo
- Participants on either DTBZ or placebo who reported "very much improved" or "much improved" had a higher mean reduction (improvement) in total motor AIMS score from baseline, compared to those who reported "minimally improved".
- The improvement in total motor AIMS score in participants who reported "very much improved" or "much improved" was greater in those taking DTBZ than placebo.
- Using a PGIC score ≤3 (treatment improvement) and a PGIC score ≤2 (treatment success), 75% of participants on DTBZ had "treatment improvement and 38% had "treatment success"

Overall, it is agreed that these findings support that the clinician's perception of the patient's improved dyskinesias on the total motor AIMS score reflected the patient's experience of improved dyskinesias.

Support of DTBZ efficacy from secondary endpoints

Teva pointed out that the secondary efficacy endpoints of Clinician Global Impression of Change (CGIC) and PGIC from Trials C-18 and C-23 were analysed using a hierarchical (fixed-sequence) testing approach. For both scales, treatment success was defined as a rating of "much improved" or "very much improved" at week 12. The CGIC and PGIC did not meet criteria for statistical significance at $p < 0.05$ level, however, across both trials and in both the CGIC and PGIC, a greater proportion of participants on DTBZ had a treatment success, compared to those taking placebo. In the *applicant*'s view, these secondary endpoint results, in conjunction with the responder analyses presented above, further support that the statistically significant effect on the primary endpoint of the total motor AIMS score for both trials is clinically meaningful to both clinicians and participants.

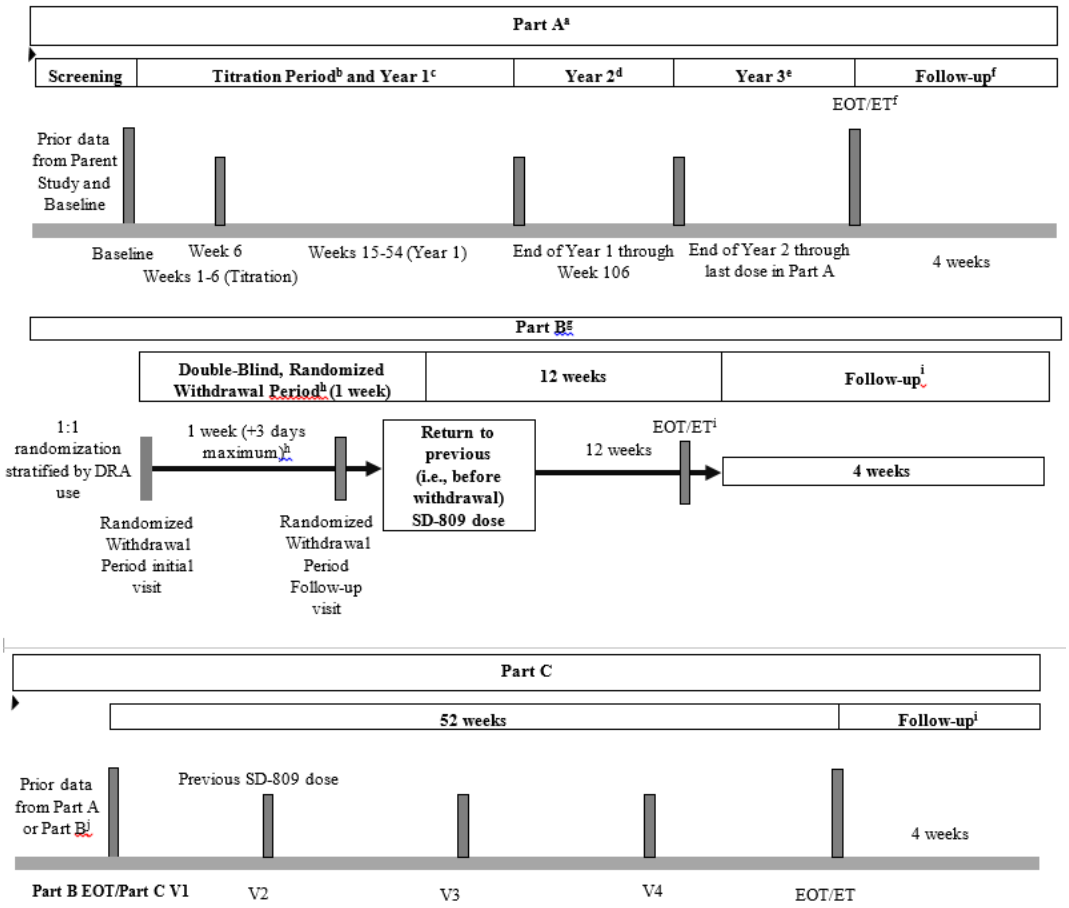
2.6.5.6. Other Supportive study(ies)

2.6.5.6.1. Trial C-20 (open label, flexible dose): An Open-label, Long-term Safety Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia

The study was conducted at 76 centers in US and Europe (Poland, Czech Republic, Hungary, Slovakia, and Germany). One center (in US) was excluded from the analyses due to fraudulent clinical study activities and data collection.

The study period was 15 October 2014 to 06 December 2019.

Figure 41: Overall study schematic (Parts A, B, and C)



Abbreviation: DRA=dopamine receptor antagonist; EOT=end of treatment; ET=early termination; SD-809=TEV-50717; V=visit.

a Patient participation in Part A ended at Week 158, at start of Part B, or ET. Patients were on a stable dose of TEV-50717 and any concomitant dopamine receptor antagonist for a minimum of 4 weeks before starting the Double-Blind, Randomized Withdrawal Period (Part B).

b Weeks 1 through 6 (telephone contact at Weeks 1, 3, and 5; clinic visit at Weeks 2, 4, and 6).

c Weeks 15 through 54 (clinic visits occurred once every 13 weeks beginning at Week 15).

d Weeks 67 through 106 (clinic visits occurred once every 13 weeks beginning at Week 67).

e Weeks 119 through 158 (clinic visits occurred once every 13 weeks beginning at Week 119).

f Patients who did not participate in Part B continued in Part A until EOT at Week 158 or until ET, completed a follow-up visit at Week 159 or 1 week after ET, and a follow-up call at Week 162 or 4 weeks after ET.

g Patients were on a stable dose of TEV-50717 and any concomitant DRA for a minimum of 4 weeks before starting the Randomized Withdrawal Period. The first visit of the Randomized Withdrawal Period of Part B (Pre-withdrawal Visit) was the patient's next scheduled visit, or a visit as determined by the Investigator. The Post-withdrawal Visit occurred approximately 1 week after the scheduled visit. After the Post-withdrawal Visit, patients returned to the previous (i.e., before withdrawal) dose of TEV-50717 and completed 12 more weeks of treatment before EOT.

h Patients who did not complete the 1 week (+3 days maximum) post-withdrawal visit will complete the ET visit.

i Follow-up after EOT is a follow-up telephone contact 4 weeks after EOT. Follow-up after ET consists of a clinic visit 1 week after ET and a telephone contact 4 weeks after ET.

j Patients who completed Part B EOT could be enrolled in Part C. Part B EOT coincided with Part C Visit 1.

Note: An unscheduled visit will require a clinic visit or telephone call.

Placebo: Placebo was used during the 1-week randomized withdrawal period of study Part B. Part A of the study was open-label TEV-50717.

Number of Patients (planned and analysed)

Of the 368 patients who had completed a parent study (Study **SD- 809-C-18** or Study **SD-809-C-23**), 343 patients rolled over into this study, of which 337 were analysed for efficacy and safety at the time of the data cut-off (06 December 2019). Six patients were not included in the analysis.

Key inclusion criteria:

- Patient was at least 18 years of age at screening.
- Patient had successfully completed Study SD-809-C-18 or Study SD-809-C-23, or any other controlled study of SD-809 for treatment of moderate to severe TD.
- Patient had a history of using a dopamine receptor antagonist for at least 3 months (or 1 month in patients 60 years of age and older).
- Patient had a clinical diagnosis of TD and had symptoms for at least 3 months prior to screening.
- For patients with underlying psychiatric illness:
    - Patient was psychiatrically stable and has had no change in psychoactive medications (including, but not limited to, neuroleptics, benzodiazepines, anticonvulsants, and mood stabilizers) for ≥30 days before screening (45 days for antidepressants).
    - Patients on long-acting (depot) medications were on stable therapy (dose, frequency) for at least 3 months before screening.
    - Patient had a healthcare provider (caregiver) who was aware of the patient's participation in the trial and did not anticipate any changes in the patient's treatment regimen (drug, dose, or frequency) in the next 3 months.

Main Criteria for Exclusion

Patients were excluded from participating in this study if one or more of the following main criteria were met (full criteria provided in the clinical study report):

- Patient had received tetrabenazine within 7 days of baseline;
- Patient had received any of the following medications within 30 days of baseline:
    - reserpine, α-methyl-p-tyrosine, botulinum toxin (within 3 months of baseline), and medications with strong anticholinergic activity (trihexyphenidyl, benztropine, orphenadrine, procyclidine, and biperiden)
    - metoclopramide, promethazine, and prochlorperazine
    - stimulants (i.e., methylphenidate, amphetamine/dextroamphetamine, and lisdexamphetamine) or monoamine oxidase inhibitors
    - levodopa or dopamine agonists
- Patient had a neurological condition other than TD that could interfere with assessing the severity of dyskinesias.
- Patient had a serious untreated or undertreated psychiatric illness at baseline.

- Patient had active suicidal ideation at baseline.
- Patient had a history of any of the following within 6 months of baseline:
    - previous intent to act on suicidal ideation with a specific plan, irrespective of the level of ambivalence at the time of suicidal thought
    - previous preparatory acts to commit suicide or suicidal behaviour
    - a previous actual, interrupted, or aborted suicide attempt
- Patient had a score ≥11 on the depression subscale of the Hospital Anxiety and Depression Scale (HADS) - Depression Subscale (HADS-D) at baseline.
- Patient was developmentally disabled or had evidence of dementia.
- Patient had a serious or unstable medical illness at baseline.
- Patient had a history (within 3 months) or presence of violent behaviour within 3 months from baseline.

Investigational Product

TEV-50717 oral tablets at strengths of 6, 9, 12, 15, and 18 mg were used. The starting dose of 12 mg/day was titrated by 6 mg not more than once per week until there was adequate control of dyskinesia, the patient experienced a protocol-defined clinically significant adverse event, or the maximal allowable dose was reached. The maximum daily dose was determined by body weight at baseline and CYP2D6 impairment status (based on CYP2D6 poor metabolizer phenotype and/or those using a strong CYP2D6 inhibitor at baseline). TEV-50717 was administered daily in 2 divided doses. The stable dose reached at the end of the 6-week titration period was used for the rest of the study. If the patient experienced an adverse event during maintenance, the investigator could reduce or suspend the dose of TEV-50717.

Placebo

Placebo was used during the 1-week randomized withdrawal period of study Part B. Part A of the study was open-label TEV-50717. During the double-blind period in Part B, patients were randomly assigned to receive treatment with TEV-50717 or a matching placebo in a 1:1 ratio stratified by concomitant dopamine receptor antagonist (DRA) usage. Patients were randomly assigned to treatment through an interactive response technology (IRT) system. Parts A and B following the randomized withdrawal were open label; however, prior treatment assignment from the parent study remained blinded.

The duration of the open-label treatment in Part A was up to 158 weeks.

After implementation of Protocol Amendment 06, patients could enter Part B if they were on a stable dose of TEV-50717 and any concomitant DRA for a minimum of 4 weeks before starting the 1-week randomized withdrawal period, followed by 12 weeks of open-label treatment. After Protocol Amendment 07, an additional 52 weeks of open-label treatment were available for patients in Europe. Parts A, B and C had a follow-up telephone contact 4 weeks after the end of treatment. A patient typically had 1 follow-up visit during the entire study.

Treatment duration in Part A plus Part B was up to 171 weeks (158 weeks [Part A] + 1 week randomized withdrawal [Part B] + 12 weeks [Part B]. Treatment duration in Part A plus Part B plus Part C was up to 223 weeks (171 weeks + 52 week [Part C]).

General Design and Methodology

All patients discontinued study drug (TEV-50717 or placebo) for 1 week at the completion of the parent study. There was no randomization in Part A of this study, and all enrolled patients were assigned to the

same treatment group at a starting dose of TEV-50717 12 mg/day (6 mg twice daily). Doses were titrated over the initial 6 weeks of therapy to identify a dose that provided adequate dyskinesia control and was well tolerated. The dose of TEV-50717 was adjusted (upward or downward) by 6 mg not more than once per week until there was adequate control of dyskinesia, the patient experienced a protocol-defined clinically significant adverse event, or the maximal allowable dose was reached. The maximal allowable dose was based on patient weight and CPY2D6 status. Patients could continue at the "maintenance dose" for up to158 weeks, 1 week follow-up visit, and a follow-up telephone contact after an additional 4 weeks (5 weeks after the end of treatment).

Protocol Amendment 06 permitted patients to enrol in Part B when they were on a stable dose of TEV-50717 and concomitant DRAs for at least 4 weeks.

During the 1-week randomized withdrawal period, patients were randomized to continued treatment at their maintenance dose of TEV-50717 or to treatment with placebo and were assessed for efficacy and safety at the pre-withdrawal visit, a post-withdrawal visit, 1-week later, and an end of treatment (EOT) visit at 12 weeks after the post-withdrawal visit.

Protocol Amendment 07 permitted patients in the EU to enrol in Part C, at the Part B EOT visit.

In Part A, efficacy was assessed with the total motor Abnormal Involuntary Movement Scale (AIMS), the Clinical Global Impression of Change (CGIC), the Patient Global Impression of Change (PGIC), and the modified Craniocervical Dystonia Questionnaire (mCDQ-24). In Part B, efficacy was assessed with the total motor AIMS.

Only safety was assessed in Part C.

Safety evaluations in Parts A and B included monitoring of adverse events, clinical laboratory tests (serum chemistry, haematology, urinalysis), physical examinations (including weight), complete neurological examinations, vital signs measurements (resting heart rate, resting blood pressure, orthostatic heart rate and blood pressure, respiratory rate, and temperature), electrocardiogram (ECG) findings, concomitant therapy or medication and rating scales. These scales included the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor), the Barnes Akathisia Rating Scale (BARS), the HADS-D, the Columbia-Suicide Severity Rating Scale (C-SSRS), the Epworth Sleepiness Scale (ESS), and the Montreal Cognitive Assessment (MoCA©). Safety measures in Part C included the same measures but excluded all scales other than the C-SSRS.

Statistical Considerations

Analysis Populations

Part A

- Intent-to-Treat (ITT) Population: All enrolled patients, regardless of whether or not the patient received a dose of TEV-50717. All efficacy analyses were performed on the ITT Population.
- Safety Population: All patients who received any TEV-50717. Patients who were enrolled but discontinued the study prior to dosing were not included in this population. All analyses of safety were performed on the Safety Population.

Part B

- Randomized withdrawal ITT population: All patients enrolled in Part B of the study
- Randomized withdrawal modified ITT (mITT) Population: All patients enrolled in Part B who received study drug during the randomized withdrawal period and had a total motor AIMS score as assessed by blinded central video rating at both the pre-withdrawal visit and the post-withdrawal visit

Summary of Results

Although 343 patients were enrolled in Part A, data are provided for 337 patients because 6 patients from 1 site were excluded due to fraudulent behaviours at that site. This site was excluded from all tables, listings and graphs, as triggered by a federal investigation that resulted in indictment of the investigator for fraudulent clinical study activities and data collection.

Patient Disposition and Demography

Disposition: Of the 368 patients with TD who had successfully completed a qualifying parent study, 337 at 75 centres met entry criteria and were enrolled into this study: 227 patients who received TEV-50717 parent study treatment and 110 patients who received placebo in the parent study. All 337 patients were evaluated for safety and efficacy.

In Part A, a total of 163 (48%) patients withdrew from the study during the 3-year treatment period. The most frequent reasons for withdrawal were "withdrawal by patient" (79 [23%] patients), followed by "adverse event" (33 [10%] patients) and "lost to follow-up" (24 [7%] patients). Nine (3%) patients discontinued the study due to lack of efficacy.

The duration of Part A was up to 158 weeks of treatment. Of the 337 patients who enrolled in Part A, 249 had at least 1 visit at ≥week 54, 194 had at least 1 visit at ≥week 106, and 160 had at least 1 visit by week 145. Discontinuations due to AEs were similar during each of the 3 years of the study (4%, 5%, and 5% prior to week 54, week 54 to before week 106, and week 106 to before week 145, respectively).

A total of 142 patients (42% of Part A patients) enrolled into Part B. A majority (81%) of patients enrolled into Part B at week 145 of the open-label treatment. Of the 142 patients who entered Part B, 134 (94%) completed it (66 [93%] patients in the placebo group and 68 [96%] patients in the TEV-50717 group). Eight (6%) patients discontinued from the study (5 [7%] patients receiving placebo and 3 [4%] receiving TEV-50717). The reasons for withdrawal were "lost to follow-up" and "withdrawal by patient" (4 [1%] patients each).

Demographics and Baseline Characteristics

All demographic and baseline characteristics values were collected at baseline of the parent studies. Among the 337 patients in the ITT population, the mean age was 56.9 years, 56% were females, 20% were black, 78% were white, mean weight was 82.6 kg, and mean BMI was 29.23 kg/m2. The mean time since TD diagnosis was 5.72 years, and the mean total motor AIMS score was 8.8. The proportion of patients with comorbid schizoaffective disorder, bipolar disorder, depression, and schizophrenia was 11%, 17%, 18%, and 50%, respectively. Seventy-five percent of patients were using DRAs, and 18% of patients had impaired CYP2D6 function.

In Part B the placebo group and the TEV-50717 group were well matched with regard to age (mean 59.7 and 62.4 years, respectively), sex (37% and 32% men, respectively), race (82% white in both treatment groups), weight (mean 80.5 and 81.7 kg, respectively), and BMI (28.62 and 30.09 kg/m2, respectively). The baseline characteristics of the placebo and TEV-50717 groups were generally similar to each other in the randomized withdrawal ITT population. Mean time since TD diagnosis for the placebo and TEV-50717 groups was 9.25 and 9.24 years, respectively. Mean total AIMS scores (centrally read) at entry into Part B for patients in the placebo group and the TEV-50717 group were 5.6 and 5.0, respectively.

Exposure

Two hundred fifty-three (75%) patients received treatment with TEV-50717 for ≥54 weeks, 203 (60%) patients received treatment for ≥106 weeks, 170 (50%) patients received treatment for ≥145 weeks, and 156 (46%) patients received treatment for ≥158 weeks. The mean duration of exposure was 783.6 days, and the median duration of exposure was 1015.0 days. The mean total daily dose was 35.7 mg at the

end of titration (week 6) and 38.3 mg at week 15 and remained stable throughout the rest of Part A: 38.7 mg at week 54, 39.3 mg at week 106, and 39.4 mg at week 145.

In Part B the mean (SE) total daily dose of TEV-50717 at the pre-withdrawal visit was 40.1 (1.18) mg in the placebo group and 39.6 (1.27) mg in the TEV-50717 group.

Efficacy Results

Part A

Prior treatment in the parent studies (TEV-50717 or placebo) did not have an impact on the efficacy results. Therefore, all efficacy results are presented for the total ITT Population. Because the number of patients who had week 158 assessments is small, week 145 data were considered representative of the 3-year efficacy data (total motor AIMS, CGIC, and PGIC scores). Because mCDQ-24 was not assessed at week 145, week 106 data have been presented. Baseline data were from the current study.

AIMS

There was an improvement in the total motor AIMS score (site rating) of patients during the overall treatment period. Decreases in the total score from baseline were indicative of an improvement from more severe to less severe dyskinesia. There was a mean (SE) decrease in the total motor AIMS score of -3.6 (0.21) from baseline to week 6 as the dose of TEV-50717 was titrated to an average of 35.7 mg/day. There was a gradual improvement thereafter, from week 6 to week 15, where the mean (SE) change from baseline in total motor AIMS score was -3.9 (0.24), and the mean daily dose was 38.3 mg. At week 54 the mean (SE) change from baseline in the total motor AIMS score was -4.8 (0.28), and the mean daily dose was 38.7 mg. At week 145, the mean (SE) change from baseline in the total motor AIMS score was -6.6 (0.37), and the mean daily dose was 39.4 mg.

The proportion of patients who had a ≥50% reduction from baseline in the total motor AIMS score increased from 31% at week 6 to 38% at week 15 and to 49% at week 54. The proportion continued to increase, reaching 54% and 67% at week 106 and week 145, respectively. The proportion of patients who had a ≥70% reduction from baseline in the total motor AIMS score increased from 13% at week 6 to 18% at week 15 and to 24% at week 54. The proportion continued to increase, reaching 29% and 42% at week 106 and week 145, respectively.

AIMS items 8, 9, and 10 are clinician-rated global judgments of the overall severity of abnormal movements, the incapacitation due to abnormal movements, and the patient's awareness of abnormal movements, respectively. Patients taking TEV-50717 experienced a mean reduction (improvement) from baseline in items 8 (-0.07 to -1.3), 9 (-0.6 to -1.3), and 10 (-0.5 to -1.3) of the AIMS score compared to baseline and a continued reduction in these parameters through week 145.

CGIC

A 7-point Likert scale was used to assess the overall response to therapy. The proportion of patients in Part A who were considered by the investigator to be a treatment success (defined as "much improved" or "very much improved") based on the CGIC increased over the treatment period from 57% at week 6 to 60% at week 15, 66% at week 54, 65% at week 106, and 73% at week 145. At week 6, over three-quarters of patients (88%) demonstrated improvement ("minimally improved," "much improved," or "very much improved"), and this was sustained or increased during the study (87% at week 15, 93% at week 54, 94% at week 106, and 94% at week 145). In most weeks, the highest proportions of patients were in the "much improved" category, ranging from 37% to 46% during treatment to week 145.

PGIC

A 7-point Likert scale was used to assess the overall response to therapy. The proportion of patients in Part A who were considered a treatment success according to self-ratings (defined as "much improved"

or "very much improved") based on the PGIC increased over the treatment period from 54% at weeks 6 and 15 to 61% at week 54, 64% at week 106, and 63% at week 145. At week 6, a majority (87%) of patients in Part A demonstrated improvement ("minimally improved," "much improved," or "very much improved"), and this was sustained through week 145.

Quality of Life: mCDQ-24

Measurement of quality of life (mCDQ-24 scale) was used to evaluate stigma, emotional well-being, pain, activities of daily living, and social/family life. Decreases (improvement) in the mean mCDQ-24 total score from baseline were observed at week 6 (first on-treatment assessment) (-3.2) and at week 15 (-5.0) of TEV-50717 treatment. After week 15, most decreases in mCDQ-24 total score were around 5.0 units. The greatest mean (SE) improvements from baseline to week 106 were seen in the subscales of stigma (-8.5 [1.56]), pain (-7.0 [1.64]), and ADL (-5.8 [1.29]).

Part B: AIMS

There was no statistically significant difference in the central reading of the total motor AIMS score between patients who continued treatment with TEV-50717 and patients who were randomized to placebo during the 1-week randomized withdrawal period. The mean change in total motor AIMS score from pre-withdrawal to post-withdrawal based on central rating was not statistically significant: LS mean difference (95% CI) of -0.6 (-1.42, 0.17) and a p-value of 0.121.

Post-hoc analysis of the total motor AIMS score, as assessed by the investigator (site rating), suggested a difference between the 2 treatment groups in the randomized withdrawal period.

The mean change in the total motor AIMS score from pre-withdrawal to post-withdrawal based on site rating suggested a difference: LS mean difference (95% CI) of -1.5 (-2.66, 0.25) and a nominal p-value of 0.018.

2.6.5.6.2. Trial SD-809-C-15: Flexible-Dose Trial in Chorea Associated with Huntington Disease

Trial C-15 was a Phase 3, randomised, double-blind, placebo-controlled, parallel-group trial designed to evaluate the efficacy of DTBZ matrix-based formulation BID to reduce HD-associated chorea and evaluate the safety and tolerability of titration and maintenance therapy in HD patients. The treatment period consisted of an 8-week titration phase and a 4-week maintenance phase. The DTBZ dose was adjusted weekly in increments of 6 mg/day, in a flexible manner based on chorea control and tolerability.

A total of 90 participants were randomised 1:1 and were treated with DTBZ (N=45) or placebo (N=45). On the primary efficacy endpoint, the trial demonstrated a 2.49-point mean reduction from baseline to maintenance therapy (defined for each participant as the mean of values from the week 9 and week 12 visits) in the Unified Huntington Disease Rating Scale (UHDRS) Total Maximal Chorea (TMC) score for participants treated with DTBZ compared with participants treated with placebo ($p<0.0001$). Trial C-15 showed that participants with HD-associated chorea could be titrated to clinical efficacy based on response over the dose range of 24 to 48 mg/day.

2.6.5.6.3. Trial SD-809-C-16: Open-Label Extension Trial in Chorea Associated with Huntington Disease

The Switch Cohort of the open-label Trial C-16 assessed treatment with DTBZ matrix-based formulation BID in participants with HD-associated chorea. This cohort included participants who transitioned from a stable dose of TBZ to DTBZ administered twice daily and provided data regarding the DTBZ doses

needed to produce a clinical response comparable to the TBZ response in participants switching from TBZ to DTBZ.

In Teva's views, the results of Trial C-16 provided clinical validation of DTBZ at a low dose and less frequent dosing than TBZ, showing that a lower C_{max} is still efficacious, and demonstrated that the shape of the PK curve does not affect efficacy as long as the extent of overall daily exposure (AUC) is maintained.

Trial SD-809-C-16 was an open-label, single-arm, 2-cohort trial designed to evaluate the long-term safety and tolerability of DTBZ matrix-based formulation BID dose adjustments/titrations for the treatment of HD-associated chorea over long term treatment.

The following 2 groups of participants were enrolled in this trial:

Rollover Cohort**:** participants had successfully completed the parent Trial C-15, including a 1-week washout period, and then initiated long-term DTBZ treatment.

Switch Cohort**:** participants were receiving an approved dosing regimen of TBZ for the treatment of chorea associated with HD-associated chorea and were switched overnight to DTBZ based on an algorithm designed to achieve comparable daily exposure to total deuterated (α+β)-HTBZ metabolites compared to the non-deuterated (α+β)-HTBZ metabolites. These participants similarly initiated a long-term DTBZ treatment regimen after the initial switch from TBZ therapy.

Participant Disposition and Exposure

A total of 119 participants received DTBZ (Rollover Cohort: 82 participants; Switch Cohort: 37 participants). A total of 36 participants discontinued DTBZ (Rollover Cohort: 26 participants; Switch Cohort: 12 participants), of which 11 in the Rollover Cohort and 1 participant in the Switch Cohort discontinued due to adverse events, and 1 in the Rollover Cohort discontinued due to death.

The mean total duration of trial drug exposure was similar across the 2 cohorts (810 and 869 days for the Rollover and Switch Cohorts, respectively). A total of 81 participants in the Rollover Cohort achieved a stable dose by a mean of 40.6 days and 35 participants in the Switch Cohort achieved a stable dose by a mean of 31.1 days.

Key Results

Rollover Cohort:

Decreases from baseline in the mean UHDRS TMC score were observed as early as week 2 of DTBZ titration and persisted through week 145 of therapy.

Decreases in Total Motor Score (TMS) from baseline were observed as early as week 2 of DTBZ titration and persisted through week 80 of therapy before reverting to baseline or worsening beyond baseline.

Switch Cohort:

The overnight switch from a stable dosing regimen of TBZ to the DTBZ regimen predicted to provide comparable AUC for total deuterated (α+β)-HTBZ metabolites resulted in maintenance of chorea control, as assessed by the UHDRS TMC score, through week 1.

At week 8, a mean decrease from baseline in TMC score was observed (−2.06 points), indicating potential improvement in chorea control following DTBZ dose adjustment. Chorea control was maintained through week 158.

The TMS was maintained at week 1, following the overnight switch from TBZ to DTBZ on day 1. The TMS remained around the baseline score through week 67.

Since many TD patients developed the disorder while being treated for HD and similar underlying diseases, the applicant was asked to discuss whether these specific conditions where DTBZ has been studied besides TD unfavourably affected the response to DTBZ. Teva provided data on HD, Tourette syndrome (TS) and dyskinesia in cerebral palsy (DCP). The applicant claimed that patients with TD were mostly excluded from HD, TS and DCP studies; therefore, data from these studies are not relevant. Still, some patients had narratives that allowed to admit TD but did not discuss to what extent the (lack) of efficacy results and the occurrence of AEs might impact TD. It was considered that not sufficient evidence was presented to support the use in patients with TD and concomitant co-morbidities of HD, TS and DCP. It is agreed that in HD and TS the effect of DTBZ may not pose efficacy or safety issues. Regarding cerebral palsy, there is not sufficient data to support its use in the paediatric DCP patients. In adults, it is agreed that, when patients with DCP reach adulthood, the risk of TD superimposing over the abnormal movements due to CP is very high. In conclusion, it was considered that no precautionary statement regarding any of these 3 potential co-morbidities is deemed necessary in the PI.

2.6.6. Discussion on clinical efficacy

To support DTBZ initial MAA the applicant provided data on two (12-weeks, randomised, double-blind, placebo-controlled) pivotal studies in adults with tardive dyskinesia (TD): C-18 (flexible dose) and C-23 (fixed dose). In addition, the results of one open label, flexible dose, long-term extension safety study in TD (C-20), and other supportive studies in Huntington's (HD) disease were submitted.

Patients enrolled in trials C-18 and C23 presented with symptoms that were bothersome or caused functional impairment (n=335). These two studies included patients who had moderate or severe abnormal movements based on Item 8 of the Abnormal Involuntary Movement Scale (AIMS) and a total motor AIMS score of ≥6 (based on Items 1 through 7)".

Background comorbid illnesses included schizophrenia/schizoaffective disorder (n=207, 62%), mood disorder (n=112, 33%), other (neurological, psychiatric and gastrointestinal conditions; n=15, 4%), and missing (n=1, <1%). With respect to concurrent dopamine receptor antagonists (DRA) use, 75.5% of the patients were on a stable DRA dose, while 24.5% were not receiving a DRA at baseline.

The primary efficacy endpoint in the trials was the total motor AIMS score (the sum of items 1 to 7 with a score range from 0 to 28).

The study population was representative of the population with the most treatment unmet need, i.e. the moderate to severe TD, especially patients still requiring psychiatric treatment, particularly with DRAs. The population of trials C-18 and C-20 was similar. Patients aged 18 to 75 years with a clinical diagnosis of TD for at least 3 months prior to screening and a history of DRAs use for at least 3 months (except in older patients for whom this duration was at least 1 month) were enrolled. The history of DRAs use prior to enrolment was consistent with the recommendations of the American Association of Psychiatry's criteria (2022). Patients with underlying psychiatric illness had to be psychiatrically stable and had no change in psychoactive medications for at least 30 days (45 days for antidepressants). Other exclusions included history of active suicidal ideation or behaviour, within 6 months of screening and score ≥11 on the depression subscale of the Hospital Anxiety and Depression Scale (HADS). As outlined in SmPC section 5.1 patients in the trials *were psychiatrically stable and had no change in psychoactive medications for at least 30 days (45 days for antidepressants)*, for HCPs to be aware that generalizability of the results to a more severely psychiatrically ill population with TD is currently not clear.

In addition, Teva provided data on DTBZ post-marketing use and discussed the results of DTBZ clinical development in Huntington disease (HD), Tourette syndrome and dyskinesia in cerebral palsy (DCP).

Study participants had moderate to severe TD. Severity was defined based on the total motor AIMS score. This score is the sum of 7 items measuring the severity of abnormal movements in distinct body areas (4 items in the orofacial region, 2 items for each upper and lower extremities and 1 item in the trunk), each rated from 0 (no severity) to 4 (severe). The total motor AIMS score had to be ≥6 at baseline. The Tardive Dyskinesia Assessment Working Group (Kane 2018) pointed out the limitation of the total motor AIMS score alone in drawing conclusions about overall TD severity. For example, a total score of 10 could only be the sum of 5 individual scores of mild severity (each equal to 2). It is noted, nevertheless, that a judgement of the overall severity had to be made based on AIMS item 8 which equals the highest score of individual items 1 to 7 (Munetz 1988). It is therefore assumed that at least one of the individual items corresponded to moderate to severe movements. It is also noted that symptoms had to be bothersome to the patient and/or cause functional impairment. However, the method used to assess this criterion was not stated, though it is assumed that item 9 of the AIMS, which evaluates incapacitation due to abnormal movements, may have been used.

The applicant requested only national scientific advice from the National Competent Authorities (NCAs) of Germany (DE), Sweden (SE) and The Netherlands (NL) for the potential HD indication and development program, between 2016 and 2017.

There are no dedicated regulatory guidelines on how to develop agents for TD. Notwithstanding, EMA guidance on clinical investigation of medicinal products in the treatment of Parkinson's disease (EMA/CHMP/330418/2012 rev. 2) discuss the treatment of motor fluctuations and might have been considered. A product specific Paediatric Investigation Plan (PIP) waiver was granted for DTBZ (EMEA-002052-PIP02-23) for the treatment of TD (EMA decision P/0205/2023 dated 14 June 2023).

The phase 3 development program showed an improvement of TD with DTBZ with AIMS measured mean treatment effect measured as compared to placebo of -1.4 in study C-18 and of -1.8 to -1.9 in the proposed dose range. However, several concerns were identified in the course of the procedure:

1) The double-blind pivotal studies were short term studies. Although the immediate symptomatic effect of DTBZ can be observed in a short period, the maintenance of effect on sustained treatment is of paramount importance in a chronic situation where most patients (about 2/3 in the enrolled pivotal population) need to continue psychiatric treatment with agents which may foster TD and negatively sum adverse event's risk, such as parkinsonism and other movement disorders or dysautonomia. From what is already known with TBZ, the sustained benefit of the treatment depends on the judicious adjustments of both TBZ and the remaining psychiatric treatment. Even if not on DRA / antidepressant medication when TBZ is started for the treatment of TD, patients frequently develop depressed mood and require initiation of antidepressants. This frequently require 6-12 months of treatment's adjustments until reaching a stable dose for symptoms control.

2) The magnitude of DTBZ treatment (after subtraction of the placebo effect) was noted as marginal and did not reach the identified minimally clinically important difference of 2 points (Stacy et al. 2019) with the primary efficacy tool, the AIMS. The use of other relevant tools to anchor the possible benefit observed with AIMS primary endpoint also failed to support the benefit of DTBZ, which appeared to be small. The key secondary endpoints were either lacking clinical significance or were not statistically significant. Of note, PROs were consistently negative. Pooling of efficacy data of the two studies considering the higher treatment arms only (from study C-23) were also not able to discriminate a positive effect.

3) The drop out rate was high, even in these short-term studies, raising tolerability issues. The reported reasons for study discontinuation did not enlighten the drop out high rate. As for the long-term study, which had a second phase with a randomized withdrawal part, also failed to demonstrate a worsening when DTBZ was withdrawn. This may be related to the short duration of the randomised withdrawal, but

a lack of effect (or similar to the placebo effect), or improvement of the initial TD condition could not be ruled out.

Also of relevance, there was not estimand policy a priori, and the type of population to be analysed and the different imputations planned and performed for the missing data were not clear.

These concerns were addressed in the course of the procedure. The reader should refer thereafter in this AR.

Design and conduct of the clinical studies

It is recognised that study design in TD trials is very challenging. The interplay between the need for sustained psychiatric treatment support and movement disorders control is difficult. While it would be ideal to keep stable the psychiatric medication while titrating DTBZ, after an initial up-titration a sequential DRA and antidepressant medication is often required for the maintenance of efficacy and tolerability of the combined medication. The applicant understood this when the slow up-titration used in the development program caused an increased drop-out, and a new faster up-titration was therefore proposed. But not only a fast up-titration, also a fast psychiatric adjustment is needed. As such, the best approach would be the assessment of the best combined treatment (DTBZ + psychiatric agents) aiming at stability between week 6 and week 12, followed by an observation period till week 24.

Both trials C-18 and C-23 were randomized, double-blind, placebo-controlled trials. Placebo control is acceptable as there is no approved standard treatment for TD in the EU. One of the limitations of trial C-18 was the modest sample size (117 patients randomized), whereas trial C-23 was larger (298 patients randomized). In addition, both studies had a short treatment duration (12-weeks). A longer treatment duration would have been preferable given that TD has a spontaneous up and down time course of severity. Nevertheless, studies published between 1982 and 2017 in this condition all presented short and similar treatment durations (6 to 20 weeks) (Kane John M et al. 2018 -DOI: 10.4088/JCP.17cs11959). In addition, the AIMS was administered at sufficiently close intervals over the course of the studies which reduces the concern that patients developing signs of TD may have been missed due to the fluctuating nature of the disease. Data on the maintenance of efficacy are also available from the 3-year long-term open label safety trial C-20.

In the safety population, there were 3/130 (2,3%) patients with AE leading to dose reduction and 7/130 (5,4%) patients with AE leading to dose suspension in the placebo group. There were 14/168 (8,3%) patients with AEs leading to dose reduction and 5/168 (3,0%) patients with AE leading to dose suspension in DTBZ (titration) group (the reader could refer to the Overview Table of Adverse Event Profile from Phase 3 Trials in Participants with Tardive Dyskinesia per Treatment Period [Safety Population, in section 2.6.8.2.1 of this AR). Due to the limited number of patients, the interpretation of the results was considered cautiously.

The applicant provided satisfactory detailed information on the participants experiencing dose adjustments, the reasons for these actions (e.g., clinically significant AEs), and the reversibility of any such AEs separately for the Phase 3 Trials C-18, C-23 and C-20. Among AE leading to dose reduction or dose suspension, no unexpected findings were identified considering the safety profile of DTBZ.

Placebo as comparator was shown to be adequate. In CNS disorders the placebo effect is always important since its magnitude is high and long-lasting. Furthermore, while tetrabenazine is a known therapeutic agent in TD, it has not been approved centrally and is not available in this indication in many EU countries. Since there is no other TD approved agent in EU, placebo is considered to be an adequate comparator.

The primary endpoint (AIMS total score from baseline [BL] to week 12) is a well established endpoint for the assessment of drug induced dyskinesias. Its Minimal Clinically Important Difference (MCID) is also

established. The AIMS was centrally rated by experts in movement disorders blinded to treatment and visit number(s) and was administered using the specific instructions for clinical practice developed by Munetz and Benjamin 1988. Therefore, bias due to interrater variability and to the potential for inflated scores at baseline and overly reduced scores at the end of trials were minimised. This represents a strength of the trials.

Teva provided results from Study C-20 of the change in the Abnormal Involuntary Movement Scale (AIMS) individual scores (items 1 through 7) from baseline of the study to each visit and discussed the clinical relevance of the results. In Trial C-20, 337 patients were enrolled and received open-label DTBZ (rolled over from Trials C-18 and C-23). Of these, 110 patients had been previously treated with placebo and 227 with DTBZ. Among the 337 patients in Part A of trial C-20, 249 s had at least one visit at ≥week 54; 194 had at least one visit at ≥week 106; and 160 by week 145. "Withdrawal by patients" was the most frequent reason for discontinuation. The applicant performed the assessment of individual AIMS item scores at each trial visit (baseline and weeks 15, 28, 54, 106 and 145), as requested. No new element regarding clinical relevance could be highlighted with this assessment in patients who completed the C-20 long term open study.

The applicant summarised and discussed Individual AIMS item scores (1 to 9) in both pivotal studies C-18 and C-23. Teva also performed descriptive sub-group analyses of changes from baseline at week 12 in individual AIMS item scores 8 and 9, in addition to 1-7 for Trial C-18 (flexible-dose trial) and Trial C-23 (fixed-dose trial). Mean changes in individual AIMS items 1 to 9 from baseline to Week 12 seemed in favour of an effect of DTBZ compared to placebo in line with the assessment of primary end points. No imbalance between groups in terms of impact on the study outcomes were observed.

Teva did not provide a statistical analysis in agreement to ICH E9(R1) (Addendum to ICH E9 Statistical Principles for Clinical Trials). The statistical analysis conducted for the C-18 trial was in accordance with the approved SAP dated 29 April 2015. The primary efficacy endpoint for C-18 was the change from baseline to Week 12 in total AIMS score (sum of items 1 through 7) as assessed by blinded central video rating.

For the primary estimand, the clinical question of interest was: "What is the treatment benefit in terms of AIMS score for a participant assigned DTBZ regardless of treatment compliance, use of concomitant medications or early discontinuation over 12 weeks?". Based on this clinical question, the estimand was defined by the following attributes.

a) **Treatment**: DTBZ or placebo BID for 12 weeks (flexible dose escalation and maintenance);

b) **Population**: Male and female adult subjects with moderate to severe TD who received trial drug and had at least one post-baseline assessment of the AIMS;

c) **Endpoint**: Change from baseline to week 12 in total motor AIMS score (items 1 through 7) as assessed by blinded central video rating;

d) **Population-level summary**: Difference between DTBZ and placebo in mean change from baseline to week 12 in total motor AIMS score by blinded central video rating.

The **treatment policy strategy** was applied for all intercurrent events, including treatment non-compliance, concomitant medication use, and early discontinuation. This implied that all observed data were used to estimate the primary estimand, regardless of any intercurrent events.

Secondary Estimand

The key secondary efficacy endpoint for C-18 was the proportion of subjects who are a treatment success at Week 12 based on the Clinical Global Impression of Change (CGIC). A treatment success was defined as "Much" or "Very Much Improved" on the CGIC at the week 12 visit. Subjects whose status at week

12 was not known, as well as subjects who were "not Much or "Very Much Improved" at the week 12 visit, were considered treatment failures for this analysis. The CGIC is a 7-point Likert Scale, ranging from "Very much worse" to "Very much improved".

For the secondary estimand, the clinical question of interest was: "What is the potential treatment success based on CGIC for a participant assigned DTBZ regardless of treatment compliance, use of concomitant medications or early discontinuation over 12 weeks?". Based on this clinical question, the estimand was defined by the following attributes.

a) Treatment: DTBZ or placebo BID for 12 weeks;

b) Population: Male and female adult subjects with moderate to severe drug-induced TD who received trial drug and had at least one post-baseline assessment of the AIMS;

c) Endpoint: CGIC at the week 12 visit;

d) Population-level summary: The proportion of subjects within each treatment group who are a treatment success at week 12 based on the CGIC.

The **treatment policy strategy** was applied for all intercurrent events, including treatment non-compliance, concomitant medication use, and early discontinuation. This implied that all observed data were used to estimate the secondary estimand, regardless of any intercurrent events.

The supportive secondary endpoints for both studies C-18 and C-23 (responder analyses, CGIC, PGIC) failed to support the efficacy primary endpoint since either not statistically significant (CGIC, PGIC) or its clinical relevance doubtful besides the multiple comparisons of different status (central rating versus local, percentage of improvement rate of responders, (proportion of responder analyses based on the amount of improvement in AIMS total score at week 12 by treatment group). Because the CGIC was rated by the investigator, it was considered the most objective and informative of the secondary efficacy assessments. Also, it may add clinical relevance to the total motor AIMS score. It should be noted though that, unlike the AIMS, the CGIC was not centrally rated and required an accurate recall of the subject's baseline presentation. So, its outcome must have included more variability compared to the AIMS. Regarding the PGIC and mCDQ-24, a limitation could be that some patients were not totally aware of their symptoms and that the underlying psychotic disorder (schizophrenia or schizoaffective disorder) might have affected their ability to assess the improvement of their disease and their quality of life. Therefore, results based on PGIC and mCDQ-24 will not be detailed below.

The conduct of the studies was overall acceptable. Most amendments did not significantly impact the study conduct or results. However, in study C-23, the co-primary endpoint of both AIMS response to the 24 and 36 mg compared to baseline was reduced to a single primary endpoint of AIMS response to 36 mg as compared to baseline. This was implemented when there were already 102 patients enrolled into the study. The reason for this relied on the fact that the mean dose in study C-18 was 38 mg. However, the amendment may have signalled investigators on the lower efficacy of lower doses, triggering suspicion regarding most of the treatment arms, since investigators did not know in which study arm participants were. The impact of this on the study was initially not discussed by the applicant. The increase in the number of study sites from approximately 60 to approximately 75 (and the number of patients from approximately 200 to approximately 288), increased in the upper limit of age for inclusion in the study to 80 years of age and the change from coprimary analyses to a single primary analysis are also aspects that may signal that the magnitude of effect between arms may be low or the study too short to detect a valuable difference. Therefore, Teva was asked to discuss to what extent investigators might have been influenced by the 3rd amendment regarding the expectation of efficacy and tolerability, namely and how this may have influenced the results.

In its response the applicant confirmed that Protocol Amendment 3 for Trial C-23 (fixed dose trial) was triggered by the results of Trial C-18 (flexible dose trial), which showed that the mean dose of DTBZ in C-18 was 38 mg. Protocol Amendment 3 for Trial C-23 was approved on 29 October 2015. Of the 206 participants in the mITT population who completed the trial (SD-809-C-23 CSR, Table 7), 82 completed the treatment period before the protocol amendment, and 124 completed it after the amendment.

The investigators, trial participants, and central (video) raters were blinded to the trial drug allocation (using a balanced 1:1:1:1 randomisation) throughout the trial duration. Therefore, any potential "expectation of efficacy and tolerability" would have affected all trial arms equally and could not have biased the comparative results. Thus, the validity and reliability of the trial were not affected. The central raters were also blinded to the local sites and timing of videos. Of note, for the primary endpoint only the ratings for the blinded central raters were considered.

Furthermore, to address any potential concerns related to a potential impact of Protocol Amendment 3 on the C-23 trial results, Teva conducted an analysis of the efficacy and safety of DTBZ (12, 24, or 36 mg/day) or placebo in participants who completed the trial before the approval of the protocol amendment compared to those who completed it after this date.

The change in total motor AIMS score (central), LS mean difference (DTBZ minus placebo) from baseline to week 12 was -1.5, -2.5, -1.9 in participants who completed the trial before the amendment and -0.2, -1.3, -2.0 in those who completed the trial after the amendment (for the 12, 24, and 36 mg/day arms, respectively). For 36 mg/day, the LS mean differences were similar before and after the amendment. However, for 24 mg/day, the LS mean difference showed a 1.2-point drop, indicating that the amendment did not introduce any bias. These results did not indicate any apparent bias related to increased expectations for the treatment effect of DTBZ resulting from Protocol Amendment 3.

The safety and tolerability of DTBZ (12, 24, or 36 mg/day) or placebo in participants who completed Trial C-23 before Amendment 3 versus after this amendment were similar, with the limitation of small subgroup sizes.

In summary, no meaningful differences in terms of efficacy and safety/tolerability were observed in participants who completed this trial before versus after the approval date of Protocol Amendment 3, indicating that the amendment did not bias the trial results.

Efficacy data and additional analyses

Trial C-18

Primary endpoint: DTBZ treatment provided a statistically significant reduction in the AIMS total score (indicating improvement) from baseline to week 12, based on central reading (a 3.0-point mean reduction compared to a 1.6-unit mean reduction in the placebo group, for a mean treatment effect difference of −1.4 points; p=0.0188).

First key secondary endpoint: DTBZ treatment resulted in a not statistically significant at the $p<0.05$ level (p=0.4001) numerically higher proportion of participants who achieved treatment success at week 12, based on CGIC ("much improved" or "very much improved": 48.2% versus 40.4% in the placebo group), a 7.8% difference of treatment success between groups.

Trial C-23

Primary endpoint: DTBZ 36 mg/day treatment provided a statistically significant reduction in the AIMS total score from baseline to week 12, based on central reading (a 3.3-point mean reduction, compared to a 1.4-point mean reduction in the placebo group, for a mean treatment effect difference of −1.9

points; p=0.001). A separation of the total motor AIMS score in the DTBZ groups from placebo was seen starting at week 2 in all treatment groups.

First key secondary endpoint: DTBZ 36 mg/day treatment resulted in a not statistically significant at the p<0.05 level (p=0.059), numerically higher proportion of participants who achieved treatment success at week 12, based on CGIC ("much improved" or "very much improved": 44% versus 26% in the placebo group), a 18% difference in the responder rate.

Therefore, the CHMP initially concluded that the magnitude of treatment effect did not reach the threshold of the clinically significant difference for AIMS, in any of the pivotal studies nor at the pooled analysis of the two studies (considering just the higher dose arm from study C-23). The Key secondary endpoints also did not support or increase the primary endpoint low magnitude of effect.

Although subgroup analyses showed some subgroups where results were more favourable (patients not on DRAs, patients with more severe disease) the studies were not powered for these subgroup analyses, nor the differences in magnitude were so striking as to be facially relevant, although it seemed that there was a higher response in patients without concomitant use of DRAs. Studies in other populations (HD and the not discussed cerebral palsy movement disorders) also failed their objectives.

Consequently, in order to identify the potential causes for the failed studies, admitting that they had failed for a short margin, the applicant was required to discuss several variables that may account for these negative results.

The CHMP requested Teva to further justify the clinical relevance of the primary endpoint results, also considering the lack of strong support from the secondary endpoints.

To address CHMP request, Teva conducted responder analyses of the reduction in the total motor Abnormal Involuntary Movement Scale (AIMS) score from baseline using 3 approaches. The first utilised the conventional responder cut-offs, and the additional 2 non-overlapping categories and anchoring to the Patient Global Impression of Change (PGIC).

As detailed in the clinical efficacy section of this AR, in Teva's view, taken together, the responder analyses based on total motor AIMS score reduction demonstrated a clear separation in responder rates between DTBZ treatment and placebo independent of the exact definition of a clinically relevant effect or MCID. Importantly, the observed separation was reversed in the category of participants with no change or worsening in total motor AIMS score.

Additionally, the applicant provided a plot showing the distributions by treatment group using non-overlapping categories of reduction in total motor AIMS score. In participants treated with DTBZ shifts in the distribution of total motor AIMS score reduction were aligned with the responder analysis results above mentioned, indicating clinical meaningfulness across various responder cut-offs.

Furthermore, Teva presented a tabulation of total motor AIMS score reduction by treatment group anchored on categories of PGIC. In general, the level of participants' reported improvement on PGIC tracked well with the level of total motor AIMS score reduction. Additionally, more participants reported improvements in TD symptoms in DTBZ treatment group compared to placebo.

The results provided showed that the mean change in total motor AIMS score from baseline at week 12 anchored to categories of PGIC for the DTBZ dose groups and placebo dose groups pooled across Trials C-18 and C-23. Specifically, the pooled DTBZ group included all dose groups from the C-18 flexible-dose trial and the 24 mg and 36 mg dose groups from the C-23 fixed-dose trial. Of note, data from the C-23 12 mg dose group were excluded because efficacy was not established for this dose.

In general, the proportion of participants who reported "very much improved" or "much improved" on PGIC was greater in DTBZ compared to placebo. Additionally, the participants who reported "very much

improved" or "much improved" on PGIC had a higher mean reduction (improvement) in total motor AIMS score on DTBZ compared to placebo. Conversely, the proportion of participants who reported "no change or worsening" on PGIC was greater on placebo compared to DTBZ.

Overall, these findings supported that the clinician's perception of the patient's improved dyskinesias on the total motor AIMS score reflected the patient's experience of improved dyskinesias.

A similar analysis of the mean change in total motor AIMS score from baseline at week 12 anchored to categories of PGIC was performed separately for Trial C-23, pooling the DTBZ doses within the efficacious dose range, i.e., 24 mg and 36 mg, compared with placebo. In general, the proportion of participants who were "very much improved" or "much improved" on PGIC and the mean reductions in total motor AIMS score were higher in the pooled DTBZ 24 mg and 36 mg group than in the placebo group. The proportions of participants who were "minimally improved" were similar in the DTBZ and placebo groups, although the mean reduction in total motor AIMS score was greater in the DTBZ group. A higher proportion of participants in the placebo group reported "no change or worsening".

An additional analysis of the DTBZ 12 mg and placebo groups in Trial C-23 showed that the mean change in total motor AIMS score from baseline at week 12 was similar for both DTBZ 12 mg and placebo groups, with comparable proportions of participants reporting being "very much improved" or "much improved" on the PGIC scale. However, slightly more participants in the DTBZ 12 mg group reported being "minimally improved" compared to the placebo group.

The applicant considered the DTBZ's effective dose range to be 24 to 48 mg daily, so the 12 mg dose was confirmed as just a starting dose and without providing significant clinical benefit. When pooling data from Trial C-23 DTBZ 12 mg, 24 mg, and 36 mg groups, the improvement rates for DTBZ were closer to placebo, indicating that the 12 mg dose reduced the overall reported improvement in TD, aligning with Teva's view that 12 mg is below the efficacious dose range.

Teva also analysed DTBZ data based on the Minimal Clinically Important Difference (MCID) method by Stacy 2019, using a Patient Global Impression of Change (PGIC) score ≤3 (named treatment improvement) and a PGIC score ≤2 (named treatment success) as anchors and the change in total motor Abnormal Involuntary Movement Scale (AIMS) score from baseline to week 12 in the pooled Trials C-18 and C-23 data: 75% of participants on DTBZ had "treatment improvement" and 38% had "treatment success" based on PGIC.

With regard to (further) support of DTBZ efficacy from secondary endpoints, Teva pointed out that the secondary endpoints of Clinician Global Impression of Change (CGIC) and PGIC from Trials C-18 and C-23 were analysed using a hierarchical (fixed-sequence) testing approach. For both scales, treatment success was defined as a rating of "much improved" or "very much improved" at week 12.

The CGIC and PGIC did not meet criteria for statistical significance at $p < 0.05$ level, however, across both trials and in both the CGIC and PGIC, a greater proportion of participants on DTBZ had a treatment success, compared to those taking placebo. These results, in conjunction with the responder analyses presented above, further supported that the (statistically significant) effect on the primary endpoint of the total motor AIMS score for both trials was clinically meaningful to both clinicians and participants.

CHMP confirmed the applicant's responses addressed accordingly the clinical efficacy MO.

The applicant was also requested to provide the cumulative exposure to antipsychotic medications at baseline of pivotal studies and clarify whether any imbalances in the cumulative exposure to antipsychotic medication between groups could have impacted the study outcomes. In the two pivotal trials, cumulative antipsychotic exposure, quantified as dose-years, was not collected in the case report forms (CRFs). In its response the applicant also mentioned that reliable calculation of cumulative exposure from the prior medication data is not feasible due to the heterogeneity of antipsychotic agents

utilised, each with distinct dose equivalencies and pharmacokinetic profiles. This precludes accurate standardisation and aggregation of dosing data across different antipsychotic medications. In lieu of this, the duration of prior antipsychotic therapy was calculated from the prior medications data and was used as a surrogate by the applicant.

Teva summarised the duration of prior exposure to antipsychotic medications at baseline as box plots in Trials C-18 and C-23 (thereafter), and as descriptive statistics in Trials C-18 and C-23 in the two following tables, respectively.

Figure 42: Antipsychotic medication exposure by treatment group - trial C-18 (Safety Population)

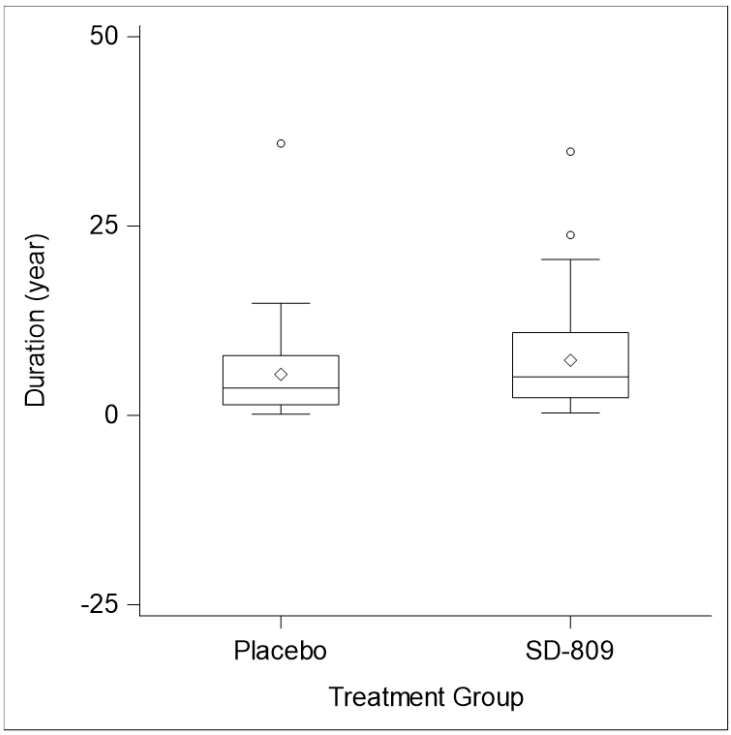


Figure 43: Antipsychotic medication exposure by treatment group - trial C-23 (Safety Population)

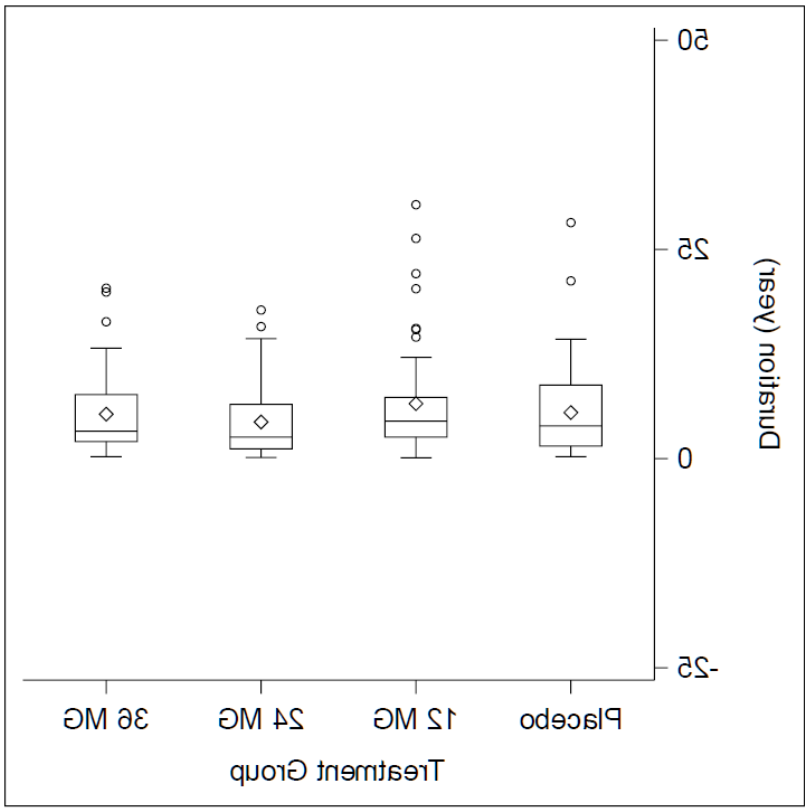


Table 48: Duration of antipsychotics medication exposure by treatment group - trial C-18 (Safety Population)

Duration (months) Prior to Trial Start Date	Placebo (N=42)	DTBZ (N=47)	Overall (N=89)
Mean	65.0	87.4	76.8
SD	73.91	85.45	80.55
SE	11.40	12.46	8.54
Median	43.5	61.1	56.9
Min, Max	2, 431	4, 418	2, 431

DTBZ=deutetrabenazine; SD=standard deviation; SE=standard error.
Participants were assigned to the above treatment groups based on the randomisation scheme, after the medical history assessment.

Table 49: Duration of antipsychotics medication exposure by treatment group - trial C-23 (Safety Population)

Duration (months) Prior to Trial Start Date	Placebo (N=56)	DTBZ 12 mg (N=58)	DTBZ 24 mg (N=52)	DTBZ 36 mg (N=56)	Overall (N=222)
Mean	66.3	79.0	52.7	63.9	65.8
SD	64.96	76.38	53.66	58.37	64.45
SE	8.68	10.03	7.44	7.80	4.33
Median	47.2	54.0	30.9	39.5	46.4
Min, Max	3, 339	1, 364	2, 213	3, 245	1, 364

DTBZ=deutetrabenazine; SD=standard deviation; SE=standard error.
Participants were assigned to the above treatment groups based on the randomisation scheme, after the medical history assessment.

In summary, according to the two Tables above, summarising the duration of antipsychotics medication exposure by treatment group the mean duration in months might be higher in DTBZ group (65 months in the placebo group versus 87,4 months in DTBZ group) in study C-18 as no difference was observed in study C-23 between groups. It was therefore not possible to conclude.

Separately, in Table 2 of the SmPC (Improvement in AIMS total score in the fixed dose study C-23, noted as Study 1), the statistically significant LS mean difference at week 12, on change from baseline total motor AIMS score at 24 mg/day, from DTBZ minus placebo (diff LS mean (SE), 95%CI, -1.8 (0.45), -3.00, -0.63, nominal p-value=0. 003), in the mITT population (N=222), was considered exploratory. CHMP commented that a nominal p-value should rather be noted in the SmPC for the change from baseline total motor AIMS score at week 12, for DTBZ 12- and 24 mg/day, due to non-adjustment for multiplicity, by following the hierarchical testing approach of key secondary endpoints planned in the protocol and the lack of statistical significance on the CGIC at week 12 for DTBZ 36 mg/day. The applicant updated section 5.1 of the SmPC as requested by CHMP. Table 2 of the SmPC was revised with the deletion of the initially included exploratory (nominal) p-values for difference DTBZ 12 and 24 mg/day compared to the placebo, in the absence of multiplicity adjustment.

The results of a responders analyses based on the change in the total motor AIMS score from baseline to week 12 were consistent with the primary analysis. In particular, in trial C-23, 35% and 38% of patients in the DTBZ 36 mg/day and 24 mg/day respectively showed ≥50% improvement versus 13% in the placebo group (odds ratio 4.10 and 4.47 respectively). 50% improvement could be suggestive of a clinical meaningfulness of the treatment effect. There was however no relevant difference between the DTBZ 12 mg/day and placebo.

Long term efficacy results from trial C-20.

In part A of trial C-20, consistent improvements across efficacy assessments based on AIMS and CGIC were observed for up to 3 years and support of a long-term benefit of DTBZ for patients who remain on treatment. A limitation of this finding is that a large number of patients, who were probably poor responders, dropped out of the study.

The total motor AIMS score (blinded central rating) was analysed in Part A both as: (1) change from the baseline of study C-20 to visits during this study, and (2) change from the baseline of the parent double-blind studies (C-18 and C-23) to visits during study C-20. In both analyses, decreases (improvement) in the mean total motor AIMS score from baseline were observed at week 15 of treatment, followed by maintenance of the reduced total motor AIMS score through week 145/158. The mean (SE) change in the total motor AIMS score from baseline of study C-20 was -2.0 (0.38) at week 145/158 (min -14, max 9). The mean (SE) change in the total motor AIMS score from baseline of the parent studies C-18 and C-20 was -4.0. (0.37) at week 145/158 (min -14, max 7).

The results were supported by the responders analysis based on the total motor AIMS score and by the proportion of patients who were treatment success based on CGIC.

The applicant was requested to provide results from Study C-20 of the change in AIMS individual scores (items 1 through 7) from baseline of the study to each visit and discussed the clinical relevance of these results. In Trial C-20, 337 patients were enrolled and received open-label DTBZ (rolled over from trials C-18 and C-23). Of these, 110 patients had been previously treated with placebo and 227 with DTBZ. Among the 337 patients in Part A, 249 patients had at least one visit at ≥week 54; 194 patients had at

least one visit at ≥week 106; and 160 patients by week 145. "Withdrawal by patients" was the most frequent reason for discontinuation.

The applicant performed the assessment of individual AIMS item scores at each trial visit (baseline and weeks 15, 28, 54, 106, and 145) as requested. No new element regarding clinical relevance could be highlighted with this assessment in patients who completed the long term open study.

Subgroup analysis

In individual studies, subgroup analysis of the primary endpoint and secondary endpoints were performed by baseline disease severity (baseline AIMS score <median, baseline AIMS score ≥median), by DRA Status ("currently taking" versus "not currently taking" a DRA), and by comorbid illness type (the disorder types were grouped into schizophrenia, schizoaffective, bipolar/depression and other). It was however difficult to derive any substantive conclusions based on the small size of the various subgroups.

Therapeutic indication claimed in the SmPC

The applicant claimed a broad therapeutic indication, irrespective of disease severity and without mentioning that symptoms must be bothersome to the patient and/or cause functional impairment. This expansion of the indication to cover the milder forms was not agreed by CHMP. As discussed, neither the definition of mild TD presented by the applicant was acceptable, nor sustained follow up of patients with mild forms was available. The post-hoc analysis in participants which scored centrally as having a possible milder form of TD was challenged, since the central assessment did not substitute the investigator's rating which considered the total impact (temporal and systemic) whereas the central assessment was only partial. Furthermore, patients with lower AIMS had an even lower magnitude of effect.

The applicant justified that the C18 / C23 included population was representative of the real world potentially benefitting patients. In fact, it covered TD patient characteristics such as age, genders, socioeconomic backgrounds and geographic locations. The efficacy results did not seem to depend upon biases from these characteristics, and refining the population did not seem to improve efficacy response. However, TD patients enrolled into the study were assessed by the investigator as being stable on concomitant psychiatric illness and psychiatric medication, and having moderate to severe symptoms, and these aspects could not be demeanoured, as well as the functional impairment that the patients had to present to be included into the study.

The results of the post-hoc analysis in mild TD subjects of trials C-18 and C-23 (n=38 for DTBZ treated with the 24 mg/day and 36 mg/day doses and n=20 for placebo) were considered exploratory, not clinically and statistically confirmatory (p=0.079, treatment effect -0.92). Therefore, the applicant agreed to align DTBZ intended therapeutic indication with the trial population in the pivotal clinical trials for TD, as requested by CHMP. Consequently, the wording in SmPC Section 4.1 e was amended as follows to reflect a restriction to "moderate to severe TD": *Austedo is indicated for the treatment of moderate to severe tardive dyskinesia in adults* thus also conveying that DTBZ should only be used in patients with bothersome movements or cause functional impairment.

Regarding psychiatric stability, it was accepted that the treating psychiatrist should be able to distinguish when the patient is sufficiently stabilized to allow use of DTBZ, meaning that the risk of psychiatric decompensation is less than the risk of TD causing impairment to the patient making the overall trade-off in favour of treatment with DTBZ. Therefore, it was agreed that psychiatric stability should be assessed by the treating physician on a routine basis, and it was not necessary to impose further boundaries on DTBZ indication.

Furthermore, while most treatment guidelines for schizophrenia regarding TD recommend to start with either dose reduction of antipsychotics or switching to clozapine or other SGAs (Takeuchi and al, 2022), it seems there is no need to add a place in therapy for DTBZ (i.e., adding pharmacological interventions to which patients are non-responders in the indication) as it might not impact the efficacy or safety of DTBZ (.e., conclusions on the benefit-risk balance can be extrapolated beyond the line of treatment).

Other concerns addressed in the course of the procedure.

Regarding concomitant use of other products besides DRAs and antidepressants, the applicant confirmed that no patient had deep brain stimulation implanted, and that the effect of opioid use did not have a blunt effect in the studied populations. Regarding the use of anticholinergics, the applicant justified that such use was excluded from the trial to avoid any confounding effect, and that anticholinergic treatment should be discouraged in TD, due to possible worsening of some movements. However, use of anticholinergics is a current clinical practice in TD. Therefore, the applicant discussed whether post-marketing data supported the concomitant use of anticholinergics or a cautionary warning should be added in the SmPC (section 4.5) against such concomitant use with DTBZ.

Teva pointed out the (known) limitations of available post-marketing data (e.g. [population] biased [data coming from patients' groups more likely to report], incomplete, under-reported AEs, lacking key information about i.e., instances of concomitant medication use, lack of detailed usage data, such as details on medication regimens and duration of concomitant usage. In addition, confounding factors such as underlying health conditions and other medications not always adequately described in these reports).

Teva also expressed that "*the PI for several anticholinergic medications adequately indicate that these medicinal products should not be used to treat TD and may even provoke or exacerbate TD symptoms. The applicant deems it inappropriate to warn about the use of this class of medicinal products to treat TD in the DTBZ SmPC, as this warning is connected to the condition (TD), but not to the use of DTBZ".* CHMP agreed with Teva's position.

Teva was requested to further elaborate on the exclusion from the trial(s) of patients who had received botulinum toxin within 3 months of screening or baseline.

Botulinum toxin (BoNT) is prescribed (mostly off-label) for certain movement disorders, such as TD, dystonia, bruxism, tremors, tics, myoclonus, restless legs syndrome, and a variety of symptoms associated with Parkinson's disease (Anandan and Jankovic 2021). Patients who received botulinum toxin within 3 months of screening or baseline were excluded from the trials, due to the potential confounding effect of the botulinum toxin on the interpretation DTBZ's effect on the TD. Ultimately, CHMP agreed that it is not probable that treatment with BoNT may adversely impact DTBZ efficacy, and that they may be synergic.

2.6.7. Conclusions on clinical efficacy

Efficacy of DTBZ in the treatment of TD was statistically significant at 12 weeks in the phase 3 trials C-18 and C-23 based on the total motor AIMS score. Still, these pivotal studies were negative (or at least failed to be positive) for the common primary endpoint (AIMS score decrease of the minimal clinically significant difference of 2 points) regarding clinical significance. Furthermore, these low magnitude findings were not improved by the first key secondary endpoints and some other secondary endpoints which also showed a smaller magnitude of effect. In the C-20 trial, consistent improvements across efficacy assessments based on AIMS and CGIC were observed for up to 3 years showing a maintenance of the effect for patients who remained on treatment. However, the effect size based on the reduction of the total motor AIMS score was not clinically significant. In the responses to the D180 LoOI, the applicant presented the requested additional analyses of the reduction in total motor Abnormal

Involuntary Movement Scale (AIMS) score from baseline using 3 approaches. Besides the classical (first approach) which utilized the conventional responder cut-offs, the additional 2 approaches utilized non-overlapping categories and anchoring to the PGIC to confirm that the patient's perception was in line with the clinician's perception.

Regarding efficacy, the applicant presented several exploratory analyses which were in favour of a clinical effect of DTBZ compared to placebo on Total Motor AIMS score, PGIC and CGIC in both C-18 and C-23 pivotal studies. They also suggested that DTBZ would benefit to the population of patients with moderate to severe TD. Therefore, the applicant agreed to align the intended therapeutic indication for DTBZ with the trial population in the pivotal clinical trials for TD, as requested by CHMP.

2.6.8. Clinical safety

The safety programme for DTBZ included **10 clinical trials**: 2 Phase 3 efficacy trials (**C-18 [flexible dose]** and **C-23 [fixed dose]**) and 1 Phase 3 (3-year) **long-term safety** trial (**C-20**) in adults with tardive dyskinesia (TD), 1 Phase 3 efficacy trial (**C-15**) and 1 Phase 3 long-term safety trial (**C-16**) in adults with HD-associated chorea (supportive data as the mechanism of action of DTBZ does not differ between patients with TD and HD; of note Teva did not seek approval for HD indication) and **5 Phase 1 BE and PK trials** in healthy adults (supportive data):

- **TV50717-BE-10179** and **TV50717-BE-10165**, comparing the commercial osmotic PR formulation QD with the clinical matrix formulation BID;
- **TV50717-PK-10175**, **TV50717-BE-10192**, and **TV50717-BE-10201** with DTBZ osmotic PR formulation QD;

All phase 3 trials in TD were conducted using a DTBZ **matrix formulation BID** and the **5 Phase 1 trials** in healthy participants were conducted using the **osmotic PR formulation QD**, for which Teva submitted the MAA.

Safety (and efficacy) of DTBZ in patients with TD were bridged from the clinical matrix formulation BID to the commercial osmotic PR formulation QD through comparison of the PK profiles by biopharmaceutic studies in conjunction with exposure response modelling and simulation of clinical data.

For the primary safety analysis, data from the Phase 3 trials in TD were presented individually and pooled resulting in the following treatment groups: placebo (integrated), fixed doses treatment with DTBZ 12-mg/day, DTBZ 24-mg/day, and DTBZ 36-mg/day (individually), DTBZ titration (integrated), DTBZ placebo-controlled trials (integrated), and long-term safety Trial C-20 (individually).

As detailed in previous sections of this assessment report, the initiation and titration scheme for DTBZ proposed by Teva differs from the one applied in the Phase 3 trials in TD. Specifically, titration to an efficacious dose range is shortened by 1 week by increasing the dose from 12 to 24 mg/day in the second week, excluding the 18 mg dosing step (for which no MAA was submitted). This dosing recommendation is based on real-world/postmarketing data, a comparison of safety events from 3 trials in HD and TD (Trial C-15, Trial C-18, and Trial C-23), along with modelling and simulation.

A total of **1270 participants** received DTBZ during the development programme, including 384 adults with TD (745.84 patient-years of treatment), 121 participants with HD-associated chorea (280.26 patient-years of treatment), and 765 healthy adults who received single or repeated DTBZ doses.

Significant post-marketing experience also contributed to define DTBZ safety profile. In the period from 03 April 2017 (US FDA approval of DTBZ for the treatment of HD associated chorea in adults) until 31

March 2023 (the cut-off date of the latest periodic safety update report - PSUR), patient exposure to DTBZ was approximately 73000 patient-years (in patients with HD and TD).

A tabular listing of all trials included in the clinical development program to establish DTBZ safety and to bridge from DTBZ matrix formulation BID to the osmotic PR formulation QD, is provided in the next tables.

Table 50: Summary of clinical trials included in the DTBZ clinical safety program

Summary of Clinical Trials Included in the DTBZ Clinical Safety ProgramTrial ID (Phase)	**No. trial centres/ Countries regions**	**Design** **control type**	**Test products** **Dosage regimen** **Route of** **Administration**	**Trial objective**	**No. participants by arm:** **entered/ completed**	**Duration of treatment**	**Sex M/F** **Age**	**Primary endpoint(s)**
Tardive Dyskinesia								
SD-809-**C-18** (**Phase 2/3**) Flexible-dose trial	29/US 7/Poland 3/Slovakia 2/Czech Republic	Randomised, double-blind. Placebo	DTBZ matrix formulation BID, oral, up to a maximum of 48 mg/day	Efficacy of DTBZ to reduce severity of abnormal involuntary movements of TD Safety and tolerability of titration and maintenance therapy	DTBZ: 58/52 Placebo: 59/52	6-week titration 6-week maintenance	M: 47.8% F: 52.2% Mean age: 54.9 years	Change from baseline (defined for each participant as the value from the Day 0 visit) to week 12 in AIMS score as assessed by blinded central video rating.
SD-809-**C-23** (**Phase 3**) Fixed-dose trial	38/US 19/Poland 7/Hungary 6/Czech Republic 3/Slovakia 2/Germany	Randomised, double-blind. Placebo	DTBZ matrix formulation BID Oral (12 mg/day, 24 mg/day or 36 mg/day)	Efficacy of fixed doses to reduce severity of abnormal involuntary movements of TD Safety and tolerability of fixed doses	DTBZ 12 mg/day: 75/67 DTBZ 24 mg/day: 74/65 DTBZ 36 mg/day: 75/65 Placebo: 74/67	4-week dose escalation 8-week maintenance	M: 45% F: 55% Mean age: 56.4 years	Change from baseline (defined for each participant as the value from the Day 0 visit) to week 12 in AIMS score as assessed by blinded central video rating.
SD-809-**C-20** (**Phase 3**) **Long-term trial**	41/US 18/Poland 6/Czech Republic 6/Hungary 3/Slovakia	Open-label, single-arm, long-term Part A: Persistence of effect (No placebo)	DTBZ matrix formulation BID, oral, up to a maximum of 48 mg/day	Safety and tolerability of long-term maintenance therapy Efficacy of long-term maintenance	DTBZ: 337/174	**Up to 158 weeks**	M: 44% F: 56% Mean age: 56.9	Change in total motor AIMS score from baseline to each visit (site rating)

Summary of Clinical Trials Included in the DTBZ Clinical Safety ProgramTrial ID (Phase)	**No. trial centres/ Countries regions**	**Design** **control type**	**Test products** **Dosage regimen** **Route of** **Administration**	**Trial objective**	**No. participants by arm:** **entered/ completed**	**Duration of treatment**	**Sex M/F** **Age**	**Primary endpoint(s)**
	2/Germany			therapy to reduce severity of abnormal involuntary movements of TD Persistence of therapeutic effect			years	

Table 51: Summary of clinical trials included in the DTBZ clinical safety program (Continued)

Trial ID (Phase)	**No. trial centres / Countries regions**	**Design** **control type**	**Test product(s)** **Dosage regimen** **Route of** **Administration**	**Trial objective**	**No. participants by arm:** **entered/ completed**	**Duration of treatment**	**Sex M/F** **Age**	**Primary endpoint(s)**
SD-809-**C-20** (**Phase 3**) **Long-term trial**	41/US 18/Poland 6/Czech Republic 6/Hungary 3/Slovakia 2/Germany	Part B: Double-blind, randomised withdrawal (placebo-controlled)	DTBZ matrix formulation BID, oral, up to a maximum of 48 mg/day	Safety and tolerability of long-term maintenance therapy Efficacy of long-term maintenance therapy to reduce severity of abnormal involuntary movements of TD Persistence of therapeutic effect	DTBZ: 71/68 Placebo: 71/66	**1-week withdrawal** **12-week back to initial DTBZ dose**	M: 35% F: 65% Mean age: 61.0 years	Change in total motor AIMS score from baseline to each visit (site rating)
SD-809-**C-20** addendum 01 (**Phase 3**) **Long-term trial**	Same as for Parts A and B, but without US	Part C: Open-label safety in EU countries	DTBZ matrix formulation BID, oral, up to a maximum of 48 mg/day	Reduced burden safety	DTBZ: 80/73	**52 weeks**	M: 35% F: 65% Mean age: 61.4 years	Change in total motor AIMS score from baseline to each visit (site rating)
Huntington's Disease								

Trial ID (Phase)	No. trial centres / Countries regions	Design control type	Test product(s) Dosage regimen Route of Administration	Trial objective	No. participants by arm: entered/ completed	Duration of treatment	Sex M/F Age	Primary endpoint(s)
SD-809-**C-15** (**Phase 3**)	33/US 3/Canada	Randomised, double-blind. Placebo	DTBZ matrix formulation BID, oral, up to a maximum of 48 mg/day	Efficacy of DTBZ to reduce chorea associated with HD Safety and tolerability of titration and maintenance therapy	DTBZ: 45/44 Placebo: 45/43	8-week titration 4-week maintenance	M: 55.6% F: 44.4% Mean age: 53.7 years	Change in TMC from Baseline (defined for each participant as the mean of values from the Screening and Day 0 visits) to maintenance therapy (defined for each subject as the mean of values from the Week 9 and Week 12 visits).

Table 52: Summary of clinical trials included in the DTBZ clinical safety program (Continued)

Trial ID (Phase)	No. trial centres / Countries regions	Design control type	Test product(s) Dosage regimen Route of Administration	Trial objective	No. participants by arm: entered/ completed	Duration of treatment	Sex M/F Age	Primary endpoint(s)
SD-809-**C-16** (**Phase 3**)	33/US 3/Canada 1/Australia	Open-label, long-term, flexible-dose 2-cohort trial: Rollover and Switch groups	DTBZ matrix formulation BID, oral, up to a maximum of 72 mg/day	Safety and tolerability of titration and maintenance therapy, and of switching from TBZ to DTBZ PK of TBZ and DTBZ (and their respective metabolites) in participants switching from TBZ to DTBZ	Rollover: 82/56 Switch: 37/25	Up to 171 weeks	M: 56.3% F: 43.7% Mean age: 53.3 years	Changes from baseline and from Week 8 in TMC score and TMS from the UHDRS motor assessment.
Phase 1 Trial in healthy participants								
TV50717-BE-10179 (**Phase 1**)	1/US	Open-label, randomised, repeated dose, 2 treatment, 2 period,	Test: 24 mg DTBZ osmotic PR tablet QD Reference: 12 mg DTBZ	BE of DTBZ (parent), and α-HTBZ and β-HTBZ metabolites, at steady state of 24 mg DTBZ osmotic PR tablet QD compared to	Test: 132/108 Reference: 130/109	20 days total (7-day treatments with a 6-day washout in	M: 66% F: 34% Mean age: 38.6 years	$AUC_{0\text{-}24h,ss}$ of DTBZ (parent) and metabolites (as a sum and individually)

Trial ID (Phase)	No. trial centres / Countries regions	Design control type	Test product(s) Dosage regimen Route of Administration	Trial objective	No. participants by arm: entered/ completed	Duration of treatment	Sex M/F Age	Primary endpoint(s)
		2 sequence crossover trial	matrix tablet BID Both the above under fed conditions and repeated oral dose	12 mg DTBZ matrix tablet BID under fed conditions		between)		
TV50717-PK-10175 (**Phase 1**)	1/US	Open-label, randomised, single dose, 4-way, 4-sequence, crossover trial	Test: 2×6 mg DTBZ 1×12 mg DTBZ 1×24 mg DTBZ 2×24 mg DTBZ Reference: N/A All the above DTBZ osmotic PR tablet QD (single oral dose) under fed conditions	To assess the dose proportionality (6 mg to 48 mg) of the PK of DTBZ and deuterated α-HTBZ and β-HTBZ metabolites (individually and as a sum) after single doses of Test DTBZ To assess the relative BA between 2x6 mg and 1x12 mg after single doses of DTBZ	Test: 116/108 In 4 sequences: ABCD: 29/23 BCAD: 29/27 CDBA: 29/28 DACB: 29/25 Reference: N/A	22 days total (4 single dose treatments with a 6-day washout between doses)	M: 56% F: 44% Mean age: 40.9 years	Dose proportionality: C_{max}, AUC_{0-36h} and $AUC_{0-\infty}$ for DTBZ and metabolites Relative BA: C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for DTBZ (parent) and metabolites

Table 53: Summary of clinical trials included in the DTBZ clinical safety program (Continued)

Trial ID (Phase)	**No. trial centres / Countries regions**	**Design** **control type**	**Test product(s)** **Dosage regimen** **Route of Administration**	**Trial objective**	**No. participants by arm:** **entered/ completed**	**Duration of treatment**	**Sex M/F** **Age**	**Primary endpoint(s)**
TV50717-BE-10165 (**Phase 1**)	1/US	Open-label, randomised, 3-period, 3-treatment, 6-sequence, crossover trial	Test: 24 mg DTBZ osmotic PR tablet QD (single oral dose) under fed and fasted conditions Reference: 12 mg DTBZ matrix tablet (single oral dose) BID (12 hrs apart) under fed conditions	To assess the relative BA of DTBZ (parent) and deuterated α- and deuterated β-HTBZ metabolites (individually and as a sum), following a single 24-mg DTBZ osmotic PR tablet QD tablet compared to 12 mg DTBZ matrix formulation BID under fed conditions To assess the relative BA of DTBZ and its active metabolites under fasting (Test) and fed (Reference) conditions following single doses of DTBZ osmotic PR tablet QD	Test and Reference: 84/84 In 6 sequences consisting of 14 participants each	15 days total (3 single dose treatments with a 6-day washout between doses)	M: 56% F: 44% Mean age: 38.4 years	For DTBZ (parent) and metabolites: AUC_{0-t} and $AUC_{0-\infty}$
TV50717-BE-10192 (**Phase 1**)	1/US	Open-label, randomised, 2-sequence, 2-period, 2-treatment, crossover trial	Test: 1×48 mg DTBZ Reference: 2×24 mg DTBZ Both the above as oral osmotic PR tablets QD, under fasted conditions	To assess BE of DTBZ (parent) and its α- and β-HTBZ metabolites (individually and as a sum), a single dose of a DTBZ 1×48 mg (Test) compared with a single dose of DTBZ 2×24 mg (Reference) under fasted conditions	Test and Reference: 190/187 In 2 sequences: Test/Reference: 95/94 Reference/Test: 95/93	8 days total (2 single dose treatments with a 6-day washout between doses)	M: 47% F: 53% Mean age: 41.1 years	For DTBZ (parent) and metabolites: C_{max}, AUC_{0-t} and $AUC_{0-\infty}$

Table 54: Summary of clinical trials included in the DTBZ clinical safety program (Continued)

Trial ID (Phase)	**No. trial centres / Countries regions**	**Design** **control type**	**Test product(s)** **Dosage regimen** **Route of Administration**	**Trial objective**	**No. participants by arm:** **entered/ completed**	**Duration of treatment**	**Sex M/F** **Age**	**Primary endpoint(s)**
TV50717-BE-10201 (**Phase 1**)	1/US	Open label, randomised, 2-period, 2-treatment, 2-sequence crossover trial	Test: 1×36 mg DTBZ Reference: 1×12 mg + 1×24 mg DTBZ Both the above as oral osmotic PR tablets QD, under fasted conditions	To assess BE of DTBZ (parent) and its α- and β-HTBZ metabolites (individually and as a sum), for 1×36 mg DTBZ (Test) compared with 1×12 mg + 1×24 mg DTBZ (Reference) under fasted conditions	Test and Reference: 132/123 In 2 sequences: Test/Reference: 66/62 Reference/Test: 66/61	8 days total (2 single dose treatments with a 6-day washout between them)	M: 48% F: 52% Mean age: 38.7 years	For DTBZ (parent) and metabolites: C_{max}, AUC_{0-t} and $AUC_{0-\infty}$

Source: CSR SD-809-C-18; CSR SD-809-C-23; CSR SD-809-C-20; CSR SD-809-C-20 addendum 01; CSR SD-809-C-15; CSR SD-809-C-16; CSR TV50717-BE-10179; CSR TV50717-PK-10175; CSR TV50717-BE-10165; CSR TV50717-BE-10192; CSR TV50717-BE-10201.
AIMS=abnormal involuntary movement scale; $AUC_{0-24h,ss}$=area under the plasma concentration-time curve over a 24-hour interval at steady state; AUC_{0-36h}=area under the plasma concentration-time curve over a 36-hour interval; AUC_{0-t}=area under the plasma concentration-time curve from time 0 to the time of the last measurable drug concentration; $AUC_{0-\infty}$=area under the plasma concentration-time curve from time 0 to infinity; BA=bioavailability; BE=bioequivalence; BID=twice daily; C_{max}=max observed plasma concentration; CSR=clinical study report; DTBZ=deutetrabenazine; EU=European Union; F=female; HD=Huntington's disease; α-HTBZ=alpha-dihydrotetrabenazine; β-HTBZ=beta-dihydrotetrabenazine; ID=identification; ITT=intent-to-treat; M=male; N/A=not applicable; PK=pharmacokinetics; PR=prolonged release; QD=once daily; TBZ=tetrabenazine; TD=tardive dyskinesia; TMC= total maximal chorea; TMS= total motor score; UHDRS=Unified Huntington's Disease Rating Scale.

Presentation of Safety Data from the Phase 3 Program in Tardive Dyskinesia

Safety data from the Phase 3 trials, **SD-809-C-18** (flexible dose; hereafter referred to as **Trial C-18**), **SD-809-C-23** (fixed dose; hereafter referred to as **Trial C-23**) **and SD-809-C-20** (hereafter referred to as **Trial C-20**) in participants with TD are presented as either integrated data or individual trial data (see table below).

Integrated Data is presented for the following groups:

- **Placebo:** placebo-treated participants in Trials C-18 and C-23 up through and including week 12;
- **DTBZ titration**: DTBZ-treated participants in Trial C-18 up through and including week 12, plus data in Trial C-20 up through and including week 15 for participants previously in the placebo treatment group in either Trial C-18 or C-23 and then switched to DTBZ;
- **DTBZ placebo-controlled trials**: DTBZ-treated participants in placebo-controlled trials, i.e. Trials C-18 and C-23 up through and including week 12.

Individual Trial Data is presented for the following groups:

- **DTBZ 12 mg, 24 mg, and 36 mg:** DTBZ-treated participants in Trial C-23 for the respective treatment group up through and including week 12;
- **DTBZ, long term safety data**: DTBZ treated participants from Trial C-20 (Parts A–C);

Table 55: Safety data presentation for the phase 3 program with Tardive Dyskinesia

Analysis Group	**Trial Data**	**Trials Included**
Participant groups		
Placebo	**Integrated**	C-18 C-23
DTBZ titration		C-18 C-20 Part A (up to week 15)
DTBZ placebo-controlled trials		C-18 C-23
DTBZ 12 mg, 24 mg, and 36 mg	**Individual**	C-23
DTBZ long-term safety data		C-20 Parts A–C

DTBZ=deutetrabenazine.

Safety of DTBZ During Initiation and Titration in Participants with Tardive Dyskinesia or Huntington's Disease

The proposed **initiation and titration scheme** for **DTBZ osmotic PR formulation QD** is based on real-world/post-marketing data, a comparison of safety events from 3 trials (**Trial C-15, Trial C-18, and Trial C-23**) with participants having either TD or HD-associated chorea, along with modelling and simulation. The safety profile of participants titrated from a daily total dose of 12 mg directly to 24 mg DTBZ did not differ from that of participants treated with an additional incremental dose of 18 mg DTBZ. These data supported exclusion of the 18 mg dosing step from initiation and titration scheme.

Phase 3 Clinical Trials in Participants with Tardive Dyskinesia

Trial SD-809-C-18: Flexible Dose Efficacy Trial in Tardive Dyskinesia

SD-809-C-18 was a Phase 2/3 randomised, double-blind, placebo-controlled, parallel-group trial in participants with TD. Participants initiated DTBZ at a low dose (12 mg) and then escalated to a dose that observed maximum benefit while minimizing side effects, up to a maximum daily dose of 48 mg.

Participants were randomised in a 1:1 ratio to receive either DTBZ BID (initiated at 12 mg with titration up to a maximum of 48 mg daily dose) or placebo. The trial included a screening period of up to 4 weeks, a 6-week titration period, a 6-week maintenance period, and a 1week washout period. During the 6-week titration period, investigators titrated the dose of trial drug (DTBZ or placebo) on a weekly basis to a dose at which adequate dyskinesia control was achieved and the participant tolerated the treatment regimen, or until the maximum permitted dose was reached.

A total of 117 participants with TD were randomised to DTBZ (N=58) or placebo (N=59) treatment and received at least 1 dose of trial drug. Six participants in the DTBZ group withdrew from the trial, including 1 participant due to an adverse event AE). Seven participants in the placebo group also withdrew from the trial, including 2 participants due to an AE.

The mean total duration of trial drug exposure was similar between the 2 treatment groups (77.39 days for DTBZ, 77.64 days for placebo).

Key Safety Results

- DTBZ was generally well tolerated during the 6 weeks of the titration period and the 6 weeks of the maintenance period for the treatment of TD.
- More serious adverse events (SAEs) occurred in the placebo group (5 participants [8.5%]) compared with the DTBZ group (3 participants [5.2%]). All these events were assessed by the investigator as unrelated or unlikely related to trial drug or placebo and all resolved or were resolving.
- The frequency of severe AEs was similar in both treatment groups (5.2% in DTBZ and 5.1% in placebo).
- No deaths were reported for Trial C-18.
- Three participants withdrew due to AEs, with 1 participant (1.7%) in the DTBZ group and 2 participants (3.4%) in the placebo group.
- The frequency of AEs leading to dose suspension or withdrawal from the trial was higher in the placebo group (8.5% and 3.4%, respectively) than the DTBZ group (5.2% and 1.7%, respectively).
- Somnolence was the most frequent AE (13.8% of participants receiving DTBZ and 10.2% of participants receiving placebo), although all events occurred during the titration period and resolved without dose reduction.
- The frequency of AEs leading to dose reduction was higher in the DTBZ group (10.3%) than in the placebo group (5.1%); all these events resolved after dose reduction, with the exception of an event of mild spinocerebellar ataxia during the titration phase.
- Impaired CYP2D6 function did not alter the incidence or severity of AEs, or the incidence of AEs that led to dose reduction, dose suspension, or withdrawal.

Trial SD-809-C-23: Fixed Dose Efficacy Trial in Tardive Dyskinesia

SD-809-C-23 was a Phase 3, double-blind, placebo-controlled, and parallel-group trial in participants with TD where all participants started at a low initial dose and then escalated to a pre-specified target dose.

Participants were randomly assigned (1:1:1:1) to receive 1 of 3 fixed target dose regimens of DTBZ BID (12 mg, 24 mg, or 36 mg) or placebo. Participants underwent dose escalation (i.e.. forced titration) over the initial 4 weeks of treatment to reach their target dose, followed by 8 weeks of maintenance therapy at that dose.

A total of 293 participants with TD were randomised and received DTBZ of 12, 24, and 36 mg/day, or placebo (74, 73, 74, and 72 participants, respectively). The trial discontinuation rate was similar for all groups. A total of 34 (11%) participants discontinued the trial during the treatment period: 8 (11%) in the DTBZ 12-mg/day group, 9 (12%) in the 24-mg/day group, 10 (13%) in the 36-mg/day groups, and 7 (9%) in the placebo group. Participants discontinued the trial because of adverse events at a similar frequency in the DTBZ groups (2.7% to 5.4%) as in the placebo group (3%).

The mean duration of exposure to DTBZ was 79.0, 77.5, and 75.8 days for participants in the DTBZ 12-, 24-, and 36-mg/day groups, respectively, and 80.5 days in the placebo group. The median number of days of treatment was 84.0 days for participants in each treatment group.

Key Safety Results

- DTBZ was generally well tolerated at all dose levels.
- The frequency of AEs was similar between the DTBZ and placebo groups, with 36 participants (48.6%), 32 participants (43.8%), and 38 participants (51.4%) in the DTBZ 12-, 24-, and 36-mg/day groups, respectively, and 34 participants (47.2%) in the placebo group experiencing at least 1 AE.
- SAEs were reported in 2.7% to 8.2% of DTBZ treated participants and 5.6% of placebo treated participants.
- The majority of AEs were mild to moderate in severity. The most frequently occurring AEs in the DTBZ-treated participants (from all 3 dose groups) were headache, diarrhoea, nasopharyngitis, and anxiety.
- The frequency of severe AEs was similar between the DTBZ and placebo groups, with a total of 7 DTBZ–treated participants (2 participants [2.7%], 4 participants [5.5%], and 1 participant [1.4%] in the DTZB 12, 24-, and 36mg/day groups, respectively) and 2 placebo treated participants (2.8%) experiencing at least 1 severe AE.
- Four DTBZ-treated participants (3 [4.1%] in the 36-mg/day group and 1 (1.4%) in the 24mg/day group) had a dose reduction due to AEs; 5 DTBZ-treated participants (2.3%) and 2 placebo treated participants (2.8%) had their trial treatment suspended due to AEs; and 11 participants were withdrawn from the trial because of AEs (9 DTBZ-treated participants and 2 placebo-treated participants).
- Two deaths occurred in this trial (1 participant treated with DTBZ 24 mg/day died due to sudden cardiac death, and 1 participant treated with DTBZ 36 mg/day died due to cardio-respiratory arrest). Both deaths were assessed as unrelated to DTBZ.

The frequency of AEs between participants with impaired cytochrome P450 2D6 (CYP2D6) function and participants without impaired CYP2D6 function was similar in all treatment groups, except for the DTBZ 36-mg/day group, which had a higher frequency of AEs in participants with impaired CYP2D6 function; most of the AEs in this group occurred in only 1 participant, and the only AE related to the central

nervous system (CNS) that occurred in more than 1 participant in the DTBZ 36-mg/day group with impaired CYP2D6 function was headache. No other differences were apparent in the frequency or severity of AEs, suggesting that DTBZ was well tolerated independently of CYP2D6 function.

Table 56: Incidence of adverse events hypertension and weight decreased in participants with Tardive Dyskinesia from trials C-18 and C-23 and participants with Huntington's Disease from trial C-15

System Organ Class **MedDRA 17.0 Preferred Term**	**Trials C-18 and C-23 grouped**		**Trial C-15**	
	Placebo (N=131)	**DTBZ (N=279)**	**Placebo (N=45)**	**DTBZ (N=45)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Participants with at least 1 AE	70 (53.4)	147 (52.7)	27 (60.0)	27 (60.0)
Investigations	9 (6.9)	18 (6.5)	3 (6.7)	6 (13.3)
Weight decreased	2 (1.5)	2 (0.7)	1 (2.2)	1 (2.2)
Vascular disorders	4 (3.1)	8 (2.9)	0 (0.0)	2 (4.4)
Hypertension	2 (1.5)	4 (1.4)	0 (0.0)	1 (2.2)

Source: TDISS, Ad Hoc Summary 5; SD-809-C-15 CSR, Table 14.3.1.1 and Table 14.3.1.3
AE=adverse event; DTBZ=deutetrabenazine; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants; n=number of participants in subgroup.

Of note, the review of cases in trial SD-809-C-23 did not provide adequate evidence to establish a causal relationship between DTBZ and hypertension and between DTBZ and weight decreased. Thus, addition of hypertension and weight decreased to the proposed list of ADRs was not justified for Teva.

The applicant was requested to discuss the impact on safety of the absence of an 18 mg dose formulation (for which Teva did not seek MA), resulting in an increment of 12 mg/day for the first increment (starting at 12 mg/day), instead of the 6 mg/day in the clinical program and for higher doses. Teva emphasised that "*the incidence of AEs during the initiation and titration period in participants treated with DTBZ (39%) was similar to that in participants treated with placebo (42%), while the incidence of treatment-related AEs was lower in participants treated with DTBZ than with placebo (17% and 27%, respectively)*". Additionally, based on data provided, the safety profile did not largely differ across 12 mg and 24 mg doses. In addition, the applicant a provided an exposure-safety modelling analysis. Although, no further detail on the construction of the model was presented, and thus further assessed, results suggested there is no increased risk when increasing the titration step from 12 mg.

Teva explained that, among the 79 patients who discontinued "due to withdrawal by participant", 62 (78%) did not report any AEs within approximately 1 month before or during the early termination visit, 17 reported AEs mainly non-serious and mild or moderate in severity. Among these 17 subjects, 2 reported SAEs (epilepsy and schizophrenia) classified as not related to DTBZ by the investigator. These data did not suggest a hidden problem of tolerance behind this high rate of discontinuations "due to withdrawal by participant".

Trial SD-809-C-20: Open-Label Trial in Tardive Dyskinesia

SD-809-C-20 was a Phase 3 open-label, single-arm trial which included participants with TD who had successfully completed one of the parent trials (C-18 or C-23). It consisted of 3 parts:

- Part A: Open-label persistence of effect
- Part B: Double-blind, randomised withdrawal

- Part C: Open-label safety in the European Union

The trial included a screening period, a 6-week titration, an open-label treatment up to 158 weeks (Part A), a 1-week randomised withdrawal period followed by 12 weeks of open-label treatment (together called Part B) and an additional 52 weeks of open-label treatment available for participants in Europe (Part C).

In Part A, flexible dose titration to effect, participants were titrated in a response-driven manner, similar to Trial C-18. They reached a stable dose through a 6-week titration period with additional dose adjustments as needed. If a participant experienced an AE during maintenance, the investigator could reduce or suspend DTBZ dose.

During the double-blind period, in Part B, participants were randomly assigned to receive treatment with DTBZ or a matching placebo in a 1:1 ratio stratified by concomitant dopamine receptor antagonist (DRA) usage. Parts A and B, following the randomised withdrawal, were open label; however, prior treatment assignment from the parent trial remained blinded.

Of the 368 participants with TD who had successfully completed a qualifying parent trial, 337 participants were enrolled into this trial (227 on DTBZ and 110 on placebo in the parent trial treatment). All 337 participants were evaluated for both safety and efficacy.

In Part A 163 (48%) participants withdrew from the trial during the 3-year treatment period. The main reasons for withdrawal were "withdrawal by participant" (79 [23%] participants), adverse event (33 [10%] participants), lost to follow-up (24 [7%] participants), and "discontinued the trial due to lack of efficacy" (9 [3%] participants). Discontinuations due to AEs were similar during each of the 3 years of the trial.

The duration of Part A was up to 158 weeks of treatment. Mean duration of exposure was 783.6 days, and the median duration of exposure was 1015.0 days. The mean total daily dose was 35.7 mg at the end of titration (week 6), 38.3 mg at week 15, and remained stable throughout the rest of Part A (39.4 mg at week 145).

From Part A 142 participants (42%) enrolled into Part B; of these 142 134 (94%) completed the trial (68 [96%] DTBZ group and 66 [93%] placebo group). Eight (6%) participants discontinued from the trial (3 [4%] DTBZ group; 5 [7%] placebo). The reasons for withdrawal were lost to follow-up and withdrawal by participant (4 [1%] participants from each reason). Eighty participants (24% of the 337 participants who enrolled in Part A) enrolled into Part C, the additional 52-week open-label safety for European Union (EU) participants. Of these 80 participants, 73 (22%) completed the trial; the reasons for withdrawal were AE (2 [<1%]), death (2 [<1%]) and withdrawal by participant (3 [<1%]).

According to Teva, out of the 368 participants who completed studies C-18 and C-23, 25 participants (7%) (8 participants from study C-18 and 17 participants from study C-23) were not enrolled into the long-term Trial C-20. Among these patients, 8 participants had been randomised to receive placebo and 17 participants had been randomised to receive DTBZ in pivotal trials. Regrettably, the applicant did not collect the reasons why these participants did not join the long-term study.

In C-18, none of the roll-over patients from DTBZ arm (n=4) experienced SAE; 1 subject experienced AEs leading to dose reduction. In C-23, none of the roll-over patients from DTBZ arm (n=13) had experienced SAE; 2 subjects experienced AEs leading to dose reduction.

Although the proportion of patients who did not roll over in the long-term study was overall slightly higher for DTZB than for placebo arm (similar in C1-18 4vs4), this proportion remained quite limited. Additionally, the safety data provided did not suggest any particular signal.

The applicant provided the AEs overview adjusted for the exposure by period (i.e., <6, ≥6 to <15, ≥15 to <54, ≥54 to <106, ≥106 to <158, ≥158). However, despite requested to provide an analysis in **number of events per patient-years**, Teva did not follow such request. Instead, it provided results in **number of participants per patient-years**. Additionally, it was indicated that "for calculating patient-years in each category, participants with an AE contributed with treatment exposure up to time of their first AE". However, this was not a time to event analysis and a patient even having an AE should continue to account for the denominator if still receiving the treatment; the rationale behind the applicant's strategy was later clarified and understood. Nevertheless, it seemed that overall, there was no worsening of tolerance over time.

The choice of the threshold of 2% to complete the list of the ADR remained unclear, and the decision of the applicant appeared purely arbitrary. However, it was indicated that "to ensure no important AEs were overlooked, the applicant reviewed AEs not surpassing the 2% threshold (i.e., occurring <2%) to identify any additional clinically-relevant ADRs". Additionally, the applicant indicated that "an additional analysis of post-marketing safety data from patients with TD and patients with HD showed no difference between rates of ADRs". Thus, all together, it was conveyed this whole approach should allow to overcome the risk of non-inclusion of safety risk of importance with a frequency below 2%.

Key Safety Results

- DTBZ at dosages of 6 to 48 mg per day was generally safe and well tolerated for up to 4 years of treatment in participants with TD. No new safety signals were identified.
- A total of 269 (79.8%) participants experienced an AE in Parts A and B of this trial. Most AEs were considered mild or moderate in severity. The most frequently reported AEs were anxiety (42 [12.5%] participants), depression (35 [10.4%] participants), and somnolence (34 [10.1%] participants). Twenty-three (28.8%) participants experienced at least 1 AE during the treatment period during Part C of this trial. All AEs in Part C were reported by 1 (1.3%) participant except for nasopharyngitis, back pain, and dyskinesia which were reported by 2 (2.5%) participants. The most frequently occurring AEs during the maintenance period in Parts A and B (i.e., anxiety, depression, weight decreased and urinary tract infection) were not reported by participants in Part C.
- Sixty-eight (20.2%) participants experienced at least 1 SAE during Part A and B. The most frequently reported SAEs period were schizophrenia (5 [1.5%] participants), pneumonia (4 [1.2%] participants), and chronic obstructive pulmonary disease (4 [1.2%] participants). In Part C, 5 (6.3%) participants experienced at least 1 SAE. All SAEs in Part C were reported once each.
- Safety scales revealed no evidence of subclinical toxicity of worsening of depression, anxiety, somnolence and sedation, parkinsonism-like events, or akathisia associated with long-term DTBZ treatment.
- Exposure-adjusted incidence rates (EAIRs) were highest during the titration period for the standardized medical dictionary for regulatory activities (MedDRA) query (SMQ) adverse events of depression, Parkinson-like events, and Torsade de pointes/QT prolongation and for somnolence and sedation compared to later time intervals. EAIRs for Akathisia SMQ adverse events were low throughout the trial.
- The incidence of suicide and self-injury SMQ adverse events, overall EAIRs and EAIRs by time period were low. Columbia Suicide Severity Rating Scale (C-SSRS) did not indicate any increase of suicidal ideation, suicidal behaviour, and self-injurious behaviour without suicidal intent during the trial. There were no completed suicides.
- A total of 42 (12.5%) participants discontinued the trial due to AEs during Part A and B. The most frequent AEs leading to discontinuation were psychiatric disorders (11 [3.3%] participants), followed

by nervous system disorders (8 [2.4%] participants), and cardiac disorders (7 [2.1%] participants). Individual AE preferred terms (PT) leading to discontinuation were reported by 1 to 2 participants each. In Part C of this trial, 3 (3.8%) participants had 4 adverse events leading to discontinuation from the trial.

- Eight deaths were reported during Parts A and B of the trial, all of which were considered unlikely related or unrelated to DTBZ. One additional participant died 56 days after DTBZ last dose , which was 25 days after being withdrawn from the trial. Two deaths were reported during Part C.
- There were no clinically meaningful changes in clinical laboratory, vital signs, electrocardiogram (ECG), or physical examination findings for up to 3 years of DTBZ treatment.
- During the 1-week randomised withdrawal period (Part B) compared to Part A, no new safety signals or clinically significant safety changes were observed.

Phase 3 Clinical Trials in Participants with Huntington's Disease

Safety data from Phase 3 trials in participants with HD-associated chorea were provided as supportive data for this MAA. These data were considered relevant for safety assessment as the mechanism of DTBZ action does not differ between patients with TD and those with HD-associated chorea.

Trial SD-809-C-15: Flexible Dose Efficacy Trial in Huntington's Disease

SD-809-C-15 was a randomised, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy, safety, and tolerability of DTBZ in adults with HD-associated chorea.

A total of 90 participants were randomised between DTBZ (N=45) and placebo (N=45) treatment groups; 44 (97.8%) participants in DTBZ group and 43 (95.6%) in the placebo group completed trial participation. Participants initiated DTBZ at a low dose (6 mg) and then escalated to a dose observed to adequately control chorea and that was well tolerated, up to a maximum daily dose of 48 mg.

The mean total duration of trial drug exposure was similar between the 2 treatment groups (84.4 days for DTBZ, 81.8 days for placebo). The mean duration for titration (defined as the time from randomisation to the time to firstly receiving the maintenance dose), was 42.2 days and 47.0 days, for participants in DTBZ-treated and placebo-treated groups, respectively.

Key Safety Results:

- The overall frequency rates of AEs were similar in participants treated with DTBZ and those receiving placebo (27 participants [60%] in each treatment group experienced at least 1 AE).
- One participant (2.2%) in the DTBZ group experienced the SAEs of chronic cholecystitis and agitated depression; 1 participant (2.2%) in the placebo group experienced an SAE of exacerbation of chronic obstructive pulmonary disease (COPD).
- The frequencies of dose reduction, dose suspension or withdrawal from the trial due to AEs were low, with the same numbers reported for both the DTBZ-treated and placebo-treated participants (dose reduction: 3 participants [6.7%], dose suspension: 1 participant [2.2%], or withdrawal from the trial: 1 participant [2.2%]).
- Two participants (4%) in the DTBZ group and 1 (2.2%) in the placebo group experienced severe AEs.
- No deaths were reported.

- A low frequency of neurologic and psychiatric AEs, such as depression, anxiety, and akathisia, were observed during treatment with DTBZ and the frequencies of these AEs in participants treated with DTBZ were similar to or lower than those in participants treated with placebo.
- Safety scales were included in the trial to monitor for symptoms of depression, suicidality, anxiety, somnolence, parkinsonism, akathisia and dysphagia. None of these scales revealed subclinical toxicity associated with DTBZ treatment.
- The trial demonstrated that DTBZ could be titrated safely in participants with HD-associated chorea.

Trial SD-809-C-16: Open-Label Trial in Huntington's Disease

SD-809-C-16 was an open-label, single-arm, 2-cohort trial designed to evaluate the long-term safety and tolerability of DTBZ dose adjustments/titrations for the treatment of HD-associated chorea over long term treatment.

The following 2 groups of participants were enrolled into this trial:

- Rollover participants / cohort who had successfully completed the parent Trial C-15, including a 1-week washout period and then initiated long-term DTBZ treatment.
- Switch participants / cohort received a stable dose of TBZ for treatment of HD-associated chorea and were switched overnight to DTBZ based on an algorithm designed to achieve comparable daily exposure to total alpha- and beta-dihydrotetrabenazine ([α+β] HTBZ) metabolites. These participants similarly initiated a long-term DTBZ treatment regimen after the initial switch from TBZ therapy.

A total of 119 participants received DTBZ (Rollover Cohort: 82 participants; Switch Cohort: 37 participants).

A total of 38 participants discontinued DTBZ: 26 participants from the Rollover Cohort (of which 11 participants discontinued due to adverse events and 1 due to death); and 12 participants from the Switch Cohort (of which 1 participant discontinued due to AE).

The mean total duration of trial drug exposure was similar across the 2 cohorts (810 days for the Rollover Cohort and 869 days for the Switch Cohort). A total of 81 participants in the Rollover Cohort achieved a stable dose by a mean of 40.6 days and 35 participants in the Switch Cohort achieved a stable dose by a mean of 31.1 days.

Key Safety Results:

- Seventy-seven Rollover (93.9%) and 35 Switch participants (94.6%) experienced at least 1 AE over the entire treatment period.
- There was 1 sudden cardiac death (1.2%) reported in the Rollover Cohort during the trial. The investigator assessed this death as unlikely related to the trial drug. The sponsor assessed this death as unrelated to the trial drug. There were no deaths in the Switch Cohort.
- Twenty-one Rollover participants (25.6%) and 11 (29.7%) Switch participants experienced at least 1 SAE. The majority of SAEs were psychiatric disorders in the Rollover Cohort and infections and infestations in the Switch Cohort. Thirteen Rollover participants (15.9%) and 3 Switch participants (8.1%) withdrew from the trial due to an AE, 20 Rollover participants (24.4%) and 10 Switch participants (27.0%) had an AE that led to a dose reduction, and 8 Rollover participants (9.8%) and 3 Switch participants (8.1%) had an AE that led to a dose suspension.

- Fall, a well-known consequence of HD, was the most frequent AE in both Rollover and Switch participants. Most of the falls were considered unrelated to the trial drug and related to the underlying disease.
- Safety scales used to monitor for symptoms of depression, suicidality, anxiety, somnolence, parkinsonism, akathisia, and dysphagia did not reveal development of any new subclinical toxicity associated with DTBZ; changes in cognitive function in a subset of participants were generally not associated with functional declines.
- There was no unique pattern of AEs during the first week of DTBZ therapy following the overnight switch from TBZ to DTBZ in the Switch participants, suggesting that overnight dose conversion can be conducted safely and is not associated with any safety concerns.
- DTBZ was generally well tolerated; the overall safety results were consistent with those in Trial C-15. There were no new safety findings or concerns.

Phase 1 Clinical Trials in Healthy Participants

Trial TV50717-BE-10179

TV50717-BE-10179 was a Phase 1, open-label, single-centre, randomised, 2-period, 2-sequence, crossover repeated dose trial using a full replicate design to compare the bioequivalence (BE) and relative bioavailability (BA) of administration of 24 mg DTBZ osmotic PR tablets QD compared to 12 mg DTBZ matrix tablets BID in healthy participants who were extensive or intermediate CYP2D6 metabolizers, or a combination of the two.

The primary objective was to assess BE with regard to area under the plasma concentration-time curve over a 24-hour interval at steady state ($AUC_{0\text{-}24h,ss}$) of DTBZ (parent), α-HTBZ and β-HTBZ metabolites (individually and as a sum) at a steady state, following repeated administration of 24 mg DTBZ osmotic PR formulation QD compared to repeated administration of 12 mg DTBZ matrix formulation BID under fed conditions.

Key Safety Results

- DTBZ appeared safe and well tolerated following oral administration of 24 mg QD (Test) and DTBZ 12 mg BID (Reference) formulations up to 7 days.
- No new safety findings emerged in this trial.

Trial TV50717-PK-10175

TV50717-PK-10175 was a Phase 1, open-label, single centre, randomised, 4-period, 4-sequence crossover trial to assess dose proportionality of the dosage strengths from 6 mg to 24 mg and to assess dose proportionality of DTBZ (parent), α-HTBZ and β-HTBZ (metabolites individually and as a sum) following a single dose of DTBZ osmotic PR tablets QD administered as 2×6 mg, 1×12 mg, 1×24 mg, and 2×24 mg under fed conditions in healthy participants, who were known extensive or intermediate CYP2D6 metabolizers (or a combination of the 2), over the recommended clinical dose range (6 mg to 48 mg).

This trial consisted of 2 primary objectives:

- Key primary objective: to assess the dose proportionality (6 mg to 24 mg) of the pharmacokinetics (PK) of DTBZ, α-HTBZ and β-HTBZ (metabolites individually and as a sum) after single doses of DTBZ osmotic PR tablet QD administered as 2×6 mg, 1×12 mg, and 1×24 mg under fed conditions;

- Co-primary objective: to assess relative BA between 2×6 mg and 1×12 mg DTBZ osmotic PR tablet QD administered as single doses in the fed state for all analytes (DTBZ, α-HTBZ and β-HTBZ [metabolites individually and as a sum]).

Key safety results

- A single dose of DTBZ administered as 2×6 mg, 1×12 mg, 1×24 mg and 2×24 mg under fed conditions appeared safe and well tolerated in healthy participants.
- No new safety findings emerged in this trial.

Trial TV50717-BE-10165

TV50717-BE-10165 was a Phase 1, open-label, single center, randomised, 3-period, 3-treatment, 6-sequence, crossover trial to assess relative BA of DTBZ (parent), deuterated α-HTBZ and deuterated β-HTBZ metabolites (individually and as a sum), following oral administration of 24 mg DTBZ osmotic PR tablet QD (Test) compared to DTBZ 12 mg matrix tablets BID dosed 12 hours apart under fed conditions in healthy participants. The trial also evaluated the effect of food on the PK of DTBZ, deuterated α-HTBZ and deuterated β-HTBZ (individually and as a sum) following a single oral dose of DTBZ 24-mg QD osmotic PR tablet.

Key safety results

- DTBZ appeared safe and well tolerated following oral administration of 24 mg (Test, under both fasted and fed conditions) and DTBZ 12 mg BID (Reference, under fed conditions).
- No new safety findings emerged in this trial.

Trial TV50717-BE-10192

TV50717-BE-10192 was a Phase 1, open label, single center, randomised, 2 period, 2 treatment, 2 sequence crossover trial to assess BE of DTBZ (parent), as well as deuterated α-HTBZ and deuterated β-HTBZ metabolites (individually and as a sum), following oral administration of single doses of 1×48 mg DTBZ osmotic PR tablet QD (Test) compared to 2×24 mg osmotic PR tablet QD DTBZ (Reference) under fasted conditions in healthy participants. The trial included healthy participants who were extensive or intermediate CYP2D6 metabolizers or a combination of the 2.

Key Safety Results:

- The safety profiles of DTBZ 1×48 mg and DTBZ 2×24 mg were similar, with a low and similar frequency of AEs for both treatments (Test and Reference).
- No new safety findings emerged in this trial.

Trial TV50717-BE-10201

TV50717-BE-10201 was a Phase 1, open label, single center, randomised, 2 period, 2 treatments, 2 sequence crossover trial to assess the BE of DTBZ (parent), as well as deuterated α-HTBZ and deuterated β-HTBZ metabolites (individually and as a sum), following oral administration of single doses of 1×36 mg DTBZ osmotic PR tablet QD (Test) compared to 1×12 mg + 1×24 mg osmotic PR tablet QD DTBZ (Reference) under fasted conditions in healthy participants. The trial included healthy participants who were extensive or intermediate CYP2D6 metabolizers or a combination of the 2.

Key Safety Results:

- The safety profiles of DTBZ 1×36 mg and DTBZ 1×12 mg + 1×24 mg were similar, with a low and similar frequency of AEs for both treatments (Test and Reference).

- No new safety findings emerged in this trial.

2.6.8.1. Patient exposure

2.6.8.1.1. Extent of Exposure

Extent of Exposure in Phase 3 Trials in Participants with Tardive Dyskinesia

In the 3 Phase 3 trials, 514 participants with TD were treated with DTBZ or placebo (DTBZ=384; placebo=130), with a mean duration of exposure of 79.4 days for placebo, 78.9 days for 12 mg, 77.4 days for 24 mg, 75.6 days for 36 mg and 92.7 days for DTBZ titration.

Exposure to DTBZ across the clinical development program in TD is summarized in the next table. Of the 384 participants, 67% received DTBZ for ≥54 weeks, 53% for ≥106 weeks, and 37% for ≥158 weeks.

Table 57: Trial drug exposure in the Tardive Dyskinesia safety population

Trial, n (%)	Any DTBZ exposure	≥6 weeks	≥15 weeks	≥28 weeks	≥54 weeks	≥106 weeks	≥158 weeks
C-18	58 (100)	53 (91.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
C-23	216 (100)	195 (90.3)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
C-20 Parts A, B and C	337 (100)	325 (96.4)	307 (91.1)	287 (85.2)	253 (75.1)	203 (60.2)	156 (46.3)
Total TD participant exposure to DTBZ[a]	384 (100)	355 (92.4)	324 (84.4)	294 (76.6)	256 (66.7)	205 (53.4)	143 (37.2)
Patient years of treatment	745.84	--	--	--	--	--	--

Source: TDISS20, MAA Ad Hoc Summary 4.
[a] Total TD participant exposure includes only C-20 Part A + parent trials.
DTBZ=deutetrabenazine; n=number of participants in subgroup; TD=tardive dyskinesia.
Note: Parent trials include Trials C-18 and C-23. The parent trials exposure is combined with Trial C-20 Part A exposure. For participants randomised to placebo in the parent trials, their exposure is only from Trial C-20 Part A. For participants randomised to DTBZ in the parent trials, their exposure is combined exposure between the parent trials and Trial C-20 Part A. For participants randomised to DTBZ in the parent trials who did not enter Trial C-20, their exposure is only from the parent trials.

Extent of Exposure in Phase 3 Trials in Participants with Huntington's disease

In support of the extent of exposure in participants with TD, data from those with HD associated chorea treated with at least 2 doses of DTBZ are presented in the next table.

Table 58: Trial drug exposure in the Huntington's Disease safety population

Trial, n (%)	Any DTBZ exposure	≥8 weeks	≥15 weeks	≥28 weeks	≥52 weeks
SD-809-C-15	45 (100.0)	45 (100.0)	0 (0)	0 (0)	0 (0)
SD-809-C-16	119 100.0)	117 (98.3)	114 (95.8)	109 (91.6)	100 (84.0)
Total HD participant exposure to DTBZ	121 (100.0)	119 (98.3)	116 (95.9)	111 (91.7)	102 (84.3)
Patient years of treatment	280.26	--	--	--	--

Source: HDISS19, Table 3.2.
DTBZ=deutetrabenazine; HD=Huntington's disease; n=number of participants.

Extent of Exposure in Phase 1 Trials in Healthy Participants

Safety analyses from the Phase 1 DTBZ trials included 765 healthy adult participants exposed to DTBZ osmotic PR formulation QD.

Table 59: Exposure to trial drug in the phase 1 trials

Trial	QD Tablet Exposure, N	Safety Analysis Set by Sequence, n	Safety Analysis Set by Treatment, n	Dose Strengths of Test Formulation Used in Clinical Trials	Reference Investigational Product
TV50717-BE-10179	243	R-T: 130 T-R: 132	243 participants received DTBZ	DTBZ 24 mg osmotic PR formulation QD	DTBZ 12 mg clinical matrix formulation BID
TV50717-PK-10175	116	29 participants per treatment sequence (4 treatment sequences in total)	116 participants received at least 1 dose of DTBZ; 103 received all 4 DTBZ treatments administered	DTBZ osmotic PR formulation QD administered as 2×6 mg, 1×12 mg, 1×24 mg, and 2×24 mg under fed conditions	Not applicable
TV50717-BE-10165	84	14 participants per treatment sequence (6 treatment sequences in total)	84 participants received a single dose of each of the 3 DTBZ treatments administered	1×24 mg DTBZ osmotic PR formulation QD fed;1×24 mg DTBZ osmotic PR formulation QD fasted	2×12 mg DTBZ clinical matrix formulation BID (12 h apart), fed
TV50717-BE-10192	190	95 participants per treatment sequence (2 treatment sequences in total)	189 participants received a single dose each of the 2 DTBZ treatments administered; an additional 1 participant received only a single dose of Reference treatment	DTBZ osmotic PR formulation QD administered as 1×48 mg fasted	DTBZ osmotic PR formulation QD administered as 2×24 mg fasted
TV50717-BE-10201	132	66 participants per treatment sequence (2 treatment sequences in total)	123 participants received a single dose each of the 2 DTBZ treatments administered; an additional 9 participants received a single dose of either Test or Reference treatment.	DTBZ osmotic PR formulation QD administered as 1×36 mg fasted	DTBZ osmotic PR formulation QD administered as 1×12 mg + 1×24 mg fasted

Source: CSR TV50717-BE-10179, Section 10; CSR TV50717-PK-10175, Section 10; CSR TV50717-BE-10165, Section 10; CSR TV50717-BE-10192, Section 10; CSR TV50717-BE-10201, Section 10.
BID=twice daily; CSR=clinical study report; DTBZ=deutetrabenazine; h=hour; N=number of participants; n=number of participants in subgroup; PR=prolonged release; QD=once daily; R-T=Reference-Test sequence; T-R=Test-Reference sequence.

2.6.8.1.2. Duration of Exposure

Duration of Exposure in Phase 3 Trials in Participants with Tardive Dyskinesia

The majority of participants in the integrated safety dataset received DTBZ matrix formulation BID for >9 weeks to ≤15 weeks. Data after week 15 was not included to assure meaningful integration of information based on equivalent treatment durations for the titration group trials (Trials C-18 and C-20): trial C-18 had a 6week titration period + 6week treatment period (12 weeks in total). The week 15 cutoff for Trial C-20 (rather than a week 12 cutoff matching Trial C-18) was based on the first visit after the titration period (there was no scheduled visit for week 12 in Trial C-20). Differences in exposure duration resulted from the difference in treatment period duration between the trials included in the integrated analysis.

At week 12/15 (which refers to the short-term data up to week 12, including the integrated data from Trial C-18 week 12 and Trial C-20 week 15) the mean total daily dose was 38.4 mg in the DTBZ titration group.

Table 60: Trial drug exposure at each visit by participant group (Safety Population) with Tardive Dyskinesia

Trial	Trials C-18 and C-23	Trial C-23			Trials C-18 and C-20
Duration/Parameter	**Placebo (N=130)**	**DTBZ 12 mg (N=72)**	**DTBZ 24 mg (N=72)**	**DTBZ 36 mg (N=72)**	**DTBZ Titration[a] (N=168)**
Weeks treated, n (%)					
≤2 weeks	6 (5)	3 (4)	2 (3)	4 (6)	2 (1)
>2 to ≤4weeks	0	2 (3)	4 (6)	3 (4)	3 (2)
>4 to ≤6 weeks	2 (2)	1 (1)	1 (1)	1 (1)	4 (2)
>6 to ≤9 weeks	3 (2)	1 (1)	2 (3)	2 (3)	4 (2)
>9 to ≤15 weeks	119 (92)	64 (89)	63 (88)	62 (86)	155 (92)
>15	0	1 (1)	0	0	0
Duration of treatment (days)					
n	130	72	72	72	168
Mean (SD)	79.4 (17.58)	78.9 (19.24)	77.4 (20.04)	75.6 (22.40)	92.7 (20.29)
Median	84.0	84.0	84.0	84.0	105.0
Min, max	3, 102	2, 110	2, 90	5, 87	10, 105

Source: TDISS20, MAA Ad Hoc Summary 6.
[a] The DTBZ titration group included data from participants receiving DTBZ in Trial C-18 through week 12 plus data from C-20 through week 15 for participants who were previously in the placebo treatment group in Trials C-18 or C-23.
DTBZ=deutetrabenazine; max=maximum; min=minimum; N=number of participants; n=number of participants in subgroup; SD=standard deviation.

The long-term drug exposure of over 4 years for participants with TD from Trial C-20 is presented in the next table.

Table 61: Total daily dose in the long-term trial C-20 (Safety Population) in participants with Tardive Dyskinesia

	Trial C-20 (N=337) Parts A, B and C
Duration of treatment (days)	
N	337
Mean (SD)	866.1 (535.56)
Median	1015.0
Min, max	14, 1700
Week 2 - total daily dose (mg)	
N	333
Mean (SD)	17.4 (1.77)
Min, max	12, 18
Week 4 - total daily dose (mg)	
N	328
Mean (SD)	27.5 (4.89)
Min, max	12, 30
Week 6 – total daily dose (mg)	
N	318
Mean (SD)	35.7 (7.88)
Min, max	12, 42
Week 15 - total daily dose (mg)	

N	295
Mean (SD)	38.3 (9.71)
Min, max	12, 48
Week 28 - total daily dose (mg)	
N	274
Mean (SD)	38.4 (9.93)
Min, max	12, 48
Week 54 - total daily dose (mg)	
N	241
Mean (SD)	38.7 (10.30)
Min, max	12, 60
N	188
Mean (SD)	39.3 (10.31)
Min, max	12, 60
Week 145 - total daily dose (mg)[a]	
N	161
Mean (SD)	39.4 (10.52)
Min, max	12, 60
Trial C-20 (N=337) Part A	
Week 158 - total daily dose (mg)[a]	
N	32
Mean (SD)	37.3 (10.96)
Min, max	12, 48

Source: TDISS20, MAA Ad Hoc Summary 7A and MAA Ad Hoc Summary 7B.
[a] In Trial C-20, participants in Part A could enrol to Part B before completing week 158 if they were on a stable dose of DTBZ and any concomitant dopamine receptor antagonist for a minimum of 4 weeks. Therefore, some of the Part A participants did not complete 158 weeks of Part A because they moved into Part B when the option was available to them.
max=maximum; min=minimum; N=number of participants; SD=standard deviation.

Duration of Exposure in Healthy Participants

- **Trial TV50717-BE-10179**: Test treatment was administered once-daily (24 mg DTBZ osmotic PR formulation QD) for 7 consecutive days and Reference (12 mg DTBZ matrix formulation BID) treatment was administered twice-daily 12 hours apart for 7 consecutive days. There was a 6-day washout period between treatments. In total, 243 participants were treated with Test (osmotic PR formulation QD) treatment and 243 participants with Reference (matrix formulation BID) treatment.
- **Trial TV50717-PK-10175**: 113, 110, 106, and 111 participants received a single dose of DTBZ osmotic PR formulation QD administered as 2×6 mg, 1×12 mg, 1×24 mg, and 2×24 mg doses of trial drug, in 1 of 4 treatment sequences, respectively. There was a 6-day wash-out period between treatments. A total of 103 participants received all 4 doses administered (23, 27, 28, and 25 participants), while 13 participants did not receive all doses administered (6, 2, 1, and 4 participants).
- **Trial TV50717-BE-10165**: 84 participants received a single dose of each of the 3 treatments administered: DTBZ 24 mg osmotic PR tablet QD in the fed state (osmotic PR formulation QD fed), DTBZ 24 mg osmotic PR tablet QD in the fasted state (osmotic PR formulation QD fasted), and DTBZ 2×12 mg matrix tablet BID, 12 mg administered 12 hours apart in the fed state (matrix formulation BID fed) in 1 of 6 treatment sequences. There was a 6-day washout period between treatments.

- **Trial TV50717-BE-10192**: 189 participants received a single dose of each of the 2 treatments administered: DTBZ 1×48 mg and 2×24 mg osmotic PR tablets QD, with a 6-day washout period between treatments, in the fasted state; and 1 participant received a single dose of 2×24 mg osmotic PR tablets QD.
- **Trial TV50717-BE-10201**: 123 participants received a single dose of each of the 2 treatments administered: DTBZ 36 mg and 1×12 mg + 1×24 mg osmotic PR tablets QD, with a 6-day washout period between treatments, in the fasted state; 9 additional participants received a single dose of either the 36 mg or 1×12 mg + 1×24 mg osmotic PR tablets QD.

2.6.8.1.3. Disposition of Participants

Disposition of Participants with Tardive Dyskinesia from Phase 3 Trials

Most participants with TD from the Phase 3 trials in the intent-to-treat (ITT) population completed up to week 12 in Trials C-18 and C-23. Data from Trial C-20 were included up to week 15 and integrated with week 12 data from C-18.

Table 62: Disposition by participant group (ITT population) for participants with Tardive Dyskinesia in phase 3 trials

Analysis group, n (%)	Trials C-18 and C-23		Trial C-23		Trials C-18 and C-20
	Placebo	DTBZ 12 mg	DTBZ 24 mg	DTBZ 36 mg	DTBZ Titration
ITT population	132 (100)	73 (100)	73 (100)	73 (100)	168 (100)
ITT population, not treated	2 (2)	1 (1)	1 (1)	1 (1)	0
Safety population	130 (98)	72 (99)	72 (99)	72 (99)	168 (100)
Completed up to week 12/15	118 (89)	65 (89)	64 (88)	63 (86)	152 (90)
Discontinued prior to week 12/15 due to:	14 (11)	8 (11)	9 (12)	10 (14)	16 (10)
Adverse event	4 (3)	4 (5)	1 (1)	2 (3)	4 (2)
Death	0	0	1 (1)	1 (1)	0
Lack of efficacy	0	0	0	0	1 (<1)
Lost to follow-up	3 (2)	1 (1)	4 (5)	0	3 (2)
Noncompliance with trial drug	1 (<1)	1 (1)	2 (3)	1 (1)	2 (1)
Protocol deviation	3 (2)	0	0	1 (1)	0
Withdrawal by subject	3 (2)	2 (3)	1 (1)	4 (5)	6 (4)
Trial terminated	0	0	0	0	0
Other	0	0	0	1 (1)	0

Source: TDISS20, MAA Ad Hoc Summary 8.
ITT=Intent-to-Treat; n=number of participants in subgroup.
Note: The denominator for calculating percentages is the number of participants in the ITT Population.

Of the 337 participants in Trial C-20, 32 (9%) completed Part A of the trial and did not enrol into Part B and 163 (48%) discontinued, leaving 142 (42%) participants to enrol to Part B. Of the 134 participants who completed Part B 80 (24% of the 337 participants who enrolled in Part A of the trial) from the EU enrolled in Part C.

Table 63: Summary of participant disposition in long-term trial C-20 Parts A, B, and C (ITT population)

Analysis Group, n (%)	DTBZ
ITT population	**337 (100)**
ITT population, not treated	0
Safety population[a]	337 (100)
Completed Part A	**32 (9)**
Discontinued during Part A due to:	163 (48)
Adverse event	33 (10)
Death	8 (2)
Lack of efficacy	9 (3)
Lost to follow-up	24 (7)
Non-compliance with trial drug	3 (<1)
Protocol deviation	1 (<1)
Withdrawal by subject	79 (23)
Trial terminated	1 (<1)
Other	5 (1)
Randomized withdrawal ITT population	142 (42)
Randomized withdrawal mITT population	128 (38)
Completed Part B	**134 (40)**
Discontinued during Part B	8 (2)
Adverse event	0
Death	0
Lack of efficacy	0
Lost to follow-up	4 (1)
Non-compliance with trial drug	0
Protocol deviation	0
Withdrawal by subject	4 (1)
Trial Terminated	0
Other	0
Part C ITT population	80 (24)
Part C safety population	80 (24)
Completed Part C	**73 (22)**
Discontinued during Part C	7 (2)
Adverse event	2 (<1)
Death	2 (<1)
Lack of efficacy	0
Lost to follow-up	0
Non-compliance with trial drug	0
Protocol deviation	0
Withdrawal by subject	3 (<1)
Trial Terminated	0
Other	0
Completed trial	**159 (47)**

Source: TDISS20, MAA Ad Hoc Summary 9.

[a] In Trial C-20, participants in Part A could enrol to Part B before completing week 158 if they were on a stable dose of DTBZ and any concomitant dopamine receptor antagonist for a minimum of 4 weeks. Therefore, some of the Part A participants did not complete 158 weeks of Part A because they moved into Part B when the option was available to them.

DTBZ=deutetrabenazine; ITT=intent-to-treat; mITT=modified intent-to-treat; n=number of participants in subgroup.
Note: The denominator for calculating percentages is the number of participants in the ITT Population.

Disposition of Healthy Participants from Phase 1 Trials

The disposition of healthy adult participants who received single or repeated doses of DTBZ is summarized in the next table.

TV50717-BE-10179: 262 participants were randomised and received at least 1 dose of either Test (osmotic PR formulation QD) or Reference (matrix formulation BID) treatment. Of the 45 early withdrawals, 24 occurred during Reference treatment (5 participants during Test-Reference [T-R] sequence and 19 participants during Reference-Test [R-T] sequence) and 21 during Test treatment (19 participants in T-R sequence, and 2 participants in R-T sequence).

TV50717-PK-10175: 116 participants were enrolled. All received at least 1 dose of 2×6 mg, 1×12mg, 1×24mg, or 2×24 mg DTBZ osmotic PR tablet QD.

TV50717-BE-10165: 84 participants were enrolled and all received all doses. The different doses of trial drug used in the trial were 24 mg osmotic PR tablet QD in the fed state; 24 mg osmotic PR tablet QD in the fasted state and 12 mg DTBZ matrix tablet BID given twice 12 hours apart, in the fed state.

TV50717-BE-10192: 190 participants were enrolled and 189 received both doses while 1 participant withdrew after receiving only a single Reference treatment dose. The different doses of trial drug used in the trial were 1×48 mg and 2×24 mg osmotic PR tablet QD in the fasted state.

TV50717-BE-10201: 132 participants were enrolled and 123 received all doses while 9 participants received a single dose of either Test or Reference treatment. The different doses of trial drug used in the trial were 1×36 mg and 1×12 mg + 1×24 mg osmotic PR tablet QD in the fasted state. Of the 9 (7%) participants who withdrew from the trial 4 were from the T-R group and 5 from the R-T group.

Table 64: Trial disposition of healthy adult participants in phase 1 trials

Trial Disposition, n (%)	TV50717-BE-10179	TV50717-PK-10175	TV50717-BE-10165	TV50717-BE-10192	TV50717-BE-10201
Screened	306	131	107	225	151
Screened but not enrolled/randomized	44	15	23	35	19
Randomized	262 (100)	116 (100)	84 (100)	190 (100)	132 (100)
Completed trial	217 (83)	103 (89)	84 (100)	187 (98)	123 (93)
Discontinued trial	45 (17)	13 (11)	0 (0)	3 (2)	9 (7)
Withdrawal by subject	23 (9)	7 (6)	0 (0)	1 (<1)	7 (5)
Participants discontinued due to AEs	11 (4)	2 (2)	0 (0)	2 (1)	2 (2)
Participants lost to follow-up	7 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Participants discontinued due to other reasons	4 (2)	4 (3)	0 (0)	0 (0)	0 (0)

Source: CSR TV50717-BE-10179, Section 10.1.1; CSR TV50717-PK-10175, Section 10.1.1; CSR TV50717-BE-10165, Section 10.1.1; CSR TV50717-BE-10192, Section 10.1.1; and CSR TV50717-BE-10201, Section 10.1.1.
AE=adverse event; CSR=clinical study report; n=number of participants.

2.6.8.2. Adverse events

2.6.8.2.1. Overview of Adverse Events by Treatment

Phase 3 Trials in Participants with Tardive Dyskinesia: AEs in the Integrated Datasets

A summary of AEs reported by treatment period is provided in the next table. AEs in the overall treatment period, up to week 12/15, showed a similar proportion of participants experiencing AEs in the DTBZ

titration and placebo groups. Participants in the fixed dose groups also showed overall similar AE proportions. Events were typically of mild or moderate severity; severe AEs were infrequent. The most frequently reported AEs for DTBZ were anxiety and somnolence.

SAEs in the short-term (up to Week 12/15) treatment period occurred in a similar proportion between placebo-treated participants and participants in the DTBZ titration group; no pattern in the frequency of SAEs was evident among DTBZ fixed-dose treatment groups. AEs leading to withdrawal were infrequent and occurred in similar proportions in DTBZ titration and placebo groups.

Two deaths were reported in Trial C-23, one sudden cardiac arrest and one cardio-respiratory arrest, both of which considered unrelated to the trial drug.

AEs leading to dose reductions occurred with lower frequency in the placebo group than in DTBZ titration group, and this pattern was reversed in AEs that led to dose suspensions. A review of these AEs did not reveal any specific pattern.

Table 65: Overview of adverse event profile from phase 3 trials in participants with Tardive Dyskinesia per treatment period (Safety Population)

Adverse event category, n (%)	**Short-Term (up to Week 12/15)**				
	Trials C-18 and C-23	**Trial C-23**			**Trials C-18 and C-20 Part A**
	Placebo	**DTBZ 12 mg**	**DTBZ 24 mg**	**DTBZ 36 mg**	**DTBZ Titration**
	(N=130)	**(N=72)**	**(N=72)**	**(N=72)**	**(N=168)**
Participants with AE	70 (53.8)	36 (50.0)	32 (44.4)	36 (50.0)	100 (59.5)
Participants with SAE	9 (6.9)	2 (2.8)	6 (8.3)	3 (4.2)	9 (5.4)
Participants with severe AE	5 (3.8)	2 (2.8)	4 (5.6)	1 (1.4)	6 (3.6)
Participants with treatment-related AE	40 (30.8)	13 (18.1)	11 (15.3)	18 (25.0)	64 (38.1)
Participants with AE leading to death	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)	0 (0.0)
Participants with AE leading to dose reduction	3 (2.3)	0 (0.0)	1 (1.4)	3 (4.2)	14 (8.3)
Participants with AE leading to dose suspension	7 (5.4)	3 (4.2)	1 (1.4)	1 (1.4)	5 (3.0)
Participants with AE leading to withdrawal	4 (3.1)	4 (5.6)	2 (2.8)	3 (4.2)	5 (3.0)
Participants with treatment-related AE leading to withdrawal	3 (2.3)	1 (1.4)	1 (1.4)	1 (1.4)	5 (3.0)
Participants with AE leading to dose reduction, suspension or withdraw	11 (8.5)	6 (8.3)	4 (5.6)	7 (9.7)	23 (13.7)

Source: TDISS20, MAA Ad Hoc Summary 11.
AE=adverse event; DTBZ=deutetrabenazine; N=number of participants; n=number of participants in subgroup; SAE=serious adverse event.
Note: Participants are counted only once for each category.

In the overall treatment period of Part A and B of the long-term safety trial (Trial C-20), 269 participants (79.8%) experienced an AE, 68 (20.2%) experienced an SAE, 57 (16.9%) experienced severe AE, and 42 (12.5%) discontinued due to AE. During C-20 Part A and B 8 deaths were reported; in all of them the cause was considered unlikely related or unrelated to the trial drug. One additional death occurred 56 days after the last dose of the trial drug and 25 days after the participant was withdrawn from the trial.

During Trial C-20 Part C, 23 (28.8%) participants reported at least 1 AE. AEs considered by the investigator as treatment related (definitely, probably, or possibly related to trial drug) were reported in 3 (3.8%) participants. There were 2 deaths reported during Part C, both of them considered unrelated to the trial drug. Five (6.3%) participants had SAEs. Three (3.8%) participants experienced an AE that led to trial drug discontinuation and dose reductions were required for 2 (2.5%) participants due to AEs.

Table 66: Overview of adverse events in the overall treatment period for phase 3 trial C-20 in participants with Tardive Dyskinesia (Safety Analysis Set)

Adverse event category, n (%)	**C-20 Parts A + B (N=337)**	**C-20 Part C (N=80)**
Participants with any AE[a]	269 (79.8)	23 (28.8)
Participants with any severe AE	57 (16.9)	3 (3.8)
Participants with any treatmentrelated AE	154 (45.7)	3 (3.8)
Participant deaths	8 (2.4)	2 (2.5)
Participants with any SAE	68 (20.2)	5 (6.3)
Participants with any AE leading to discontinuation	42 (12.5)	3 (3.8)
Participants with any AE leading to dose suspension	34 (10.1)	0
Participants with any AE leading to dose reduction	53 (15.7)	2 (2.5)

Source: CSR SD-809-C-20 addendum 01, Table 8; CSR SD-809-C-20, Table 24.
[a] Adverse events summarized are those that began or worsened after treatment with trial drug.
AE=adverse event; CSR=clinical study report; N=number of participants; n=number of participants in subgroup; SAE=serious adverse event.

Phase 3 Trials in Participants with Tardive Dyskinesia - Exposure-Adjusted Incidence Rates of Adverse Events

To enable comparison of AE frequencies among short-term treatments (12/15 weeks in Trial C-23 fixed dose groups and the integrated titration group) and the long-term safety trial (up to and including 158 weeks in Trial C-20), AE rates were adjusted based on duration of exposure. This Exposure-adjusted incidence rates (EAIR) analysis provided the number of participants with events per patient-years of exposure. For most types of AEs, the EAIR observed with long-term DTBZ treatment was lower than those observed during short-term DTBZ or placebo treatment.

Table 67: Exposure-adjusted incidence rates of adverse events from phase 3 trials in participants with Tardive Dyskinesia per treatment period (Safety Population in trials C-18, C-23, and C-20)

Adverse event category	Short-Term (up to Week 12/15)					Long-Term (up to Week 158)
	Trials C-18 and C-23	Trials C-23			Trials C-18 and C-20[a]	Trial C-20 Part A
	Placebo (N=130)	DTBZ 12 mg (N=72)	DTBZ 24 mg (N=72)	DTBZ 36 mg (N=72)	DTBZ Titration (N=168)[a]	DTBZ (N=337)
	EAIR (No. of Participants/Patient-years)					
Any AE	3.97 (70/17.6)	3.19 (36/11.3)	2.91 (32/11.0)	3.63 (36/9.9)	4.07 (100/24.6)	1.24 (268/215.8)
Any SAE	0.33 (9/27.3)	0.13 (2/15.5)	0.40 (6/15.1)	0.2 (3/14.9)	0.22 (9/41.5)	0.11 (67/617.6)
Any severe AE	0.18 (5/27.8)	0.13 (2/15.6)	0.26 (4/15.2)	0.07 (1/15.0)	0.14 (6/42.3)	0.09 (55/629.9)
Any treatment-related AE	1.83 (40/21.9)	0.91 (13/14.3)	0.78 (11/14.1)	1.45 (18/12.4)	2.03 (64/31.5)	0.36 (153/428.5)
Any AE leading to death	0 (0/28.3)	0 (0/15.6)	0.06 (1/15.4)	0.07 (1/15.0)	0 (0/42.9)	0.01 (7/687.7)
Any AE resulting in dose reduction	0.11 (3/27.8)	0 (0/15.6)	0.07 (1/15.3)	0.2 (3/14.7)	0.35 (14/40.5)	0.09 (53/572.4)
Any AE resulting in dose suspension	0.25 (7/27.6)	0.2 (3/15.3)	0.06 (1/15.4)	0.07 (1/14.9)	0.12 (5/42.5)	0.04 (29/657.7)
Any AE leading to withdrawal	0.14 (4/28.3)	0.26 (4/15.6)	0.13 (2/15.4)	0.2 (3/15.0)	0.12 (5/42.7)	0.06 (41/683.3)
Any treatment-related AE leading to withdrawal	0.11 (3/28.3)	0.06 (1/15.6)	0.06 (1/15.4)	0.07 (1/15.0)	0.12 (5/42.7)	0.02 (14/685.8)
Participants with AE leading to dose reduction, suspension or withdrawal	0.40 (11/27.4)	0.39 (6/15.3)	0.26 (4/15.3)	0.48 (7/14.6)	0.58 (23/40.0)	0.19 (103/543.8)

Source: TDISS20, MAA Ad Hoc Summary 12.

[a] The DTBZ titration group included data from participants receiving DTBZ in Trial C-18 through week 12 plus data from Trial C-20 through week 15 for participants who were previously in the placebo treatment group in Trials C-18 or C-23.

AE=adverse event; DTBZ=deutetrabenazine; EAIR=exposure-adjusted incidence rate; N=number of participants; SAE=serious adverse events.

Note: Participants are counted only once for each category. For calculating patient-years in each category, participants with an AE contribute with treatment exposure up to the day of their first AE in Part A, and participants without an AE contribute with their entire treatment exposure in Part A.

Note: EAIR is calculated as the number of participants/patient-years.

Phase 1 Trials in Healthy Participants – Adverse Events by Treatment

For all Phase 1 trials using DTBZ osmotic PR formulation QD in healthy participants, no deaths, serious or severe adverse events were reported.

TV50717-BE-10179 – Adverse Events by Treatment

In the repeated dose trial TV50717-BE-10179, the frequency of AEs was slightly higher when comparing Test (24 mg DTBZ osmotic PR tablets QD) to Reference (DTBZ 12 mg matrix tablets BID) treatments, with AEs reported by 28 (12%) participants treated with the Test drug and 22 (9%) participants treated with the Reference drug. There was a similar frequency of AEs assessed as related to trial treatment by the investigator across Test and Reference arms (13 participants [5%] treated with Test drug and 12 participants [5%] treated with Reference drug). A total of 11 participants (4%) withdrew or discontinued the trial due to AEs.

TV50717-PK-10175 – Adverse Events by Treatment

In the single dose, cross-over trial TV50717-PK-10175, the frequency of AEs was similar when comparing the 4 different trial drug doses, with AEs reported by 5 (4%), 3 (3%), 2 (2%), and 4 (4%) participants receiving 2×6 mg, 1×12 mg, 1×24 mg, and 2×24 mg (DTBZ osmotic PR formulation QD) treatment, respectively. Additionally, there was a similar frequency of AEs when comparing trial periods, with a total of 3 (3%), 4 (4%), 3 (3%), and 4 (4%) participants with at least 1 AE during Periods 1, 2, 3 and 4, respectively (CSR TV50717-PK-10175). AEs assessed as related to trial treatment by the investigator were reported in 2 (2%) participants, both while receiving 2×6 mg trial drug. There were 2 (2%) participants who were withdrawn or discontinued from the trial due to AEs; 1 participant while receiving 2×6 mg trial drug (vomiting) and 1 participant while receiving 2×24 mg trial drug (coronavirus disease 2019 [COVID-19]) (CSR TV50717PK10175).

TV50717-BE-10165 – Adverse Events by Treatment

In the single dose cross-over trial TV50717-BE-10165, the frequency of AEs was similar when comparing the 3 different trial drug regimens, with AEs reported by 2 (2%), 4 (5%), and 2 (2%) participants receiving 1×24 mg DTBZ osmotic PR tablet QD (fed state), 1×24 mg DTBZ osmotic PR tablet QD (fasted state) and 2×12 mg DTBZ matrix tablets BID (fed state). When comparing trial periods, a similar frequency of AEs was observed, with a total of 3 (4%), 2 (2%), and 3 (4%) participants with at least 1 AE during Periods 1, 2, and 3, respectively (CSR TV50717-BE-10165). AEs considered by the investigator to be treatment-related were reported for 3 (4%) participants in total: 1 (1%) participant while receiving 1×24 mg QD (fed), and 2 (2%) participants while receiving 1×24 mg QD (fasted). No participants were withdrawn from or discontinued the trial due to AEs (CSR TV50717-BE-10165).

TV50717-BE-10192 – Adverse Events by Treatment

In the single dose, cross-over trial TV50717-BE-10192, the frequency of AEs was similar when comparing the 1×48 mg (Test) and 2×24 mg (Reference) DTBZ osmotic tablets QD (fasted state). At least one AE was reported for 6 (3%) participants while on Test treatment, and by 7 (4%) participants when receiving the Reference treatment. When comparing trial periods, a similar frequency of AEs was observed, with a total of 6 (3%) and 7 (4%) participants with at least 1 AE in periods 1 and 2, respectively. The only AE by preferred term (PT) that occurred in more than 1 participant was headache, experienced by 3 (2%) participants in total. Headache was reported once during the 1×48 mg (Test) treatment and 3 times during the 2×24 mg (Reference) treatment, with 1 participant experiencing headache twice (once during the Test and once during the Reference treatment period). AEs that necessitated withdrawal from the trial were reported in 1 participant in each treatment group (1%; Test and Reference).

TV50717-BE-10201 – Adverse Events by Treatment

In the single dose cross-over trial TV50717-BE-10201, the frequency of AEs was similar when comparing the 1×36 mg (Test) and 1×12 mg + 1×24 mg (Reference) DTBZ osmotic PR formulation QD (fasted state): at least one AE was reported for 3 (2%) participants receiving Test treatment, and by 6 (5%) participants receiving Reference treatment. There was a slightly higher frequency of AEs during period 1 when comparing treatment periods, with a total of 6 (5%) and 3 (2%) participants with at least 1 AE in periods 1 and 2, respectively. Two AEs by PT occurred in more than 1 participant: back pain (1 participant receiving Test treatment and 2 participants receiving Reference treatment), and presyncope (in 2 participants, both during the Reference treatment period). An AE that necessitated withdrawal was reported in 1 (<1%) participant from the reference treatment group and 1 (<1%) in the test treatment group.

2.6.8.2.2. Most Common Adverse Events

Phase 3 Trials in Participants with Tardive Dyskinesia – Most Common Adverse Events

The most frequent AEs during the titration/dose escalation and maintenance periods are presented in the next table.

Somnolence was the most frequent AE, more frequent during the titration/dose escalation period (11.3% in the DTBZ titration treatment group) than during the maintenance period (0% in the titration treatment group up to week 12/15) or the long-term safety Trial C-20 (4.2% up to week 158). Anxiety was the most frequently reported AE during the maintenance period (9.8% in the long-term Trial C-20).

EAIRs for AEs that occurred in ≥4% of any treatment group are summarised below.

Table 68: Adverse events occurring in ≥4% of Tardive Dyskinesia participants in the titration/dose-escalation or maintenance period in any participant group (Safety Population in trials C-18, C-23, and C-20)

Preferred Term, n (%)	Titration/Dose-Escalation Period						Maintenance Period					
	Short-Term (Up to Week 12/15)					Long-Term[a]	Short-Term (Up to Week 12/15)					Long-Term[a]
	Trials C-18 and C-23	Trial C-23			Trials C-18 and C-20[b]	Trial C-20 Part A	Trials C-18 and C-23	Trial C-23			Trials C-18 and C-20[b]	Trial C-20 Part A
	Placebo (N=130)	DTBZ 12mg (N=72)	DTBZ 24mg (N=72)	DTBZ 36mg (N=72)	DTBZ Titration (N=168)	DTBZ (N=337)	Placebo (N=130)	DTBZ 12mg (N=72)	DTBZ 24mg (N=72)	DTBZ 36mg (N=72)	DTBZ Titration (N=168)	DTBZ (N=337)
Participants with at least 1 AE	56 (43.1)	24 (33.3)	26 (36.1)	28 (38.9)	83 (49.4)	161 (47.8)	33 (25.4)	20 (27.8)	16 (22.2)	21 (29.2)	55 (32.7)	232 (68.8)
Anxiety	4 (3.1)	1 (1.4)	2 (2.8)	1 (1.4)	6 (3.6)	12 (3.6)	2 (1.5)	2 (2.8)	0	2 (2.8)	2 (1.2)	33 (9.8)
Bradykinesia	0	0	0	0	0	4 (1.2)	0	0	0	0	1 (0.6)	14 (4.2)
Depression	0	0	3 (4.2)	0	3 (1.8)	10 (3.0)	1 (0.8)	1 (1.4)	0	1 (1.4)	2 (1.2)	27 (8.0)
Diarrhoea	5 (3.8)	1 (1.4)	3 (4.2)	4 (5.6)	3 (1.8)	6 (1.8)	0	0	1 (1.4)	1 (1.4)	4 (2.4)	21 (6.2)
Dry mouth	6 (4.6)	3 (4.2)	0	2 (2.8)	3 (1.8)	3 (0.9)	0	0	0	0	0	2 (0.6)
Dyskinesia	0	0	0	0	0	3 (0.9)	0	0	1 (1.4)	1 (1.4)	0	15 (4.5)
Fall	0	0	0	0	0	3 (0.9)	0	1 (1.4)	0	0	0	14 (4.2)
Fatigue	6 (4.6)	0	2 (2.8)	2 (2.8)	5 (3.0)	10 (3.0)	0	1 (1.4)	0	1 (1.4)	2 (1.2)	7 (2.1)
Headache	8 (6.2)	2 (2.8)	2 (2.8)	5 (6.9)	6 (3.6)	15 (4.5)	2 (1.5)	3 (4.2)	1 (1.4)	0	3 (1.8)	9 (2.7)
Hypertension	1 (0.8)	0	0	3 (4.2)	5 (3.0)	7 (2.1)	1 (0.8)	0	0	0	2 (1.2)	16 (4.7)
Influenza	1 (0.8)	0	0	0	0	0	0	0	0	1 (1.4)	0	16 (4.7)
Nasopharyngitis	2 (1.5)	3 (4.2)	1 (1.4)	2 (2.8)	1 (0.6)	5 (1.5)	0	1 (1.4)	2 (2.8)	0	2 (1.2)	15 (4.5)
Nausea	7 (5.4)	1 (1.4)	1 (1.4)	0	4 (2.4)	5 (1.5)	4 (3.1)	0	0	0	0	11 (3.3)
Somnolence	9 (6.9)	0	0	2 (2.8)	19 (11.3)	23 (6.8)	0	0	1 (1.4)	2 (2.8)	0	14 (4.2)
Tremor	0	0	0	0	1 (0.6)	1 (0.3)	1 (0.8)	0	0	0	2 (1.2)	14 (4.2)
Urinary tract infection	1 (0.8)	2 (2.8)	0	0	3 (1.8)	6 (1.8)	1 (0.8)	0	1 (1.4)	2 (2.8)	0	24 (7.1)
Weight decreased	2 (1.5)	0	0	0	4 (2.4)	4 (1.2)	0	0	0	0	0	26 (7.7)

Source: TDISS20, MAA Ad Hoc Summary 15.
[a] Long term is up to Week 158

[b] The DTBZ titration group included data from participants receiving DTBZ in Trial C-18 through week 12 plus data from Trial C-20 through week 15 for participants who were previously in the placebo treatment group in Trial C-18 or C-23.
AE=adverse event; DTBZ=deutetrabenazine; N=number of participants; n=number of participants in subgroup.
Note: Participants are counted only once in each preferred term category, and only once in each system organ class category.

Table 69: Exposure-adjusted incidence rate for adverse events that occurred in ≥4% in any Tardive Dyskinesia participant group in the overall treatment period by participant group (Safety population in trials C-18, C-23, and C-20)

Preferred Term	**Short-Term (up to Week 12/15)**										**Long-Term (up to Week 158)**	
	Trials C-18 and C-23		**Trial C-23**						**Trials C-18 and C-20**		**Trial C-20 Part A**	
	Placebo (N=130)		**DTBZ 12mg (N=72)**		**DTBZ 24mg (N=72)**		**DTBZ 36mg (N=72)**		**DTBZ Titration (N=168)**		**DTBZ (N=337)**	
	n (%)	**EAIR**	**n (%)**	**EAIR**	**n (%)**	**EAIR**	**n (%)**	**EAIR**	**n (%)**	**EAIR**	**n (%)**	**EAIR**
Participants with at least 1 AE	70 (53.8)	3.97	36 (50.0)	3.19	32 (44.4)	2.91	36 (50.0)	3.63	100 (59.5)	4.07	268 (79.5)	1.24
Anxiety	6 (4.6)	0.22	3 (4.2)	0.20	2 (2.8)	0.13	3 (4.2)	0.20	8 (4.8)	0.19	42 (12.5)	0.07
Back pain	0	0.00	2 (2.8)	0.13	1 (1.4)	0.07	1 (1.4)	0.07	2 (1.2)	0.05	14 (4.2)	0.02
Bradykinesia	0	0.00	0	0.00	0	0.00	0	0.00	1 (0.6)	0.02	15 (4.5)	0.02
Depressed mood	0	0.00	1 (1.4)	0.06	0	0.00	0	0.00	1 (0.6)	0.02	14 (4.2)	0.02
Depression	1 (0.8)	0.04	1 (1.4)	0.06	3 (4.2)	0.20	1 (1.4)	0.07	5 (3.0)	0.12	33 (9.8)	0.05
Diarrhoea	5 (3.8)	0.18	1 (1.4)	0.07	3 (4.2)	0.20	5 (6.9)	0.35	7 (4.2)	0.17	27 (8.0)	0.04
Dizziness	5 (3.8)	0.18	0	0.00	0	0.00	2 (2.8)	0.14	4 (2.4)	0.09	14 (4.2)	0.02
Dry mouth	6 (4.6)	0.22	3 (4.2)	0.20	0	0.00	2 (2.8)	0.14	3 (1.8)	0.07	5 (1.5)	<0.01
Dyskinesia	0	0.00	0	0.00	1 (1.4)	0.06	1 (1.4)	0.07	0	0.00	18 (5.3)	0.03
Fall	0	0.00	1 (1.4)	0.06	0	0.00	0	0.00	0	0.00	17 (5.0)	0.03
Fatigue	6 (4.6)	0.22	1 (1.4)	0.06	2 (2.8)	0.13	3 (4.2)	0.21	7 (4.2)	0.17	16 (4.7)	0.02
Headache	10 (7.7)	0.37	5 (6.9)	0.33	2 (2.8)	0.13	5 (6.9)	0.36	8 (4.8)	0.19	23 (6.8)	0.04
Hypertension	2 (1.5)	0.07	0	0.00	0	0.00	3 (4.2)	0.21	7 (4.2)	0.17	23 (6.8)	0.04
Influenza	1 (0.8)	0.04	0	0.00	0	0.00	1 (1.4)	0.07	0	0.00	16 (4.7)	0.02
Insomnia	1 (0.8)	0.04	2 (2.8)	0.13	2 (2.8)	0.13	2 (2.8)	0.13	7 (4.2)	0.17	14 (4.2)	0.02
Muscle spasms	1 (0.8)	0.04	0	0.00	0	0.00	3 (4.2)	0.21	0	0.00	5 (1.5)	<0.01

Nasopharyngitis	2 (1.5)	0.07	4 (5.6)	0.27	3 (4.2)	0.20	2 (2.8)	0.14	3 (1.8)	0.07	20 (5.9)	0.03
Nausea	9 (6.9)	0.33	1 (1.4)	0.06	1 (1.4)	0.07	0	0.00	4 (2.4)	0.10	15 (4.5)	0.02
Somnolence	9 (6.9)	0.34	0	0.00	1 (1.4)	0.06	3 (4.2)	0.21	19 (11.3)	0.48	34 (10.1)	0.05
Tremor	1 (0.8)	0.04	0	0.00	0	0.00	0	0.00	3 (1.8)	0.07	14 (4.2)	0.02
Urinary tract infection	2 (1.5)	0.07	2 (2.8)	0.13	1 (1.4)	0.06	2 (2.8)	0.13	3 (1.8)	0.07	29 (8.6)	0.05
Weight decreased	2 (1.5)	0.07	0	0.00	0	0.00	0	0.00	4 (2.4)	0.09	30 (8.9)	0.05
Weight increased	4 (3.1)	0.14	0	0.00	1 (1.4)	0.07	2 (2.8)	0.13	2 (1.2)	0.05	15 (4.5)	0.02

Source: TDISS20, MAA Ad Hoc Summary 14.
AE=adverse event; DTBZ=deutetrabenazine; EAIR=exposure-adjusted incidence rate; N=number of participants; n=number of participants in subgroup.
Note: Participants are counted only once for each category. To calculate patient-years in each preferred term, participants with an adverse event contribute with treatment exposure up to the day of their first adverse event, and participants without an adverse event contribute with their entire treatment exposure.

In the long-term safety trial (Trial C-20) the most frequently reported AEs (≥10%) were anxiety, depression and somnolence. The next table presents a list of the most frequent AEs in descending order in ≥4% of participants in the long-term Trial C-20 Part A and B.

Table 70: Adverse events in ≥4% of participants in long-term trial C-20 overall treatment period (Safety population)

Preferred Term, n (%)	**Trial C-20 (Parts A and B)**
	DTBZ
	(N=337)
Participants with at least 1 AE	269 (79.8)
Anxiety	42 (12.5)
Depression	35 (10.4)
Somnolence	34 (10.1)
Weight decreased	32 (9.5)
Urinary tract infection	31 (9.2)
Diarrhoea	27 (8.0)
Headache	24 (7.1)
Hypertension	23 (6.8)
Dyskinesia	22 (6.5)
Nasopharyngitis	20 (5.9)
Fall	18 (5.3)
Fatigue	16 (4.7)
Influenza	16 (4.7)
Nausea	16 (4.7)
Weight increased	16 (4.7)
Back pain	15 (4.5)
Bradykinesia	15 (4.5)
Depressed mood	15 (4.5)
Dizziness	15 (4.5)
Insomnia	14 (4.2)
Tremor	14 (4.2)
Upper respiratory tract infection	14 (4.2)

Source: TDISS20, MAA Ad Hoc Summary 13.
AE=adverse event; DTBZ=deutetrabenazine; N=number of participants; n=number of participants in subgroup.
Note: Participants are counted only once in each preferred term category.

In Trial C-20 Part C (the 52-week additional treatment period for participants in the EU countries), 23 (28.8%) participants experienced at least 1 AE during the treatment period. All AEs were reported by 1 (1.3%) participant with the exception of nasopharyngitis, back pain, and dyskinesia which were reported by 2 (2.5%) participants. The most frequently occurring AEs during the maintenance period in Trial C-20 Parts A and B (i.e. anxiety, depression and somnolence) were not reported by participants in Part C.

Phase 1 Trials in Healthy Participants – Most Common Adverse Events

TV50717-BE-10179 - Most Common Adverse Events

By PT, the most common AEs occurring in more than 2 participants were headache (13 participants, 5%), influenza-like illness (5 participants, 2%), oropharyngeal pain (4 participants, 2%), diarrhoea, dizziness, rhinorrhoea (each in 3 participants [1%]).

Table 71: Adverse events by MedDRA system organ class and MedDRA preferred term in trial TV50717-BE-10179

System Organ Class MedDRA 23.1 Preferred Term[a], n (%)	Test 24 mg QD (N=243)	Reference 12 mg BID (N=243)	Total (N=262)
Participants with at least 1 AE	28 (12)	22 (9)	46 (18)
Eye disorders	**0**	1 (<1)	1 (<1)
Chalazion	0	1 (<1)	1 (<1)
Gastrointestinal disorders	**5 (2)**	**4 (2)**	**9 (3)**
Diarrhoea	2 (<1)	1 (<1)	3 (1)
Constipation	1 (<1)	1 (<1)	2 (<1)
Abdominal discomfort	1 (<1)	0	1 (<1)
Dyspepsia	1 (<1)	0	1 (<1)
Epigastric discomfort	0	1 (<1)	1 (<1)
Nausea	1 (<1)	0	1 (<1)
Vomiting	0	1 (<1)	1 (<1)
General disorders and administration site conditions	**4 (2)**	**2 (<1)**	**6 (2)**
Influenza-like illness	3 (1)	2 (<1)	5 (2)
Asthenia	1 (<1)	0	1 (<1)
Infections and infestations	**3 (1)**	**2 (<1)**	**5 (2)**
COVID-19	1 (<1)	1 (<1)	2 (<1)
Acute sinusitis	1 (<1)	0	1 (<1)
Asymptomatic COVID-19	1 (<1)	0	1 (<1)
Upper respiratory tract infection	0	1 (<1)	1 (<1)
Injury, poisoning and procedural complications	1 (<1)	0	1 (<1)
Arthropod bite	1 (<1)	0	1 (<1)
Investigations	2 (<1)	2 (<1)	4 (2)
Alanine aminotransferase increased	1 (<1)	1 (<1)	2 (<1)
Aspartate aminotransferase increased	1 (<1)	0	1 (<1)
Blood creatine phosphokinase increased	0	1 (<1)	1 (<1)
Blood creatinine increased	1 (<1)	0	1 (<1)
Musculoskeletal and connective tissue disorders	1 (<1)	2 (<1)	3 (1)
Back pain	0	1 (<1)	1 (<1)
Neck pain	0	1 (<1)	1 (<1)
Pain in extremity	1 (<1)	0	1 (<1)
Nervous system disorders	8 (3)	9 (4)	16 (6)
Headache	7 (3)	7 (3)	13 (5)
Dizziness	1 (<1)	2 (<1)	3 (1)
Psychiatric disorders	3 (1)	0	3 (1)
Anxiety	2 (<1)	0	2 (<1)
Nightmare	1 (<1)	0	1 (<1)
Reproductive system and breast disorders	1 (<1)	1 (<1)	2 (<1)
Dysmenorrhoea	1 (<1)	1 (<1)	2 (<1)
Respiratory, thoracic and mediastinal disorders	5 (2)	2 (<1)	7 (3)
Oropharyngeal pain	3 (1)	1 (<1)	4 (2)
Rhinorrhoea	2 (<1)	1 (<1)	3 (1)

Source: CSR TV50717-BE-10179, Table 19. PTs are sorted by descending order of incidence within a SOC for the total group. Participants are counted only once in each PT category, and only once in each SOC category.
AE=adverse event; BID=twice daily; COVID-19=coronavirus disease 2019; CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants; n=number of participants in subgroup; PT=preferred term; QD=once daily; SOC=system order class.
Note: one or more participants experienced AEs during both periods (Test and Reference). As a result, the number of participants in Test and Reference columns does not always add up to the number in "total` for each preferred term.

TV50717-PK-10175 - Most Common Adverse Events

By PT the only AE that occurred in more than 2 participants was Influenza-like illness (3 participants, 3%).

TV50717-BE-10165 - Most Common Adverse Events

The only AE that occurred in more than 2 participants was Headache (3 participants, 4%).

TV50717-BE-10192 - Most Common Adverse Events

The only AE that occurred in more than 1 participant was Headache, reported for 3 (2%) participants (once during the 48 mg [Test] treatment and 3 times during the 2×24 mg [Reference] treatment).

TV50717-BE-10201 - Most Common Adverse Events

The only AEs by PT reported for more than 1 participant were back pain and presyncope. Back pain was reported for 3 (2%) participants (once during the 36 mg [Test] treatment and 2 times during the 1×12 mg + 1×24 mg [Reference] treatment) and presyncope reported for 2 (2%) participants (both during the 1×12 mg + 1×24 mg [Reference] treatment).

2.6.8.2.3. Attribution of Adverse Events

Phase 3 Trials in Participants with Tardive Dyskinesia - Attribution of Adverse Events

Treatment-related AEs in the short-term treatment period (up to week 12/15) for both integrated data sets and individual trials are shown in the next table. These AEs (considered by the investigator as possibly, probably, or definitely related to trial drug) were reported in higher frequencies in DTBZ titration group than the placebo group. Within the individual fixed-dose groups, frequencies of treatment-related AEs were lower than either the titration or placebo groups.

Somnolence was the most frequently reported treatment-related AE, with 9 participants (6.9%) in the placebo-treated group and 18 participants (10.7%) in the titration group; a much lower frequency was reported in the 3 fixed-dose groups.

Treatment-related psychiatric disorders and nervous system disorders were more common in DTBZ titration than in the placebo group whereas gastrointestinal disorders occurred more frequently in placebo group than those in DTBZ titration group.

In Trial C-20 a higher frequency of treatment-related AEs was reported during long-term treatment compared with the titration group, which was much shorter in duration. The event of somnolence (30 participants [8.9%]) was the most frequently reported treatment-related AE in this trial.

Table 72: Treatment-related adverse events in ≥2% of participants with Tardive Dyskinesia in the overall treatment period by system organ class, preferred term, and participant group (Safety population in trials C-18, C-23, and C-20)

System Organ Class Preferred Term, n(%)	Short-Term (up to Week 12/15)					Long-Term (up to Week 158)
	Trials C-18 and C-23	Trial C-23			Trials C-18 and C-20[a]	Trial C-20 Part A
	Placebo (N=130)	DTBZ 12mg (N=72)	DTBZ 24mg (N=72)	DTBZ 36mg (N=72)	DTBZ Titration (N=168)	DTBZ (N=337)
Participants with at least 1 treatment-related AE	40 (30.8)	13 (18.1)	11 (15.3)	18 (25.0)	64 (38.1)	153 (45.4)
Eye disorders	1 (0.8)	0	2 (2.8)	0	2 (1.2)	2 (0.6)
Gastrointestinal disorders	16 (12.3)	4 (5.6)	2 (2.8)	2 (2.8)	10 (6.0)	22 (6.5)
Diarrhoea	3 (2.3)	0	2 (2.8)	0	2 (1.2)	4 (1.2)
Dry mouth	4 (3.1)	3 (4.2)	0	1 (1.4)	3 (1.8)	2 (0.6)
Nausea	6 (4.6)	1 (1.4)	0	0	3 (1.8)	3 (0.9)
Salivary hypersecretion	1 (0.8)	0	0	1 (1.4)	1 (0.6)	8 (2.4)
General disorders and administration site conditions	6 (4.6)	1 (1.4)	2 (2.8)	2 (2.8)	6 (3.6)	18 (5.3)
Fatigue	4 (3.1)	1 (1.4)	1 (1.4)	1 (1.4)	5 (3.0)	10 (3.0)
Investigations	4 (3.1)	1 (1.4)	3 (4.2)	2 (2.8)	7 (4.2)	25 (7.4)
Weight decreased	0	0	0	0	3 (1.8)	10 (3.0)
Metabolism and nutrition disorders	1 (0.8)	0	1 (1.4)	2 (2.8)	3 (1.8)	9 (2.7)
Musculoskeletal and connective tissue disorders	3 (2.3)	1 (1.4)	0	3 (4.2)	5 (3.0)	13 (3.9)
Muscle spasms	1 (0.8)	0	0	2 (2.8)	0	1 (0.3)
Nervous system disorders	17 (13.1)	4 (5.6)	3 (4.2)	9 (12.5)	35 (20.8)	78 (23.1)
Bradykinesia	0	0	0	0	1 (0.6)	14 (4.2)
Dyskinesia	0	0	0	0	0	8 (2.4)
Headache	7 (5.4)	3 (4.2)	0	3 (4.2)	5 (3.0)	8 (2.4)
Somnolence	9 (6.9)	0	1 (1.4)	2 (2.8)	18 (10.7)	30 (8.9)
Tremor	0	0	0	0	3 (1.8)	8 (2.4)
Psychiatric disorders	6 (4.6)	6 (8.3)	4 (5.6)	5 (6.9)	14 (8.3)	42 (12.5)
Anxiety	2 (1.5)	1 (1.4)	0	2 (2.8)	3 (1.8)	12 (3.6)
Depression	1 (0.8)	1 (1.4)	1 (1.4)	1 (1.4)	2 (1.2)	10 (3.0)
Insomnia	1 (0.8)	2 (2.8)	2 (2.8)	1 (1.4)	4 (2.4)	5 (1.5)
Skin and subcutaneous tissue disorders	3 (2.3)	1 (1.4)	0	0	3 (1.8)	3 (0.9)
Vascular disorders	3 (2.3)	1 (1.4)	0	0	4 (2.4)	8 (2.4)

Source: TDISS20, MAA Ad Hoc Summary 16.
AE=adverse event; DTBZ=deutetrabenazine; N=number of participants; n=number of participants in subgroup.
[a] The DTBZ titration group included data from participants receiving DTBZ in Trial C-18 through week 12 plus data from Trial C-20 through week 15 for participants who were previously in the placebo treatment group in Trials C-18 or C-23.
Note: Participants are counted only once in each preferred term category and only once in each system organ class category.

In Trial C-20 Part C there were 4 treatment-related AEs reported for 3 (3.8%) participants (CSR SD-809-C-20 addendum 01). One (1.3%) experienced an event of tardive dyskinesia, 1 (1.3%) experienced tremor and 1 (1.3%) reported both asthenia and bradykinesia.

Phase 1 Trials in Healthy Participants - Attribution of Adverse Events

TV50717-BE-10179

Treatment-related (possibly, probably, or definitely related) AEs were reported for 13 participants (5%) treated with the Test drug (24 mg DTBZ osmotic PR formulation QD) and 12 participants (5%) treated with the Reference drug (12 mg DTBZ clinical matrix formulation BID). Most treatment-related AEs were mild. AEs of moderate severity considered treatment-related were reported in both Test (anxiety; 1 participant) and Reference treatment (headache; 2 participants). By PT the most common treatment related AE reported was headache (12 participants [5%].

TV50717-PK-10175 - Attribution of Adverse Events

Treatment-related AEs were reported for 2 participants (2%), both while receiving 2×6 mg trial drug. These AEs included dizziness in 1 participant (<1%) and headache in 1 participant (<1%), both of which classified under the SOC nervous system disorders. Both events were mild in severity. No treatment-related moderate or severe AEs were reported in this trial.

TV50717-BE-10165 - Attribution of Adverse Events

AEs considered treatment-related by the investigator were reported for 3 (4%) participants: 1 (1%) while receiving 1×24 mg DTBZ osmotic PR tablets QD fed and 2 (2%) receiving 1×24 mg DTBZ osmotic PR tablets QD fasted. All treatment-related AEs were headaches. The event for 1×24 mg DTBZ osmotic PR tablets QD fed treatment was classified as mild in severity while both cases from 1×24 mg DTBZ osmotic PR tablets QD fasted treatment were classified as moderate in severity. No treatment-related severe AEs were reported in this trial.

TV50717-BE-10192 - Attribution of Adverse Events

Treatment-related AEs were reported for 4 (2%) participants each during treatment with 1×48 mg (Test) and 2×24 mg (Reference) DTBZ osmotic PR formulation QD, respectively. All events were classified as mild, other than headache in 2 participants (reported in 1 participant during the 1×48 mg [Test] treatment and in 2 participants during the 2×24 mg [Reference] DTBZ osmotic PR formulation QD treatment), classified as moderate in severity. One participant experienced headache twice: once during the Test and once during the Reference treatment period.

TV50717-BE-10201 - Attribution of Adverse Events

An AE (Headache) considered treatmentrelated by the investigator was reported for 1 (<1%) participant during treatment with 1×36 mg DTBZ osmotic PR formulation QD (Test). This event was moderate in severity. There were no severe treatment-related AEs reported in this trial.

2.6.8.3. Adverse drug reactions

Phase 3 Trials in Participants with Tardive Dyskinesia

Active treatments were pooled for the 2 double-blind, placebo-controlled trials (Trial C-18 [flexible dose] and Trial C-23 [fixed dose]) and compared to pooled placebo treatment to determine the adverse drug reactions (ADRs; defined as >2% and more common in active treatment than in placebo). The frequently reported AEs listed in the next table were defined as ADRs. The grouped terms of akathisia, agitation, and restlessness occurred at a rate close to 2% (1.8%) in participants treated with DTBZ versus 0.8% in participants treated with placebo in the 2 pooled placebo-controlled TD trials. Therefore, these terms were also included in the ADR section of the SmPC section 4.8.

Table 73: Adverse drug reactions occurring in >2% in participants with Tardive Dyskinesia from trials C-18 and C-23

System Organ Class MedDRA 17.0 Preferred Term, n (%)	Placebo (N=131)	DTBZ (N=279)
Participants with at least 1 AE	70 (53.4)	147 (52.7)
Gastrointestinal disorders	32 (24.4)	40 (14.3)
Diarrhoea	5 (3.8)	12 (4.3)
Infections and infestations	17 (13.0)	42 (15.1)
Nasopharyngitis	2 (1.5)	11 (3.9)
Urinary tract infection	2 (1.5)	6 (2.2)
Psychiatric disorders	15 (11.5)	38 (13.6)
Depression[a]	1 (0.8)	5 (1.8)
Dysthymic disorder[a]	0	1 (0.4)
Insomnia	1 (0.8)	10 (3.6)

Source: TDISS, Ad Hoc Summary 5.
[a] Depression and Dysthymic disorder were grouped (2.2%).
AE=adverse event; DTBZ=deutetrabenazine; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants; n=number of participants in subgroup.

Phase 3 Trials in Participants with Huntington's Disease

As the mechanism of action of DTBZ does not differ between patients with TD and those with HD-associated chorea, clinical trial data from the placebo-controlled HD Trial C-15 (using the DTBZ matrix formulation BID) were used to support ADR determination for DTBZ in participants with TD. Due to the overall lower number of participants in Trial C-15 (45 participants in the DTBZ-treatment arm and placebo-treatment arm each) ADRs were defined for this analysis as >4% and more common in DTBZ treatment group than in the placebo group. The analysis resulted in the additional ADRs listed in the next table, included in the ADR section of the SmPC section 4.8.

Table 74: Adverse reactions occurring in >4% in participants with Huntington's Disease from trial C-15

System Organ Class MedDRA 17.0 Preferred Term, n (%)	Placebo (N=45) n (%)	DTBZ (N=45) n (%)
Gastrointestinal disorders	10 (22.2)	10 (22.2)
Constipation	1 (2.2)	2 (4.4)
Diarrhoea	0 (0.0)	4 (8.9)
Dry mouth	3 (6.7)	4 (8.9)
General disorders and administration site conditions	8 (17.8)	8 (17.8)
Fatigue	2 (4.4)	4 (8.9)
Infections and infestations	5 (11.1)	7 (15.6)
Urinary tract infection	1 (2.2)	3 (6.7)
Injury, poisoning and procedural complications	8 (17.8)	4 (8.9)
Contusion	1 (2.2)	2 (4.4)
Nervous system disorders	10 (22.2)	9 (20.0)
Somnolence	2 (4.4)	5 (11.1)
Psychiatric disorders	8 (17.8)	8 (17.8)
Anxiety	1 (2.2)	2 (4.4)
Insomnia	2 (4.4)	3 (6.7)

Source: CSR SD-809-C-15, Table 14.3.1.3.

Safety data based on post-marketing reports received from patients with TD and HD showed no difference between ADRs rates, confirming a similar DTBZ safety profile of in both indications.

2.6.8.4. Serious adverse events, deaths, and other significant events

2.6.8.4.1. Severity of Adverse Events

Phase 3 Trials in Participants with Tardive Dyskinesia- Severity of Adverse Events

More than 90% of the AEs reported in the DTBZ and placebo groups were mild or moderate in severity (integrated data) during the first 12/15 weeks of the trials. During the overall treatment period, severe AEs were reported for the same proportion of participants in the placebo group (5 participants [3.8%]) and DTBZ titration group (6 participants [3.6%]). In the fixed-dose DTBZ 12-, 24-, and 36-mg groups, participants experienced 2, 4, and 1 severe AEs, respectively (TDISS20). The only severe AEs reported in more than 1 participant were depression (1 participant receiving placebo and 1 receiving DTBZ 24 mg) and headache (1 participant in the titration group and 1 receiving DTBZ 12 mg, respectively).

In the long-term safety trial (Trial C-20), severe AEs occurring in more than 1 participant were fall (6 participants [1.8%]), anaemia, urinary tract infection (3 participants [0.9%]), abdominal pain, cardiovascular insufficiency, COPD, dehydration, depression, mental status changes, pneumonia, renal failure acute, respiratory failure, sepsis and suicidal ideation (each reported in 2 participants [0.6%]). Based on the long-term safety data from titration and maintenance period (C-20 Parts A and B) there was no evidence of increased severity of AEs.

In Trial C-20 Part C there were 3 (3.8%) participants with 6 severe AEs: acute myocardial infarction and coronary artery disease (experienced by 1 [1.3%] participant), severe dehydration and cardiac failure (experienced by 1 [1.3%] participant), acute respiratory failure and circulatory collapse (experienced by 1 [1.3%] participant). AEs of moderate severity were reported by 8 (10%) participants. These included back pain and dyskinesia each reported by 2 (2.5%) participants. All other AEs of moderate severity were reported by 1 (1.3%) participant: sinus tachycardia, blood pressure increased, gout, tardive dyskinesia, schizophrenia and schizophrenia paranoid type. All other AEs of mild severity were reported by 12 (15%) participants.

Phase 1 Trials in Healthy Participants - Severity of Adverse Events

TV50717-BE-10179: all AEs were reported as mild (31 participants [12%]) or moderate (15 participants [6%]) in severity. Events of moderate severity by PT were reported in the Test group for 1 participant (<1%) each: dyspepsia, asthenia, acute sinusitis, COVID-19, arthropod bite, anxiety, and dysmenorrhea. In the Reference group events of moderate severity by PT were reported for 1 participant (<1%) each: chalazion, blood creatine phosphokinase increased, neck pain and dysmenorrhea. The only AEs of moderate severity by PT reported by at 2 participants (<1%) was oropharyngeal pain in the Test group, influenza-like illness and headache in the Reference group (CSR TV50717-BE-10179). No severe AEs were reported.

TV50717-PK-10175: all AEs were reported as mild (9 participants [8%]) or moderate (5 participants [4%]) in severity. The only AE of moderate severity by PT reported by at least 2 participants was influenza-like illness, recorded in 2 (2%) while receiving 2×24 mg trial drug. There were no severe AEs.

TV50717-BE-10165: all AEs (8 participants [10%]) were reported as mild (4 participants [5%]) or moderate (4 participants [5%]) in severity. By PT the only moderate AE that occurred in at least 2 participants within a treatment was headache, reported for 2 participants (2%) receiving 1×24 mg DTBZ QD osmotic tablet fasted (CSR TV50717BE10165). No severe AEs were reported.

TV50717-BE-10192: all AEs (12 participants [6%]) were reported as mild (8 participants [4%]) or moderate (4 participants [2%]) in severity. By PT the only moderate AE that occurred in at least 2 participants (1%) receiving 2×24 mg QD (Reference) was headache, No severe AEs were reported in the trial.

TV50717-BE-10201: all AEs (9 participants [7%]) were reported as mild (4 participants [3%]) or moderate (5 participants [4%]) in severity. By PT moderate AEs occurred in only 1 participant. No severe AEs were reported in the trial.

2.6.8.5. Deaths

Deaths of Participants with Tardive Dyskinesia Treated with DTBZ in the Phase 3 Trials

Trial C-18: no deaths reported

Trial C-23: 2 deaths reported

Trial C-20: 10 deaths reported

Eight participants died during Parts A and B of the trial. Two participants died during C-20 Part C. One additional death was reported for a participant who died 56 days after the last dose of trial drug and 25 days after being withdrawn from the trial.

Deaths of Participants with Huntington's Disease Treated with DTBZ in the Phase 3 Trials

Trial C-15: no deaths were reported

Trial C-16: 1 death was reported

Deaths of Healthy Participants Treated with DTBZ in the Phase 1 Trials

There were no reported deaths in any of the trials including healthy participants treated with DTBZ osmotic PR formulation QD.

2.6.8.6. Other Serious Adverse Events (SAEs)

Participants with Tardive Dyskinesia

Twenty-nine participants with TD reported at least 1 SAE up to week 12/15 (9 participants in the placebo group, 11 participants receiving 12 to 36 mg DTBZ, and 9 participants in the titration group); 67 in the long-term safety Trial C-20 reported SAEs anytime during Part A.

SAEs were reported in a similar proportion between participant in the placebo-treated and DTBZ titration groups. Fewer SAEs were reported in the fixed dose groups overall, with participants receiving the 24mg fixed dose showing a slightly higher frequency of SAEs than for the 12- or 36-mg groups. A summary of SAEs for the TD trials is presented in the next table (any event occurring in ≥2 participants in any treatment group).

SAEs of psychiatric disorders were infrequent in the short-term trials. One placebo-treated participant (0.8%) experienced 1 SAE of bipolar disorder, 3 in the DTBZ titration group experienced an SAE in the psychiatric disorder SOC (hypomania, mania, and schizophrenia), 1 (1.4%) in the 12-mg group experienced an SAE of psychotic disorder and 1 participant (1.4%) each in the 24-mg group experienced an SAE of depression and suicidal ideation. The frequency of psychiatric SAEs in the long-term open label trial was similar to those in the short-term trials, aside from schizophrenia which was only slightly higher.

No pattern was observed between treatment groups for the type of SAEs reported, and the only SAE reported in more than 1 participant in Trials C18 and C-23 was pneumonia.

Table 75: Serious adverse events in the overall treatment period by preferred term and participant group in ≥2 participants with Tardive Dyskinesia

Preferred Term, n (%)	**Short-Term (up to Week 12/15)**					**Long-Term (up to Week 158)**
	Trials C-18 and C-23	**Trial C-23**			**Trials C-18 and C-20**	**Trial C-20 Part A**
	Placebo (N=130)	**DTBZ 12 mg (N=72)**	**DTBZ 24 mg (N=72)**	**DTBZ 36 mg (N=72)**	**DTBZ Titration (N=168)**	**DTBZ (N=337)**
Participants with at least 1 SAE	9 (6.9)	2 (2.8)	6 (8.3)	3 (4.2)	9 (5.4)	67 (19.9)
Cardiac failure	0	0	0	0	0	2 (0.6)
Cardiovascular insufficiency	0	0	0	0	0	2 (0.6)
Chronic obstructive pulmonary disease	0	0	0	0	0	4 (1.2)
Depression	0	0	1 (1.4)	0	0	2 (0.6)
Hypomania	0	0	0	0	1 (0.6)	2 (0.6)
Mania	0	0	0	0	1 (0.6)	2 (0.6)
Pneumonia	1 (0.8)	0	1 (1.4)	1 (1.4)	1 (0.6)	3 (0.9)
Psychotic disorder	0	1 (1.4)	0	0	0	2 (0.6)
Schizophrenia	0	0	0	0	1 (0.6)	5 (1.5)
Schizoaffective disorder	0	0	0	0	0	2 (0.6)
Suicidal ideation	0	0	1 (1.4)	0	0	3 (0.9)
Renal failure acute	0	0	0	0	0	2 (0.6)

Source: TDISS20, MAA Ad Hoc Summary 17.

In Trial C-18 3 participants treated with DTBZ and 5 treated with placebo experienced 1 SAE each during the treatment period. The events in the DTBZ-treated participants were pneumonia, manic episode (leading to hospitalization) and schizophrenia (suspected exacerbation). All these events were assessed by the investigator as unrelated or unlikely related to trial drug and all resolved. The events in the placebo-treated participants were overdose, jaw fracture, jaw abscess, pneumonia and laryngeal hypertrophy. All of these events were assessed by the investigator as unrelated or unlikely related to trial drug and all had outcomes of recovered/resolved or recovering/resolving. The event of overdose also led to trial withdrawal.

In Trial C-23, the most frequently reported SAE in the DTBZ treated participants was pneumonia (2 participants: 1 [1.4%] participant each); the other events occurred in 1 DTBZ treated participant each. The SAE of suicidal ideation reported in a participant treated with DTBZ 24 mg/day was considered possibly related to trial drug; all other SAEs were assessed as unrelated or unlikely related to the trial drug.

In Part A and B of the long-term safety trial C-20 the most common SAEs experienced during the overall treatment period were schizophrenia (5 participants [1.5%]), COPD, pneumonia (4 participants each [1.2%]) and suicidal ideation (3 participants [0.9). Four SAEs in 3 participants were considered by the investigator as possibly related to DTBZ (1 participant with intentional overdose and suicide attempt, and 1 participant each exacerbation of mania and exacerbation of hypomania); all other SAEs were

considered unrelated or unlikely related to DTBZ, and most events resolved without change in DTBZ dosage.

A total of 8 participants (2.4%) in Part A and B of Trial C-20 experienced 9 SAEs of cardiac disorders, including cardiac arrest, cardiopulmonary failure, myocardial infarction, and ventricular tachycardia each reported by 1 participant (0.3%). Cardiac failure and cardiovascular insufficiency were each reported by 2 participants (0.6%). All of these participants entered Trial C20 with a history of cardiovascular disorder. The investigator considered these (cardiac) events as unlikely related to DTBZ. Seven of the 8 cardiac events (cardiac arrest, cardiopulmonary failure, myocardial infarction, 2 cases of cardiac failure, ventricular tachycardia, and cardiovascular insufficiency) had fatal outcomes. Three events () each in 1 participant were reported as resolved: angina pectoris, acute myocardial infarction and cardiovascular insufficiency.

In Part C of Trial C-20 5 participants had 1 or more SAE. No PT for a SAE occurred in more than 1 participant. Two participants each reported 2 SAE: cardiac failure and dehydration in 1 (1.3%) participant and acute respiratory failure and circulatory collapse in 1 (1.3%) participant. These 2 (2.5%) participants had SAEs that were fatal.

Healthy Participants Treated with DTBZ

There were no reported SAEs in any of the trials including healthy participants treated with DTBZ osmotic PR formulation QD.

2.6.8.7. Other Significant Adverse Events

VMAT2-Inhibition-Related AEs in Participants with TD in the Phase 3 Trials

Signs and symptoms observed with TD and vesicular monoamine transporter type 2 (VMAT2) inhibition-related AEs included depression, anxiety, somnolence, parkinsonism, and akathisia. These categories of class related AEs are described in further detail in the following sections through analysis of related AE preferred terms.

In addition to AE reporting, safety scales were incorporated into the trials to regularly monitor for subclinical toxicity related to VMAT2 inhibition. Analysis of the safety scales revealed no evidence of subclinical toxicity in TD participants.

Overall, the frequencies of AEs in these categories of interest were not significantly different between DTBZ groups compared to the placebo group during the short-term treatment (up to week 12/15) period or long term open-label trial (C-20).

In the long-term Trial C-20 Part C, data from the analyses of AEs demonstrated that in participants with TD treated with DTBZ for ≥171 weeks, the risk of developing VMAT2-inhibition-related AEs did not increase with long exposure. During C-20 Part C, 2 participants reported AEs grouped under Parkinson-like events SMQ. No other VMAT2-inhibition-related AEs were reported for Trial C-20 Part C.

2.6.8.7.1. Depression

Depression was evaluated through monitoring of AEs and Hospital Anxiety and Depression Scale - Depression Subscale (HADS-D).

Depression (excluding suicide and self-injury) SMQ AEs were reported for fewer placebo-treated participants than participants in the DTBZ titration group, with a higher frequency in the long-term open label (C-20) trial. The EAIRs for depression (excluding suicide and selfinjury) SMQ AEs were highest in

the titration and fixed-dose groups compared to the long-term open label (C-20) trial and placebotreated groups.

Most depression (excluding suicide and self-injury) SMQ events were mild or moderate. Severe depression was reported in 1 participant (in Trial C-18, receiving placebo), and considered by the investigator as probably related to the trial drug, consequently suspended for 6 days. No further treatment was administered and the event resolved. One event of severe depression (in Trial C-23) was assessed as serious and considered by the investigator unlikely related to DTBZ.

Table 76: Depression (Excluding Suicide and Self-Injury) SMQ adverse events in the overall treatment period by preferred term and participant group (Safety population in Tardive Dyskinesia trials C-18, C-23, and C-20)

Preferred Term, n (%)	**Short-Term (up to Week 12/15)**					**Long-Term (up to Week 158)**
	Trials C-18 and C-23	**Trial C-23**			**Trials C-18 and C-20[a]**	**Trial C-20 Part A**
	Placebo (N=130)	**DTBZ 12 mg (N=72)**	**DTBZ 24 mg (N=72)**	**DTBZ 36 mg (N=72)**	**DTBZ Titration (N=168)**	**DTBZ (N=337)**
Participants with at least 1 AE	1 (0.8)	2 (2.8)	3 (4.2)	2 (2.8)	6 (3.6)	50 (14.8)
EAIR (No. of participants/ patient-years)	0.04 (1/28.3)	0.13 (2/15.6)	0.20 (3/15.1)	0.14 (2/14.8)	0.14 (6/41.8)	0.08 (50/611.5)
Adjustment disorder with depressed mood	0	0	0	0	0	1 (0.3)
Depressed mood	0	1 (1.4)	0	0	1 (0.6)	14 (4.2)
Depression	1 (0.8)	1 (1.4)	3 (4.2)	1 (1.4)	5 (3.0)	33 (9.8)
Dysthymic disorder	0	0	0	1 (1.4)	0	5 (1.5)

Source: TDISS20, MAA Ad Hoc Summary 22.

[a] The DTBZ titration group included data from participants receiving DTBZ in Trial C-18 through week 12 plus data from Trial C-20 through week 15 for participants who were previously in the placebo treatment group in Trials C-18 or C-23.

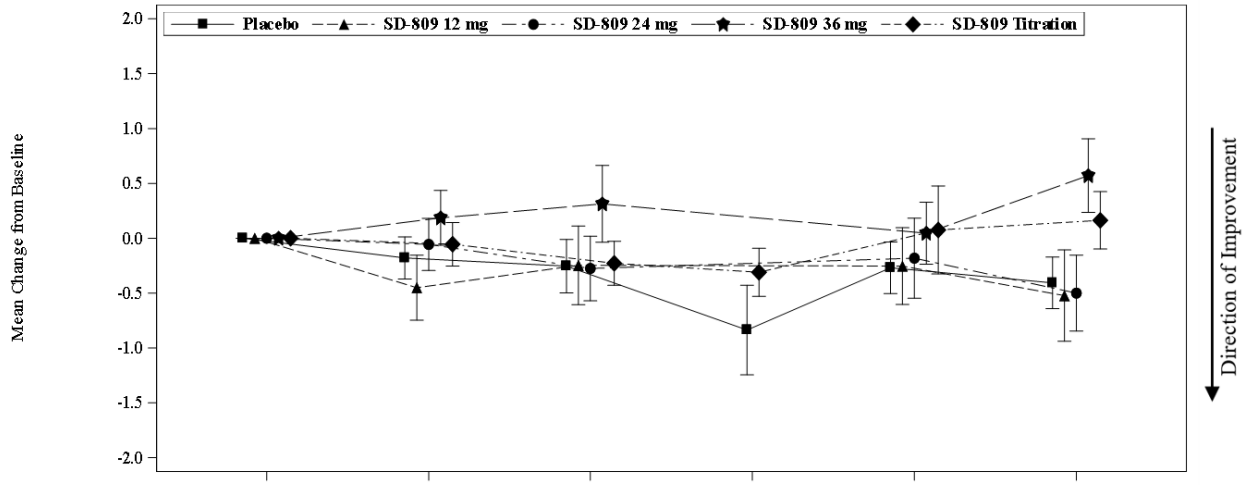
Note: Participants are counted only once in each preferred term category. For calculating patient-years in each preferred term, participants with an adverse event contribute with treatment exposure up to the day of their first adverse event and participants without an adverse event contribute with their entire treatment exposure.

The EAIR for depression AEs in Trial C20 was 0.08, indicating no increase in depression over this longer period when compared with the EAIR in the 12/15-week DTBZ titration group (0.14).

HADS-D subscale scores (changes from baseline) generally remained constant for most participant groups up to week 12/15, indicating no increase in depressive symptoms and this trend continued in the long-term safety trial (Trial C-20), which includes data up to week 158.

Figure 44: Mean (±SE) HADS-D subscale score changes from baseline to each visit by participant group (Safety population in Tardive Dyskinesia trials)

Parameter: Depression Total

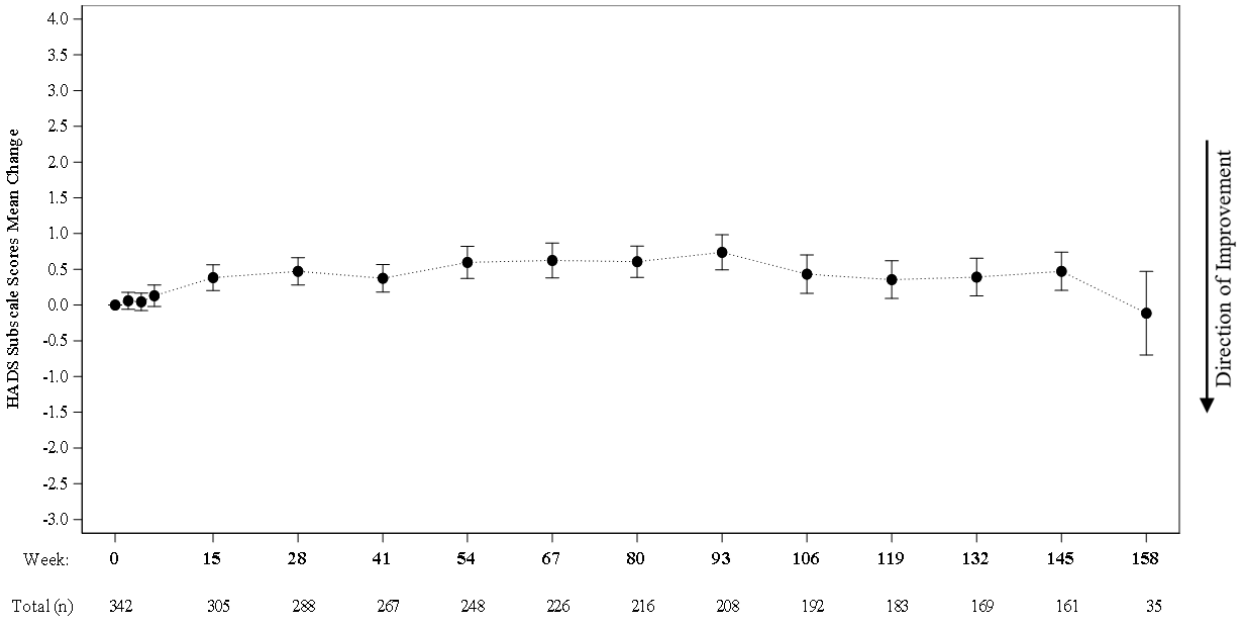


Visit:	Baseline	Week 2	Week 4	Week 6	Week 8/9	Week 12/15
SD-809 Titration (N)	168	165	162	158	53	153
SD-809 36 mg (N)	72	70	67		65	63
SD-809 24 mg (N)	72	71	69		66	64
SD-809 12 mg (N)	72	71	69		67	65
Placebo (N)	130	128	122	55	119	118

Source: TDISS20, Graph 9.
HADS-D=Hospital Anxiety and Depression Scale – Depression Subscale; N=number of participants; SD-809=Deutetrabenazine; SE=standard error; TD=tardive dyskinesia.
Note: Week 8/9 is the combination of Trial C-23 week 8 data and Trial C-18 week 9 data. Week 12/15 is the combination of Trials C-18 and C-23 week 12 data and Trial C-20 week 15 data.

Figure 45: Mean (±SE) HADS-D Subscale Score Changes from Baseline of this Trial to Each Part A Visit (Trial C-20, Safety population)

Parameter: Depression Total



Week:	0	15	28	41	54	67	80	93	106	119	132	145	158
Total (n)	342	305	288	267	248	226	216	208	192	183	169	161	35

Source: SD-809-C-20, Graph 17.18.
HADS-D=Hospital Anxiety and Depression Scale – Depression Subscale; n=number of participants; SD-809=deutetrabenazine; SE=standard error.
Note: Higher scores indicate greater motor impairment.

Anxiety

Anxiety was evaluated through monitoring of AEs and the Hospital Anxiety and Depression Scale - Anxiety Subscale (HADS-A). Anxiety AEs were reported for a similar proportion of placebo-treated participants and participants in the DTBZ titration group. The overall EAIR for the anxiety AE PT is presented in the next table. Most anxiety events were mild or moderate. Severe anxiety was reported for 1 participant (Trial C23, 12 mg), considered by the investigator probably related to the trial drug and resolved without change in the l drug dose. One moderate anxiety AE, considered by the investigator possibly related to the trial drug, led to withdrawal from the trial (Trial C-20). One participant had the dose reduced due to mild anxiety.

Table 77: Anxiety adverse events in the overall treatment period by preferred term and participant group with Tardive Dyskinesia (Safety population)

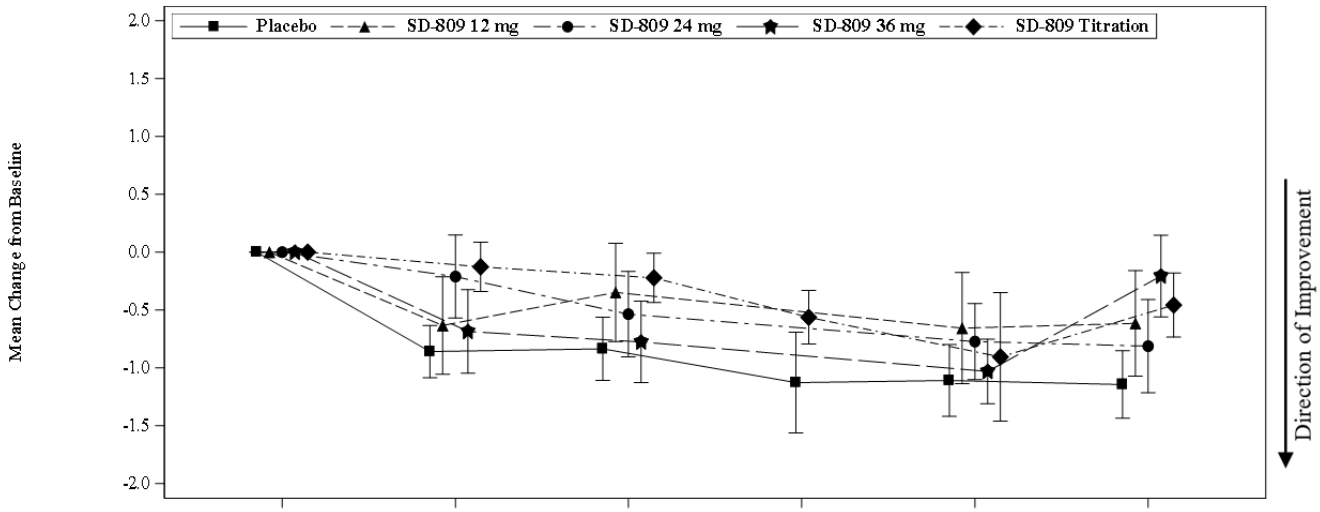
Preferred Term, n (%)	**Short-Term (up to Week 12/15)**					**Long-Term (up to Week 158)**
	Trials C-18 and C-23	**Trial C-23**			**Trials C-18 and C-20[a]**	**Trial C-20 Part A**
	Placebo (N=130)	**DTBZ 12 mg (N=72)**	**DTBZ 24 mg (N=72)**	**DTBZ 36 mg (N=72)**	**DTBZ Titration (N=168)**	**DTBZ C-20 (N=337)**
Anxiety	6 (4.6)	3 (4.2)	2 (2.8)	3 (4.2)	8 (4.8)	42 (12.5)
EAIR	0.22	0.20	0.13	0.20	0.19	0.07
(No. of participants/ patient-years)	(6/27.8)	(3/15.4)	(2/15.0)	(3/14.7)	(8/41.5)	(42/636.0)

Source: TDISS20, MAA Ad Hoc Summary 23.
[a] The DTBZ titration group included data from participants receiving DTBZ in Trial C-18 through week 12 plus data from Trial C-20 through week 15 for participants who were previously in the placebo treatment group in Trials C-18 or C-23.
DTBZ=deutetrabenazine; EAIR=exposure-adjusted incidence rate; N=number of participants; n=number of participants in the subgroup.
Note: Participants are counted only once in each preferred term category. For calculating patient-years in each preferred term, participants with an adverse event contribute with treatment exposure up to the day of their first adverse event and participants without an adverse event contribute with their entire treatment exposure.

In the long-term safety trial C-20 42 participants (12.5%) had an anxiety AE. The EAIR for anxiety AEs was 0.07, indicating no increase in anxiety over this longer period compared with EAIR in the 12/15-week DTBZ titration group (0.19). All anxiety events reported in Trial C-20 were mild or moderate in severity, except for 1 participant who reported drug abuse (PT) and anxiety (descriptive term) secondary to amphetamine abuse. One participant experienced a SAE of anxiety (anxiety aggravated), considered moderate and unrelated to DTBZ. Two participants discontinued from the trial due to anxiety. Slight decreases in the HADS-A subscale scores were observed for all participant groups up to week 12/15, indicating no generalized worsening in anxiety symptoms (TDISS20), and this trend continued in the long-term safety trial (Trial C-20), which includes data up to week 158.

Figure 46: Mean (±SE) HADS-A subscale score changes from baseline to each visit by participant group (Safety population in Tardive Dyskinesia trials)

Parameter: Anxiety Total

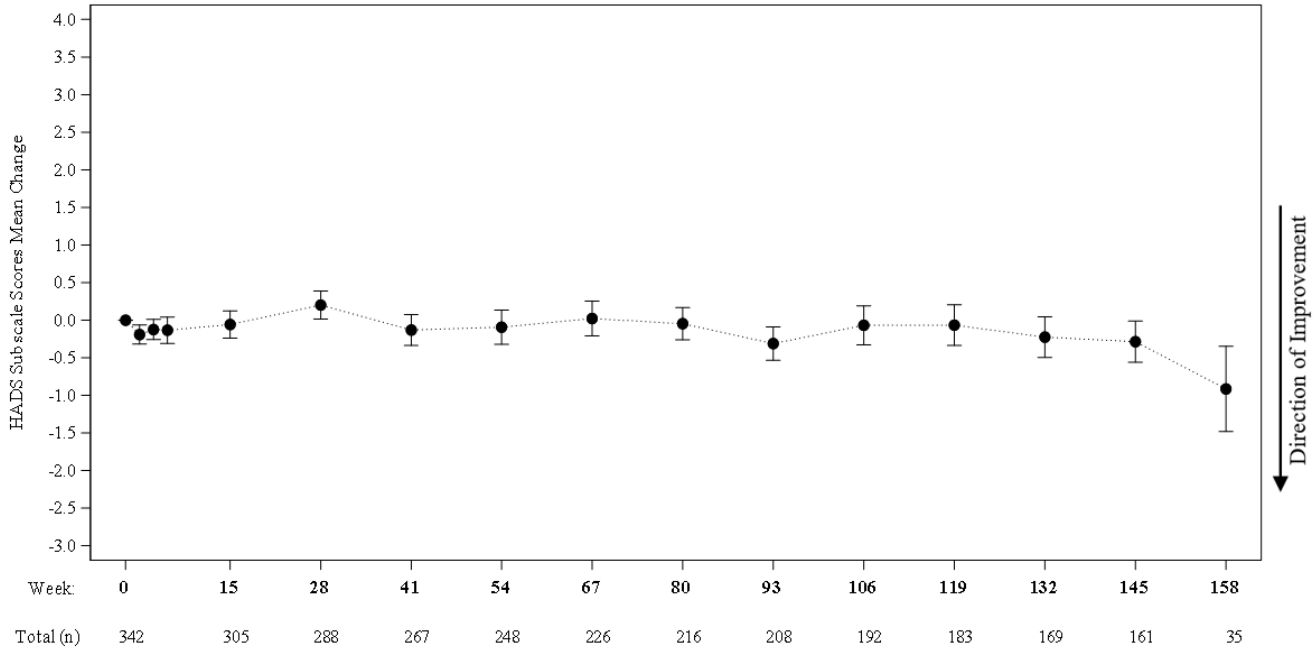


Visit:	Baseline	Week 2	Week 4	Week 6	Week 8/9	Week 12/15
SD-809 Titration (N)	168	165	162	158	53	153
SD-809 36 mg (N)	72	70	67		65	63
SD-809 24 mg (N)	72	71	69		66	64
SD-809 12 mg (N)	72	71	69		67	65
Placebo (N)	130	128	122	55	119	118

Source: TDISS20, Graph 9.
HADS-A=Hospital Anxiety and Depression Scale – Anxiety Subscale; N=number of participants; SD-809=deutetrabenazine; SE=standard error; TD=tardive dyskinesia.
Note: Week 8/9 is the combination of Trial C-23 week 8 data and Trial C-18 week 9 data. Week 12/15 is the combination of Trials C-18 and C-23 week 12 data and Trial C-20 week 15 data.

Figure 47: Mean (±SE) HADS-A subscale score changes from baseline to each part A visit (Trial C-20, Safety population)

Parameter: Anxiety Total



Source: SD-809-C-20, Graph 17.18.
HADS-A=Hospital Anxiety and Depression Scale – Anxiety Subscale; n=number of participants; SD-809=deutetrabenazine; SE=standard error.
Notes: Higher scores indicate more motor impairment.

2.6.8.7.2. Somnolence and Sedation

Somnolence and sedation were evaluated through monitoring of AEs and ESS. Somnolence AEs were reported for fewer participants in the placebo and fixed-dose groups than in DTBZ titration group. The overall EAIR for somnolence and sedation AE preferred terms is presented in the next table. The AEs generally occurred early during treatment, with most being reported during the first 2 to 3 weeks of treatment or during titration.

All were considered mild or moderate; 4 of these events led to dose reduction and most of them were considered by the investigator related to the trial drug.

Table 78: Somnolence and sedation adverse events in the overall treatment period by preferred terms and participant group (Safety Population in Tardive Dyskinesia trials C-18, C-23, and C-20)

Preferred Term, n (%)	Short-Term (up to Week 12/15)					Long-Term (up to Week 158)
	Trials C-18 and C-23	Trial C-23			Trials C-18 and C-20[a]	Trial C-20 Part A
	Placebo (N=130)	DTBZ 12 mg (N=72)	DTBZ 24 mg (N=72)	DTBZ 36 mg (N=72)	DTBZ Titration (N=168)	DTBZ (N=337)
Participants with at least 1 AE	9 (6.9)	0	1 (1.4)	4 (5.6)	21 (12.5)	41 (12.2)
EAIR (No. of participants/ patientyears)	0.34 (9/26.5)	0.0 (0/15.6)	0.06 (1/15.4)	0.28 (4/14.4)	0.54 (21/39.0)	0.07 (41/621.3)
Lethargy	0	0	0	0	0	2 (0.6)
Sedation	0	0	0	1 (1.4)	2 (1.2)	6 (1.8)
Somnolence	9 (6.9)	0	1 (1.4)	3 (4.2)	19 (11.3)	34 (10.1)

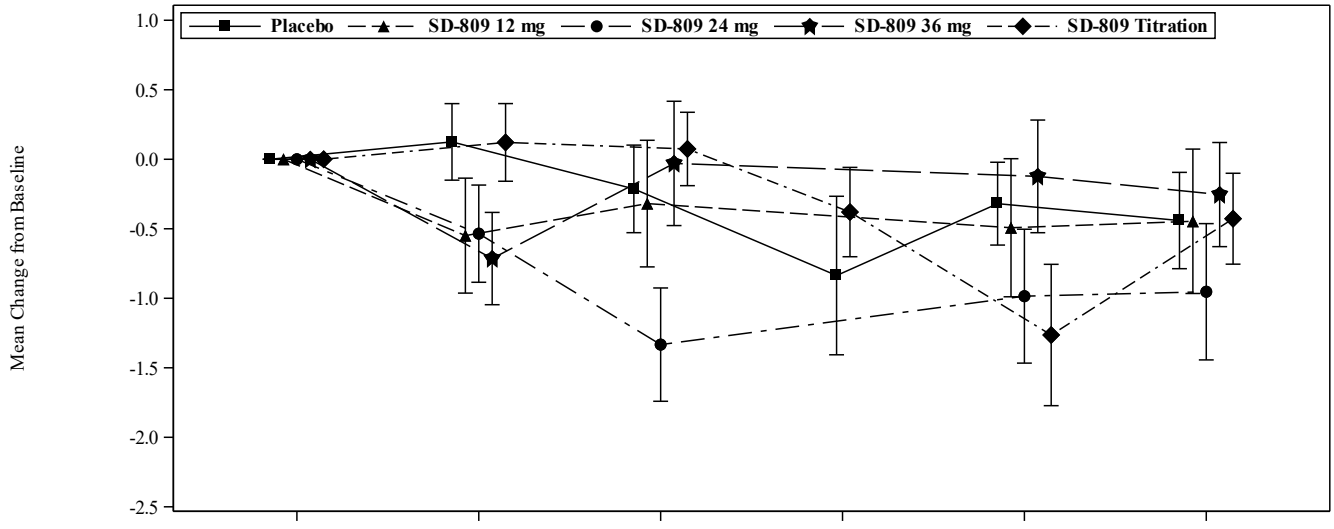
Source: TDISS20, MAA Ad Hoc Summary 24.
[a] The DTBZ titration group included data from participants receiving DTBZ in Trial C-18 through week 12 plus data from Trial C-20 through week 15 for participants who were previously in the placebo treatment group in Trials C-18 or C-23.
AE=adverse event; DTBZ=deutetrabenazine; EAIR=exposure-adjusted incidence rate; N=number of participants; n=number of participants in the subgroup.
Note: Participants are counted only once in each preferred term category. For calculating patient-years in each preferred term, participants with an adverse event contribute with treatment exposure up to the day of their first adverse event and participants without an adverse event contribute with their entire treatment exposure.

In the long-term safety trial C-20 34 participants (10.1%) experienced an AE of somnolence. The exposure-adjusted incidence rate (EAIR) for somnolence AEs in this trial was 0.07, indicating no increase in somnolence with long-term exposure. The EAIR of somnolence was highest in the DTBZ titration and placebo groups, suggesting that this event may be reported more frequently when titrating the trial drug to a clinical response. All events of somnolence or sedation reported in Trial C-20 were mild or moderate in severity; 1 event of moderate somnolence led to discontinuation from the trial.

The Epworth Sleepiness Scale (ESS) summary scores showed no trends or consistent changes in any of the participant groups up to week 12/15, indicating no observed general increase in somnolence in the study population. This is consistent with the observations in the long-term safety trial C-20 which includes data up to week 158.

Mean ESS total score values and changes from baseline to each visit by participant group are presented the table below for the safety population enrolled in TD trials and thereafter specifically for the safety population enrolled in Trial C-20.

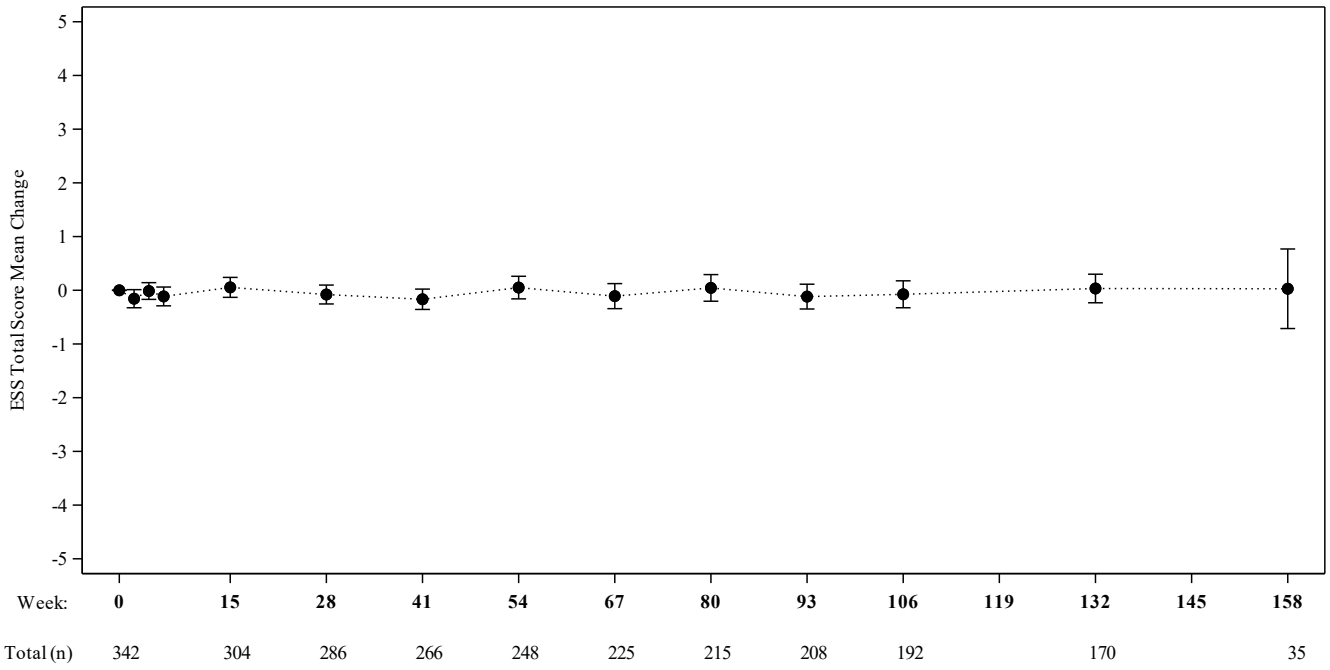
Figure 48: Mean (±SE) ESS Total Score change from baseline to each visit by participant group (Safety population in Tardive Dyskinesia trials)



Visit:	Baseline	Week 2	Week 4	Week 6	Week 8/9	Week 12/15
SD-809 Titration (N)	168	165	162	158	53	152
SD-809 36 mg (N)	72	70	67		65	63
SD-809 24 mg (N)	72	71	69		66	64
SD-809 12 mg (N)	72	71	69		67	65
Placebo (N)	130	128	122	55	119	118

Source: TDISS20, Graph 10.
ESS=Epworth Sleepiness Scale; N=number of participants; SD-809=deutetrabenazine; SE=standard error.
Note: Week 8/9 is the combination of Trial C-23 week 8 data and Trial C-18 week 9 data. Week 12/15 is the combination of Trials C-18 and C-23 week 12 data and Trial C-20 week 15 data.

Figure 49: Mean (±SE) ESS total score change from baseline of this trial to each part A visit (Trial C-20, Safety population)



Source: SD-809-C-20, Graph 17.19.
ESS=Epworth Sleepiness Scale; n=total number of participants; SE=standard error.
Note: Higher scores indicate higher levels of daytime sleepiness.

2.6.8.7.3. Parkinsonism

Parkinsonism was evaluated through monitoring of AEs and motor assessment score of the Unified Parkinson's Disease Rating Scale (UPDRS). Parkinson-like (SMQ) AEs were thoroughly searched and analysed by PT as indicated in the TD integrated summary of safety (ISS) statistical analysis plan (SAP).

Parkinson-like (SMQ) AEs were reported higher in DTBZ titration group compared to the placebo-treated group. One participant in the fixed-dose groups (receiving DTBZ 36 mg) experienced an AE of parkinsonism. Because there were few events, no trends could be observed with regard to timing of events' onset. EAIRs for the overall Parkinson-like (SMQ) AEs were low in the integrated data and in the long-term Trial C-20.

All of the Parkinson-like (SMQ) AEs were considered mild or moderate in severity, none was serious or led to discontinuation from the trial. The events of parkinsonian gait and parkinsonism led to dose reduction.

Table 79: Parkinson-like (SMQ) adverse events in the overall treatment period by preferred term and by participant group (Safety population in Tardive Dyskinesia trials C-18, C-23, and C-20)

Preferred Term, n (%)	Short-Term (up to Week 12/15)					Long-Term (up to Week 158)
	Trials C-18 and C-23	Trial C-23			Trials C-18 and C-20[a]	Trial C-20 Part A
	Placebo (N=130)	DTBZ 12 mg (N=72)	DTBZ 24 mg (N=72)	DTBZ 36 mg (N=72)	DTBZ Titration (N=168)	DTBZ (N=337)
Participants with at least 1 AE	2 (1.5)	1 (1.4)	1 (1.4)	5 (6.9)	10 (6.0)	51 (15.1)
EAIR (No. of participants/ patient-years)	0.07 (2/28.1)	0.06 (1/15.4)	0.07 (1/15.3)	0.35 (5/14.5)	0.24 (10/41.7)	0.08 (51/606.1)
Bradykinesia	0	0	0	0	1 (0.6)	15 (4.5)
Bradyphrenia	0	0	0	0	0	2 (0.6)
Cogwheel rigidity	1 (0.8)	0	0	0	0	0
Drooling	0	1 (1.4)	0	2 (2.8)	0	5 (1.5)
Extrapyramidal disorder	0	0	0	0	0	1 (0.3)
Gait disturbance	0	0	1 (1.4)	1 (1.4)	1 (0.6)	3 (0.9)
Hypokinesia	0	0	0	0	1 (0.6)	1 (0.3)
Micrographia	0	0	0	0	0	1 (0.3)
Muscle rigidity	0	0	0	0	0	3 (0.9)
Musculoskeletal stiffness	0	0	0	1 (1.4)	3 (1.8)	8 (2.4)
Parkinson's disease	0	0	0	0	0	1 (0.3)
Parkinsonian gait	0	0	0	0	1 (0.6)	0
Parkinsonian rest tremor	0	0	0	0	0	1 (0.3)
Parkinsonism	0	0	0	1 (1.4)	0	7 (2.1)
Postural tremor	0	0	0	0	0	1 (0.3)
Tremor	1 (0.8)	0	0	0	3 (1.8)	14 (4.2)

Source: TDISS20, MAA Ad Hoc Summary 25.
[a] The DTBZ titration group included data from participants receiving DTBZ in Trial C-18 through week 12 plus data from Trial C-20 through week 15 for participants who were previously in the placebo treatment group in Trials C-18 or C-23.
AE=adverse event; DTBZ=deutetrabenazine; EAIR=exposure-adjusted incidence rate; N=number of participants; n=number of participants in the subgroup; SMQ=Standardized MedDRA Query.
Note: Participants are counted only once in each preferred term category. For calculating patient-years in each preferred term, participants with an adverse event contribute with treatment exposure up to the day of their first adverse event and participants without an adverse event contribute with their entire treatment exposure.

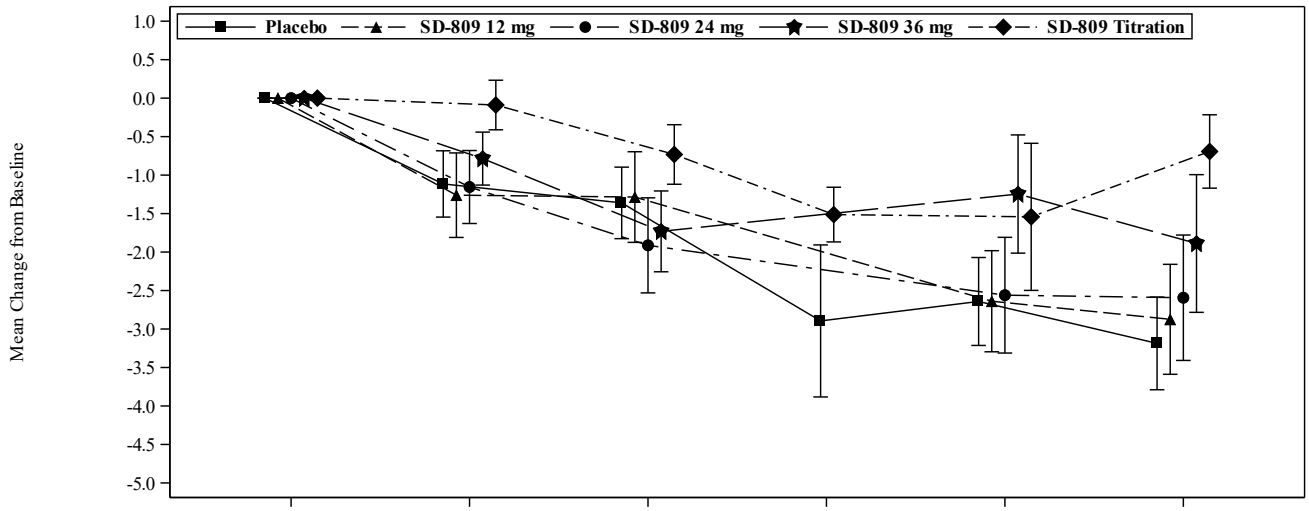
With regard to Parkinson-like (SMQ) AEs in the overall treatment period by PT and by participant group (Safety Population in Tardive Dyskinesia Trials C-18, C-23, and C-20), as summarised in the table above, one participant (1.4%) in the DTBZ 36 mg group and 7 participants (2.1%) in the long-term safety trial C-20 had an AE that mapped to Parkinsonism.

The EAIR for Parkinson-like (SMQ) AEs in Trial C-20 was 0.08, indicating no increase in parkinsonism related AEs over this longer period when compared with the EAIR in the 12/15week DTBZ titration group (0.24) and placebo group (0.07).

Small decreases in the UPDRS motor scores were observed for all participant groups up to week 12/15. Participants receiving DTBZ 36 mg and within the DTBZ titration group experienced less benefit, which could be indicative of parkinsonism effect. There was also no evidence of increased motor impairment over time in the long-term safety trial C-20, which includes data up to week 158.

In trial C-20 Part C, 2 participants reported Parkinson-like events: 1 reported bradykinesia (starting on day 1322) that was mild in severity, required a dose reduction and medication, was resolving and considered possibly related to the trial drug by the investigator. One participant reported (left hand) tremor (starting on day 1381) that was mild in severity, did not require a dose modification or other treatment, was resolving and considered probably related to the trial drug by the investigator. This participant reported 4 other tremor AEs (right hand tremors) of varying severity (mild, moderate, and severe) starting at day 105 and ongoing on day 378. The severe tremor resulted in dose reduction of the trial drug, and all these 4 events of right-hand tremor required medication. These right-hand tremor was considered probably related to the trial drug by the investigator.

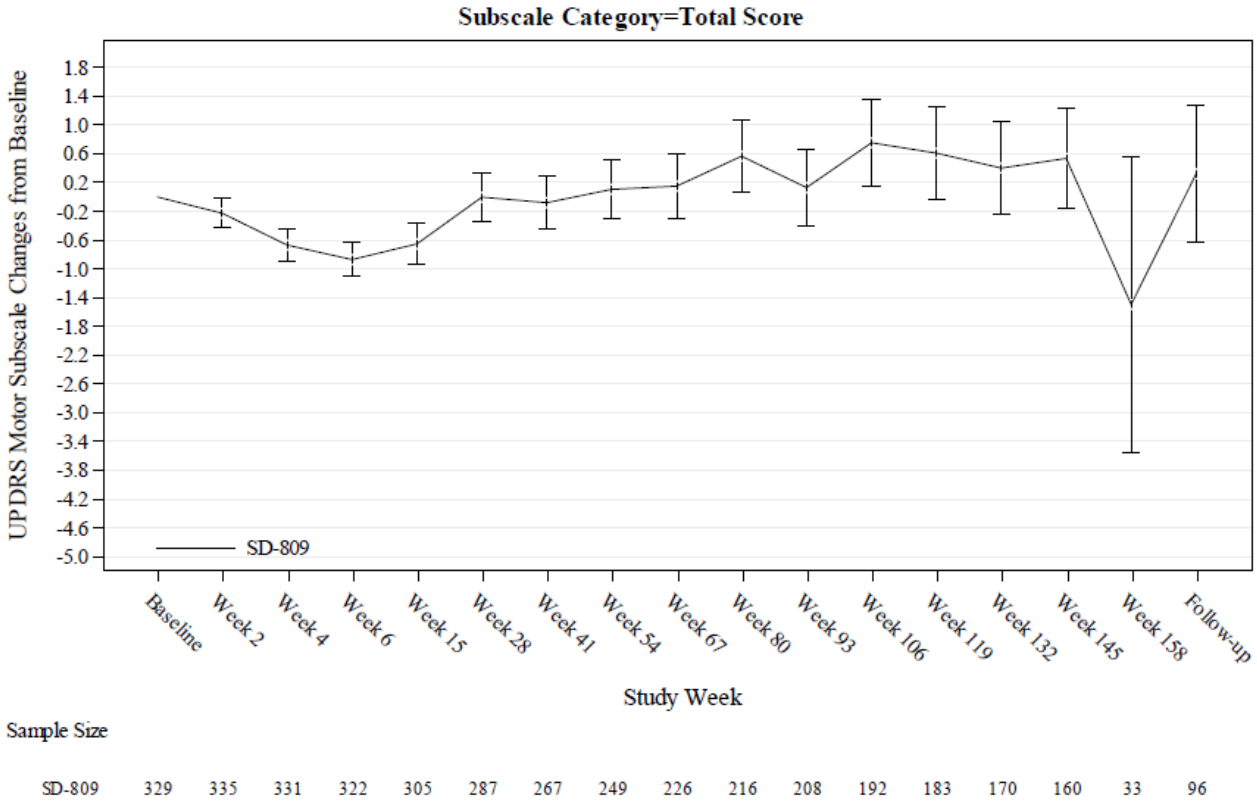
Figure 50: Mean (±SE) UPDRS motor score change from baseline to each visit by participant group (Safety population in Tardive Dyskinesia trials)



Visit:	Baseline	Week 2	Week 4	Week 6	Week 8/9	Week 12/15
SD-809 Titration (N)	168	165	162	158	53	153
SD-809 36 mg (N)	72	70	67		65	63
SD-809 24 mg (N)	72	71	69		66	64
SD-809 12 mg (N)	72	71	69		67	65
Placebo (N)	130	128	122	55	120	118

Source: TDISS20, Graph 7.
N=number of participants; SD-809=deutetrabenazine; SE=standard error; UPDRS=Unified Parkinson's Disease Rating Scale.
Note: Week 8/9 is the combination of Trial C-23 week 8 data and Trial C-18 week 9 data. Week 12/15 is the combination of Trials C-18 and C-23 week 12 data and Trial C-20 week 15 data.

Figure 51: Mean (±SE) UPDRS motor subscale score change from baseline to each part A visit (Trial C-20, Safety population)



Source: TDISS20, Ad Hoc Graph 3.
Sd-809=deutetrabenazine; SE=standard error; UPDRS =Unified Parkinson's Disease Rating Scale.
Notes: Higher scores indicate greater motor impairment.

The applicant clarified that Parkinsonism was evaluated through monitoring of AEs and motor assessment score of UPDRS. The SMQ Parkinson-like events was applied to identify and analyse relevant AEs.

The review of clinical data from the TD development programme did not identify parkinsonism as an ADR. However, review of post-marketing experience reports in patients with TD resulted in the classification of parkinsonism as an ADR. To determine this ADR adequate frequency category for SmPC section 4.8, the applicant reviewed the placebo-controlled trials in TD, C-18 and C-23. Among DTBZ-treated participants in these trials (N=279), 1 event of parkinsonism (0.4%) was reported. Based on this, the frequency category of uncommon (≥1/1,000 to <1/100) was selected.

2.6.8.7.4. Akathisia and Restlessness

Akathisia and restlessness were evaluated through AEs monitoring, including all PTs that could map to akathisia SMQ (TDISS statistical analysis plan) and Barnes Akathisia Rating Scale (BARS) summary assessment scores.

Akathisia (SMQ) AEs were reported in 4 participants in the DTBZ titration group compared to none in the placebo-treated group. Additionally, 1 participant in each of the DTBZ 12-, 24-, and 36-mg dose groups experienced AEs that could be mapped to akathisia and restlessness. The EAIRs for the overall akathisia (SMQ) AEs were low in the integrated data and in the long-term Trial C-20. Occurrence of akathisia and restlessness events was sporadic and no trends could be observed with regard to timing of these events. All akathisia (SMQ) AEs were considered mild or moderate and none led to dose reduction or suspension. One participant (Trial C23; 36 mg) experienced an SAE of psychomotor hyperactivity, considered

moderate in severity and unlikely related to the trial drug. This event led to patient's withdrawal from the trial.

Table 80: Akathisia (SMQ) adverse events in the overall treatment period by preferred term and participant group (Safety population in Tardive Dyskinesia trials C-18, C-23, and C-20)

Preferred Term, n (%)	**Short-Term (up to Week 12/15)**					**Long-Term (up to Week 158)**
	Trials C-18 and C-23	**Trial C-23**			**Trials C-18 and C-20[a]**	**Trial C-20 Part A**
	Placebo (N=130)	**DTBZ 12mg (N=72)**	**DTBZ 24mg (N=72)**	**DTBZ 36mg (N=72)**	**DTBZ Titration (N=168)**	**DTBZ (N=337)**
Participants with at least 1 AE	0	1 (1.4)	1 (1.4)	1 (1.4)	4 (2.4)	10 (3.0)
EAIR (No. of participants/ patient-years)	0.0 (0/28.3)	0.06 (1/15.4)	0.07 (1/15.3)	0.07 (1/15.0)	0.09 (4/42.7)	0.01 (10/675.2)
Akathisia	0	0	1 (1.4)	0	4 (2.4)	9 (2.7)
Extrapyramidal disorder	0	0	0	0	0	1 (0.3)
Psychomotor hyperactivity	0	0	0	1 (1.4)	0	0
Restlessness	0	1 (1.4)	0	0	0	1 (0.3)

Source: TDISS20, MAA Ad Hoc Summary 26.
[a] The DTBZ titration group included data from participants receiving DTBZ in Trial C-18 through week 12 plus data from Trial C-20 through week 15 for participants who were previously in the placebo treatment group in Trials C-18 or C-23.
AE=adverse event; DTBZ=deutetrabenazine; EAIR=exposure-adjusted incidence rate; N=number of participants; n=number of participants in the subgroup; SMQ=Standardized MedDRA Query; TD=Tardive Dyskinesia.

Note: Participants are counted only once in each preferred term category. For calculating patient-years for each preferred term, participants with an adverse event contribute with treatment exposure up to day of their first adverse event, and participants without an adverse event contribute with their entire treatment exposure.

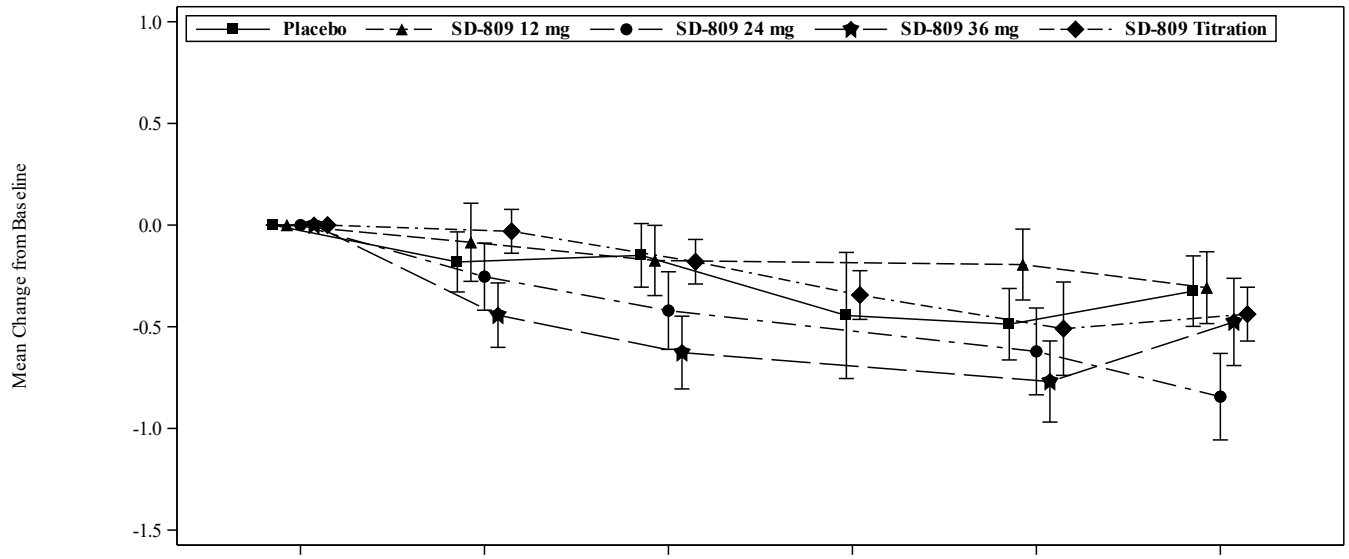
Note: EAIR is calculated as the number of participants/patient-years.

The EAIR for akathisia (SMQ) AEs in Trial C-20 was 0.01, as outlined in the table above, indicating no increase in akathisia related AEs over this longer period compared with the EAIR in the 12/15-week DTBZ titration group (0.09). All events of akathisia and restlessness reported in Trial C-20 (Part A) were mild in severity; none was serious or led to discontinuation.

Small decreases in the BARS summary scores were observed for all participant groups up to week 12/15, indicating there was no overall increase in akathisia and restlessness symptoms (TDISS20), and this trend continued in the long-term safety trial C-20, which includes data up to week 158.

Taken together, available data demonstrate that, in participants with TD, the risk of akathisia or restlessness during treatment with DTBZ was low.

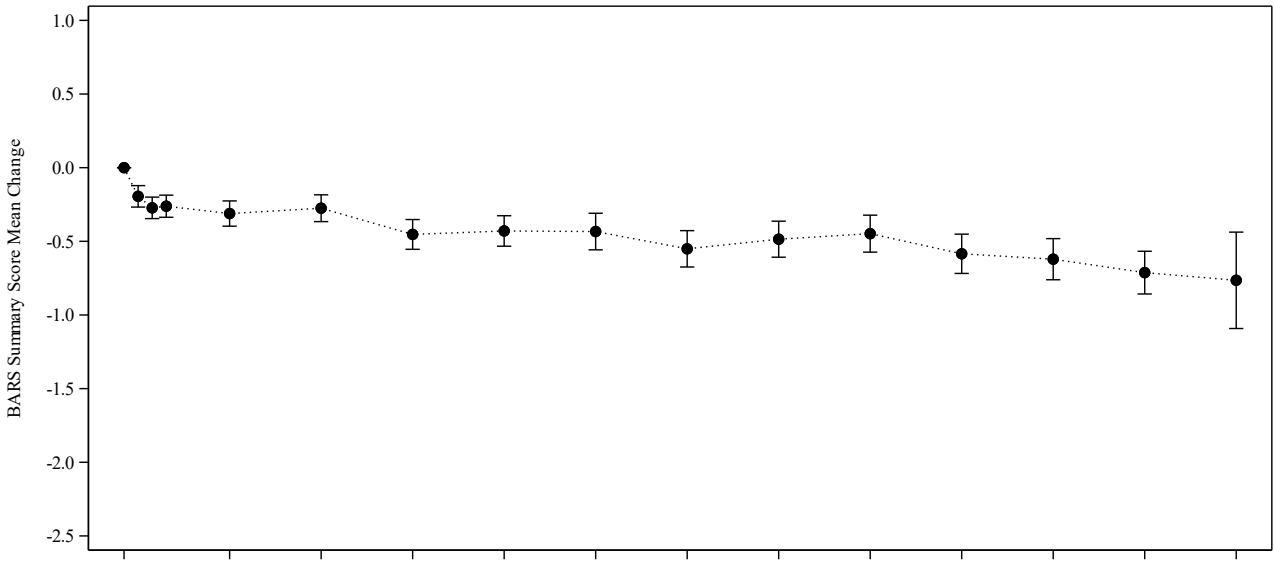
Figure 52: Mean (±SE) BARS summary score change from baseline to each visit by participant group (Safety population Tardive Dyskinesia trials)



Visit:	Baseline	Week 2	Week 4	Week 6	Week 8/9	Week 12/15
SD-809 Titration (N)	168	164	161	157	53	153
SD-809 36 mg (N)	72	70	67		65	63
SD-809 24 mg (N)	72	71	69		66	64
SD-809 12 mg (N)	72	71	69		67	65
Placebo (N)	129	127	121	54	119	117

Source: TDISS20, Graph 8.
BARS=Barnes Akathisia Rating Scale; N=total number of participants; SD-809=deutetrabenazine; SE=standard error.
Note: Week 8/9 is the combination of Trial C-23 week 8 data and Trial C-18 week 9 data. Week 12/15 is the combination of Trials C-18 and C-23 week 12 data and Trial C-20 week 15 data.

Figure 53: Mean (±SE) BARS summary score change from baseline of this trial to each part A visit (Trial C-20, Safety population)



Week:	0	15	28	41	54	67	80	93	106	119	132	145	158
Total (n)	342	305	287	267	249	226	216	208	192	183	169	160	34

Source: SD-809-C-20, Graph 17.17.
BARS=Barnes Akathisia Rating Scale; n=total number of participants; SE=standard error.

2.6.8.8. Additional Safety Assessments

2.6.8.8.1. Suicidality

Suicidality is a known risk in the predominantly psychiatric population of patients with TD; it was therefore systematically evaluated through monitoring of C-SSRS and AE reporting in TD trials. Review of the aggregate clinical data in the TD population presented below did not reveal any safety signal with respect to DTBZ having a differential effect on causing or worsening suicidality compared to placebo. The incidence of suicidality was low in all trials using the DTBZ matrix formulation BID.

Phase 1 Trials in Healthy Participants

For participants in the Phase 1 trials who were administered DTBZ osmotic PR formulation QD, no suicidal ideation or suicide attempt was reported in any of these trials.

Phase 3 Trials in Participants with Tardive Dyskinesia

At screening, positive responses in the C-SSRS related to suicidal ideation and suicidal behaviour were recorded for a similar proportion of placebo-treated participants and participants in the DTBZ titration group. Post baseline positive C-SSRS responses related to suicidal ideation and suicidal behaviour were reported for more placebo-treated participants than participants in the DTBZ titration group. There were no completed suicides.

Table 81: Columbia suicide severity rating scale by participant group (Safety population in Tardive Dyskinesia trials)

	Short-Term (up to Week 12/15)					Long-Term (up to Week 158)
	Trials C-18 and C-23		Trial C-23		Trials C-18 and C-20[a]	Trial C-20 Part A
	Placebo (N=130)	DTBZ 12 mg (N=72)	DTBZ 24 mg (N=72)	DTBZ 36 mg (N=72)	DTBZ Titration (N=168)	DTBZ (N=337)
C-SSRS, screening (participants with an assessment), n (%)						
Suicidal ideation	30 (23)	17 (24)	21 (29)	18 (25)	37 (22)	82 (24)
Suicidal behaviour	22 (17)	12 (17)	16 (22)	13 (18)	28 (17)	61 (18)
Self-injurious behaviour without suicidal intent	7 (5)	1 (1)	4 (6)	0	7 (4)	11 (3)
C-SSRS, anytime post baseline, n (%)						
Suicidal ideation	5 (4)	1 (1)	4 (6)	2 (3)	3 (2)	22 (7)
Suicidal behaviour	1 (<1)	0	1 (1)	0	0	2 (<1)
Self-injurious behaviour without suicidal intent	0	0	1 (1)	0	0	0

Source: TDISS20, MAA Ad Hoc Summary 27.
[a] The DTBZ titration group included data from participants receiving DTBZ in Trial C-18 through week 12 plus data from Trial C-20 through week 15 for participants who were previously in the placebo treatment group in Trials C-18 or C-23.
C-SSRS=Columbia Suicide Severity Rating Scale; DTBZ=deutetrabenazine; N=number of participants; n=number of participants in the subgroup.
Notes: The denominator for calculating the percentages is the number of participants with an assessment at that time point. Participants are counted only once for each category and once for each item within a category at each time point. All time points come from the last visit version of the scale.

In the long-term safety **trial C-20**, Parts A-C, **3 participants** reported Suicidal ideation SAEs; all these SAEs were considered unrelated or unlikely related to DTBZ. One participant reported an SAE of suicide attempt, considered possibly related to DTBZ.

Thirteen participants had suicidal ideation post-baseline; no participant had completed suicide at any post-baseline time point.

Suicide/self-injury (SMQ) AEs were reported in 1 placebo-treated participant and in no participants in DTBZ titration group. The event reported in the placebo-treated participant led to temporary dose suspension and it subsequently resolved. **One participant in Trial C-23** experienced an SAE event of suicidal ideation that was **moderate in severity** and led to discontinuation. The 2 other AEs of suicidal ideation in Trial C-23 were considered mild and non-serious.

The EAIR for suicide/self-injury (SMQ) adverse events in Trial C-20 was 0.02, indicating no increase in suicidality over this longer period of treatment compared with the EAIR over the 12/15-week period in the DTBZ 24 mg and 36 mg fixed-dose groups or placebo. No pattern or trend in the time to first occurrence of the suicidality was observed when data was evaluated over time.

Table 82: Suicide/Self-Injury (SMQ) adverse events in the overall treatment period by preferred term and participant group in (Safety population in Tardive Dyskinesia trials C-18, C-23, and C-20)

Preferred Term, n (%)	Short-Term (up to Week 12/15)					Long-Term (up to Week 158)
	Trials C-18 and C-23	Trial C-23			Trials C-18 and C-20[a]	Trial C-20
	Placebo (N=130)	DTBZ 12 mg (N=72)	DTBZ 24 mg (N=72)	DTBZ 36 mg (N=72)	DTBZ titration (N=168)	Part A (N=337)
Participants with at least 1 AE	1 (0.8)	0	2 (2.8)	1 (1.4)	0	14 (4.2)
EAIR (No. of participants/ patient-years)	0.04 (1/28.3)	0.0 (0/15.6)	0.13 (2/15.3)	0.07 (1/14.9)	0.0 (0/42.9)	0.02 (14/673.1)
Suicidal ideation	1 (0.8)	0	2 (2.8)	1 (1.4)	0	13 (3.9)
Intentional overdose	0	0	0	0	0	1 (0.3)
Suicide attempt	0	0	0	0	0	1 (0.3)

Source: TDISS20, MAA Ad Hoc Summary 28.
[a] The DTBZ titration group included data from participants receiving DTBZ in Trial C-18 through week 12 plus data from Trial C-20 through week 15 for participants who were previously in the placebo treatment group in Trials C-18 or C-23.
AE=adverse event; DTBZ=deutetrabenazine; EAIR=exposure-adjusted incidence rate; N= number of participants; n= number of participants in the subgroup.
Note: Participants are counted only once in each preferred term category. For calculating patient-years in each preferred term, participants with an adverse event contribute with treatment exposure up to the day of their first adverse event and participants without an adverse event contribute with their entire treatment exposure.

The CHMP considered that the 4 cases of suicidal ideation reported during the clinical trial programme (1 case in Trial C-23 and 3 cases in Trial C-20, Part A, as above pointed out) required further attention, questioning whether suicidality, a known risk in the general psychiatric population (and patients with TD are a predominantly psychiatric patient population) could be increase with DTBZ. Therefore, as requested, the applicant provided further details (including narratives) about these cases to support the conclusion that no increased incidence of suicidality had been identified in comparison with the expected background of suicidality in the psychiatric TD population.

In Trial C-18, the exposure-adjusted incidence rates for suicide/self-injury (SMQ) AEs over the 12/15-week period were higher in the DTBZ 24 mg/day (0.13) and 36 mg/day fixed-dose groups (0.07) versus placebo (0.04). In the long-term Trial C-20, the EAIR was 0.02. No AE were reported in C18.

Concomitant medications with known risk of suicidality and medical history were reviewed. In all 4 cases, medical history included depression (with 2 participants having 2 or more suicide attempts) and all participants received concomitant medications to treat underlying depression. No trend was observed in the time to event, as well as no dose-dependent pattern was identified. In addition, in all these cases, the suicidality event resolved (DTBZ was discontinued in 3 cases; action taken was unknown in the fourth one). In 3 cases, causality was confirmed as not related to DTBZ by both the investigator and Teva. The assessment of causality in these cases took into consideration confounding factors (like medical history of depression and suicide attempts), as well as concomitant medications with known risk of suicidality. In 1 of the cases, the time to event onset (latency) was very long (546 days) and in another case the participant had not received DTBZ for at least 3 months prior to the event. In the case where both investigator and Teva considered the event as possibly related to DTBZ, there was a close temporal relationship between the event and exposure to DTBZ, as well as positive dechallenge. However, history of borderline personality disorder and schizoaffective disorder with previous suicide attempts, as well as multiple concomitant medications associated with an increased risk of suicidality, represented significant confounding factors.

Of note, as outlined in SmPC section 4.9, although experience with dosages higher than the recommended maximum daily dose of 48 mg is limited, isolated cases of deutetrabenazine overdose (up to 240 mg per day) had been derived from post-marketing reports and literature. Among the most frequently observed symptoms suicidal ideation was noted. Quantitative scales to assess VMAT2-inhibition-related subclinical toxicity indicated no AEs with DTBZ treatment. There was no increase of motor score of UPDRS in the treated participants in TD Trials.

An integrated analysis of the AEs of interest in participants with TD showed that the frequencies of AEs in the categories of interest were not significantly different between participants who received DTBZ compared to those who received placebo during short-term treatment period (up to week 12/15) or the long-term open-label Trial C-20. This indicated that the risk of developing VMAT2-inhibition-related AEs does not increase with longer-term exposure.

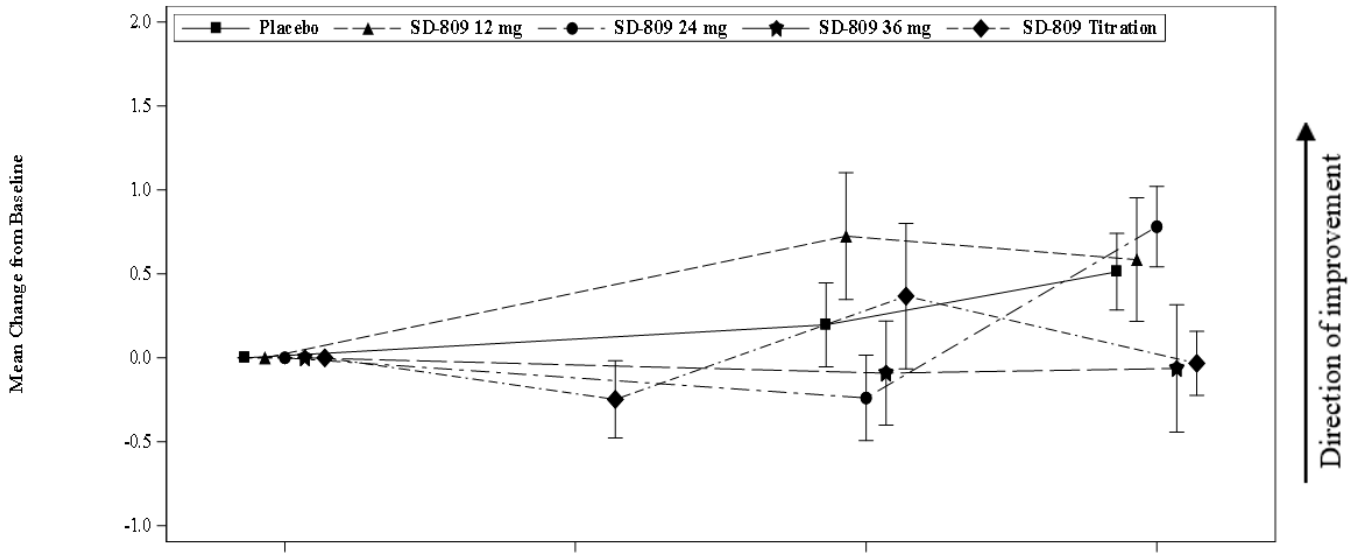
The applicant reported that active treatments were pooled for the 2 double-blind, placebo-controlled trials (Trial C-18 [flexible dose] and Trial C-23 [fixed dose]) and compared these data to the pooled placebo treatment to determine adverse drug reactions (defined as >2% and more common in active treatment than in placebo). The choice of the threshold of 2% to complete the list of the ADR remains unclear, and this applicant's decision appears purely arbitrary. However, it was also indicated that "*to ensure no important AEs were overlooked, Teva had reviewed AEs not surpassing the 2% threshold (i.e., occurring <2%) to identify any additional clinically-relevant ADRs*". Additionally, the applicant indicated that "an additional analysis of post-marketing safety data from patients with TD and patients with HD showed no difference between the rates of the proposed ADRs". Thus, all together, this whole approach should allow to overcome the risk of non-inclusion of safety risk of importance with a frequency below 2%.

Ultimately, the incidence of suicidality was low in Trials C-18 and C-23, based on both AE reporting and scale assessment. Long-term administration of DTBZ in participants with TD in Trial C-20 did not identify any increased incidence of suicidality in comparison with the expected background of suicidality in this psychiatric participant population in TD trials.

2.6.8.8.2. Cognitive Function

Cognitive function was evaluated through the Montreal Cognitive Assessment (MoCA) and AEs monitoring. MoCA total scores were generally stable or trended upward in all participant groups up to week 12/15 (mean change 0.5), indicating that DTBZ did not adversely affect cognitive function. A similar observation was made in the long-term safety trial C-20) which included data up to week 158.

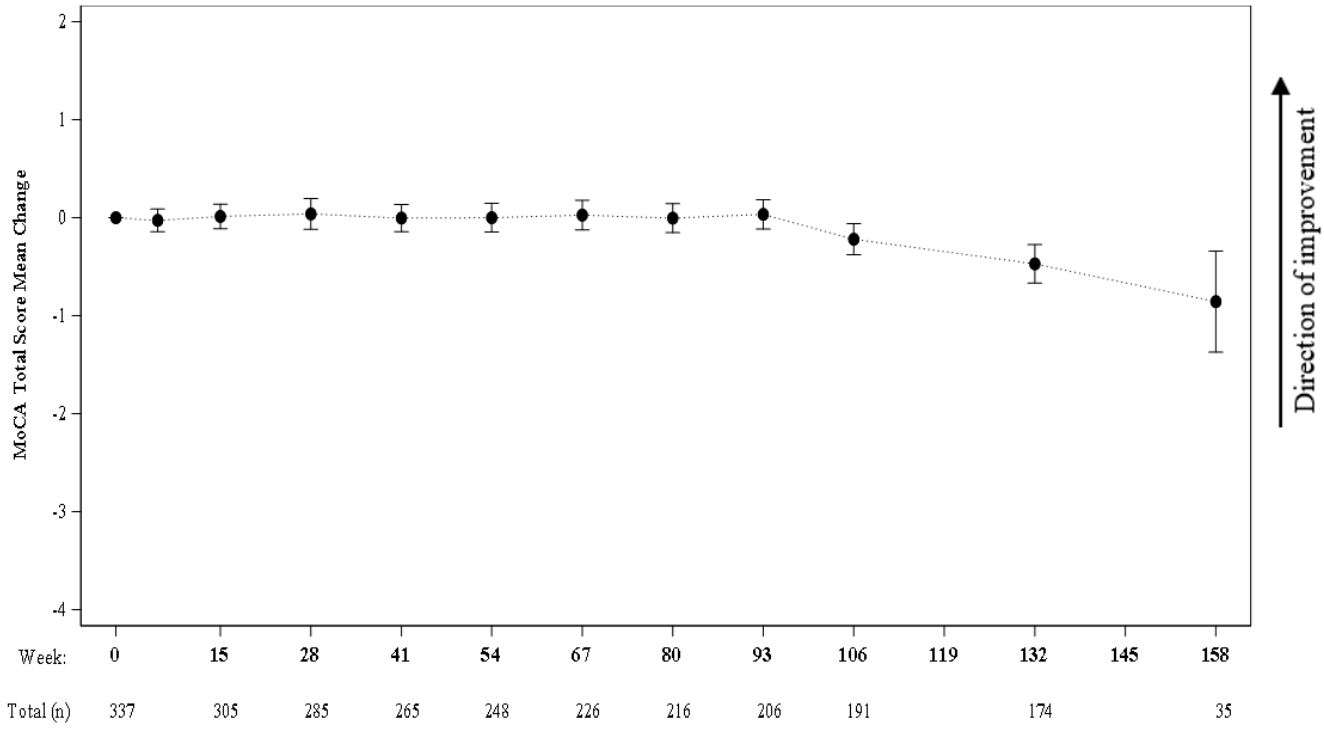
Figure 54: Mean (±SE) MoCA total score change from baseline to each visit by participant group (Safety population in Tardive Dyskinesia trials)



Visit:	Baseline	Week 6	Week 8/9	Week 12/15
SD-809 Titration (N)	168	105	49	153
SD-809 36 mg (N)	72		66	63
SD-809 24 mg (N)	72		67	64
SD-809 12 mg (N)	72		69	65
Placebo (N)	130		122	119

Source: TDISS20, Graph 11.
MoCA=Montreal Cognitive Assessment; N=total number of participants; sd-809=deutetrabenazine; SE=standard error; SD-809=DTBZ; TD=tardive dyskinesia.
Note: Week 8/9 is the combination of Trial C-23 week 8 data and Trial C-18 week 9 data. Week 12/15 is the combination of Trials C-18 and C-23 week 12 data and Trial C-20 week 15 data.

Figure 55: Mean (±SE) MoCA total score change from baseline of this trial to each part A visit (Trial C-20, Safety population)



Source: SD-809-C-20, Graph 17.20.
MoCA=Montreal Cognitive Assessment; SE=standard error.

One placebo-treated participant and 1 participant in Trial C-20 experienced AEs related to cognitive function. Both events were mild/moderate in severity and not serious.

Table 83: Cognitive disorder adverse events in the overall treatment period (Safety population in Tardive Dyskinesia trials C-18, C-23 and C-20)

	Short-Term (up to Week 12/15)					Long-Term (up to Week 158)
	Trials C-18 and C-23	Trial C-23			Trials C-18 and C-20[a]	Trial C-20 Part A
	Placebo (N=130)	DTBZ 12 mg (N=72)	DTBZ 24 mg (N=72)	DTBZ 36 mg (N=72)	DTBZ Titration (N=168)	Part A (N=337)
EAIR	0.04	0.0	0.0	0.0	0.0	<0.01
(Participants/patient-years)	(1/28.3)	(0/15.6)	(0/15.4)	(0/15.0)	(0/42.9)	(1/687.5)

Source: TDISS20, MAA Ad Hoc Summary 29.

[a] The DTBZ titration group included data from participants receiving DTBZ in Trial C-18 through week 12 plus data from Trial C-20 through week 15 for participants who were previously in the placebo treatment group in Trials C-18 or C-23.
DTBZ=deutetrabenazine; EAIR=exposure-adjusted incidence rate; N=number of participants.

Note: Participants are counted only once for each preferred term category. For calculating patient-years for each preferred term, participants with an adverse event contribute with treatment exposure up to the day of their first adverse event, and participants without an adverse event contribute with their entire treatment exposure.

Note: EAIR is calculated as number of participants/patient-years.

2.6.8.8.3. Overdose

No overdose has been reported for participants in TD trials. In the HD Trial C-16, potential overdose was reported for multiple participants, due to "return of an incorrect number of pills" during at least one of their scheduled visits. Subsequently, it was difficult to determine if these missing pills were misplaced, lost, or truly taken by the participants. Taking a conservative approach, a potential overdose was considered for these cases in which medication was not returned. None of the participants received more than 72 mg/day DTBZ matrix formulation BID as their protocol defined dose. None of them reported an AE of overdose with the trial drug. One patient in the HD Trial C-16 Rollover Cohort increased the dose of 48 to 72 mg/day for 4 days, without the investigator's knowledge: this was considered a potential overdose of trial drug, with no AEs in the time period immediately following the reported overdose.

Post-marketing reports (received up to 31 October 2023) suggestive of DTBZ overdose were identified using search criteria of a highest reported daily dose greater than 48 mg/day together with inclusion of one of the following PTs: Accidental overdose, Intentional overdose, Overdose, Prescribed overdose and suicidality-related PTs (Suicidal ideation, attempt, behaviour, completed suicide, suicide threat, suspected suicide attempt). Overall, 69 cases were identified. In most of these reports (55 cases), no specific AEs related to intake of doses over 48 mg/day were identified. The remaining 14 cases included the following 23 additional AEs: somnolence (reported in 3 cases), dyskinesia, hypersomnia, insomnia, and suicidal ideation (each reported in 2 cases), anxiety, apathy, dizziness, fatigue, feeling jittery, movement disorder, muscle twitching, psychotic disorder, restlessness, sedation, stress, and weight increased (each reported once). In addition, 2 literature articles describing DTBZ overdose were identified. The first by Obadeyi et al 2021 reported about a 59-years-old female patient with a history of hypertension, type 2 diabetes, hypothyroidism, TD, Parkinson's disease, schizophrenia, bipolar disorder, and ischemic stroke, who unintentionally took 240 mg of DTBZ and denied any suicidality attempt. The only co-reported events were depression (not known if a pre-existing condition) and somnolence. The second literature article (Sidlak et al 2019) described a 21-year-old male patient hospitalized with toxic encephalopathy, dyskinesia, and psychomotor hyperactivity following an ingestion of 720 mg of DTBZ. The patient was initially treated with diazepam and midazolam, and after 6 hours received benztropine and lorazepam. Urine gas chromatography/mass spectroscopy revealed no other co-ingestion. ECG revealed a normal sinus rhythm, with normal QT and QRS intervals. Twenty-four hours after the ingestion, the toxic encephalopathy resolved, and his ataxia returned to baseline.

Overall, most events co-reported with DTBZ overdose were consistent with DTBZ safety profile.

2.6.8.8.4. Drug Abuse

The trials in DTBZ clinical development program did not reveal any tendency for drug-seeking behaviour, although these assessments were not made in a systematic manner. There are no reports of DTBZ drug abuse in either clinical trials or in the post-marketing phase. As triggered by FDA request dated 13 September 2017, the applicant had conducted regular post-marketing assessments of AEs suggestive of DTBZ abuse-potential in the treatment of TD. Based on this request, Teva analysed cases DTBZ in its safety database for almost 6 years in several periodic safety reports submitted to FDA. Cumulatively, until 31 March 2023, none of the post-marketing cases found in the analyses was suggestive of DTBZ abuse-potential in TD (PSUR No. 727/03/23).

2.6.8.8.5. Withdrawal and Rebound

The long-term safety Trial C-20 included, a double-blinded placebo controlled randomised withdrawal period (Part B). Of the 142 participants randomised to the withdrawal ITT population, 2 (1 from the placebo group and 1 from DTBZ matrix formulation BID group) did not receive the trial drug and were consequently excluded from the safety summary data. The mean (SE) total daily dose of DTBZ at the pre-withdrawal visit was 40.1 (1.18) mg in the placebo group and 39.6 (1.27) mg in the DTBZ group.

During the randomised withdrawal period, no AEs were assessed as serious and all were considered unlikely related or unrelated to the trial drug with the exception of 2 participants with dyskinesia (probably and possibly related to the trial drug in the placebo group and DTBZ group, respectively) and 1 participant in DTBZ group with headache (possibly related to the trial drug). The dyskinesia in the participant treated with DTBZ was considered severe. One participant discontinued due to ALT increased and AST increased. The trial drug was interrupted for 3 participants: 1 with blood magnesium decreased, 1 with blood potassium decreased and 1 with renal failure. All AEs that led to drug interruption and withdrawal resolved except for ALT and AST increased, still unresolved at the last laboratory assessment.

There were no new safety signals or clinically significant safety changes observed during the 1week randomised withdrawal period.

Table 84: Adverse drug reactions reported in adult and elderly patients with Tardive Dyskinesia based on postmarketing reports

Event Preferred term MedDRA version 27.1	**Adult patients (<65 years)**		**Elderly patients (≥65 years)**	
	n	**%**	**n**	**%**
Total number of events	23071	100	19283	100
Constipation	69	0.30	55	0.29
Diarrhoea	212	0.92	224	1.16
Dry mouth	130	0.56	120	0.62
Fatigue	475	2.06	443	2.30
Nasopharyngitis	93	0.40	54	0.28
Urinary tract infection	41	0.18	79	0.41
Contusion	42	0.18	36	0.19
Akathisia	47	0.20	24	0.12
Parkinsonism	35	0.15	45	0.23
Sedation and Somnolence	626	2.71	519	2.69
Agitation and Restlessness	211	0.91	136	0.71
Anxiety	328	1.42	249	1.29
Depression	457	1.98	330	1.71
Insomnia*	574	2.49	433	2.25

Source: data on file
*Insomnia is a grouped term including PTs Initial insomnia, Middle insomnia, Terminal insomnia, and Insomnia
MedDRA=Medical Dictionary for Regulatory Activities; n=number of events

In Trials C-18, C-23, and C-20, there were 16 (14%), 72 (24%), and 79 (23%) elderly participants, respectively.

The applicant provided an additional analysis of AEs by SOC and age group (<65 and ≥65 years) in Trials C-18 and C-23, and an analysis of post-marketing reports from its safety database. In summary, no clinically meaningful differences were observed in the rates of reported AEs by SOC and ADRs between elderly participants/patients and adult participants/patients, as well as the overall population participants in Trials C-18 and C-23 and in the post-marketing setting.

The applicant agreed that DTBZ may slightly prolong the QT interval but argued that the degree of QT prolongation is not clinically significant when DTBZ is administered within the recommended dose range. Teva point out that this aspect is reflected in Section 4.4 of the SmPC. There is a warning in this section that DTBZ should be used with caution in combination with other medicinal products that prolong the QTc interval and in patients with congenital long QT syndrome, a history of cardiac arrhythmias, bradycardia, hypokalaemia or hypomagnesaemia. Further details about the potential interaction with medicines known to prolong the QTc interval are included in Section 4.5 of the SmPC together with specific examples of such medicines.

In Teva's view these RMMs are considered sufficient. Furthermore, the applicant provided a comparative table of SmPC section 4.4 of the authorized tetrabenazine product in Europe, based on a search on the Mutual Recognition Information Product Index database, along with a dedicated discussion for each warning. Two products were identified: Dystardis 25 mg tablets and Tetrabenazine Aristo 25 mg tablets, approved via the decentralised procedure for both indications of hyperkinetic motor disorders with HD and TD.

Suicidality, depression, Parkinsonism, pheochromocytoma and prolactin-dependent tumours, such as prolactin-dependent pituitary tumours or breast cancer are listed as contraindications in the two TBZ products above noted.

Suicidality is described in sub-section 2.6.8.8.1 (Additional safety assessments), 2.6.9 (discussion on clinical safety) and 2.7.1 (risk management plan – safety concerns). Depression and Parkinsonism have also been extensively discussed in different sections of this AR.

Pheochromocytoma was not identified as a risk associated with DTBZ treatment based on available clinical and post-marketing data. With regard to prolactin-dependent pituitary tumours or breast cancer, relevant considerations (such as amenorrhoea, galactorrhoea, gynecomastia. and impotence), which may be associated with hyperprolactinemia, were not reported in DTBZ development program. Therefore, Teva did not consider necessary to include pheochromocytoma or prolactin-dependent tumours as a contraindication in DTBZ SmPC. Overall, CHMP agreed that there is no sufficient evidence at this stage to support these contraindications for DTBZ.

It was also considered whether to categorise somnolence, anxiety, and Parkinsonism as SAEs. Safety data collected during the TD clinical development programme via AE reporting, the HADS-Anxiety Subscale, the Epworth Sleepiness Scale, and UPDRS motor scores demonstrated a low risk for these events in TD participants treated with DTBZ. Anxiety and somnolence were identified as ADRs based on supportive safety data from the HD Trial C-15. Parkinsonism was identified as an uncommon ADR based on postmarketing reports. It is agreed that these ADRs can be adequately followed up via routine pharmacovigilance activities, do not require implementation of additional RMM and do not impact the benefit-risk profile of DTBZ.

2.6.8.9. Laboratory findings

Clinical Laboratory Evaluations – Participants with Tardive Dyskinesia in the Phase 3 Trials

Clinical laboratory tests (haematology, chemistry, and urinalysis) were performed in Trial C-18 and Trial C-23 at screening, baseline, and weeks 6/8 and 12. In Trial C20, they were conducted at weeks 6, 28, 54, and 106 and 158/early termination (ET). Change from baseline and shift tables were provided for all clinical laboratory test results. Values that were outside of the reference range were interpreted by the investigator as either clinically significant or not clinically significant.

No safety signals related to laboratory findings were observed. No clinically meaningful trends were observed for any clinical laboratory parameters, and no clinically meaningful trends were observed for any clinical assessment parameters, including ECGs, for DTBZ.

In long-term Trial C-20 Part C, clinical laboratory assessments were not performed as part of the reduced burden scope of the trial. One participant had a laboratory-related AE during Part C: hypercholesterolemia, that was mild in severity, did not require dose modification, was ongoing (and resolving, with medication). and considered unlikely related to the trial drug.

Haematology

There were no clinically meaningful changes of mean haematology parameter values from baseline to each visit, and no clinically meaningful shifts from normal to abnormal mean haematology parameters were observed. There were no notable changes in mean haematology parameter values over time in either placebo- or DTBZ-treated participants. AEs related to haematology abnormalities (anemia and leukocytosis) were occasionally reported, but these were infrequent. In the placebo-controlled trials, haematology abnormalities occurred at similar frequencies in placebo-treated and DTBZ-treated participants.

Chemistry

No clinically meaningful changes from mean chemistry parameter values at baseline, and no clinically meaningful shifts from normal to abnormal mean chemistry parameter values were observed. There were no notable changes in mean chemistry parameter values over time in placebo- or DTBZ-treated participants.

In Trial C-23, 5 DTBZ treated participants (2 participants in the DTBZ 12 mg and 24 mg fixed-dose group each and 1 participant in the 36 mg fixed-dose group) experienced an AE of abnormal liver function test (LFT), increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), or increased blood alkaline phosphatase (ALP). All events were non-serious. In 4 participants, the severity of the AEs was mild and did not result in treatment changes. The remaining participant experienced AEs of moderate severity (ALT and AST increased), which resolved after drug interruption.

There was no observation of clinically significant laboratory tests abnormalities related to LFTs in Trial C-18.

In Trial C-20, 14 participants had AEs of increased ALT, increased blood ALP, increased AST, increased hepatic enzyme, or abnormal LFT. All these events were non-serious. No AE was assessed as severe (7 participants each experienced mild or moderate adverse events). These AEs resulted in no dose changes in 11 participants, drug interruption in 1 participant (due to abnormal LFT) and drug withdrawal in 2 participants (due to increased ALT and AST in one participant and increased ALT in the other participant).

Urinalysis

No clinically meaningful changes in mean urinalysis parameter values (pH, specific gravity) from baseline, and no clinically meaningful shifts from normal to abnormal mean urinalysis parameters were observed. There were no notable changes in mean urinalysis parameter values over time in either placebo- or DTBZ-treated participants. Clinical Laboratory Evaluations – Healthy Participants in the Phase 1 Trials**.**

For all healthy participants treated with DTBZ osmotic PR formulation QD in the Phase 1 trials, comparable changes in laboratory parameters were recorded across treatment groups and sequences (as applicable). There were no clinically meaningful trends in mean changes from baseline for any clinical laboratory variable in any of the trials. Clinically significant abnormal laboratory measurements were

reported as AEs. In trials **TV50717-PK-10175**, **TV50717-BE-10165**, and **TV50717-BE-10201** no laboratory findings were reported as AEs.

During trial **TV50717-BE-10179**, 5 AEs under the SOC *Investigations* were reported for 4 participants (2%): 2 participants with 3 AEs in the Test treatment (24 mg DTBZ osmotic PR formulation QD) and 2 participants with 1 AE each in the Reference treatment (DTBZ 12 mg matrix formulation BID) treatments:

- In the Test treatment, the AEs of ALT increased, AST increased, and blood creatinine increased were reported;
    - In the Reference treatment, the AEs of ALT increased and CPK increased were each reported for a single participant.

During trial **TV50717-BE-10192**, significant increases in ALT and AST values were reported for 1 participant during treatment with 2×24 mg DTBZ osmotic PR formulation QD (Reference) and evaluated by the investigator as clinically significant (CSR TV50717-BE-10192).

2.6.8.10. Vital Signs, Physical Findings, and other observations related to safety

Vital Signs, Physical Findings, and Other Observations Related to Safety – Participants with Tardive Dyskinesia in the Phase 3 Trials

Vital Signs

There were no notable effects of DTBZ on vital signs, such as blood pressure or pulse, including orthostatic values, in participants with TD in the Phase 3 trials using the matrix formulation BID. Changes from baseline in all blood pressure and heart rate measurements were minimal at week 12/15 and were similar regardless of treatment group. During the long-term TD Trial C-20 (Part A, B, C), no clinically meaningful trends or changes from baseline were observed in vital signs.

Body Weight

Body weight was measured at baseline, periodically during the trial, and at final visit in TD Trials C-18, C-23, and in the long-term Trial C-20. No meaningful changes in mean body weight were observed up to week 12/15 in the placebo and any of the DTBZ groups. No meaningful change in mean body weight was observed in the long-term Trial C-20 ≤week 145. Part C of this latter trial, mean changes in body weight from baseline at visit 1 to visits during the 1 year of Part C ranged from 0.0 to 0.5 kg.

Electrocardiogram Findings

ECGs were performed as follows:

- In **Trial C-18**, a 12-lead ECG was conducted at screening, baseline, and weeks 2 and 12 or the last postbaseline observation. For participants on drugs that prolong the QT interval, a 12lead ECG was also performed at weeks 4, 6, and 9;
- In **Trial C-23**, a 12lead ECG conducted at screening, baseline, and all clinic visits;
- In **Trial C-20**, a 12-lead ECG was conducted at baseline and weeks 2, 4, 6, 28, 41, 54, 106, and 158/ET or the last postbaseline observation. For Part B, a 12-lead ECG was conducted at the pre-withdrawal visit and end of treatment (EOT) visit 12 weeks after the post-withdrawal visit or ET.

For all trials, a qualified physician at a central diagnostic centre was responsible for assessing the ECG intervals (i.e., PR, QRS, QT, and QTcF) and providing clinical interpretation of the ECG. Any ECG finding judged by the investigator as a clinically meaningful change (worsening) compared with a baseline value

was considered an AE, recorded on the case report form, and monitored. All ECGs were to be performed after at least 5 minutes of rest in a supine or semi-supine position.

Overall, no safety signals were observed in ECG parameters. Of the participants with normal QTcF at baseline, QTcF values >450 ms were observed in a similar proportion of placebo-treated participants and participants in the DTBZ titration group (11 participants [9%] versus 10 participants [6%], respectively). In the fixed-dose groups, QTcF values >450 ms were recorded for 7 participants (10%), 3 participants (5%), and 3 participants (4%) who received DTBZ 12 mg, 24 mg, and 36 mg, respectively. The frequency of QTcF values >450 ms recorded in the long-term Trial C-20 was similar as in the blinded trials with 31 (10%) participants recorded. Two additional QT trials (SD-809-C-21 and TV50717-SAD-10132) dedicated to evaluating QTc showed that no QTcF prolongation was observed.

ECG findings were reported during the long-term Trial C-20 Part C as following, at any time post-baseline (EOT Part B/visit 1 of Part C):

- 2 (3%) participants had QTcF >450 ms and 1 (1%) of these participants had QTcF >480 ms. No participant had QTcF >500 ms;

- 3 (4%) participants had a change in the QTcF >30 ms, and 1 (1%) of these participants had a change in the QTcF >60 ms. There were no cardiac-related AEs reported for this participant.

Shifts in ECG from normal at baseline to abnormal not clinically significant (NCS) and abnormal clinically significant (CS) were reported at visits during long-term C-20 Part C. The number of participants with shifts was consistent over time but not considered to be clinically meaningful.

Shifts from normal to abnormal NCS were reported for 11 participants during long-term Trial C-20 Part C. Shifts from normal to abnormal potentially CS were reported for 3 participants during Part C. Cardiac-related AEs were reported for 1 participant with an ECG shift from normal to abnormal potentially CS and 1 participant with an ECG shift from normal to abnormal NCS.

Healthy Participants in the Phase 1 Trials

In Trial **TV50717-BE-10179**, no clinically meaningful trends in mean changes from baseline for any vital sign variable were recorded. Three participants had ECG findings that fell under the pre-defined criteria for potential clinical significance. None of these findings was evaluated by the investigator as clinically significant. There were no clinically meaningful trends in mean changes from baseline at discharge for any ECG parameter and no clinically significant ECG findings were reported by the investigator at discharge. No participants met discontinuation criteria based on QTcF. None of the participants reported suicidal behaviour/ideation assessed using the C-SSRS Since Last VisitIn Trial **TV50717-PK-10175**, no clinically significant abnormal vital sign values throughout the trial were recorded. There were 2 potentially clinically significant abnormal QTcF results, neither of which was evaluated as clinically significant by the trial investigator.

There were no clinically significant abnormal physical examination findings and no clinically significant abnormal neurological examination findings observed in the trial. There was no suicidality, and no deterioration in suicidal tendency scores reported in the trial. Elevated serum β-HCG levels were reported for 1 participant; however, this finding was interpreted as "false positive" attributed to post-menopausal reproductive status.

In Trial **TV50717-BE-10165**, no clinically meaningful trends in mean changes from baseline for any vital sign variable were recorded. There was a single potentially clinically significant abnormal QTcF result, evaluated as not clinically significant by the trial investigator. No meaningful trends of change in mean ECG results over time in the trial were observed for any of the treatment sequences or any of the ECG parameters evaluated. There were no clinically significant abnormal physical examination findings

in the trial. No clinically significant abnormal neurological examination findings, no observations of suicidality, and no deterioration in suicidal tendency scores were reported in the trial.

In trial **TV50717-BE-10192**, no clinically meaningful trends in mean changes from baseline for any vital sign variable were recorded. There was a single potentially clinically significant abnormal QTcF result which was considered as not clinically significant by the trial investigator. No meaningful consistent trend in the change in mean ECG results over time in the trial was observed for any of the treatment sequences or any of the ECG parameters evaluated. The percentage of participants with abnormal ECG findings increased at EOT compared to baseline (from 17% to 49% for 1×48 mg DTBZ osmotic PR formulation QD [Test], and from 25% to 43% for 2×24 mg DTBZ osmotic PR formulation QD [Reference]). However, only a single QTcF value for 1 participant (during treatment with the 2×24 mg DTBZ osmotic PR tablets QD [Reference]) met the criteria for a potentially clinically significant finding.

There were no clinically significant abnormal physical examination findings; no clinically significant abnormal neurological examination findings were observed in the trial; no observations of suicidality, and no deterioration in suicidal tendency scores reported in the trial.

In **Trial TV50717-BE-10201**, no clinically meaningful trends in mean changes from baseline for any vital sign variable were recorded. There were no potentially clinically significant abnormal vital sign values reported (. No meaningful trends of change in mean ECG results over time in the trial were observed for any of the treatment sequences or any of the ECG parameters evaluated. The percentage of participants with abnormal ECG findings increased at EOT compared to baseline (from 30% to 50% for 1×36 mg DTBZ osmotic PR formulation QD [Test], and from 32% to 60% for 1×12 mg + 1×24 mg DTBZ osmotic PR formulation QD [Reference]). None of the QTcF values met the criteria for a potentially clinically significant finding. There were no clinically significant abnormal physical examination findings; no clinically significant abnormal neurological examination findings, no observations of suicidality, and no deterioration in suicidal tendency scores were reported in the trial.

2.6.8.11. In vitro biomarker test for patient selection for safety

Based on the established non-clinical safety profile of DTBZ (with scientifically sound comparability to VMAT2 inhibitor TBZ), the wealth of available clinical safety data and post-marketing experience (with more than 73000 patient-years in both TD and HD patients), and in line with 3R principles of animal research, additional animal studies would not provide any additional meaningful information to assess the safety profile of DTBZ and, therefore, they were considered not necessary.

2.6.8.12. Safety in special populations

Intrinsic Factors

To increase the sensitivity of the evaluation of DTBZ safety in relation to intrinsic factors, the incidence of AEs in the Phase 3 trials using the matrix formulation BID was evaluated in the short-term trials as follows.

The mean total daily dose and duration of exposure to trial drug are listed for DTBZ titration group in the next table.

In the DTBZ titration group, the largest differences in duration of exposure (≥1 week) were seen in race, CYP2D6 phenotype, use of strong CYP2D6 inhibitor, and comorbid illness subgroups. Mean drug exposure was consistent within subgroups, with the exception of the CYP2D6 phenotype.

Table 85: Mean (SD) total daily dose at week 12/15 and trial drug exposure (days) in the DTBZ titration group (Safety population in Tardive Dyskinesia trials)

	N	Total daily dose (mg) mean (SD)	Duration of treatment (days) mean (SD)
Age			
<65 years	140	38.9 (8.84)	92.9 (20.24)
≥65 years	28	36.0 (11.58)	91.3 (20.83)
Sex			
Male	78	38.9 (9.43)	90.7 (21.81)
Female	90	38.0 (9.30)	94.4 (18.81)
Race			
White	124	38.3 (9.76)	94.7 (17.68)
Non-White	44	38.6 (8.07)	86.9 (25.67)
Time since TD diagnosis			
<Median (4.2 years)	73	38.3 (10.01)	91.3 (22.53)
≥Median (4.2 years)	95	38.5 (8.84)	93.7 (18.43)
CYP2D6 phenotype			
Poor metabolizer	10	42.0 (7.59)	65.6 (34.55)
Non-poor metabolizer	158	38.3 (9.39)	94.4 (17.88)
Yes	22	34.0 (8.76)	96.5 (10.60)
No	146	39.1 (9.26)	92.1 (21.33)
Impaired CYP2D6 function			
Yes	32	35.8 (9.04)	86.8 (25.19)
No	136	39.0 (9.33)	94.0 (18.80)
Total motor AIMS score			
<Median (8.0)	59	38.0 (9.85)	92.8 (20.53)
≥Median (8.0)	108	38.7 (9.08)	92.5 (20.31)
Baseline weight			
<Median (81.6 kg)	80	39.6 (8.63)	92.2 (22.12)
≥Median (81.6 kg)	88	37.4 (9.86)	93.1 (18.58)
Baseline BMI			
<Median (28.1 kg/m^2)	80	39.5 (9.00)	91.4 (22.93)
≥Median (28.1 kg/m^2)	88	37.6 (9.57)	93.8 (17.60)

	N	Total daily dose (mg) mean (SD)	Duration of treatment (days) mean (SD)
Region			
US	115	38.2 (9.01)	91.0 (20.68)
Non-US a	53	38.9 (10.10)	96.3 (19.10)
DRA use			
Currently taking	131	38.3 (9.22)	91.3 (22.14)
Not currently taking	37	38.8 (9.82)	97.4 (10.42)
Comorbid illness			
Psychotic disorders b	107	39.3 (9.00)	89.0 (23.63)
Mood disorders c	60	37.2 (9.67)	99.0 (9.71)

Source: TDISS20, MAA Ad Hoc Summary 30.

a Non-US refers to EU countries only

b Schizophrenia/schizoaffective disorder.

c Bipolar/depression/other.

AIMS=Abnormal Involuntary Movement Scale; BMI=body mass index; CYP2D6=cytochrome P450 2D6; DRA=dopamine receptor antagonist; DTBZ=deutetrabenazine; N=number of participants; n=number of participants in the subgroup; SD=standard deviation; TD=tardive dyskinesia; US=United States.

Intrinsic factors including sex, body weight, disease duration, total motor AIMS score, and impaired CYP2D6 function had no notable effect on the overall incidence of AEs when comparing the DTBZ titration group with the placebo-treated participants.

Like impaired CYP2D6 function, concomitant use of a strong CYP2D6 inhibitor at baseline also had no notable effect on AE frequency.

The safety and efficacy of DTBZ in children and adolescents below the age of 18 years with TD has not been established; no data are available.

The overall incidence of AEs in all treatment groups appeared generally higher in White participants than in non-White participants, in participants from the United States (US) compared with non-US participants, in participants not taking DRA at baseline compared with those receiving concomitant DRA, and in participants with comorbid illness of mood disorders compared with those with psychotic disorder. In the DTBZ titration group, AEs were more frequent in participants ≥65 years of age than in participants <65 years of age; however, a similar observation was not made in the DTBZ fixed-dose groups. Insufficient numbers of participants aged 65 and over did not allow to determine whether they respond differently from younger participants. Other reported clinical experience has not identified differences in responses between the elderly and younger participants. Overall, AEs were generally evenly distributed across subgroups or were reported in numbers too small to show any patterns or trends.

Table 86: Incidence of adverse events by subgroup (Safety population in Tardive Dyskinesia trials C-18, C-23 and C-20) category, % (n/N)

Incidence of Adverse Events by Subgroup (Safety Population in Tardive Dyskinesia Trials C-18, C-23 and C-20) Category, % (n/N)	**Trials C-18 and C-23**		**Trial C-23**		**Trials C-18 and C-20[a]**
	Placebo	**DTBZ 12 mg**	**DTBZ 24 mg**	**DTBZ 36 mg**	**DTBZ Titration**
Age					
<65 years	55.0 (61/111)	47.3 (26/55)	46.3 (25/54)	47.9 (23/48)	53.6 (75/140)
>=65 years	47.4 (9/19)	58.8 (10/17)	38.9 (7/18)	54.2 (13/24)	89.3 (25/28)
Sex					
Male	50.8 (31/61)	51.6 (16/31)	34.4 (11/32)	41.9 (13/31)	52.6 (41/78)
Female	56.5 (39/69)	48.8 (20/41)	52.5 (21/40)	56.1 (23/41)	65.6 (59/90)
Race					
White	55.9 (57/102)	50.0 (28/56)	49.1 (26/53)	54.2 (32/59)	62.9 (78/124)
Non-white	46.4 (13/28)	50.0 (8/16)	31.6 (6/19)	30.8 (4/13)	50.0 (22/44)
CYP2D6 phenotype					
Poor metabolizer	40.0 (2/5)	100.0 (1/1)	0	57.1 (4/7)	80.0 (8/10)
Non-poor metabolizer	54.4 (68/125)	50.0 (35/70)	43.7 (31/71)	49.2 (32/65)	58.2 (92/158)
Use of a strong CYP2D6 inhibitor					
Yes	61.1 (11/18)	54.5 (6/11)	40.0 (4/10)	100.0 (5/5)	63.6 (14/22)
No	52.7 (59/112)	49.2 (30/61)	45.2 (28/62)	46.3 (31/67)	58.9 (86/146)
Impaired CYP2D6 function					
Yes	56.5 (13/23)	58.3 (7/12)	40.0 (4/10)	75.0 (9/12)	68.8 (22/32)
No	53.3 (57/107)	49.2 (29/59)	44.3 (27/61)	45.0 (27/60)	57.4 (78/136)
Baseline weight					
<Median (81.6 kg)	48.3 (28/58)	44.7 (17/38)	45.5 (15/33)	46.7 (21/45)	63.8 (51/80)
>=Median (81.6 kg)	58.3 (42/72)	55.9 (19/34)	43.6 (17/39)	55.6 (15/27)	55.7 (49/88)
Total motor AIMS score					
<Median (8.0)	45.5 (20/44)	50.0 (12/24)	34.1 (14/41)	35.5 (11/31)	59.3 (35/59)
>=Median (8.0)	58.8 (50/85)	50.0 (24/48)	58.1 (18/31)	61.0 (25/41)	59.3 (64/108)
Baseline BMI					
<Median (28.1 kg/m2)	50.8 (32/63)	40.5 (15/37)	40.6 (13/32)	45.5 (20/44)	61.3 (49/80)
>=Median (28.1 kg/m2)	56.7 (38/67)	60.0 (21/35)	47.5 (19/40)	57.1 (16/28)	58.0 (51/88)
Region					
US	61.9 (52/84)	56.1 (23/41)	45.9 (17/37)	66.7 (24/36)	63.5 (73/115)
Non-US[b]	39.1 (18/46)	41.9 (13/31)	42.9 (15/35)	33.3 (12/36)	50.9 (27/53)
DRA use					
Currently taking	52.4 (55/105)	50.9 (28/55)	48.2 (27/56)	45.3 (24/53)	55.0 (72/131)
Not currently taking	60.0 (15/25)	47.1 (8/17)	31.3 (5/16)	63.2 (12/19)	75.7 (28/37)
Comorbid illness					
Psychotic disorders[c]	47.0 (39/83)	45.0 (18/40)	44.9 (22/49)	40.9 (18/44)	54.2 (58/107)
Mood disorders[d]	65.2 (30/46)	56.3 (18/32)	43.5 (10/23)	64.3 (18/28)	68.3 (41/60)
Time since TD diagnosis					
<Median (4.2 years)	56.1 (32/57)	47.6 (20/42)	43.9 (18/41)	42.9 (15/35)	68.5 (50/73)
>=Median (4.2 years)	52.1 (38/73)	53.3 (16/30)	45.2 (14/31)	56.8 (21/37)	52.6 (50/95)

Source: TDISS20, MAA Ad Hoc Summary 31.

[a] The DTBZ titration group included data from participants receiving DTBZ in Trial C-18 through week 12 plus data from Trial C-20 through week 15 for participants who were previously in the placebo treatment group in Trials C-18 or C-23.

[b] Non-US refers to EU countries only.

[c] Schizophrenia/schizoaffective disorder.

[d] Bipolar/depression/other.

AIMS=Abnormal Involuntary Movement Scale; BMI=body mass index; CYP2D6=cytochrome P450 2D6; DRA=dopamine receptor antagonist; DTBZ=deutetrabenazine; n=total number of participants in the subgroup; N=total number of participants; US=United States.

Hepatic impairment

The effect of hepatic impairment on the PK of DTBZ and its primary metabolites has not been studied. The use of DTBZ in patients with hepatic impairment is contraindicated which is considered acceptable although the lack of data in a specific subgroup of patients is not an automatic reason for a contraindication. Nevertheless, patients with TD who had impaired hepatic function were excluded from pivotal clinical trials and in fact this contraindication is already reflected in the SmPC since the tetrabenazine (TBZ) formulation, through the immediate release (IR) of DTBZ, to the actual prolonged-release (PR) formulation. As the approval of the current PR tablets is based on a bridging / extrapolation approach, and in the absence of new PK data (either with the IR and PR formulations) allowing to lift this contraindication, it appears more appropriate and prudent to maintain the same recommendation to guarantee consistency between available SmPCs of the different pharmaceutical forms. This will avoid misinterpretation by prescribers regarding any clinical advantage or flexibility that the new formulation would have over the existing one.

Renal impairment

No clinical trials have been conducted to assess the effect of renal impairment on the PK of DTBZ and its active metabolites. However, the major route of elimination of the active moieties is non-renal (<10% active moieties excreted in urine) and the dosing instructions, based on up-titration guided by tolerability and efficacy responses, minimize potential risks. Limited data in patients with mild to moderate renal impairment from the Phase 3 trials did not indicate safety concerns.

In all DTBZ Phase 3 trials, participants were to be included if they had a creatinine clearance ≥50 mL/min, as estimated by the Cockroft-Gault formula. A post-hoc analysis of estimated glomerular filtration rate (eGFR), using the Modification of Diet in Renal Disease formula (Levey et al 2006) with adjustment for body surface area (Mosteller 1987) was performed. Renal impairment categories were determined according to the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) guidelines for renal impairment: an eGFR≥90 mL/min indicates normal renal function; an eGFR of 60 to 89 mL/min is classified as mild renal impairment, and an eGFR of 30 to 59 mL/min is classified as moderate renal impairment (European Medicines Agency 2015).

Overall, in trials C-18 and C-23, out of 404 participants, 130 received placebo and 274 received DTBZ. Of them, 217 (54%) participants had normal eGFR, 146 participants (36%) had mild and 39 participants (10%) moderate renal impairment. There were only 2 participants with eGFR corresponding to severe and end stage renal disease (one in each category).

Table 87: Estimated Glomerular Filtration Rate (eGFR) and renal function categories at baseline for Tardive Dyskinesia participants (Safety population from trials C-18 and C-23)

Renal function category, n (%)	Placebo (N=130)	DTBZ (N=274)	Total (N=404)
Normal (eGFR ≥90 mL/min)	76 (58%)	141 (51%)	217 (54%)
Mild renal impairment (eGFR ≥60 to <90 mL/min)	47 (36%)	99 (36%)	146 (36%)
Moderate renal impairment (eGFR ≥30 to <60 mL/min)	7 (5%)	32 (12%)	39 (10%)
Severe renal impairment (eGFR ≥15 to <30 mL/min)	0 (0%)	1 (<1%)	1 (<1%)
End stage renal disease (ESRD) (<15 mL/min)	0 (0%)	1 (<1%)	1 (<1%)

Source: TDISS20, Post Hoc Summary 15.
DTBZ=deutetrabenazine; eGFR=estimated renal filtration rate; MDRD= modification of diet in renal disease; n=number of participants in subgroup
Note: eGFR (mL/min) is calculated as eGFR (mL/min/1.73m^2) × BSA / 1.73, where eGFR (mL/min/1.73m^2) is estimated using the MDRD formula and body surface area (BSA) is estimated using the Mosteller formula.

To evaluate the safety in participants with renal impairment, AEs were compared between participants based on their renal function category. AEs in participants with TD from Trials C-18 and C-23, with mild and moderate renal impairment at baseline were comparable to AEs in participants with normal renal function, regardless of treatment group. No safety signals were observed with respect to renal function across all treatment groups.

Table 88: Overall adverse events - incidence by preferred term, and renal function category (Tardive Dyskinesia trials C-18 and C-23)

MedDRA 17.0 PT,	**DTBZ**			**Placebo**		
n (%)	**Normal renal function**	**Mild renal impairment**	**Moderate renal impairment**	**Normal renal function**	**Mild renal impairment**	**Moderate renal impairment**
Number of participants	141	99	32	76	47	7
Any AE	70 (49.6)	55 (55.6)	19 (59.4)	46 (60.5)	22 (46.8)	2 (28.6)
Insomnia	4 (2.8)	6 (6.1)	0	1 (1.3.)	0	0
Depression/ Depressed mood/ Dysthymic disorder	2 (1.4)	4 (4.0)	2 (6.3)	0	1 (2.1)	0

Akathisia /Agitation /Restlessness	2 (1.4)	3 (3.0)	0	0	1 (2.1)	0
Suicidal ideation	1 (0.7)	2 (2.0)	0	0	1 (2.1)	0
Somnolence/Sedation/ Hypersomnia	8 (5.7)	5 (5.0)	2 (6.3)	8 (10.5)	0	1 (14.3)

Source: TDISS20, Post Hoc Summary 17.

AE=adverse event; DTBZ=deutetrabenazime; n=number of participants in subgroup.

Note: Glomerular filtration rate (eGRF) in unit mL/min is used for determining renal function categories. Normal renal function=eGFR ≥90 mL/min; Mild renal impairment=eGFR ≥60 to <90 mL/min; Moderate renal impairment=eGFR ≥30 to <60 mL/min.

Note: Participants are counted only once in each preferred term category, and only once in each system organ class category, both within each renal function category.

Extrinsic Factors

The effect of food on PK parameters of the osmotic PR tablet QD was evaluated in a separate trial as part of the DTBZ osmotic formulation QD trials and no effect of food on safety parameters was identified.

An *in vitro* trial demonstrated that there was no alcohol-induced dumping when the drug release dissolution profiles of DTBZ osmotic tablets QD 12 mg, 24 mg, 30 mg, 36 mg, 42 mg, and 48 mg were compared in dissolution media with or without 40% ethanol. These results indicate that the presence of ethanol in the gastric fluid during dosing with DTBZ will not accelerate drug release.

2.6.8.13. Safety related to drug-drug interactions and other interactions

CYP2D6 inhibitors

Concomitant use of a strong CYP2D6 inhibitor at baseline had no notable effect on AE frequency. Because DTBZ is titrated in a response-driven manner to a tolerable dose that controls TD, DTBZ can be titrated safely, independent of possible CYP2D6 phenotype or concomitant use of a strong CYP2D6 inhibitor. Nevertheless, patients who are concomitantly using a strong CYP2D6 inhibitors, as well as patients who are known CYP2D6 poor metabolizers, should not exceed a total daily dosage of 36 mg DTBZ osmotic PR tablet QD or DTBZ matrix tablet BID. Concomitant use of strong CYP2D6 inhibitors (e.g., quinidine, antidepressants such as paroxetine, fluoxetine and bupropion) has been shown to increase the systemic exposure to the active dihydro-metabolites of DTBZ by approximately 3-fold. The maximum daily dose of 36 mg when DTBZ is co-administered with strong CYP2D6 inhibitors is outlined accordingly in SmPC section 4.2, with cross-reference to section 4.5 and 5.2.

Alcohol and other sedating drugs

Concomitant use of alcohol or other sedating drugs may have additive effects and worsen sedation and somnolence (SmPC section 4.5).

Reserpine

Reserpine binds irreversibly to VMAT2 and the duration of its effect is several days. Prescribers should wait for chorea or dyskinesia to re-emerge before administering deutetrabenazine to help reduce the risk of overdosage and major depletion of serotonin and noradrenaline in the central nervous system. At least 20 days should elapse after stopping reserpine before starting deutetrabenazine. Deutetrabenazine and reserpine should not be used concomitantly (SmPC section 4.3, 4.5).

Monoamine oxidase inhibitors

Deutetrabenazine is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). Deutetrabenazine should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI (SmPC section 4.3, 4.5).

Neuroleptic medicinal products

The risk of parkinsonism, neuroleptic malignant syndrome (NMS), and akathisia may be increased by concomitant use of deutetrabenazine and medicinal products that reduce the dopaminergic transmission. Therefore, the following text has been included in SmPC section 4.4: *"There is a potential risk of NMS associated with medicinal products that reduce dopaminergic transmission (see section 4.5). Main symptoms of NMS are mental changes, rigidity, hyperthermia, autonomic dysfunction and elevated creatinine phosphokinase levels. If NMS is suspected, deutetrabenazine should be discontinued immediately and appropriate symptomatic treatment should be initiated"*.

Levodopa and other dopaminergic medicinal products

Since DTBZ can lead to monoamine depletion, concurrent use with levodopa or other dopaminergic medicinal products could lead to antagonizing effects. Levodopa and other dopaminergic medicinal products (e.g. pramipexole, ropinirole) may reduce the effect of deutetrabenazine (see SmPC section 4.5).

Concomitant use of other VMAT2 inhibitors

DTBZ must not be used in patients currently taking other VMAT2 inhibitors. DTBZ can be started the day after the discontinuation of tetrabenazine at a dose which is approximately half the tetrabenazine daily dose (see SmPC section 4.3, 4.5).

Medicinal products known to prolong the QTc interval

Deutetrabenazine may prolong the QTc interval. DTBZ should be used with caution in combination with other medicinal products that prolong the QTc interval (see SmPC section 4.4, 4.5, 5.1).

2.6.8.14. Discontinuation due to adverse events

Adverse Events Leading to Discontinuation of Participants with Tardive Dyskinesia in the Phase 3 Trials

AEs leading to withdrawal from this trial occurred with similar frequency in placebo treated participants (3.1%) and participants in the DTBZ titration group (3.0%). The frequency of AEs leading to withdrawal was lower for the DTBZ 24mg dose group (2.8%) compared with the 36mg (4.2%) or 12mg (5.6%) dose groups (TDISS20). No AEs that led to withdrawal were reported for more than 1 participant, and most of the events were considered by the investigator as related to the trial drug.

In Part A and B of the long-term safety trial (Trial C-20), the most common reason for discontinuation was "Withdrawal by subject". Overall, 42 participants (12.5%) discontinued due to at least 1 AE. All AEs leading to discontinuation were reported by 1 or 2 participants (<1% of participants); the following AEs leading to discontinuation were reported by 2 participants each: alanine aminotransferase increased, anxiety, depression, diarrhoea and dyskinesia.

In the long term Trial C-20 Part C, 3 (3.8%) participants had 4 AEs leading to discontinuation. Of these 4 AEs, 3 events in 2 [2.5%] participants were fatal.

Adverse Events Leading to Dose Reduction in Participants with Tardive Dyskinesia in the Phase 3 Trials

AEs leading to dose reduction were less frequent in placebo-treated participants (2.3%) and in participants receiving fixed doses of DTBZ (0% for 12 mg, 1.4% for 24 mg, and 4.2% for 36 mg) than in participants in the DTBZ titration group (8.3%). The only AEs that occurred in more than 1 participant were somnolence, dizziness and insomnia in the DTBZ titration group.

In Part A and B of the long-term safety trial (Trial C-20), 53 participants (15.7%) had AEs that led to dose reduction. The most frequent AEs leading to dose reduction (≥1%) included bradykinesia (3.9%), somnolence (3.3%), parkinsonism (1.5%), tremor (1.2%) and insomnia (1.2%).

In Trial C-20 Part C, a total of 2 (2.5%) participants had at least 1 AE that led to a dose reduction. The AEs leading to dose reduction were asthenia, muscle weakness and bradykinesia. One (1.3%) participant had the DTBZ dose reduced for both asthenia and bradykinesia.

Adverse Events Leading to Dose Suspension in Participants with Tardive Dyskinesia in the Phase 3 Trials

AEs leading to dose suspension were more frequent in placebo-treated participants (5.4%) than in participants in the DTBZ titration group (3.0%). These AEs were less frequently reported by participants receiving the stable doses of 24 mg (1.4%) and 36 mg (1.4%) compared with participants receiving the 12 mg daily dose of DTBZ matrix formulation BID (4.2%).

Nausea (2 participants, both on placebo) was the only AE leading to dose suspension experienced by more than 1 participant in Trials C-18 and C-23.

In Part A and B of Trial C-20, 34 participants (10.1%) experienced at least 1 AE leading to dose suspension. These AEs in 2 or more participants were: blood magnesium decreased (1.2%), and prolonged ECG QT, atrial fibrillation, blood potassium decreased, schizoaffective disorder, myalgia and renal failure (0.6% each).

In Trial C-20 Part C there were no participants with AEs that led to dose suspension or interruption.

Other Significant Adverse Events in Healthy Participants in the Phase 1 Trials

Two healthy participants with AEs of vomiting were withdrawn from the Phase 1 trials (1 each from trials TV50717-PK-10175 and TV50717-BE-10192). Of note, emesis within 24 hours of dose intake falls under participant withdrawal criteria per protocol for these phase 1 trials.

During trial **TV50717-BE-10179**, 11 participants (4%) were withdrawn from the trial due to AEs: 6 participants (2%) treated with the Test drug (24 mg DTBZ osmotic PR tablets QD) and 5 (2%) treated with the Reference drug (12 mg DTBZ matrix tablets BID). In addition, COVID-19 related events were reported in both treatment arms (1 participant receiving the Test drug reporting asymptomatic COVID-19, and 1 participant each in the Test and Reference arms reporting COVID-19). Anxiety in the Test treatment arm and headache in the Reference treatment arm resulted in drug withdrawal and trial discontinuation in 2 participants each (<1%). All other AEs leading to drug withdrawal or trial discontinuation were reported by 1 participant each.

During trial **TV50717-PK-10175**, 2 (2%) participants were withdrawn from the trial due to AEs, including an AE of vomiting (24 minutes after trial drug dosing) in 1 (<1%) participant while receiving 2×6 mg, and an AE of COVID-19 in 1 (<1%) participant while receiving 2×24 mg DTBZ osmotic PR tablets QD. No AEs lead to drug withdrawal in participants while receiving the 1×12 mg or 1×24 mg trial drug doses each.

In trial **TV50717-BE-10165**, no AEs leading to drug withdrawn or trial discontinuation were reported.

In trial **TV50717-BE-10192**, 2 (1%) participants were withdrawn from the trial due to AEs, including vomiting (approximately 15 hours after trial drug dosing) in 1 (<1%) participant during treatment with the 1×48 mg DTBZ osmotic PR tablet QD (Test), and headache in 1 (<1%) participant during treatment with the 2×24 mg DTBZ osmotic PR tablets QD.

In trial **TV50717-BE-10201**, 2 (2%) participants experienced AEs that resulted in drug withdrawal or trial discontinuation. One participant experienced influenza-like illness during treatment with the 1×36 mg QD tablet (Test). The other participant experienced limb discomfort during treatment with the 1×12mg + 1×24 mg QD tablets.

2.6.8.15. Post marketing experience

In the period from 03 April 2017 (US FDA approval of DTBZ for the treatment of HD-associated chorea in adults) until 31 March 2023 (cut-off date of the latest periodic safety update report - PSUR), patient's exposure to DTBZ was approximately 73000 patient-years (in patients with HD and TD). Following several post-marketing reports of parkinsonism in patients with TD receiving DTBZ, in July 2019 the United States prescribing information (USPI) of DTBZ (Xenazine) was revised: section 5.6 under "Warnings and Precautions", was updated with Parkinsonism in TD (in addition to HD). Besides this revision, no new safety findings resulted from the post-marketing experience.

The following periodic ADR reports have been prepared for DTBZ:

- 12 quarterly Periodic Adverse Drug Experience Reports (PADERS) for the clinical matrix formulation BID covering period from 03 April 2017 through 31 March 2020;
- 3 Periodic Safety Update Reports (PSURs) for the clinical matrix formulation BID covering the period from 01 April 2020 to 31 March 2023;
- 3 PADERs for the osmotic PR formulation QD covering the period from 17 February 2023 (date of DTBZ osmotic PR formulation QD US market approval) through 16 November 2023.

The safety results are presented in the next table and show no significant difference between reporting rates of the proposed ADRs in the post-marketing setting for TD and HD patients, confirming a similar safety profile of DTBZ for both indications. The most commonly reported event among the proposed ADRs in both populations (with TD or HD) was somnolence/sedation/lethargy. This is consistent with data originated from the placebo-controlled trials.

Table 89: Comparison of postmarketing reporting rates for proposed adverse drug reactions in patients with TD and HD (Data Cut-off 31 March 2023)

	TD		HD	
Preferred Terms	**N**	**% of all reported events**	**N**	**% of all reported events**
Total number of AEs	30182	100	12265	100
Akathisia/Agitation/Restlessness	308	1.0	208	1.7
Anxiety	434	1.4	175	1.4
Constipation	87	0.3	52	0.4
Contusion	68	0.2	46	0.4
Depression/Dysthymic disorder	555	1.8	195	1.6
Diarrhoea	347	1.1	195	1.6
Dry mouth	187	0.6	76	0.6

Preferred Terms	TD		HD	
	N	% of all reported events	N	% of all reported events
Fatigue	630	2.1	284	2.3
Insomnia	631	2.1	197	1.6
Nasopharyngitis	114	0.4	33	0.3
Somnolence/Sedation/Lethargy	871	2.9	465	3.8
Urinary tract infection	84	0.3	45	0.4

Note: Data does not include reports for osmotic PR formulation QD since the data lock point precedes the date of launch in the US (May 2023).

2.6.9. Discussion on clinical safety

The TD safety programme for DTBZ included **10 clinical trials**: 2 Phase 3 efficacy trials (**C-18** and **C-23**) and 1 Phase 3 long-term safety trial (**C-20**) in adult participants with TD, 1 Phase 3 efficacy trial (**C-15**) and 1 Phase 3 long-term safety trial (**C-16**) in adult participants with HD-associated chorea and **5 Phase 1 BE and PK trials** in healthy adult participants providing supportive data.

A total of 1270 participants received DTBZ during the development programme, including 384 adult participants with TD (745.84 patient-years of treatment), 121 participants with HD-associated chorea (280.26 patient-years of treatment), and 765 healthy adults who received single or repeated DTBZ doses.

Before describing the extent of the exposure, it is reminded that the posology claimed by the applicant indicates an efficacious dose range from 24 to 48 mg, and a maximum recommended daily dose of 48 mg.

The **titration regiment** was studied in **trials C-18 and C-20**. In these studies, the adjusted weekly increment was 6 mg/day. However, Teva did not plan to register the 18 mg dose (i.e. instead it considered: 12, 24, 30, 36, 42 and 48 mg). Thus the first titration step would be an increment of 12 mg/day. The applicant emphasised that "the incidence of AEs during the initiation and titration period in participants treated with DTBZ (39%) was similar to that in participants treated with placebo (42%), while the incidence of treatment-related AEs was lower in participants receiving DTBZ than placebo (17% and 27%, respectively)". Additionally, based on data provided, the safety profile did not largely differ across 12 and 24 mg doses. Teva also produced an exposure-safety modelling analysis. Although no further detail on the model construction was presented (and therefore further assessed), results suggested there is no increased risk when increasing the titration step from 12 mg. Overall, these data did not raise any (safety) concern.

In phase 3 trials in TD patients, the proportion of AEs up to week 12/15 was generally similar in DTBZ and placebo groups. Most AEs were mild to moderate in severity. Somnolence was the most common AEs up to week 12/15 and occurred mainly during the titration/dose escalation period.

With regard to selection criteria, subjects were excluded from the study/ies based on criteria referring to, among others, psychiatric illness, depression, suicidal ideation, violent behaviour, QTcF value, or significant renal impairment.

To be enrolled in the long-term study C-20, a patient had to successfully complete study C-18, Study C-23, or any other controlled study of DTBZ for treatment of moderate to severe TD. As requested, the applicant clarified that, from the 368 participants who completed studies C-18 and C-23, 25 (7%) (8 participants from study C-18 and 17 participants from study C-23) were not enrolled into the long-term Trial C-20. Among these 25 subjects, 8 had been randomised to receive placebo and 17 randomised to

receive DTBZ in the pivotal trials. Regrettably, the applicant did not collect the reasons for these subjects not to enrol into the long term study C-20.

In study C-18, none of the roll-over patients from DTBZ arm (n=4) had experienced SAEs; 1 subject experienced AEs leading to dose reduction.

In C-23, none of the roll-over patients from DTBZ arm (n=13) had experienced SAE; 2 subjects experienced AEs leading to dose reduction.

Although the proportion of patients who did not roll over in the long term study C-20 was overall slightly higher for DTZB than for placebo (similar in C1-18 4vs4), this proportion remained quite limited. Additionally, the safety data provided did not suggest e.g., any particular signal.

In the long-term safety trial C-20, the most frequently reported AEs (≥10%) were anxiety (12.5), depression (10.4%) and somnolence (10.1%). Of note, the most frequently reported AEs related to psychiatric and nervous system disorders were anxiety, depression, somnolence, and headache. Weight decreased was reported in 32 (9.5%), urinary tract infection in 31 (9.2%), diarrhoea in 27 (8.0%) patients. Headache was also reported in 24 (7.1%), hypertension in 23 (6.8%), dyskinesia in 22 (6.5%) and nasopharyngitis in 20 (5.9%) patients.

The applicant provided an additional analysis of data from participants who experienced hypertension and weight decreased including evaluation of causality from individual case reports, performed based on data from trial C-20. Teva concluded that the review of cases did not provide adequate evidence to establish a causal relationship between DTBZ and hypertension or weight decreased. Consequently, available data and analyses did not justify addition of hypertension and weight decreased to the list of ADRs. This was agreed by CHMP.

In trial C-20 Part C, there were 4 treatment-related AEs reported for 3 (3.8%) participants. One (1.3%) experienced an event of tardive dyskinesia, 1 (1.3%) experienced tremor, and 1 (1.3%) reported both asthenia and bradykinesia.

The applicant clarified that parkinsonism was evaluated through AEs monitoring and the motor assessment score of the Unified Parkinson's Disease Rating Scale (UPDRS) Teva used the SMQ Parkinson-like events to identify and analyse relevant AEs. Review of clinical data from the TD development programme did not identify parkinsonism as an ADR. However, review of reports based on post-marketing experience in patients with TD resulted in the classification of parkinsonism as an ADR. To determine the adequate frequency category of this ADR for the SmPC, the applicant reviewed the placebo-controlled trials in TD, C-18 and C-23. Among DTBZ-treated participants in these trials (N=279), 1 event of parkinsonism (0.4%) was reported. Based on this, the frequency category of uncommon (≥ 1/1,000 to <1/100) was selected for the ADR table in SmPC section 4.8.

In the DTBZ Phase 1 trials in healthy participants, the AE profiles and overall tolerability were similar between the osmotic PR formulation QD compared to the reference matrix formulation BID. The most frequently reported AEs across all 5 trials were headache (21 participants) and influenza-like illness (11 participants).

In the pooled analysis for the 2 double-blind, placebo-controlled trials, the frequently reported AEs (2% and more common in active treatment than in placebo) were diarrhoea, nasopharyngitis, urinary tract infection and psychiatric disorders (depression, dysthymic disorder, insomnia). The grouped terms of akathisia, agitation, and restlessness occurred at a rate of 1.8% in participants treated with DTBZ versus 0.8% in participants treated with placebo in the 2 pooled placebo-controlled TD trials. These terms were included accordingly in the ADR section of the SmPC.

Treatment discontinuation prior to Week 12/15, in the overall 3 pivotal trials seems overall close across the different fixed dose arms, and also titration arms. However, looking more specifically at the C-20

trial, in part A it was observed a high-rate proportion of discontinuation (i.e., 48%) which seemed driven by patient's withdrawal (23%) and AE (10%). The applicant explained that among the 79 patients who discontinued "due to withdrawal by participant", 62 (78%) did not report any AEs within approximately 1 month before or during the early termination visit, 17 reported AEs mainly non-serious and mild or moderate in severity. Among these 17 subjects, 2 reported SAEs (epilepsy and schizophrenia, assessed as not related to DTBZ by the investigator). These data did not suggest a hidden problem of tolerance behind this high rate of discontinuations due to "withdrawal by participant".

It was noted that SAE and events leading to discontinuation of the trial drug occurred infrequently and with similar incidences among participants in the placebo-controlled trials who received DTBZ or placebo The applicant detailed that AEs were collected and recorded until 4 weeks after the last dose of study drug. This appeared as a reasonable period.

The safety profile in terms of SAE and AE leading to treatment discontinuation remained consistent with long-term exposure to DTBZ. No safety signal was identified from individual case evaluations of SAE or AE leading to discontinuation.

During the TD phase 3 program, 13 deaths were reported, including 1 post-trial. The applicant indicated that none of them was assessed as treatment-related. However, among these deaths, 10 were due to cardio-vascular events. is The CHMP noted that abnormal and clinically significant ECG, and for 3 of them abnormal ECG, were reported.

The applicant agreed that DTBZ may slightly prolong the QTc interval but argued that the degree of QTc prolongation is not clinically significant when DTBZ is administered within the recommended dose range. This was reflected accordingly in section 4.4 of the SmPC via a warning: DTBZ "*should be used with caution in combination with other medicinal products that prolong the QTc interval (see section 4.5) and in patients with congenital long QT syndrome, bradycardia, hypokalaemia, hypomagnesaemia or a history of cardiac arrhythmias*". Further details about the potential interaction with medicines known to prolong the QTc interval are included in SmPC section 4.5 with specific examples of such medicines.

Due to the risk of QT interval prolongation with DTBZ treatment, it was considered whether a normal ECG (QTc< 450 ms) would be necessary when starting treatment and tapering the dose. In the applicant's view, the above detailed RMMs are considered sufficient to address the concern of potential clinically insignificant QTc interval prolongations; therefore, ECG records are not deemed required for all patients when starting DTBZ treatment or tapering the dose. DTBZ prolongs QT segment. Thus, concomitant treatment with other prolonging QT medicinal products should be used with caution and patients monitored accordingly. The applicant revised SmPC section 4.5 to add interactions with QTc prolonging medicinal products.

Moreover, as requested, the applicant discussed accordingly the 4 cases of suicidal ideation reported during the clinical trial programme (1 case in Trial C-23 and 3 cases in Trial C-20, Part A) and concluded that no increased incidence of suicidality had been identified in comparison with the expected background of suicidality in the psychiatric TD population.

The incidence of suicidality was low in Trials C-18 and C-23, based on both AE reporting and scale assessment. Long-term administration of DTBZ in participants with TD in Trial C-20 did not identify any increased incidence of suicidality in comparison with the expected background of suicidality in this psychiatric participant population.

Nevertheless, suicidality is a known risk in the general psychiatric population, and patients with TD are a predominantly psychiatric patient population. It was therefore questioned (and evaluated) whether this risk could be increase with DTBZ, particularly in light of the reported 4 cases of suicidal ideation, for which complete narratives were provided. Concomitant medications with known risk of suicidality and medical history were reviewed in all of these 4 cases; causality was assessed as not related to DTBZ by

both the investigator and Teva. Ultimately, it appeared not possible at this stage to characterise an increased risk of suicidality with DTBZ at therapeutic dosages. On the other hand, as outlined in SmPC section 4.9, although experience with dosages higher than the recommended maximum daily dose of 48 mg is limited, isolated cases of DTBZ overdose (up to 240 mg per day) had been derived from post-marketing reports and literature and, among the most frequently observed symptoms, suicidal ideation was noted. Quantitative scales to assess VMAT2-inhibition-related subclinical toxicity indicated no AEs with DTBZ treatment. There was no increase of motor score of UPDRS in the treated participants in TD Trials.

An integrated analysis of the AEs of interest in participants with TD showed that the frequencies of AEs in the categories of interest were not significantly different between participants who received DTBZ compared to those who received placebo during short-term treatment period (up to week 12/15) or the long-term open-label Trial C-20. This indicated that the risk of developing VMAT2-inhibition-related AEs does not increase with longer-term exposure.

The applicant reported that active treatments were pooled for the 2 double-blind, placebo-controlled trials (Trial C-18 [flexible dose] and Trial C-23 [fixed dose]) and compared these data to the pooled placebo treatment to determine adverse drug reactions (defined as >2% and more common in active treatment than in placebo). The choice of the threshold of 2% to complete the list of the ADR remains unclear, and this applicant's decision appears purely arbitrary. However, it was also indicated that "*to ensure no important AEs were overlooked, Teva had reviewed AEs not surpassing the 2% threshold (i.e., occurring <2%) to identify any additional clinically-relevant ADRs*". Additionally, the applicant indicated that "an additional analysis of post-marketing safety data from patients with TD and patients with HD showed no difference between the rates of the proposed ADRs". Thus, all together, this whole approach should allow to overcome the risk of non-inclusion of safety risk of importance with a frequency below 2%.

The low incidence of parkinsonism did not correspond with the known safety profile of TBZ, where parkinsonism occurs in >10% of the subjects. Moreover, the US PL contains several specific warnings regarding parkinsonism, which is indicative for a high frequency of reported incidences. Parkinsonism is an AEs that takes time to emerge and is also dependent upon concomitant medication, especially DRAs. The applicant did not agree to include 'Parkinsonism' as an important identified risk in the list of RMP safety concerns. Teva argued that parkinsonism is an identified and well-characterised risk of DTBZ and other VMAT2-inhibitors; therefore, in its view, no additional pharmacovigilance (PhV) activities are required to further characterise it. In addition, information about this ADR was is included in DTBZ SmPC sections 4.4 and 4.8. Teva considered that no additional RMMs are likewise required for parkinsonism. In summary, e.g., accordance with the principles in GVP V rev 2.0, in the absence of additional PhV activities and / or RMM, it is agreed that "parkinsonism" does not require inclusion in the list of RMP safety concerns. Safety data from post-marketing experience, based on more than 73000 patient-years of exposure, were noted as consistent with the observed safety profile in the TD development programme, bearing in mind the risk of underreporting AEs, since (especially psychiatric) patients tend to abandon the medication(s) without reporting the reason. Following several post-marketing reports of parkinsonism in TD patients receiving DTBZ, the US Prescribing Information (2023) was revised in July 2019, and Section 5.6 on "Parkinsonism" updated under "Warnings and Precautions" to include TD in addition to HD.

With regard to 'Use in patients older than 65 years of age', initially considered for inclusion as missing information in the list of RMP safety concerns , it was agreed by CHMP that, although limited data is currently available on DTBZ use in the elderly (and, consequently, no definitive pharmacokinetic conclusions can be made for these patients), the results of the population PK analysis are sufficient to confirm that (as mentioned in SmPC section 4.2, with cross reference to section 5.2) no dose adjustment is required in patients ≥ 65 years of age. Sub-group analysis of participants with TD receiving DTBZ

revealed that intrinsic factors including sex, body weight, disease duration, AIMS total score, and CYP2D6 impairment had no meaningful impact on AEs incidence.

In Trials C-18, C-23, and C-20, there were 16 (14%), 72 (24%), and 79 (23%) elderly participants, respectively.

The applicant provided an additional analysis of AEs by SOC and age group (<65 and ≥65 years) in Trials C-18 and C-23, an analysis of post-marketing reports from the applicants safety database. In summary, no clinically meaningful differences were observed in the rates of reported AEs by SOC and ADRs between elderly participants/patients and adult participants/patients, as well as the overall population participants in Trials C-18 and C-23 and based on the post-marketing experience.

Teva also argued that the titration process minimises the risk of potential ADRs and the results from the population PK analyses did not identify age as a covariate. In its view, available data for elderly patients (≥65 years) were considered sufficient to confirm a warning in SmPC section 4.4 of DTBZ SmPC is not warranted whereas safety and efficacy of DTBZ in paediatric patients with TD, in the absence of data was not established.

No clinical trials were conducted to assess the effect of renal impairment on DTBZ PK. Limited data in patients with mild to moderate renal impairment, obtained from the Phase 3 trials, did not indicate any safety concern(s).

The applicant also outlined that the effect of hepatic impairment on the PK of DTBZ and its primary metabolites had not been studied; consequently, the use of DTBZ in patients with hepatic impairment is contraindicated, as detailed in SmPC section 4.3, in accordance with EMA Guideline CPMP/EWP/2339/02, 2005.

Drug interaction studies did not demonstrate CYP-enzyme inhibition or induction, as well as substrate and inhibition potential of DTBZ, deuterated α-HTBZ, and deuterated β-HTBZ with transporter proteins at clinically relevant concentrations. A trial in healthy volunteers showed that co-administration of DTBZ with strong CYP2D6 inhibitors results in a significantly higher systemic exposure. Patients who are concomitantly using strong CYP2D6 inhibitors, as well as patients who are known CYP2D6 PM, should therefore not exceed a total daily dosage of 36 mg DTBZ.

Alcohol, sedating drugs, and neuroleptics may increase the risk of, or worsen known and potential unfavourable effects of DTBZ. Due to a potential risk of overdose, the concomitant use of DTBZ with reserpine, monoamine oxidase inhibitors, and other VMAT2 inhibitors is contraindicated.

No safety signals related to laboratory findings were observed in patients with TD. There were no clinically meaningful changes from normal to abnormal mean values or trends in haematology, chemistry, or urinalysis parameters in the DTBZ TD development programme.

2.6.10. Conclusions on clinical safety

The results of the clinical program in patients with TD suggest that deutetrabenazine has an acceptable tolerability. Additionally, data from the HD and Phase 1 program are supportive of the safety profile. The main identified safety concerns (e.g., anxiety, depression, or down titration of DRAs and risk of psychotic flare ups), that may become more relevant in case a modest response is observed, were adequately discussed by the applicant, together with (routine) risk minimisation measures. Also of note, DTBZ dose can be easily titrated to reach a satisfactory equilibrium between benefit and risk of tetrabenazine treatment.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 90: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

The inclusion of different safety concerns into the RMP as important identified or potential risk of missing information was discussed accordingly by Teva.

The applicant signalled that, in the framework of post-marketing activities in the United States, the risk of Parkinsonism was noted. This is in line with what is known from TBZ and the identical mechanism of aciton (MoA) of DTBZ. Notwithstanding, the short to median term pivotal study duration did not allow to properly identify such risk, and the fact that many patients were concomitantly taking DRAs, which also cause parkinsonism, made it difficult for investigators to acknowledge differences in the extrapyramidal characteristics.

Teva was requested to consider inclusion of Parkinsonism in the list of important identified risks. The applicant considered that Parkinsonism is an identified and well-characterised risk of DTBZ and other VMAT2-inhibitors. Relevant and sufficient information about this ADR is provided in DTBZ SmPC (sections 4.4 and 4.8). Furthermore, Teva was of the view that, aside for routine activities, no additional PhV activities or RMM are deemed necessary. This was agreed by CHMP.

The DRAs + DTBZ AE theoretical risk is higher in the elderly (e.g., ≥ 65 years of age). Inclusion of "Use in patients older than 65 years of age" to the list of missing information was discussed. Data presented by the applicant, supporting the safety of DTBZ in the elderly, was considered sufficient for not including "Use in patients older than 65 years of age" in the list of safety concerns. As detailed in SmPC section 4.2 (with cross reference to section 5.2), "*based on the results of population pharmacokinetic analysis, no dose adjustment is required"* in the elderly population.

With tetrabenazine use in TD, depression is a limitation to its use in the most efficacious dose, not only as worsening concurrent depression, but also as contributing to initiation of depressed mood. Considering DTBZ PK with longer duration of action, and limited available data from the clinical trials, the CHMP agreed that depression does not classify as an important identified risk from a risk management (RM) perspective. The causal association is proven and depression is listed in the SmPC as a known ADR. Routine RMMs are considered sufficient to minimise the risk of depression in clinical practice. In addition, a warning in SmPC section 4.4 details that DTBZ "*may cause depression or worsen pre-existing depression. Patients should be closely monitored for the emergence of such adverse reactions. Patients and their caregivers should be informed of the risks and instructed to report any concerns to their doctor immediately. If depression does not resolve, discontinuing treatment with deutetrabenazine should be considered".*

Regarding neuroleptic malignant syndrome (NMS), while it is expected to occur, given the MoA and the use in patients concomitantly treated with DRAs, its severity and rarity lead to an early identification in EU patients. Therefore, the CHMP agreed not to included it in the list of important potential risks. A warning in SmPC section 4.4 details that "*there is a potential risk of NMS associated with medicinal products that reduce dopaminergic transmission. Main symptoms of NMS are mental changes, rigidity,*

hyperthermia, autonomic dysfunction and elevated creatinine phosphokinase levels. If NMS is suspected, deutetrabenazine should be discontinued immediately and appropriate symptomatic treatment should be initiated".

In addition, "Use in pregnancy and lactation" was removed from the list of safety concerns, given recommendations in the PI and the fact that this risk is not expected to be high.

Furthermore, in the course of the procedure, as requested, the applicant (further) discussed (providing also the narratives) the relatedness of four cases of suicidality, especially considering that this effect is known for tetrabenazine and, consequently, detailed in SmPC section 4.4. Suicidality is a known risk in the general psychiatric population, and patients with TD are a predominantly psychiatric patient population. It was however an important question whether this risk could be increased with DTBZ. In Trial C-18, the exposure-adjusted incidence rates for suicide/self-injury (SMQ) AEs over the 12/15-week period were higher in the DTBZ 24 mg/day (0.13) and 36 mg/day fixed-dose groups (0.07) versus placebo (0.04). In the long-term Trial C-20, the EAIR was 0.02. No AE were reported in study C18. Regarding the four cases, concomitant medications with known risk of suicidality and medical history, together with the fact that the causality was assessed as "*not related*" to DTBZ by both the investigator and the applicant, it appears no possible at this stage to characterise an increased risk of suicidality. Consequently, "suicidality" was not included in the list of safety concerns.

2.7.2. Pharmacovigilance plan

The CHMP, having considered data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product and to monitor the effectiveness of the risk minimisation measures (RMMs).

No additional pharmacovigilance activities are deemed necessary.

2.7.3. Risk minimisation measures

The CHMP is of the opinion that the applicant's proposed (routine) RMMs are sufficient to minimise the risks of the product in the agreed indication.

No additional RMMs are deemed necessary.

2.7.4. Conclusion on the RMP

The CHMP considers that the RMP version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive

2001/83/EC and any subsequent updates published on the European medicines web-portal.

Based on the new indication of moderate to severe tardive dyskinesia, the CHMP agreed with the PRAC recommendation that a separate entry in the EURD list for Austedo is needed, as the PSUR cycle cannot follow the already existing entry for tetrabenazine. The requirements for submission of PSURs for this medicinal product are set out in Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The new EURD list entry uses the EURD PSUR data lock point (DLP) with 31 March (DLP for Austedo global PSUR cycle) to determine the forthcoming DLPs. The PSUR cycle for Austedo should follow a yearly cycle.

2.9. Product information

2.9.1. User consultation

Overall, the methodology of the user test was considered satisfactory and the results meet the success criteria for all questions posed. Therefore, the results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Austedo (deutetrabenazine) is not included in the additional monitoring list as deutetrabenazine is not to be qualified as new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet do not include a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information.

3. Benefit-Risk Balance

3.1. Therapeutic context

3.1.1. Disease or condition

Tardive dyskinesia (TD) is a disabling, potentially irreversible, delayed onset, hyperkinetic movement disorder in which predisposed patients experience abnormal involuntary movements (dyskinesias), resulting from chronic or even episodic exposure to dopamine receptor antagonists (DRAs), such as antipsychotics and some antiemetics.

TD is generally not progressive even with continued antipsychotic treatment. It can persist for years after discontinuation of the causative agent, although some patients can experience partial or complete remission of symptoms a few years after discontinuation of the causative agent (Savitt and Jankovic 2018).

Dyskinesias are often bothersome and incapacitating. The impact of the movements is multifactorial, significantly affecting the patient's physical, psychological, social, and professional functioning and overall quality of life.

Moreover, TD affects how patients manage their underlying condition, which can interfere with effective treatment (Jain et al 2023). Thus, management of TD should not be based solely on the severity of

movements, but also on the control of the underlying condition (Jackson et al 2021). To minimize TD, the approach of stopping the dopamine receptor antagonist (DRA) (e.g., an antipsychotic) carries the risk of worsened underlying disease (e.g., schizophrenia).

The risk of treatment-emergent TD with newer-generation antipsychotics is lower than with first-generation antipsychotics, in line with the observed global mean prevalence in adults of 30% for first-generation antipsychotics exposure versus 21% for second-generation antipsychotics exposure (Carbon et al 2017). Despite the decreased use of first-generation antipsychotics, the incidence of TD remains high in the antipsychotic-treated population.

3.1.2. Available therapies and unmet medical need

Vesicular monoamine transporter type 2 (VMAT2)-inhibitors are regarded as treatment options for TD.

Several products with similar mechanism of action (MoA) and efficacy have been marketed in the EU, none has (yet) been centrally approved, and their efficacy and tolerability are far from perfect, leading to insufficient treatment, significant AEs, such as depression or Parkinsonism, and interaction with the concomitant psychiatric medication. As such, there is an unmet medical need for new efficacious treatments with a favourable safety profile, including not compromising the stability or control of the underlying disorder.

Cessation or reduction of the DRA to the lowest efficacious dose for controlling the underlying condition, or switching to a different DRA (e.g., from first- to second-generation antipsychotic) is the first-line therapeutic approach in TD (Bhidayasiri et al 2018). However, these actions do not guarantee the resolution of TD and they risk compromising the stability of the underlying condition for which the DRA is being used.

Deutetrabenazine (DTBZ) aims at reducing bothersome involuntary movements caused by previous or concomitant treatment with DRA(s) and improve patient's quality of life. The proposed therapeutic indication of this medicinal product is: treatment of moderate to severe tardive dyskinesia in adults.

3.1.3. Main clinical studies

Two pivotal trials, C-18 with best tolerated ascending dose, and C23 with fixed dose, have been conducted by the applicant. Study treatment maintenance duration was of 6 and 8 weeks, respectively. One long-term, open label extension study in tardive dyskinesia (C-20) and other supportive studies in Huntington's disease were also submitted.

3.2. Favourable effects

Deutetrabenazine showed a statistically significant and clinically meaningful improvement in the Abnormal Involuntary Movement Scale (AIMS) total score from baseline compared to placebo, as detailed thereafter.

The mean AIMS improvement at week 12 for study C18 was -1.6 for placebo and -3.0 for DTBZ, with a treatment effect of -1.4. Similarly, the mean AIMS improvement in study C23 was -1.4 for placebo and -3.3 for the 36 mg arm of DTBZ. The treatment effect did not reach the minimally clinically significant threshold of -2.0 points in the Abnormal Involuntary Movement Scale (AIMS), the identified minimally clinically important difference of 2 points (Stacy et al. 2019) with this primary efficacy tool.

Efficacy at 12 weeks: primary and key secondary endpoint

At week 12 of study C-18, the LS mean change in the total motor AIMS score (primary efficacy endpoint) in the mITT population (N=113) was -3.0 (SE 0.45) in the DTBZ group compared with -1.6 (SE 0.46) in

the placebo group, the mean difference was -1.4 (95% CI: -2.6, -0.2, p=0.0188, a multiplicity-adjusted p value for difference from placebo, statistically significant).

In study C-23, the LS mean change in total motor AIMS score at week 12 (primary efficacy endpoint) in the mITT population (N=222) was-3.2 (SE 0.45) for the 24 mg/day arm and -3.3 (SE 0.42) in the DTBZ 36 mg/day group compared with -1.4 (SE 0.41) in the placebo group. The mean difference was -1.9 (95% CI: -3.09, -0.79, p=0.001, a multiplicity-adjusted p-value for difference from placebo, statistically significant) between placebo and DTBZ 36 mg/day group.

In study C-23, because of the hierarchical testing approach, the analysis based on the change in total motor AIMS score at week 12 for the DTBZ 24 mg/day group was exploratory. Nevertheless, the efficacy estimate with DTBZ 24 mg/day is of the same magnitude as with DTBZ 36 mg/day (mean difference -1.8; 95% CI -3.00, -0.63, p=0.003). This supports the claim that the two doses of 24 mg/day and 36 mg/day are efficacious.

Long term efficacy

Consistent improvements across efficacy assessments (AIMS and CGIC - Clinical Global Impression of Change) were observed in study C-20 for up to 3 years. The mean (SE) change in the total motor AIMS score from baseline of study C-20 was -2.0 (0.38) at week 145/158 (min -14, max 9). The mean (SE) change in the total motor AIMS score from baseline of the parent studies C-18 and C-20 was -4.0 (0.37) at week 145/158 (min -14, max 7).

Also, of note, in the clinical development programme, the Phase 3 trials were conducted using a clinical matrix-based gastro erosional formulation for twice daily (BID) dosing. Thereafter, an osmotic drug delivery formulation was developed, resulting in a prolonged release formulation for once daily (QD) dosing, which can be beneficial for patients with TD, who are likely receiving one or more neuropsychiatric medications (e.g. an antipsychotic, an antidepressant, a mood stabilizer, and/or medications to control some drug-induced adverse effects) as treatment adherence and persistence are generally expected to be higher with a long-term treatment taken QD versus a more frequent dosing.

3.3. Uncertainties and limitations about favourable effects

A limitation of trial C-18 is the modest sample size whereas trial C-23 was larger. Both studies had a short treatment duration (12-weeks including dose adjustment), bearing in mind that TD has a spontaneous up and down time course of severity. Nevertheless, the Abnormal Involuntary Movement Scale (AIMS) was evaluated at sufficiently close intervals over the course of the studies which reduces the concern that patients developing signs of TD may have been missed due to the fluctuating nature of the disease.

In individual studies and in the pooled analysis, the effect size was borderline compared to the minimal clinically important difference (MCID) of 2 points reported in the literature (Stacy et al. 2019). Therefore, further analyses were provided to confirm that the patients who managed to fine tune their treatment achieved a reasonable improvement.

The key secondary efficacy endpoint for both C-18 and C-23 was the proportion of patients rated by the investigator as treatment success based on the Clinical Global Impression of Change (CGIC) at Week 12. In C-18, the results only showed a favourable trend of DTBZ over placebo (48.2% and 40.4% respectively, p=0.4001). In C-23, although a greater proportion of patients were considered a treatment success at week 12 after treatment with DTBZ 36 mg/day versus placebo, the result was not statistically significant (44% vs 26% respectively, odds ratio=2.11, p=0.059). The results of the CGIC analysis at 24-mg/day dose were similar to those at 36 mg/day (49% vs 26% respectively, odds ratio=2.71, p=0.014) although considered exploratory because of the hierarchical testing approach.

The point estimate of the primary endpoint was -1.4 and -1.9 in trials C-18 and C-23 respectively. It was -1.8 in the pooled analysis from trial C-18 and the efficacious doses from trial C-23 (36 mg/day and 24 mg/day). Therefore, the effect size was lower or borderline compared to the MCID of 2 points reported in the literature (Stacy et al. 2019). This issue remained not solved until the applicant provided further data including an analysis of AIMS response anchored to the Patient Global Impression of Change (PGIC), together with the class improvement of 2, 3, 4, 5, 6 or more AIMS points. These have shown that most patients who improved 3 points or more sensed "very much" or "much improved". Likewise, patients who scored "very much improved" in PGIC had a mean 5 points improvement in AIMS.

DTBZ proposed therapeutic indication initially included all patients irrespective of disease severity and without mentioning that symptoms must be bothersome to the patient and/or cause functional impairment.

The claim was based on a pooled post-hoc subgroup analysis of the primary endpoint, that compared patients with a centrally read total motor AIMS score ≤6 (mild TD) at baseline of studies C18 and C23 to those with a centrally read total motor AIMS score >6 (moderate to severe TD) at baseline. However, the treatment effect in the subgroup of patients with mild TD was not statistically significant. Also considering the exploratory nature of the presented pooled post-hoc analysis on the one hand, and the unconvincing treatment effect in the mild TD subgroup on the other hand, the therapeutic indication was ultimately restricted to "treatment of moderate to severe TD in adults", as requested by CHMP.

DTBZ should only be used in patients who had their underlying psychiatric condition stable for some time as unstable patients may have higher suffering with treatment-related adverse events such as depression or worsening psychiatric condition. It is at the clinician's discretion to decide if the patient is sufficiently stable to endure a treatment with DTBZ.

3.4. Unfavourable effects

The safety data from the TD development programme demonstrated that DTBZ was generally well tolerated for up to ~4 years. In the placebo-controlled trials, the overall safety profile was similar between DTBZ and placebo, with similar numbers of participants experiencing 1 or more adverse event (AE), serious AE (SAE), or severe AEs in the treatment groups. The discontinuation rate due to AEs for DTBZ was low and comparable to that of placebo.

The most common side effects of DTBZ, identified in clinic trials and post-marketing use are: urinary tract infection, nasopharyngitis, anxiety, insomnia, restlessness, somnolence, akathisia, Parkinsonism, diarrhoea, constipation, dry mouth, fatigue, and depression. Other (potential) risks carefully considered were: neuroleptic malignant syndrome and QTc prolongation. These are adequately characterised and managed via routine risk minimisation measures (RMMs).

There were no new safety findings resulting from the post-marketing experience besides several reports of parkinsonism. While review of the clinical trial data did not identify parkinsonism as an ADR, evaluation of post-marketing reports resulted in the classification of parkinsonism as an ADR.

3.5. Uncertainties and limitations about unfavourable effects

QT prolongation

DTBZ may prolong the QTc interval, but the degree of QTc prolongation is not clinically significant when DTBZ is administered within the recommended dose range. Overall, no safety signals were observed in ECG parameters in clinical trials.

In an *in vitro* study, deuterated α-HTBZ and β-HTBZ inhibited the human ether-à-go-go-related gene (hERG) potassium channel. The corresponding safety margins, calculated as ratio of 50% inhibitory effect

and the predicted unbound $C_{max,ss}$ of deuterated α-HTBZ and β-HTBZ at the maximum recommended doses were 216- and 242-fold, respectively, in EM and 172- and 52-fold, respectively, in PM.

Despite these observations, a risk cannot be excluded when DTBZ is used in combination with other products that prolong the QTc interval and in patients with congenital long QTc syndrome, a history of cardiac arrhythmias, bradycardia, hypokalaemia or hypomagnesaemia. Risk minimisation measures include (routine risk management activities): a warning in SmPC Sections 4.4 and PL (accordingly) and the legal status of "medicinal product subject to restricted medical prescription".

Further details about the potential interaction with medicines known to prolong the QTc interval are included in SmPC section 4.5 together with specific examples of such medicines. These RMMs are sufficient to address the concern of potential clinically insignificant QTc interval prolongations and therefore ECG records (e.g. a normal ECG [QTc< 450 ms] when starting treatment and tapering the dose) are not deemed required for all patients when starting DTBZ treatment or tapering the dose.

Dose Recommendations

The dose selection for DTBZ in the Phase 3 programme in TD was based on targeting similar exposure (AUC) for the deuterated active metabolites of DTBZ as for the nondeuterated active metabolites of TBZ following TBZ administration. In early PK trials, this was achieved with approximately 50% lower DTBZ doses compared to TBZ. The therapeutic benefit of these doses was confirmed in the Phase 3 efficacy trials in participants with TD.

The TD Phase 3 programme, using the DTBZ matrix formulation BID, supports a treatment initiation and titration scheme ranging from 12 to 48 mg/day and demonstrated the efficacy of DTBZ treatment at the efficacious dose range of 24 to 48 mg/day in adult patients with TD. The titration to effect in 6 mg/day steps showed that, although a considerable portion of participants were titrated up to 48 mg/day, for other participants treatment effect was achieved at dose levels below 48 mg/day starting from 24 mg/day.

The initiation phase is important to allow monitoring of safety and tolerability in each patient while they reach their efficacious dose level. However, as supported by US market research and real-world experience with DTBZ, the duration of initiation and titration phases can be a driver for lack of treatment adherence or even drop-out of patients from the therapy before clinical efficacy is reached (Caffrey and Borrelli 2020). An integrated safety analysis and subsequent modelling analyses supports treatment initiation by increasing the dose from 12 mg/day in the first week to 24 mg/day in the second week and thereby skipping the 18 mg/day dosing step applied in the TD Phase 3 programme. This allows patients to reach the efficacious dose range of 24 to 48 mg/day sooner and potentially increase adherence and persistence to treatment without adversely affecting the safety profile. This approach is expected to have a positive impact on patients' outcomes and ultimately in controlling the highly debilitating symptoms of TD.

The osmotic drug delivery formulation for QD dosing was shown to match PK exposures to that of the clinical matrix formulation BID, and thereby generate an equivalent therapeutic effect in TD. Based on matched PK exposures, dose proportionality established for both formulations over the full clinical dose range, and modelling and simulations, the dosing recommendation for the commercial osmotic PR tablet QD is the same as for the clinical matrix tablet BID.

In summary, DTBZ dosing should be determined individually for each patient, based on adequate reduction of TD symptoms and tolerability. The applicant did not plan to register the 18 mg dose (i.e. 12 mg, 24 mg, 30 mg, 36 mg, 42 mg and 48 mg). Thus, the first increment in the titration phase will be an increment of 12 mg/day, instead of 6 mg/day in the clinical program. Therapy should be initiated at 12 mg QD for one week, and the dose then increased to 24 mg QD for another week. After the second week, the dose should be titrated at weekly intervals in increments of 6 mg QD, based on reduction of

TD symptoms and tolerability. The efficacious dose range is considered to be 24 mg to 48 mg. The maximum recommended daily dose is 48 mg.

As higher exposures are observed in patients receiving strong CYP2D6 inhibitors or who are known poor CYP2D6 metabolisers, the total daily dose of DTBZ should not exceed 36 mg in these patients. This recommendation is in line with the maximum daily dose of 36 mg used in the Phase 3 efficacy trials in TD patients who received concomitant treatment with strong CYP2D6 inhibitors.

3.6. Effects table

Table 91: Effects table for deutetrabenazine

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Change in total AIMS score (Items 1 through 7) during the 12-week treatment period	AIMS	Point scale	-3.0	-1.6	Treatment effect below the minimal clinically significant difference of 2 points Key secondary endpoints not aligned with primary and not statistically significant	Study C18
Change in total AIMS score (Items 1 through 7) during the 12-week treatment period	AIMS	Point scale	-0,7 (12 mg dose) -3.0 (24 mg dose) -3.3 (36 mg dose)	-1.4	Treatment effect below the minimal clinically significant difference of 2 points Key secondary endpoints not aligned with primary and not statistically significant	Study C23
Unfavourable Effects						
Depression	Incidence of depression	%	8.0	N/A*		X1. Data from open label maintenance Study C-20 part A
Anxiety	Incidence of anxiety	%	9.8	* N/A		X1. Data from open label maintenance Study C-20 part A
Somnolence	Incidence of somnolence	%	11.3***	6.9**	more frequent during the titration/dose escalation period	X1

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Urinary tract infection	Incidence of Urinary tract infection	%	7.1	N/A*		X1 Data from open label maintenance Study C-20 part A
Nasopharyngitis	Incidence of Nasopharyngitis	%	4.5	N/A*		X1 Data from open label maintenance Study C-20 part A
Insomnia	Incidence of Insomnia	%	4.2	N/A		X3
Agitation / Akathisia / Restlessness	Incidence of Agitation / Akathisia / Restlessness	%	1.8	0.8		X4
Diarrhoea	Incidence of Diarrhoea	%	6.2	N/A*		X1 Data from open label maintenance Study C-20 part A
Constipation	Incidence of Constipation	%	4.4	2.2		X5
Dry mouth	Incidence of Dry mouth	%	8.9	6.7		X5
Fatigue	Incidence of Fatigue	%	4.4	8.9		X5
Parkinsonism	Incidence of Parkinsonism	%	0.4 / UNK	0 / N/A		**** Pooled data from C18 and C23/Post marketing

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Weight decreased	Incidence of Weight decreased	%	7.7	N/A		X1 Data from open label maintenance Study C-20 part A
QT prolongation					DTBZ may prolong the QT interval, but the degree of QT prolongation seems to be not clinically significant when DTBZ is administered within the recommended dose range; a risk cannot be excluded when DTBZ is used in combination with other products that prolong the QT interval and in patients with congenital long QT syndrome, a history of cardiac arrhythmias, bradycardia, hypokalaemia or hypomagnesaemia	X6
Neuroleptic Malignant Syndrome					The risk is associated with products that reduce dopaminergic transmission	X6

Abbreviations: AIMS (Abnormal Involuntary Movement Scale), DTBZ (deutetrabenazine)

Notes:
X1 - Table: Adverse Events Occurring in ≥4% of Tardive Dyskinesia Participants in the Titration/Dose-Escalation or Maintenance Period in Any Participant Group (Safety Population in Trials C-18, C-23, and C-20)
X2 - Table: Exposure-Adjusted Incidence Rate for Adverse Events That Occurred in ≥4% in Any Tardive Dyskinesia Participant Group in the Overall Treatment Period by Participant Group (Safety Population in Trials C-18, C-23, and C-20)
X3 - Table: Adverse Events in ≥4% of Participants in Long-Term Trial C-20 Overall Treatment Period (Safety Population)
X4 – Pooled analysis for the 2 double-blind trials in TD patients
X5 - Adverse Reactions Occurring in >4% in Participants with Huntington's Disease from Trial C-15
X6 – Summary of clinical safety

*- Study C20 Part A maintenance did not run a placebo arm.

**- Placebo values are from C-18 and C-23 titration period and the adverse event value is for the C-20 Part A open label maintenance period.

***- Pooled titration data from C18 and Part A C20.

****- Pooled data from C18 and C23

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There is no centrally approved therapy for the treatment of tardive dyskinesia (TD) in the EU, although tetrabenazine is marketed in some EU member states.

There is an improvement in the severity of abnormal involuntary movements based on the primary efficacy endpoint, the total motor AIMS score, in the pivotal studies of DTBZ (C-18 and C-23). The primary analysis was statistically significant and was supported by the key secondary endpoint of treatment success based on CGIC where a trend favoured DTBZ over placebo. Both the total motor AIMS score and the CGIC are rated by the clinician and can therefore be considered objective. It is also noteworthy that the total motor AIMS score was centrally rated by experts in movements disorders. PGIC failed to demonstrate benefit. However, AIMS improvement when anchored to PGIC showed that the two endpoint tools were related, and most patients with 4 or more points improvement in AIMS scored improved "much" or "very much". Although a higher response was identified in patients not treated with dopamine receptor antagonists (DRA), the very low number of patients as compared to those recently treated with DRA precludes a restriction to patients not currently treated with DRAs.

The applicant agreed to align the intended therapeutic indication of DTBZ with the population in the pivotal clinical trials for TD, as requested by CHMP. Consequently, the indication wording in SmPC section 4.1 was amended to reflect a restriction to "moderate to severe TD".

The safety profile of DTBZ is overall well characterised. This includes among others a risk of depression, somnolence, parkinsonism, and QT prolongation. Overall, the frequencies of serious adverse events remained limited based on the comparative data. Several effects observed with other inhibitors of VMAT2 were not observed with deutetrabenazine.

3.7.2. Balance of benefits and risks

There is no centrally approved therapy for the treatment of tardive dyskinesia (TD) in the EU, although TBZ is marketed in some EU member states.

The applicant provided sufficient evidence of DTBZ statistically significant and clinically meaningful improvement in the AIMS total score from baseline compared to placebo in the trial population of adult patients with moderate to severe tardive dyskinesia.

DTBZ dosing should be determined individually for each patient, based on adequate reduction of TD symptoms and tolerability. The efficacious dose range is considered to be 24 mg to 48 mg (maximum recommended daily dose). The dose can be easily titrated to reach a satisfactory equilibrium between benefit and risk of the treatment.

DTBZ safety profile is well characterised. Data from the TD development programme demonstrated that DTBZ was generally well tolerated for up to ~4 years. In addition, no new safety findings resulted from the post-marketing experience in the United States, besides several reports of Parkinsonism.

3.7.3. Additional considerations on the benefit-risk balance

In the context of the CHMP early contact methodology (process and FAQ at www.ema.europa.eu/en/documents/other/chmp-early-contact-patient-and-healthcare-professional-organisations-process-and-faqs_en.pdf), Austedo (deutetrabenazine) had been identified by the CHMP core group as a procedure that would benefit from input from patient and healthcare professional (HCP) groups.

Input was received from the European Academy of Neurology (EAN) and the European Psychiatric Association (EPA), requested to comment on any aspects of particular importance to HCP, such as information on:

- The standard of care or available treatments and to what extent they cover the intended indication of tardive dyskinesia in adults;
- The treatment duration; and, if in your view, the duration needs to be optimised;
- Any possible therapeutic/unmet medical needs;
- What benefits you would hope for in new medicines; as well as what level of side-effects you would consider manageable for patients;
- Considerations for pregnant people/people of child-bearing potential, where applicable.

Comments from the Assessor:

Both EAN and EPA are European organizations committed to the diagnosis, prevention and treatment of TD. Both encompass the need for adequate therapeutics, as no centrally approved agent is available throughout the EU. Both have been guided in their interpretation with the publicly available data for DTBZ, where the focus was on the maximum effect in the responders, with a broad definition of responder, and the higher doses arms, together with the long-term open-label study with up to 3 years of follow up.

EPA alludes to the Solmi et al meta-analysis, but in this tetrabenazine was excluded since trial was not meta-analysable according to the study criteria. Therefore, their conclusions are only about DTBZ and valbenazine.

In conclusion, the information provided in both responses is in line with the clinical perception of an unmet medical need, with tailored treatment centred in the patient. This point is crucial since most patients will require simultaneous DRA treatment, and down titration of these along with up titration of VMAT2 blockers is the key to success.

3.8. Conclusions

The overall benefit/risk balance of Austedo is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Austedo is favourable in the following indication(s):

- Treatment of moderate to severe tardive dyskinesia in adults

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive

2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 1 year following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

  Not applicable

- **Obligation to conduct post-authorisation measures**

  Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that deutetrabenazine is **not** to be qualified as a new active substance in itself as it is a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS) claim.

5. Re-examination of the CHMP opinion of 19 June 2025

Following the CHMP conclusion that deutetrabenazine (DTBZ) is **not** a new active substance (NAS) the applicant submitted detailed grounds for the re-examination of the CHMP recommendation to refuse the NAS request.

5.1. Detailed grounds for re-examination submitted by the applicant

It is Teva's position that DTBZ is to be classified as a NAS, primarily, under the **first indent** of the NAS definition because DTBZ and tetrabenazine (TBZ) do not expose the patient to the same therapeutic moiety at the site of biological activity. If the CHMP is of the opinion that DTBZ cannot be classified as a NAS under the first indent, it is Teva's position that DTBZ is to be classified as a NAS under the second indent, because DTBZ and TBZ differ significantly in properties with regard to safety.

Teva's grounds for re-examination on the CHMP Opinion based on the conclusions in the Day 210 Assessment Report, are as follows:

1. Teva maintains its position that DTBZ is to be classified as a NAS under the first indent of the NAS definition on the basis that:

a. DTBZ is not an isomer, mixture of isomers, complex, derivative, ester, ether, or salt of TBZ;

b. DTBZ is an isotopologue of TBZ, with 6 deuterium atoms in place of 6 hydrogen atoms at the equivalent positions in TBZ;

c. The therapeutic moiety of DTBZ is comprised of DTBZ and its deuterated active metabolites. These are different to TBZ and its non-deuterated active metabolites and are chemically stable entities that are not converted to the non-deuterated counterparts;

d. Therefore, DTBZ and TBZ do not expose the patient to the same therapeutic moiety at the site of biological activity; and

e. If administration of 2 chemical active substances does not expose patients to the same therapeutic moiety at the site of biological activity, the active substances are by definition different. Hence DTBZ is to be considered as a NAS under the first indent of the NAS definition.

2. Teva maintains its position that DTBZ is to be classified as a NAS under the **second indent** of the NAS definition on the basis that it has a significantly improved PK profile compared to TBZ, with a longer half-life (t½, terms used interchangeably throughout document) and less fluctuating concentrations, resulting in a clinically relevant improvement in safety and tolerability. In relation to the specific issues raised by the CHMP in the Day 210 Assessment Report, it is Teva's position that:

a. The indirect comparison of safety data provides robust evidence supporting improved tolerability of the DTBZ molecule over TBZ.

- Teva disagrees that the methodological issues listed in the Day 210 Assessment Report negatively impacted the robustness and conclusions from the indirect comparison;
- Teva disagrees that the use of different formulations in the 2 indirectly compared trials (First-HD [DTBZ] and TETRA-HD [TBZ]) do not allow to attribute a potential difference on the clinical effect between DTBZ and TBZ to the active substance DTBZ.

b. The improved pharmacokinetic (PK) profile of DTBZ compared to TBZ results in an improved pharmacodynamic (PD) profile with regard to QTc interval, which results in improved safety of DTBZ compared to TBZ.

5.2. Grounds submitted by the applicant in Relation to NAS Assessment Under Indent 1

General Observations on the Applicable Legal Framework

According to the European Union (EU) pharmaceutical legislation, specifically Article 10(2)(b) of Directive 2001/83/EC read in conjunction with the Annex I to this Directive (Part II under 3), and from the 2015 CHMP Reflection Paper (EMA/CHMP/QWP/104223/2015) which is based on this legislation, DTBZ is to be classified as a NAS under the first indent of the NAS definition. In the applicant's opinion, the different position of the CHMP, according to which DTBZ and TBZ are considered to have the same therapeutic moiety because hydrogen and deuterium are isotopes of the same element, has no basis in the law and is inconsistent with the rationale and principles on which Article 10(2)(b) of Directive 2001/83/EC is based.

In this respect, the applicant respectfully submits that the CHMP, being a scientific committee tasked with the drawing up of scientific opinions for the purposes of the implementation of the provisions of the EU pharmaceutical legislation, cannot, in doing so, exercise discretion that goes beyond this legislation. For the case at hand, it means that the CHMP cannot introduce new elements to the

assessment of active substances designated as new or the same, which have no basis in the law and that are not compatible with how the law has been applied and explained so far.

The EU legislation does not provide for a definition of NAS, but it does provide for a definition for the determination of whether chemical active substances, despite their structural differences, should be considered as the same or a different active substance. Article 10(2)(b) of Directive 2001/83/EC as amended provides:

> "*the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy*".

The background and rationale of Article 10(2)(b) of Directive 2001/83/EC is that the determination of whether 2 active substances are the same or different should not be based on a comparison of the active substances concerned in the form in which they are manufactured and presented in a medicinal product when placed on the market. Rather, this should be based on a comparison of the molecule that, after administration to the patient, reaches the site of activity where it exerts the intended therapeutic effect. The principles of Article 10(2)(b) of Directive 2001/83/EC and Part II under 3 of the Annex to this Directive, make clear that active substances that do not share the same therapeutic moiety at the site of biological activity cannot be considered as the same active substance *by definition*.

The key concept of Article 10(2)(b) of Directive 2001/83/EC, which is the only legal basis for the determination of whether chemical active substances shall be considered to be the 'same' or 'different' (or in the context of the case at hand: 'new'), is thus to assess the differences between active substances, not on the level of the active substance that is present in the medicinal product once it is placed on the market, but on the level of the molecule that *in vivo* arrives at the site where the biological activity takes place. If the molecule, in the form in which it *in vivo* arrives at the site of biological activity, is different, it follows that the therapeutic moiety of that active substance is different and, therefore, it is a NAS.

This is how Article 10(2)(b) of Directive 2001/83/EC is designed and intended. It does not mandate, or allow for, a further analysis and characterisation of the (part of the) molecule that has arrived at the site of biological activity in terms of the role and function of the different parts of that molecule in the interaction that takes place with the cellular tissue that forms the receptor. Any such further analysis and characterisation of the therapeutic moiety cannot be based on Article 10(2)(b) of Directive 2001/83/EC, or any other provision of pharmaceutical law, and cannot be introduced in scientific guidelines or in ad-hoc assessments of medicinal products, as it will only lead to uncertainty and render the application of Article 10(2)(b) of Directive 2001/83/EC as basis for NAS assessments unpredictable.

Principles Applied to the Distinction Between DTBZ and TBZ

DTBZ and TBZ are different in that DTBZ is an isotopologue of TBZ, with 6 deuterium atoms in place of 6 hydrogen atoms at the equivalent positions in TBZ. The part of the DTBZ molecule that arrives at the site of biological activity is different from TBZ. Indeed, DTBZ and its deuterated active metabolites are different to TBZ and its non-deuterated active metabolites and are chemically stable entities that are not converted to the non-deuterated counterparts. As such, there can be no other conclusion than that DTBZ and TBZ do not expose the patient to the same therapeutic moiety at the site of biological activity and that, therefore, they are not the same active substance in the meaning of Article 10(2)(b) of Directive 2001/83/EC.

Accordingly, the applicant considers that the CHMP is incorrect to conclude that DTBZ and TBZ are considered as derivatives of each other, which share the same therapeutic moiety at the site of

biological activity. As to "Derivatives", Section 2.4 of the 2015 Reflection Paper refers to the following situations:

a. Where the original substance or its active metabolite(s) *in vivo* will be derived from the new applied substance in such a manner that the patients are exposed to the same therapeutic moiety of the original substance (the applied substance is a prodrug).

b. Where the new applied active substance is the same substance as the therapeutic moiety that the patients were exposed to when treated with the original active substance (the applied substance is a metabolite).

Neither of these situations applies. DTBZ is not a prodrug in the meaning of situation a. Apparently, the CHMP's conclusion that DTBZ and TBZ are to be considered to be derivatives of each other is based on its misrepresentation that DTBZ and TBZ expose patients to the same therapeutic moiety, which, for the reasons set out above, is not the case.

In addition, the conclusion that DTBZ is a NAS was made also in earlier scientific advice and cannot be called into question by scientific considerations about if the deuterium atoms in DTBZ and the hydrogen atoms in TBZ are "sufficiently different". Any additional assessment, different from what under the common understanding of Article 10(2)(b) of Directive 2001/83/EC and the Annex to the Directive has been understood to be the therapeutic moiety of an active substance, will undermine legal certainty and make NAS assessments unpredictable. This is especially the case where these additional assessments rely on vague concepts of "sufficiently different" for which no legal basis or even guidance exists.
That, as the CHMP has stated, its existing guidance does not constitute an exhaustive compilation of cases when chemical active substances can be considered a NAS, does not mean that the CHMP has the scientific discretion to introduce new elements and criteria for NAS assessments for new categories of chemical active substances that go beyond the legal principles that apply for NAS assessments, and that follow for EU pharmaceutical legislation and its clarification by the European Courts.

Overall Conclusion of assessment under Indent 1

For all these reasons, Teva respectfully concludes that:

- DTBZ and TBZ are structurally different due to the presence of deuterium atoms instead of hydrogen atoms, which also confers physicochemical differences such as a higher molecular weight, a different molecular formula, and distinct pKa value.

- As a consequence, the form of DTBZ that arrives at the site of biological activity and that exerts its pharmacological action is different from that of TBZ.

- Which means that DTBZ and TBZ do not expose the patient to the same therapeutic moiety at the site of biological activity.
- From which it follows that DTBZ and TBZ cannot be considered to be the same active substance.

- There is no legal basis for additional or different criteria for assessment of NAS under indent 1.

It is Teva's opinion that DTBZ is to be classified as NAS under the first indent of the NAS definition in the Notice to applicants, in accordance with the legal basis of this definition in Article 10(2)(b) of Directive 2001/83/EC read in conjunction with the Annex to this Directive, Part II under 3.

5.3. CHMP position on NAS status claim under Indent 1

General Observations on the Applicable Legal Framework

Annex 1 of Chapter 1 of Volume 2A of the European Commission's Notice to applicants (NtA), on the procedures for marketing authorisation, defines a new chemical, biological or radiopharmaceutical active substance as including:

> 'a chemical, biological or radiopharmaceutical substance not previously authorised in a medicinal product for human use in the European Union;' (so called 'first indent' of the NtA definition).

Unlike other indent criteria, this classification does not require proof of significantly different safety or efficacy profiles when compared to an existing substance, as it inherently applies to a substance with no prior authorisation for human use in the EU. Therefore, the first indent addresses the structure of the active substance in itself. Of note, such substance is considered to be new in itself provided that the administration of the applied active substance would not expose patients to the same therapeutic moiety at the site of the biological activity as already authorised active substance(s) in a medicinal product in the European Union.

Principles Applied to the Distinction Between DTBZ and TBZ

DTBZ is an isotopologue of TBZ, with 6 deuterium atoms in place of 6 hydrogen atoms at the equivalent positions in TBZ, with the same arrangements, and therefore DTBZ is structurally related to TBZ. An isotope of an element is not a different element. Deuterium is a naturally occurring isotope of hydrogen, but it concerns the same element. DTBZ will already be present in TBZ at a level based on the natural abundance of deuterium in 1H-hydrogen, as will TBZ in DTBZ as a function of the synthetically enriched abundance of 1H-hydrogen in the deuterated raw material used to manufacture DTBZ.

So, regardless of the replacement of one or more hydrogen atoms with deuterium atoms in the molecule, DTBZ is structurally related to TBZ and is considered a derivative of TBZ. Indeed, deuterium and hydrogen are the same element, they share the same electronic configuration. The applicant argues that since DTBZ and TBZ are converted into different active metabolites *in vivo*, patients would be exposed to different therapeutic moieties. The CHMP does not agree with this argument as DTBZ and TBZ metabolites (the active metabolites of TBZ are α-HTBZ (α-dihydrotetrabenazine) and β-HTBZ and the active metabolites of DTBZ are deuterated α-HTBZ and deuterated β-HTBZ) share the same **chemical structure.** Indeed, the only difference between the metabolites is the presence of 6 deuterium atoms in place of 6 hydrogen atoms on the same backbone structure. This indicates that the deuteration does not alter the *in vivo* metabolic pathway. The CHMP is of the view that the replacement of 6 hydrogen atoms with 6 deuterium atoms in the active substance and in the active metabolites qualifies DTBZ as a derivative of TBZ, but not as a change of the therapeutic moiety. Thus, both DTBZ and TBZ, as well as their respective active metabolites, are considered to expose patients to the same therapeutic moiety.

Although deuterium and hydrogen are the same element, it is acknowledged that the mass difference may lead to different chemical-physical properties such as a higher molecular weight and a different molecular formula, and both molecules have different CAS numbers as mentioned by the applicant.

However, this is not relevant. For example, a metabolite can also have these differences and will have a unique CAS number, and this does not mean that it constitutes a NAS with respect to its authorised pro-drug. Different salts, esters, ethers, isomers, mixture of isomers, complexes or derivatives of an active substance are also different molecules which can be distinguished through identification testing, but this does not automatically qualify them as a NAS. Different salts, esters, ethers, isomers, mixture of isomers, complexes or derivatives of an active substance are only considered to be NAS when they differ significantly in properties with regard to safety and/or efficacy.

The applicant's argumentation that DTBZ cannot be converted to TBZ and vice versa due to the covalent C-H and C-D bonds is acknowledged but, as mentioned above, DTBZ has exactly the same **molecular structure** as TBZ, with the same elements in the same places. An isotope of an element is not a different element. So, regardless of the replacement of one or more hydrogen atoms with deuterium atoms in the

molecule, DTBZ does not constitute a different **chemical structure** compared to TBZ and neither the active metabolites of DTBZ compared to the active metabolites of TBZ. As specified above, this replacement qualifies DTBZ as a derivative of TBZ but not as a change in the therapeutic moiety. Thus, the therapeutic moiety that patients are exposed to is considered the same.

The applicant's claim that CHMP introduced new elements and criteria for NAS assessments of new categories of chemical substances is not agreed. As stated above, DTBZ and TBZ are considered derivatives and expose the patient to the same therapeutic moiety.

The applicant argues that, as per the 2015 Reflection Paper, the term "derivatives" refers to specific situations where the applied substance is either a prodrug or a metabolite of the previously authorised substance, neither of which applies in the present case. However, these examples do not represent an exhaustive list of cases when related active substances are considered derivatives. This is reflected in section 2.4 Derivative of the paper, where it is stated that "The term derivative, in the context of this reflection paper, includes related active substances which expose the patient to the same therapeutic moiety. This notably includes situations: (…)" . Moreover, the Introduction section of that paper clearly indicates that it cannot cover every scenario *a priori*. At the time of writing of the Reflection Paper, the experience with isotopically modified active substances was limited, hence they were not specifically covered in the Reflection Paper. However, this does not mean that the term 'derivative' does not apply to isotopically modified substances.

Conclusion on NAS status claim under Indent 1

DTBZ does not constitute a different **chemical structure** compared to TBZ, DTBZ and TBZ are considered derivatives and the therapeutic moiety that patients are exposed to, is considered the same. The replacement of specific hydrogen atoms by deuterium atoms (which are the same element) is not sufficient to consider DTBZ as a NAS based on indent 1 of Annex I, Volume 2A, Chapter 1 of the Notice to applicants. So, as the presence of deuterium in DTBZ does not constitute a new active substance vs TBZ (indent 1 not met), unless it can be demonstrated that the isotope enrichment in specific positions results into significant differences in safety and/or efficacy (indent 2), the NAS claim cannot be accepted.

Point not resolved

5.4. Grounds submitted by the applicant in relation to NAS Assessment under indent 2

Teva concludes, based on the information provided below, that DTBZ is to be classified as a NAS under the indent 2 of the NAS definition in the Annex of the Notice to applicants, Volume 2A, Chapter 1.

EMA note: Tables and Figures numbering in sub-section 5.4 and 5.5 is aligned with the numbering included in the applicant's detailed grounds for re-examination documents.

DTBZ differs significantly from TBZ with regards to PK properties (applicant's position)

Increased strength of the carbon-deuterium bond in DTBZ confers a greater resistance to enzymatic modification, resulting in a slower metabolism and a profound improvement of the PK properties of DTBZ compared to TBZ. The initial metabolism of DTBZ to its active deuterated α-HTBZ and β-HTBZ metabolites, both of which highly contribute to the antichoreic effect of DTBZ, is catalysed by carbonyl reductase. The circulating deuterated (DTBZ) or non-deuterated (TBZ) active α-HTBZ and β-HTBZ metabolites are metabolized principally by CYP2D6 to yield O-demethylated metabolites. Because of the deuterium presence in DTBZ, the metabolism by CYP2D6 is attenuated compared to that of TBZ. This results in longer circulating half-lives for the deuterated α-HTBZ and β-HTBZ following DTBZ administration compared to the analogous non-deuterated TBZ metabolites.

In vitro studies in human liver systems, comparing metabolic stability of deuterated and non-deuterated active metabolites, showed a significant half-life prolongation (by 48.5% and 105% to 138% for deuterated α- and β-HTBZ, respectively) in human liver S9 fraction. Furthermore, the increased metabolic stability of the deuterated metabolites significantly attenuated the formation of deuterated 9-O-desmethyl β-HTBZ relative to the non-deuterated counterpart, showing a 2-fold reduction after incubation of 5 µM DTBZ and TBZ with human S9 liver fraction and following administration of single 25 mg doses of radiolabelled DTBZ and TBZ to healthy participants (Trial SD-809-C-12). These findings were further corroborated by human *in vivo* trials (Trials CTP-06 and CTP-07), which confirmed the significant prolongation of half-lives for the deuterated active metabolites.

Extended half-life of DTBZ is attributed to its intrinsic properties and is independent of formulation (applicant's position)

The applicant disagrees that the use of different formulations in the 2 indirectly compared trials, First-HD (DTBZ matrix-based gastro-erosional tablet) and TETRA-HD (TBZ immediate-release tablet) does not allow for attributing a difference on the clinical effect between DTBZ and TBZ to the active substance, DTBZ. The DTBZ formulation used in the indirectly compared Phase 3 First-HD trial (referenced as evidence for indent 2) was a matrix-based gastro-erosional formulation/tablet to be administered twice daily (BID), and not the osmotic prolonged-release formulation/tablet for once daily (QD) dosing, which is the commercial formulation for EU. The dissolution data of matrix-based gastro-erosional tablets reflects a controlled release over approximately 3-4 hours under standard test conditions (pH 3). For immediate-release dosage forms (Xenazine® 25 mg tablets, and TBZ and DTBZ as powder-in-capsules), active substance release (dissolved) was greater than 80% within 30 minutes at pH 3 (for Xenazine®) or pH 3.5 (powder-in-capsules). Similar DTBZ matrix-based gastro-erosional tablets were used in Trial CTP-07 and the First-HD trial.

Increased AUC and extended $t_{1/2}$ are intrinsic properties of the DTBZ active substance conferred by selective deuterium placement in the molecule and is independent of the drug product formulation. There was no impact of the matrix-based gastro-erosional formulation on effective half-life or dosing frequency, which are driven by the inherent properties of the active substance. This includes comparison of the different formulations and presentation of PK data from 2 comparative Phase 1 trials (DTBZ matrix-based gastro-erosional formulation are compared with TBZ immediate-release tablets in Trial CTP-07 and DTBZ and TBZ as powder-in capsule are studied in Trial CTP-06).

PK parameters of total (α+β)-HTBZ from TBZ and total deuterated (α+β)-HTBZ from DTBZ, observed from the single dose administration in Trial CTP-06 and Trial CTP-07, are presented in Table 2, Table 3 and Table 4, respectively.

Table 2: PK parameters for total (α+β)-HTBZ following single dose administration of DTBZ or TBZ unformulated powder-in-capsule (Trial CTP-06; PK population, N=19) or TBZ tablets (Trial CTP-07, part 2; per-protocol PK analysis set, N=12/treatment)

Parameter (Unit)	Formulation and Dose			
	Unformulated Powder-in-capsule (Trial CTP-06)		Tablet (Trial CTP-07)	
	DTBZ[a] 25 mg	TBZ[a,b] 25 mg	DTBZ[c] 22.5 mg	TBZ[c,d] 25 mg
C_{max} (ng/mL)	74.6 (37.1)	61.6 (38.2)	67.5 (25)	55.5 (39)
$AUC_{0-\infty}$	542 (53.8)	261 (69.6)	610 (48)	320 (69)
$t_{½}$ (hours)	8.62 (38.2)	4.82 (50.8)	8.38 (26)	5.57 (34)

Source: AUS-SD-809-CTP-06 CSR Table 8 and AUS-SD-809-CTP-07 CSR Table 14.
[a]DTBZ and TBZ were administered via unformulated powder-in-capsule following an overnight fast.
[b]TBZ unformulated powder-in-capsule was synthesised by Auspex Pharmaceuticals, Inc.
[c]DTBZ matrix-based gastro-erosional tablets (7.5 mg×1 + 15 mg×1) were administered following consumption of a standardised meal, and TBZ immediate-release tablets were administered following an overnight fast.
[d]TBZ tablets were Australia-sourced.
$AUC_{0-\infty}$=area under the plasma drug concentration-time curve from time 0 to infinity; C_{max}=maximum observed plasma drug concentration; CSR=clinical study report; CV=coefficient of variation; DTBZ=deutetrabenazine; HTBZ=dihydrotetrabenazine (deuterated for DTBZ); TBZ=tetrabenazine; PK=pharmacokinetic; $t_{½}$=half-life.
Note: Results presented as mean (%CV).

Table 3: PK parameters of TBZ and DTBZ (Both 25 mg powder-in-capsule formulations) in trial CTP-06

PK Parameter (Unit)	(α+β)-HTBZ (Deuterated for DTBZ)			
	Extensive Metabolisers (EM)		All Evaluable Participants	
	DTBZ 25 mg (n=13)	TBZ 25 mg (n=13)	DTBZ 25 mg (n=19)	TBZ 25 mg (n=19)
C_{max} (ng/mL)[a]	67.9 (36.3)	60.1 (41.9)	74.6 (37.1)	61.6 (38.2)
tmax (hours)[b]	1.50 (0.67-2.00)	1.00 (0.67-2.00)	1.50 (0.67-2.00)	1.00 (0.67-2.50)
$AUC_{0-\infty}$ (ng×hours/mL)[a]	414 (45.1)	177 (50.3)	542 (53.8)	261 (69.6)
$t_{½}$ (hours)[a]	7.61 (37.8)	4.05 (57.4)	8.62 (38.2)	4.82 (50.8)

Source: AUS-SD-809-CTP-06 CSR Table 8.
[a]Mean (%CV) calculated.
[b]Median (range) calculated.
$AUC_{0-\infty}$=area under the plasma drug concentration-time curve from time 0 to infinity; C_{max}=maximum observed plasma drug concentration; CSR=clinical study report; CV=coefficient of variation; DTBZ=deutetrabenazine; HTBZ=dihydrotetrabenazine (deuterated for DTBZ); PK=pharmacokinetic; TBZ=tetrabenazine; $t_{½}$=elimination half-life; tmax=time to maximum observed plasma concentration.

Table 92: PK parameters of TBZ and DTBZ (25 mg TBZ and 15 mg DTBZ tablet formulations) in trial CTP-07

PK Parameter (Unit)	(α+β)-HTBZ (Deuterated For DTBZ) (Mean [CV%] – EM vs IM)					
	DTBZ 15 mg[a] Fed		DTBZ 15 mg[a] Fasted		TBZ 25 mg	
	EM (n=15)	IM (n=10)	EM (n=15)	IM (n=10)	EM (n=15)	IM (n=9)
C_{max} (ng/mL)	31.4 (29)	38.4 (37)	22.4 (39)	22.2 (33)	62.7 (31)	69.3 (36)
tmax (hours)	4.70 (41)	4.76 (30)	2.27 (47)	3.25 (78)	1.03 (28)	1.28 (35)
t_{lag} (hours)	0.93 (92)	0.60 (110)	0.20 (127)	0.25 (141)	0.07 (264)	0.06 (300)
$AUC_{0-\infty}$ (ng×hours/mL)	246 (24)	400 (44)	240 (28)	321 (51)	196 (41)	359 (68)
$t_{½}$ (hours)	6.54 (17)	7.81 (25)	9.12 (26)	9.78 (23)	3.71 (24)	5.73 (66)

Source: AUS-SD-809-CTP-07 CSR Table 11.
[a]15 mg ×1 tablet.
$AUC_{0-\infty}$=area under the plasma drug concentration-time curve from time 0 to infinity; C_{max}=maximum observed plasma drug concentration; CSR=clinical study report; CV=coefficient of variation; DTBZ=deutetrabenazine; EM=extensive metaboliser; HTBZ=dihydrotetrabenazine (deuterated for DTBZ); IM=intermediate metaboliser; PK=pharmacokinetic; TBZ=tetrabenazine; $t_{½}$=elimination half-life; t_{lag}=time to the first observation with a measurable (non-zero) concentration; tmax=time to maximum observed plasma concentration.

According to the applicant, comparing the PK parameter values (for fasted extensive metabolisers [EMs]) obtained for the TBZ powder formulation (Trial CTP-06, EMs, Table 3) to that obtained for the TBZ tablet formulation (Trial CTP-07, fasted EMs, Table 4), similar values were obtained for t½ (4.05 vs 3.71), tmax (1.00 vs 1.03), Cmax (60.1 vs 62.7), and AUC0-∞ (177 vs 196.0).

Comparing the PK parameter values (for fasted EMs) obtained for the DTBZ powder formulation (Trial CTP-06, EMs, Table 3) to that obtained for the DTBZ tablet formulation (Trial CTP-07, fasted EMs, Table 4), shows similar values for t½ (7.61 vs 9.12) and slightly longer tmax for the tablet formulation (1.50 vs 2.27). Please note that for approximately half the dose (25 mg vs 15 mg), the AUC0-∞ (414 vs 240) was comparable, however, the Cmax (67.9 vs 22.4) was higher for the powder-in-capsule formulation.

Overall, similar trends were thus observed for both TBZ and DTBZ: t½ values were similar for the tablet and powder-in-capsule formulations. For both DTBZ and TBZ, the formulation thus had no significant impact on AUC and t½.

PopPK model (applicant's position)

PopPK models were constructed to quantify the PK of total (α+β)-HTBZ (TBZ) and total deuterated (α+β)-HTBZ (DTBZ) from the powder-in-capsule formulation and tablet formulation. Three different analysis contribute to the final analysis:

i) report AUSP-PCS-100 TBZ including data for powder-in-capsule formulation and tablet formulation;

ii) PMXM-2025-21 for DTBZ powder-in-capsule formulation;

and iii) PMX 20-14 for DTBZ tablet formulation.

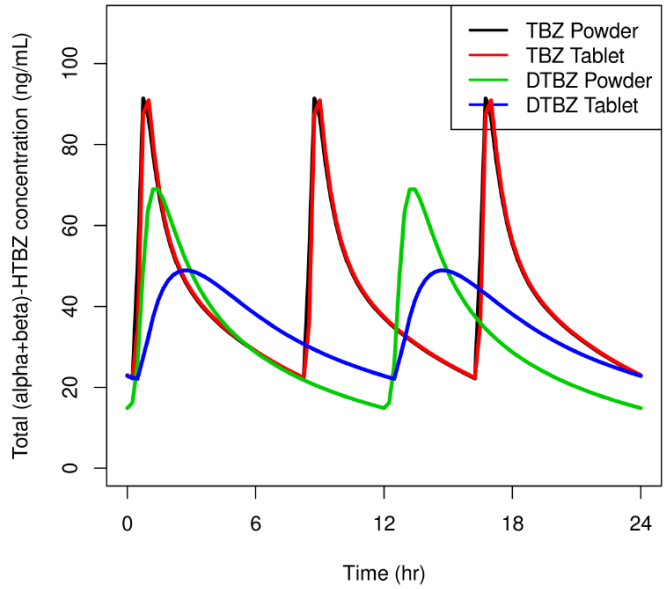
The TBZ PopPK models consisted of a 2-compartment structure with customised absorption model for the powder-in-capsule formulation and the tablet formulation, and relevant covariates. Significant covariates included CYP2D6 genotype, food, formulation, and daily dose amount.

The DTBZ PopPK models consisted of a 2-compartment structure with 2-path absorption model, both for deuterated α-HTBZ and deuterated β-HTBZ. Significant covariates included CYP2D6 genotype, body weight, sex, and co-administration of paroxetine.

The simulated concentration profiles of total (α+β)-HTBZ from TBZ and total deuterated (α+β)-HTBZ from DTBZ were obtained by use of the PK models of α-HTBZ, β-HTBZ, deuterated α-HTBZ, and deuterated β-HTBZ, for the powder-in-capsule formulation and the tablet formulation, for comparison of the key PK parameters.

Shown in popPK report's Figure 7, Tables 8, 9 and 10 are the simulated concentration profiles and PK parameters (AUC, Cmax, Cmin, Tmax and half-life) for multiple dose administration of 25 mg TID (75 mg/day) TBZ and 21 mg BID (42 mg/day) DTBZ, for a typical fasted extensive metabolizer for fair cross comparison. The 42 mg/day dose of DTBZ is expected to produce similar AUC of total (Alpha+Beta)-HTBZ compared with the 75 mg/day TBZ. The calculation was done using mean profile from n=14 extensive metabolizers for powder DTBZ. For the other cases, the calculation was done using a typical subject profile.

Figure 7: Concentration profiles following multiple dose administration



TBZ=tetrabenazine; DTBZ=deutetrabenazine, hr=hour.

Table 8: PK parameters following multiple dose administration

Regimen	AUC_{0-24} (ng×hours/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)	tmax (hours)	$t_{½}$ (hours)
TBZ Powder 25 mg TID (75 mg/day)	989	91.4	22.9	0.75	5.58
TBZ Tablet 25 mg TID (75 mg/day)	985	90.9	23.0	1.00	5.57
DTBZ Powder 21 mg BID (42 mg/day)	778	68.9	14.9	1.44	6.60
DTBZ Tablet 21 mg BID (42 mg/day)	845	48.9	22.9	2.60	8.50

Source: PMXM-2025-21 Table 8.
AUC_{0-24}=area under the plasma drug concentration-time curve for a dosing interval of 24 hours; BID=twice daily; C_{max}=maximum observed plasma drug concentration; C_{trough}=concentration reached immediately before the next dose interval starts; DTBZ=deutetrabenazine; HTBZ=dihydrotetrabenazine (deuterated for DTBZ); PK=pharmocokinetic; $t_{½}$=elimination half-life; TBZ=tetrabenazine; TID=thrice daily; tmax=time to maximum observed plasma concentration.
Note: Based on extensive metabolisers under fasted conditions. Also, poor metabolizers are in general very few (e.g., 5.3% in the C-18 study).

Table 9: Comparison of PK parameters for powder DTBZ versus powder TBZ following multiple dose administration

Regimen	AUC[a] (ng·hr/mL)	Cmax (ng/mL)	Ctrough (ng/mL)	Tmax (hr)	Thalf (hr)
TBZ Powder 25 mg TID (75 mg/day)	1	1	1	1	1
TBZ Tablet 25 mg TID (75 mg/day)	NA	NA	NA	NA	NA
DTBZ Powder 21 mg BID (42 mg/day)	1.40	0.897	0.775	1.92	1.18
DTBZ Tablet 21 mg BID (42 mg/day)	NA	NA	NA	NA	NA

[a] AUC(0-24hr)
TBZ=tetrabenazine; DTBZ=deutetrabenazine; hr=hour; NA=not applicable; NR=not relevant.

Table 10: Comparison of PK parameters for tablet DTBZ versus powder DTBZ following multiple dose administration

Regimen	AUC[a] (ng·hr/mL)	Cmax (ng/mL)	Ctrough (ng/mL)	Tmax (hr)	Thalf (hr)
TBZ Powder 25 mg TID (75 mg/day)	NA	NA	NA	NA	NA
TBZ Tablet 25 mg TID (75 mg/day)	NA	NA	NA	NA	NA
DTBZ Powder 21 mg BID (42 mg/day)	1	1	1	1	1
DTBZ Tablet 21 mg BID (42 mg/day)	1.09	0.710	1.54	1.81	1.29

[a] AUC(0-24hr)
TBZ=tetrabenazine; DTBZ=deutetrabenazine; hr=hour; NA=not applicable; NR=not relevant.

According to modelling analysis results, steady state concentration profiles and PK parameters show similar trends as was observed from the single dose simulation.

Compared with TBZ powder PK, DTBZ powder PK demonstrates (i.e., effect of deuteration) 1.4x AUC, 1.9x Tmax, and 1.2x terminal half-life. The difference in AUC between TBZ and DTBZ compared with single dose simulation, if any, is due to the separately developed powder DTBZ models (i.e., in this work using CTP-06 study data only) and tablet DTBZ models (i.e., in PMX-20-14 using 14 study data, not including CTP-06 study).

As for the comparison between powder and tablet formulations of DTBZ (i.e., effect of formulation), tablet formulation PK shows 1.1x AUC, 0.71x Cmax, 1.5x Ctrough, 1.8x Tmax and 1.3x half-life.

The applicant's conclusions are the following: the modelling analysis results combined with simulations using other models (i.e., powder and tablet PK models of TBZ, tablet PK models of DTBZ) provide valuable insight on the PK characteristics of TBZ versus DTBZ due to deuteration effect and of powder formulation versus table formulation, which is confirmatory as well as definitive. However, the applicant acknowledges also model limitations: the PopPK models of powder formulation DTBZ were constructed using limited amount of data (i.e., only 21 healthy subject treated with 15 mg powder-in-capsule formulation single-dose from AUS-SD-809-CTP-06 study), this limitation had an impact on covariates analysis, inter alia, some covariate sub-groups might not have been sufficient to produce robust and definitive parameter estimates. There were challenges in fitting the PK models to the only one study data leading to, e.g. negative estimate of allometric exponent for CL, though with large RSE, and extremely small RSE for BSV, to name a few. Though modelling of one study data with limitations, the prediction matched the observed data.

Substantially Better Tolerability of DTBZ Versus TBZ Based on a Robust Indirect Comparison of Safety Data from Clinical Trial Evidence (applicant's position)

The applicant concludes that based on the different PK profiles resulting from different half-lives of TBZ vs DTBZ, it can plausibly be predicted that following titration to optimal dose, the achieved relatively stable plasma concentrations of DTBZ lead less frequently to those adverse drug reactions that can be regarded as consequence of exaggerated VMAT2 inhibition.

Teva maintains its position that the better tolerability of DTBZ compared to TBZ was robustly demonstrated following indirect comparison of the 2 pivotal clinical trials, First-HD and TETRA-HD.

An indirect treatment comparison of the tolerability of DTBZ and TBZ, based on 2 similarly designed, placebo-controlled Phase 3 trials in Huntington's disease (HD) associated chorea, First-HD for DTBZ and TETRA-HD for TBZ, was performed. Given that the mechanism of action of DTBZ does not differ between patients with tardive dyskinesia (TD) and those with HD-associated chorea, data from HD trials are considered relevant for assessing tolerability. Additionally, a direct comparison of DTBZ and TBZ for the treatment of TD is not feasible due to the limited evidence supporting TBZ, which includes a lack of randomised, placebo-controlled trials, variability in dosing and patient selection, absence of standardised outcome measures, and a predominance of open-label or retrospective studies.

The comparability of the 2 pivotal clinical trials, First-HD and TETRA-HD, is supported by multiple factors demonstrating their similarity with respect to patient population, baseline disease characteristic, trial design, and study sites. It is further shown that similar rates of AEs in the placebo arms of the trials further support the indirect treatment comparison between DTBZ and TBZ.

In the table below an exploratory side-by-side comparison between the active arms of the 2 trials shows substantially higher AE rates for TBZ than for DTBZ.

Table 8: AE rates in DTBZ (First-HD) and TBZ (TETRA-HD) based on unadjusted data

Parameter	AE Rates (%)		P-value (Active Arms)
	First-HD DTBZ (n=45)	TETRA-HD TBZ (n=54)	
Any AE	60.0	90.7	<0.001
Moderate to severe AE	22.2	68.5	<0.001
Discontinuation due to AE	2.2	9.3	0.144
Dose reduction due to AE	6.7	44.4	<0.001
Dose reduction/suspension due to AE	8.9	44.4	<0.001

Source: Claassen et al 2017 (Table 2).
AE=adverse event, DTBZ=deutetrabenazine, TBZ=tetrabenazine.

Unadjusted rates of the most common specific AEs reported in the 2 trials, including VMAT2 inhibition-related AEs include depression, anxiety, somnolence, parkinsonism, and akathisia, sorted by rates in the TBZ arm are shown in Table 9.

Table 9: Unadjusted rates of the most common specific AEs that occurred in First-HD and Tetra-HD

Percentage of Patients Affected				
AE, MedDRA PT	**First-HD (%)**		**TETRA-HD (%)**	
	DTBZ (n=45)	**Placebo (n=45)**	**TBZ (n=54)**	**Placebo (n=30)**
Drowsiness, somnolence	11.1	4.4	31.5	3.3
Insomnia	6.7	4.4	25.9	0.0
Fatigue	6.7	4.4	22.2	13.3
Akathisia	2.2	2.2	18.5	0.0
Fall	4.4	8.9	16.7	13.3
Agitation	2.2	0.0	14.8	0.0
Anxiety	2.2	2.2	14.8	3.3
Depression	2.2	6.7	14.8	0.0
Depression, agitated depression	4.4	6.7	14.8	0.0
Parkinsonism	0.0	0.0	14.8	0.0
Nausea	2.2	4.4	13.0	6.7
Coughing	0.0	0.0	7.4	10.0
Diarrhoea	8.9	0.0	7.4	10.0
Vomiting	0.0	6.7	5.6	3.3

Source: Claassen et al 2017 (Table 2)
AE=adverse event; DTBZ=deutetrabenazine; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; TBZ=tetrabenazine.
Notes: Specific AEs occurring in >10% of patients

A matching-adjusted indirect comparison (MAIC) is presented that uses propensity score weighting to adjust for differences in baseline factors between the 2 trials. The analysis used **patient-level data from First-HD and aggregate data from TETRA-HD** to conduct a MAIC comparison of AEs.

Matching adjustment was separately performed, by matching DTBZ subjects treated in First-HD trial with corresponding TBZ-treated subjects summary data from the TETRA-HD trial, and similarly matching the placebo subjects from the 2 respective studies, for up to 3 different baseline characteristics between the 2 trials; **age, Total Functional Capacity (TFC) score, and Total Maximal Chorea (TMC) score.** These variables were considered most clinically relevant for adjustment, where advancing age, reduced TFC, and increased TMC may portend a more advanced disease with an increased likelihood of developing certain AEs. After weighting based on those 3 baseline characteristics, most of the other recorded baseline characteristics were comparable (nominal p-value >0.05) between the 2 trials. The risk of chance findings is ruled out by the following considerations, which will be fully presented below:

- The magnitudes of the observed and calculated treatment differences are consistent regardless of propensity score matching (ie, matching for none, all, or any subset of the 3 factors).
- The likelihood of chance findings is quantitatively assessed by the calculation of E-values. The resulting E-values are of a magnitude that rule out the plausibility of a chance finding as an explanation for the observed results.

After adjustment, the only 2 baseline characteristics that were nominally statistically significantly different between trials were Caucasian % and Epworth Sleepiness scale (ESS). The Caucasian % factor (p=0.04) was virtually unchanged from the unadjusted data (DTBZ arm unchanged at 100%, placebo arm changed from 84.4% to 80%). The Epworth Sleepiness scale (p=0.001) mean increased in the DTBZ arm and decreased in the placebo arm, which would have the effect of inflating the apparent relative rate of sleepiness-related AEs in the DTBZ arm. The remaining (non-significant) baseline factors were in close balance and could not have appreciably affected the calculated treatment differences in AE rates.

The potential impact of an unmeasured confounding baseline characteristic on safety/tolerability outcomes was assessed by estimating E-values.

The ESS in this MAIC analysis (12.6 for DTBZ arm and 30.1 for placebo) is somewhat reduced, as expected when applying weighting to improve comparability between trials. A lower ESS increases variance and widens confidence intervals, reflecting appropriate adjustment for reduced precision. Despite this, the treatment difference for tolerability remains highly statistically significant, demonstrating that the effect is robust and the analysis fully accounts for the smaller ESS.

For both the active arm and the placebo arm, the weights are mostly clustered below 2, with very few outliers. As a sensitivity analysis, the indirect treatment comparisons were repeated with the outliers removed, yielding similar results, confirming the robustness of the comparisons.

In addition, sensitivity analyses were performed with adjustments for all possible subsets of those baseline characteristics (age, TFC score, and TMC) to test the robustness of the findings. Results and conclusions were consistent regardless of the combinations of factors that were adjusted.

An additional sensitivity analysis, truncated MAIC, was performed that excluded the patients with outlying weights but otherwise followed the same procedure as the original analysis. The resulting ESS values were relatively high, and distribution of weights were more clustered around the value of 1, indicating more equal contributions of First-HD patients in the comparisons.

Categories of AEs that occurred during the titration and maintenance periods are summarised below in the table below.

Table 11: AE Rates for phase 3 trials First-HD (DTBZ) and TETRA-HD (TBZ), propensity score adjusted data

Parameter	AE Rates (%)		P-value (Active Arms)
	First-HD DTBZ (n=45)	TETRA-HD TBZ (n=54)	
Any AE	41.2	90.7	<0.001
Moderate to severe AE	15.7	68.5	<0.001
Discontinuation due to AE	0.6	9.3	0.030
Dose reduction due to AE	6.3	44.4	<0.001
Dose reduction/suspension due to AE	6.8	44.4	<0.001

Source: Claassen et al 2017 (Table 2).
AE=adverse event; DTBZ=deutetrabenazine; TBZ=tetrabenazine.

To fully account for any differences in AE rates in the placebo arms of the 2 trials, Bucher's method for indirect treatment comparison was used to placebo-adjust the data for the active arms within each trial before comparing active arms between trials. This was done using both matching-adjusted and unadjusted data. Using this method, summary risk differences between DTBZ and TBZ were calculated.

Table 12: Placebo-adjusted risk differences in AE rates, Butcher's method on propensity score Adjusted data

Parameter	DTBZ vs TBZ (% difference)	95% CI	P-value
Any AE	-35.3	-72.4 to 1.8	0.063
Moderate to severe AE	-46.4	-79.4 to -13.3	0.006
Discontinuation due to AE	-10.4	-20.3 to -0.4	0.041
Dose reduction due to AE	-40.5	-62.0 to -19.0	<0.001
Dose reduction/suspension due to AE	-41.6	-63.9 to -19.3	<0.001

Source: Claassen et al 2017 (Table 3).
AE=adverse event; CI=confidence interval; DTBZ=deutetrabenazine; TBZ=tetrabenazine.

Relative to TBZ, DTBZ was also associated with a lower frequency of the following neuropsychiatric AEs, as shown in the Table below.

Table 14: Relative difference in risk of AEs for DTBZ (Phase 3 trial FIRST-HD) versus TBZ (Phase 3 trial TETRA-HD), propensity score adjusted data

Adverse Event, MedDRA PT	Difference in Risk in DTBZ vs TBZ by Bucher's Method	P-value
Insomnia	-24.3%	0.004
Drowsiness, somnolence	-22.9%	0.042
Depression	-20.8%	0.002
Depression, agitated depression	-20.2%	0.004
Akathisia	-18.9%	0.005
Parkinsonism	-14.8%	0.002
Agitation	-14.2%	0.007

Source: Claassen et al 2017 (Table 3).
AE=adverse event; DTBZ=deutetrabenazine; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; TBZ=tetrabenazine.

As a sensitivity analysis, the robustness of the conclusions to any artifacts of propensity score weighting is confirmed below by the version of the comparisons without propensity score adjustment and for individual AEs. The results again demonstrate that, relative to TBZ, DTBZ was associated with significantly lower placebo-adjusted rates of any AEs, moderate to severe AEs, and discontinuations and dose reductions/suspensions due to AEs.

The analysis results above provide compelling evidence for substantially better tolerability of DTBZ vs TBZ using robust statistical methodology based on all measured baseline data in First-HD and TETRA-HD.

Finally, to quantify the potential impact of unmeasured confounders, E-values were calculated on the propensity score adjusted event rates from First-HD and TETRA-HD to further quantify the potential impact of any unmeasured confounders. The E-value quantifies, on the risk ratio scale, the minimum strength of association that an unmeasured confounder would need to simultaneously have with both the treatment and the outcome to account for an observed treatment-outcome association, after adjusting for measured confounders. It will be shown that, given the similar trial designs and populations, and the exceptional magnitude of E-values on both adjusted and unadjusted data, it is not plausible that unmeasured confounding explains the observed AE rate differences. Large observed E-values with respect to the corresponding risk values thus indicate the implausibility that unmeasured confounding explains the observed AE rate differences.

Table 17: E-values calculated on the propensity score adjusted event rates from First-HD and TETRA-HD (Propensity Score Adjusted Data)

Adverse Event, MedDRA PT	DTBZ Rate	TBZ Rate	Risk Difference	Risk Ratio	E-value For Direction Reversal
Drowsiness, somnolence	8.9	31.5	-22.6	3.5	6.5
Insomnia	3.9	25.9	-22.0	6.6	12.7
Akathisia	1.4	18.5	-17.1	13.2	25.9
Agitation	0.6	14.8	-14.2	24.7	48.9
Depression	0.2	14.8	-14.6	74.0	147.5
Depression, agitated depression	0.8	14.8	-14.0	18.5	36.5
Parkinsonism	0.1	14.8	-14.7	148.0	295.5

Source: SD-809-EU-MAA Day 180 Oral Explanation Table 3.
AE=adverse event; DTBZ=deutetrabenazine; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; TBZ=tetrabenazine.

As a sensitivity analysis, E-values were also calculated based on the unadjusted data (see table below).

Table 18: Large E-values indicate the implausibility that unmeasured confounding explains the observed AE Rate difference (Unadjusted data)

Adverse Event, MedDRA PT	DTBZ Rate	TBZ Rate	Risk Difference	Risk Ratio	E-value For Direction Reversal
Drowsiness, somnolence	11.1	31.5	-20.4	2.8	5.0
Insomnia	6.7	25.9	-19.2	3.9	7.3
Akathisia	2.2	18.5	-16.3	8.4	16.3
Agitation	2.2	14.8	-12.6	6.7	12.9
Depression	2.2	14.8	-12.6	6.7	12.9
Depression, agitated depression	4.4	14.8	-10.4	3.4	6.3
Parkinsonism	0.1	14.8	-14.7	148.0	295.5

Source: SD-809-EU-MAA Day 180 Oral Explanation Table 4.
AE=adverse event; DTBZ=deutetrabenazine; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term;TBZ=tetrabenazine.

Given the similar trial designs and populations, and the exceptional magnitude of E-values on both adjusted and unadjusted data, it is not plausible that unmeasured confounding explains the observed differences in AE rates.
In summary, robust and well-accepted statistical methodology was used to demonstrate substantially better safety and tolerability of DTBZ vs TBZ. Specifically:

- Data from the randomised, placebo-controlled, Phase 3 clinical trials, First-HD and TETRA-HD, were used for an indirect treatment comparison in safety between DTBZ and TBZ;

- Comparability of the 2 trials is supported by multiple factors demonstrating their similarity with respect to patient population, baseline disease characteristic, trial design, study sites, and AE rates in the placebo groups of both studies;

- Differences in baseline characteristics between the trials were systematically adjusted using propensity score matching;

- Bucher's method was used to produce summary risk differences accounting for any differences between the 2 trials in placebo AE rates;

- Multiple sensitivity analyses were performed and presented on the propensity score matching, all confirming the robustness of the results and conclusions;

- Calculated E-values indicated the implausibility that unmeasured confounding could explain the observed AE rate differences;

- All analyses consistently demonstrated substantially better safety and tolerability of DTBZ vs TBZ, with reduced AE rates linked to VMAT2 inhibition and hence expected to be impacted by the difference in PK profiles (see Section 2.2.2.5);

- Calculated E-values indicated the implausibility that unmeasured confounding could explain the observed AE rate differences.

These results provide compelling evidence of a clinically relevant difference in the safety profile of DTBZ compared to TBZ, fulfilling the clinical criterion for DTBZ to be classified as a NAS under the second indent of the NAS definition.

Improved QT Interval Corrected for Heart Rate Using Fridericia's Correction (QTcF) Safety of DTBZ Versus TBZ

The MAH maintains its position that the improved PK profile of DTBZ compared to TBZ results in an improved PD profile with regard to QTcF, which also contributes to an improved safety of DTBZ compared to TBZ.

In Trial SD-809-C-21 (hereafter referred to as Trial C-21), a randomised, double-blind, placebo- and positive-controlled, 6-period, crossover study, the effects of DTBZ (matrix-based gastro-erosional formulations tablets, 12 mg and 24 mg) on cardiac repolarisation were evaluated. The analysis consisted of placebo-adjusted, time-matched change from baseline in the QTc interval. Assay sensitivity was verified with moxifloxacin as the positive control. In addition, the effects of TBZ on cardiac repolarisation were also assessed at a dose (50 mg) expected to provide comparable total exposure to active metabolites to 24 mg DTBZ. The results at doses that yield similar AUC exposure (24 mg DTBZ vs 50 mg TBZ) indicate less impact of DTBZ compared to TBZ on QTc prolongation (Table 20).

Table 20: *Maximal placebo-adjusted change from baseline in QTcF (Trial C-21)*

Parameter	DTBZ 12 mg (N=45)	DTBZ 24 mg (N=44)	TBZ 50 mg (N=46)	Moxifloxacin 400 mg (N=47)
Placebo-adjusted Change from Baseline (msec)	2.8	4.5	7.6	14.0
90% 2-sided CI	0.7, 4.8	2.4, 6.5	5.6, 9.5	11.9, 16.0

Source: SD-809-C-21 CSR Table 16.
CI=confidence interval; CSR=clinical study report; DTBZ=deutetrabenazine; QTcF=QT interval corrected for heart rate using Fridericia's correction; TBZ=tetrabenazine.
Notes: The placebo-adjusted change from baseline (ΔΔQTcF) is the difference between the least squares mean change from baseline for the active drug and placebo. DTBZ was compared with the DTBZ placebo (administered under fed conditions), and TBZ was compared with the TBZ placebo (administered under fasted conditions). The maximal ΔΔQTcF was observed at Hour 8 for DTBZ and at Hour 3 for TBZ. The upper limit of the 95% 1-sided confidence interval is the upper limit of the 90% 2-sided confidence interval.

At the maximum recommended dose of 48 mg, DTBZ and its deuterated active metabolites do not prolong the QT interval to any clinically relevant extent. An exposure-response analysis on QTc prolongation, using data from a trial conducted at single doses up to 72 mg in extensive or intermediate and poor CYP2D6 metabolisers, demonstrated that a clinically relevant effect on QTcF

(<10 ms) can be excluded following daily doses of 48 mg of DTBZ at steady state in both CYP2D6 extensive and poor metabolisers (Trial TV50717-SAD-10132 CSR Section 13.2).

However, as can be observed for TBZ at doses of 50 mg, the 90% 2-sided CI for QTcF was 5.6-9.5 msec. This suggests a potential for increased QTc prolongation risk, particularly in poor CYP2D6 metabolisers or with concomitant administration of CYP2D6 inhibitors. Administration of TBZ with CYP2D6 inhibitors or in poor metabolisers may result in patients administered with TBZ at even therapeutically relevant doses to exceed the 10 msec threshold.

Overall Conclusion of assessment under Indent 2

DTBZ's greater metabolic stability and consequently improved intrinsic PK properties lead to reduced clearance, reduced dosing frequency, more stable plasma concentrations, and improved safety and tolerability. In combination, this means that DTBZ and TBZ differ significantly in properties with regard to safety. This fulfils the clinical criterion for DTBZ to be classified as NAS under the second indent of the NAS definition.

5.5. CHMP position on NAS status claim under indent 2

Indent 2 of Annex 1 of chapter 1 of volume 2A of the European Commission's Notice to applicants (NtA), on the procedures for marketing authorisation, defines a new active substance as including:

> 'an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised in a medicinal product for human use in the European Union but differing significantly in properties with regard to safety and/or efficacy from that chemical substance previously authorised.

The MAH reaffirms its claim that DTBZ qualifies as a NAS under indent 2 of the specified definition. The argumentations in support of its position are summarised in the following four points:

1. DTBZ differs significantly from TBZ with regards to PK properties;

2. Extended Half-life of DTBZ is Attributed to Its Intrinsic Properties and is Independent of Formulation;

3. Substantially Better Tolerability of DTBZ Versus TBZ Based on a Robust Indirect Comparison of Safety Data from Clinical Trial Evidence;

4. Improved QT Interval Corrected for Heart Rate Using Fridericia's Correction (QTcF) Safety of DTBZ Versus TBZ.

1. DTBZ differs significantly from TBZ with regards to PK properties, and

2. Extended Half-life of DTBZ is Attributed to Its Intrinsic Properties and is Independent of Formulation

To support its position, the MAH submitted the results of two Phase 1 clinical trials (CTP-06, CTP-07) in healthy subjects and a PopPK model simulation. Within such trials, multiple dosages of several immediate-release (IR) and extended-release (ER) formulations have been used and directly/indirectly compared to each other. However, for the sake of clarity, the DTBZ formulation to be marketed in the EU (i.e. osmotic prolonged-release formulation/tablet for one daily dosing) was used neither in the two above mentioned studies nor in the model analysis.

Of note, considering the high degree of metabolism of TBZ and DTBZ and resulting relatively low exposures to these parent drugs, exposure to the active metabolites (deuterated) α-HTBZ and (deuterated) β-HTBZ metabolites, and not parent TBZ and DTBZ, is critical for efficacy and safety of TBZ and DTBZ. PK comparisons are therefore solely based on these metabolites.

CTP-06 clinical trial allows a direct comparison between DTBZ and TBZ since both substances were administered as equal single dose through the same powder-in-capsule formulation (IR). Based on the

results, it is acknowledged that the differences in mean AUC and mean plasma half-life of the deuterated metabolites (respectively higher and longer after DTBZ administration in respect to TBZ) could result from the slower metabolism of DTBZ compared to that of TBZ. Tmax resulted to be slightly increased (i.e. 1.50 vs 1.00 hrs). On the other hand, Cmax was found to be almost comparable between products, confirming that absorption is not significantly influenced by the presence of deuterated functional groups (e.g. in extensive metabolisers Cmax for DTBZ was 67.9 ng/mL vs 60.1 ng/mL for TBZ). Results show that the presence of deuterium could be a plausible factor responsible for the observed PK profiles differences for the drug metabolism due to increased strength of the carbon-deuterium bond, which is more resistant to enzymatic modification by CYP2D6.

In the CTP-07 clinical trial single (7.5 mg, 15 mg and 22.5 mg) and multiple ascending doses (7.5 mg BID, 15 mg BID and 22.5 mg BID) of DTBZ ER matrix-based gastro-erosional tablets (responsible for a controlled release over approximately 3-4 hours) were compared to 25 mg dose of TBZ IR tablets. Dissolution data showed that matrix-based gastro-erosional tablets reflects a controlled release over approximately 3-4 hours under standard test conditions, while for IR dosage forms active substance release (dissolved) was greater than 80% within 30 minutes.

At an indirect comparison of the results of CTP-06 and CTP-07 studies in terms of PK parameters of total active metabolites, i.e. (α + β)-HTBZ, the following is found:

- In the whole PK population, when comparing 25 mg DTBZ powder-in-capsule data from CTP-06 study versus DTBZ 22.5 mg extended-release matrix CTP-07 (part 2), the PK profile seems to be almost comparable, i.e. DTBZ as capsule Cmax 74.6 ng/mL vs DTBZ as matrix Cmax 67.5 ng/mL; DTBZ as capsule AUC 542 ng*h/mL vs DTBZ as matrix AUC 610 ng*h/mL.

- Focusing on extensive metabolisers data in fasted condition, when comparing 25 mg DTBZ powder-in-capsule data from CTP-06 study versus DTBZ 15 mg extended-release matrix CTP-07 (part 2), assuming dose-normalization to balance the different dosages used, a similar exposure profile for total (α + β)-HTBZ is confirmed, particularly in terms of AUC and t½. However, for DTBZ administered as extended-release matrix, a non dose-proportional reduction in Cmax and an increase in tmax was found (i.e. DTBZ as capsule Cmax 67.9 ng/mL vs DTBZ as matrix Cmax 22.4 ng/mL; DTBZ as capsule tmax 1.50 hrs vs DTBZ as matrix tmax 2.27 hrs). Also, the half-life appears to be longer for the ER tablet given in CTP-07 (i.e. 9.12 hrs) than for the IR formulation in CTP-06 (i.e. 7.61).

Results of these two comparisons may lead to divergent interpretations: the first suggesting that in the whole PK population, the PK profile remains nearly the same independently from the formulation; the second indicating that, in the extensive metabolisers, while the formulation change does not significantly influence AUC, it does affect the peak concentration and the time required to reach it. However, considering the limits of the indirect comparison, the results derived from the comparison of a more homogeneous population, namely extensive metabolisers in fasted condition, could be considered more reliable compared to data observed in the whole PK population.

The impact of the different formulations (i.e. IR vs ER) on absorption is further corroborated by results of the PopPK model simulating concentration profiles and PK parameters for multiple dose administration of 25 mg TID (75 mg/day) TBZ and 21 mg BID (42 mg/day) DTBZ, for a typical fasted extensive metaboliser. The 42 mg/day dose of DTBZ is expected to produce similar AUC of total (α+β)-HTBZ compared with the 75 mg/day TBZ. The calculation was done using mean profile from n=14 extensive metabolisers for powder DTBZ (please, refer to table 8 for PK parameters statistics). Although the small sample size (n=21), together with all the several limitations underlined by the applicant itself, the model shows a difference in the PK profile between IR encapsulated powder and ER matrix formulations for DTBZ in fasted extensive metabolisers and not for TBZ (please, refer to PopPK report Figure 7). Namely, absorption profile in terms of Cmax (approximately 30% lower for the DTBZ ER matrix formulation as compared to the DTBZ IR encapsulated powder) and tmax for DTBZ administered as IR encapsulated

powder vs ER matrix tablet were represented as two different curves suggesting a formulation influence. On the contrary, for TBZ administered as capsules and tablets (both IR) the two profiles overlap, confirming no formulation's impact on its PK profile.

Moreover, in the comparison of simulated PK parameters (to note, values provided without variability estimate) following multiple dose administrations the following is observed:

- An increased ratio for AUC (1.40 - see Table 3 page 288) while Cmax value (ratio 0.89 – see Table 3 page 288) seems comparable for IR encapsulated-powder DTBZ vs IR encapsulated-powder TBZ (deuterium effect);

- Similar AUC values (ratio 1.09 – see Table 4 page 288) and a more pronounced decreased Cmax ratio (0.71 – see Table 4 page 288), when comparing ER matrix tablet DTBZ vs IR encapsulated-powder DTBZ (formulation effect).

Considering all the above, an influence of deuterium can be observed on AUC with no impact on Cmax, while the different formulations lead to similar AUC with a decrement in Cmax value.

In conclusion, based on the evidence provided by the applicant, it can be agreed that the presence of deuterium could be a plausible factor responsible for the metabolism/excretion change in terms of AUC and plasma half-life. Nevertheless, at least considering data in extensive metabolisers in fasting condition, a potential impact of the pharmaceutical formulation on the DTBZ PK profile, to a larger extent than the impact of deuteration, is considered plausible, especially in terms of Cmax and tmax absorption parameters.

All the above, in the lack of compelling data from a direct comparison between different DTBZ formulations administered at the same dosage and based on the evidence provided by the applicant, it is not possible to clearly characterise and quantify the impact of the deuteration, versus the pharmaceutical formulation, on the PK profile. Moreover, it should be noted that in line with the provisions of the Reflection paper EMA/651649/2010, changes to pharmacokinetics alone, not altering elements as outlined in section 2.3.1 of the said paper, are unlikely to be sufficient for justifying NAS status

3. Substantially Better Tolerability of DTBZ Versus TBZ Based on a Robust Indirect Comparison of Safety Data from Clinical Trial Evidence

According to current legislation for NAS designation, a significant difference in properties with regard to safety and/or efficacy from the chemical substance previously authorised, is required. Though the decision is made on a case-by-case basis, the preferred type of evidence required to show significant differences justifying NAS status is clinical head-to-head comparison of active substances, unless compelling evidence can be derived from pre-clinical and/or clinical data, including pharmacologic or pharmacodynamic studies (EMA/651649/2010).

A double-blinded head-to-head comparison between DTBZ and TBZ to compare safety profiles has not been performed in the context of tardive dyskinesia (the target indication of Austedo) or any other similar indication. To overcome this important gap in the evidence, the Applicant proposed extrapolation between studies by using a retrospective indirect comparison of DTBZ and TBZ published in an article by Claassen et al. (2017). The indirect treatment comparison included previously reported clinical data coming from two Phase 3, 12-week, placebo-controlled, randomised clinical trials (FIRST-HD, n=90) and TETRA-HD, n=84) that, respectively, evaluated DTBZ vs TBZ for treatment of Huntington disease-associated chorea.

A series of well-established statistical methods were applied to demonstrate that lower rates of Adverse events (AEs) were found for DTBZ as compared to TBZ and to highlight a better tolerability:

- A matching-adjusted indirect comparison (MAIC) used propensity score to adjust for differences in baseline factors between the 2 trial populations.

- Bucher's method for indirect treatment comparison was used to calculate a summary risk difference of the 2 treatments. A placebo-adjustment data was performed within each trial before comparing active arms between trials. This was done using both matching-adjusted and unadjusted data.

- Sensitivity analyses were conducted using different subsets of variables for propensity score matching and alternate methods for performing the matching.

- Finally, E-values were calculated on both adjusted and unadjusted data to quantify the potential impact of unmeasured confounders.

The results of the indirect comparative analyses of the two trials show that all AEs rates (any AE, moderate to severe AE, Discontinuation due to AE, dose reduction due to AE, and dose reduction/suspension due to AE) were lower in the First-HD DTBZ study when compared to the TETRA-HD TBZ study at unadjusted and propensity score-adjusted analyses. Additionally, relative risk difference between DTBZ and TBZ at Bucher's method on adjusted propensity score data confirmed reduced rates in DTBZ for overall AEs and 7 neuropsychiatric AEs. Calculated E-values seem to rule out effect of unmeasured confounding variables.

The indirect comparison meta-analysis is crucial when direct evidence is lacking, but it relies on the assumption that the patient populations and trial designs across the separate studies are similar and that the evidence is consistent. In this regard, important considerations apply to the specific case that pertain to clinical and methodological aspects of the generated evidence in support of the claim:

1. As a general consideration, evaluating safety across therapeutic indications could lead to misrepresenting the true safety profile, because both the context of use and the patient characteristics may significantly influence the nature, frequency and reporting of adverse events (AEs). This aspect is strictly related to the well-described concept of individual susceptibility to AEs, which is known to be influenced by the underlying disease and drug-to-drug interactions, among other factors, which are seen as important factors hampering the generalizability from one indication to another. With specific reference to the extrapolability of results from Huntington chorea (HC) to tardive dyskinesia (TD), additional concerns are represented by the study duration of the trials considered in the indirect comparison; although recognising similarity in the mode of action of the concerned products between diseases, a 12-week evaluation in HC can hardly reflect the long-term effect of a treatment in an iatrogenic condition underlying variations in concomitant medications, which can modulate the toxicity profile of the concerned drug. Moreover, considering that the dose to be administrated is tailored to the efficacy goals and tolerability of individual patients, a dose-exposure relationship cannot be reported for DTBZ or TBZ, implying that response to treatment, and consequently dose ranges with the associated safety profile, could vary between indications. This is particularly noted for adverse events such as depression, agitation and nausea.

2. The comparability between trials is further weakened by the fact that different drug formulations were tested in the First-HD (DTBZ matrix-based gastro-erosional tablet) and TETRA-HD (TBZ immediate-release tablet) trials. This aspect introduces a bias in data interpretation due to the formulation-dependent difference in pharmacological profile between products, which could influence the observed safety profile. Therefore, the indirect trial comparison cannot be taken as definitive demonstration of a clinical advantage of DTBZ over TBZ that would be solely ascribed to the deuterated active substance.

3. In the presence of confounding, baseline covariates are related to outcomes. Propensity score matching entails forming matched sets of treated and untreated subjects who share a similar value of the propensity score. The most common implementation of propensity score matching is one-to-one or pair matching, in which pairs of treated and untreated subjects are formed, such that matched subjects

have similar values of the propensity score (*Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011*). However, in the study by Claasen et al. raw patient data coming from the FIRST-HD were incorporated into the analysis, whereas only aggregated data from the TETRA-HD trial were included, limiting the accuracy and reliability of the analysis. In addition, multiplicity control adjustment is missing, inflating the type 1 error rate. Moreover, subsets of variables significantly impact propensity scores by altering the probability. The most important principle is to include all baseline covariates that are associated with both the treatment assignment and the outcome. In general, statistical models are applied to select variables based on their significant correlations with the outcome. Instead, only three variables deemed clinically significant (age, TFC score and TMC score) were included in the statistical model for propensity score probabilities, with no supporting evidence coming specifically from the study.

4. Discrepancies in apparently statistically significant findings emerged when evaluating the treatment comparison by odds ratios instead of risk differences; indeed, the odds ratio analysis did not confirm the Claasen's report on risk differences (*Rodrigues FB et al. Meta-research metrics matter: letter regarding article "indirect tolerability comparison of Deutetrabenazine and Tetrabenazine for Huntington disease". Journal of Clinical Movement Disorders 2017*) due to the well-described statistical phenomenon called rank reversal. It stems from the fact that different measures are affected differently by dissimilar baseline risks. The rank reversal phenomenon in indirect comparison refers to the situation where the relative superiority of treatments changes depending on the choice of the statistical measure used (e.g. risk ratio, risk difference or odds ratio) for comparison, despite using the same data from indirect meta-analysis. This occurs because different measures are affected differently by variations in baseline risks, leading to different rankings of treatments and potentially inconsistent conclusions (*Norton EC et al. Rank reversal in indirect comparisons. Value Health. 2012*).

5. Bucher's model of indirect treatment comparisons was originally designed for odds ratios, but others have applied it to risk ratios and risk differences, with proper adjustment. Bucher's model is a method for performing adjusted indirect comparisons when direct head-to-head trials are unavailable, allowing for a comparison of two treatments by evaluating their separate effects against a comparator. However, the Bucher method is susceptible to bias if there are significant differences in important baseline characteristics between the trials.

6. An option to deal with unmeasured confounding in observational research is to use the E-value, a readily calculated and easily interpreted statistical tool that assesses the minimum strength of potential unmeasured confounding needed to explain away an effect. A higher E-value suggests greater robustness, indicating that a stronger unmeasured association is required to negate the observed effect; conversely, a low E-value implies that weak unmeasured confounding could potentially explain the findings. Although the E-value method is easy to implement and does not require assumptions to assess the minimum strength of unmeasured confounding needed to explain an association, its use in interpreting the results of observational studies is not widespread due to its limitations. A high E-value does not always rule out unmeasured confounding. For example, confounding by indication might strongly confound an association even when the E-value is high. Some unmeasured confounders (e.g., those with a low prevalence) that fulfil the requirements of the E-value might not explain the observed effect. Thus, the prevalence of a particular confounder should be considered carefully (*Gaster T. et al. Quantifying the impact of unmeasured confounding in observational studies with the E value. BMJ Med 2023*).

7. The effective sample size (ESS) is a descriptive statistic that can be used to accompany MAIC weighted statistical analysis. The ESS compares the variances of weighted (population-adjusted) and unweighted (unadjusted) estimates. The variance of weights used for matching refers to the variability in the calculated weights applied to control and treated units to balance them between trials. Higher variance indicates that a few control units receive very large weights, potentially leading to unreliable treatment

effect estimates. A higher (ESS) value (e.g., 70-80 of the original sample size) indicates that the matching procedure successfully preserved a larger portion of the original study population and maintained greater statistical power and reliability for the comparison (*Zhang L et al. Three new methodologies for calculating the effective sample size when performing population adjustment. BMC Med Res Methodol. 2024*). Notably, for the matching between the active arms of the 2 trials, the ESS was only 12.6, while for the placebo was 30.1, indicating low precision of the adjusted estimates.

In conclusion, while DTBZ in respect to TBZ appears to have a more favourable overall safety profile with lower frequency of certain neuropsychiatric AEs, the uncertainties deriving from the abovementioned limitations of the indirect comparison between products, as presented by the applicant, hamper the robustness of data and prevents any firm conclusion on the clinical relevance of the reported data in the sought indication. Therefore, the clinical evidence, as currently presented, cannot be deemed satisfactorily addressing the requirement for a compelling demonstration of clinical difference of DTBZ over TBZ that would be expected to justify a NAS claim under indent 2.

4. Improved QT Interval Corrected for Heart Rate Using Fridericia's Correction (QTcF) Safety of DTBZ Versus TBZ

The applicant's claim on the improved cardiotoxicity profile for the deuterated medicinal product is based upon results of Trial C-21, testing the effect of a single dose of DTBZ 12 mg and 24 mg versus TBZ 50 mg on the QTcF interval in healthy individuals with moxifloxacin 400 mg used as a positive control. The study could be considered satisfactorily addressing the requirement under ECH14 guidelines to evaluate the drug effect on cardiac repolarisation. Although recognising the reduced effect of DTBZ on QT prolongation in terms of maximal mean variations (ΔΔQTcF), that were below 5 msec for both doses compared to the 7.6 msec of TBZ, the study results show that, at all tested doses of the investigated products, including TBZ 50 mg, the upper bound of the 95% one-sided confidence interval (CI) excludes 10 ms, which is the CI threshold for regulatory concern. In addition, the overlapping 90% CIs on the effect (2.4, 6.5 vs 5.6, 9.5 for DTBZ 24 mg vs TBZ 50 mg) indicate that the impact on QT interval may not be considered significantly different between products. Moreover, results cannot exclude that at higher exposures as those achieved in the presence of intrinsic and extrinsic factors affecting drug metabolism, a clinically relevant effect can be exerted by DTBZ on the QT interval. The evidence provided by the exposure-response analysis on QTc prolongation, using data from a trial conducted at single doses up to 72 mg in extensive or intermediate and poor CYP2D6 metabolisers, are also inconclusive. It is unclear if the proposed concentration-response analysis covers the requirement for reaching at least twice the high clinical exposure achieved with the maximum therapeutic dose administered in the presence of factors with the largest effect on increasing Cmax,ss. (EMA/CHMP/ICH/415588/2020).

Similarly to TBZ, CYP2D6 is the main enzyme that metabolises the active metabolites of DTBZ into minor metabolites with reduced activity. Deuterated substances tend to be more resistant to CYP2D6 metabolism than non deuterated products. On the other side, in individuals lacking CYP2D6 function ('poor metabolizers'), exposure to active metabolites is estimated to be approximately 3- to 4-fold higher than in normal metabolizers when treated with the recommended standard doses of DTBZ (*Dean l. Deutetrabenazine Therapy and CYP2D6 Genotype. Medical Genetics Summaries. 2019*).

Consequently, it cannot be excluded that in CYP2D6 poor metabolizers or individuals who are taking a strong CYP2D6 inhibitor the concomitant administration of DTBZ is safer than TBZ due to lack of clinically relevant QT prolongation at the recommended posology. In any case, effects on the QT interval do not provide evidence of a drug pro-arrhythmic action but rather inform on the likelihood of proarrhythmic effects and serve as a guidance on the level of monitoring to be adopted as a risk minimization measure during the following drug development and/or clinical use. In the absence of a documented reduction of clinical events induced by DTBZ with respect to TBZ, establishing a safety advantage of DTBZ versus TBZ based on the different magnitude of effect on QT interval cannot be concluded.

Moreover, it is worth noting that DTBZ, unlike TBZ, was tested as a matrix-based gastro-erosional tablet in Trial C-21, thus introducing a bias in data interpretation due to the uncertain contribution of formulation-dependent differences in pharmacology between products to the observed pharmacodynamics. In keeping with this, the SmPC for Austedo reports statements and warnings regarding QTc prolongation: i.e. in section 4.2 a maximum daily dose of 36 mg of DTBZ in patients receiving strong CYP2D6 inhibitors or who are poor CYP2D6 metabolisers is recommended, and in section 4.4 warnings and precautions for use are provided.

Notably, the information included in the SmPC for Austedo does not substantially differ from what is provided for nationally authorised TBZ products, thus further supporting the conclusion that the described variation in QT interval effects does not translate into a change in contraindications and warnings or allow the product to be used in a wider patient population with a more attenuated safety concern than TBZ.

In summary, the applicant's conclusion on the improved cardiac safety profile of DTBZ compared to TBZ is not adequately substantiated. First, differences in drug formulation between products tested in the Thorough QT (TQT) study introduce a bias in data interpretation hampering definitive conclusions. Secondarily, the proposed exposure-response analysis does not exclude the risk of DTBZ-induced clinically relevant QTc prolongation in "poor metabolisers" and patients taking strong CYP2D6 inhibitors, so that the same applicant proposes relevant risk minimisation measures in Austedo SmPC at sections 4.2 and 4.4.

In any case, relying on a QT prolongation analysis in the absence of a demonstrated advantage in terms of clinical events, especially for borderline results, is a weak argumentation since TQT studies are not intended to provide direct evidence of drug arrhythmogenic effects but rather help in the definition of the likelihood of proarrhythmic effects. This latter remains a concern also for DTBZ to the point that the same warnings and precaution of use are reported in the SmPC for both products. Overall, the claimed improvement in cardiac tolerability of DTBZ versus TBZ cannot be considered adequately substantiated on clinical grounds.

Overall conclusions on NAS status claim under Indent 2

Under Directive 2001/83/EC, new active substance status is justified only where significant differences in safety and/or efficacy are demonstrated for the intended active substance relative to the reference active substance. For this reason, ideally, results coming from a clinical head-to-head comparison of DTBZ with TBZ - preferably in the same therapeutic indication - would have been the preferred source of evidence to demonstrate a clinically significant difference between the active substances. However, according to Reflection paper EMA/651649/2010 evaluation and decision should be made based on a case-by-case basis, and in cases where a head-to-head clinical study is not feasible, compelling evidence deriving from pre-clinical or other clinical data (i.e., PK/PD studies) mandated by significant changes in safety and/or efficacy properties is necessary.

The applicant argues that for DTBZ the changes in PK profile leading to lower doses (48 mg maximum vs 200 mg) and less frequent dosing (once daily vs. 2-3 times daily) in respect to TBZ are likely to translate into improved tolerability. To demonstrate a clinically significant different safety profile for DTBZ over TBZ an indirect comparison of the two medicinal products is proposed.

Based on the submitted data, it is recognised that deuteration has an impact on the PK metabolism and excretion of DTBZ versus TBZ. At the same time, it also appears that the different pharmaceutical formulations have an impact on the pharmacological profile through an impact on the drug absorption phase, therefore impacting on Cmax. Based on the data provided, it is considered that the lower metabolites C_{max} for DTBZ, as compared to TBZ, with metabolites AUC being comparable for both, is mainly the consequence of the ER formulation rather than the deuteration. Nevertheless, because

interpretation of data is hampered by extrapolation issues due to indirect comparisons and use of diverse formulations and dosage, results are not regarded as compelling.

It should be noted that, in Reflection paper EMA/651649/2010 a significant change to the dosing (e.g., lower dose or less-frequent dosing) is not considered by itself enough to justify NAS status. A clear demonstration that posology translates into a clinically meaningful safety and/or efficacy advantage is expected.

To support the claim that DTBZ significantly differs regarding safety compared to TBZ the MAH proposed an indirect comparison of studies conducted for the treatment of Huntington's disease chorea. In the article published by Claasen et al. an improved safety profile is found in the DTBZ study when compared to the TBZ study. However, inconsistency of findings is established in the article by Rodrigues et al. that - although based on the same data - showed different results. More in general, the safety extrapolation exercise lacks in generalisability between indications and entails several important clinical and methodological limitations in the trial comparison. Moreover, the impact of the difference in pharmaceutical formulation cannot be excluded.

The analysis of the cardiotoxicity also fails to establish a clinically relevant difference between DTBZ and TBZ as it relies on the evaluation of the magnitude of effect of drugs on the QT interval that is of ambiguous clinical interpretability in the absence of a demonstrated difference on cardiac events. The potential for a pro-arrhythmic effect remains a concern also for DTBZ, to the point that similar warnings and precautions of use are reported in the SmPC of the two products.

In conclusion, while it is recognised that deuteration has an impact on the PK metabolism and excretion of DTBZ compared to TBZ, it is also considered that the different pharmaceutical formulations have an impact on the pharmacological profile, due to their effect on absorption observed in terms of Cmax. The attenuation in drug fluctuation with DTBZ that is claimed by the applicant as responsible for improved safety compared to TBZ cannot be entirely ascribed to the deuterated substance but rather appears also an effect of the ER matrix formulation applied for DTBZ. This adds to the uncertainties of the clinical relevance of the observed differences in toxicity, which anyway were not considered significant, based on the data provided. Indeed, safety results are not regarded as compelling due to a number of limitations in clinical and methodological aspects regarding the proposed indirect comparison between studies and extrapolation between indications, as well as the analysis of cardiac toxicity. Overall, the evidence currently submitted are deemed insufficient to demonstrate that PK changes are solely attributable to the deuterated substance and in any case, it has not been demonstrated that the observed PK changes translate into a clinically meaningful safety difference of DTBZ over TBZ.

The NAS status for DTBZ under indent 2 is not agreed.

Point not resolved

5.6. CHMP Overall conclusion on the grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant in writing and during the oral explanation in front of the CHMP held on 15 October 2025.

Based on the review of available data on the active substance, the CHMP considers that deutetrabenazine is **not** to be qualified as a new active substance in itself.

Based on the review of data on the quality and clinical properties of the active substance, the CHMP considers that deutetrabenazine in comparison to tetrabenazine, previously authorised as a medicinal product in the European Union, is **not** to be qualified as a new active substance as insufficient evidence has been provided to demonstrate that it differs significantly in properties with regard to safety and/or efficacy from the previously authorised substance.

5.7. Other considerations in the assessment of the grounds for refusal of the NAS status

Within the scope of this re-examination procedure, the applicant submitted an updated Risk Management Plan (RMP) version 1.1 (dated 01 August 2025) and a revised PI. Besides an updated date of sign off and version, in RMP Part 1 Teva changed the proposal for additional monitoring in the EU from "No" to "Yes". Accordingly, this latter change was triggered by an update of the Product Information (PI) to include the reverted black triangle symbol and related text on the requirement of additional monitoring in the EU for a New Active Substance (NAS).

Based on the CHMP conclusion on the submitted grounds requesting re-examination of the Committee's opinion on the NAS status claim, and pursuant to Article 23(1) of Regulation No (EU) 726/2004, Austedo (deutetrabenazine) should **not** be included in the additional monitoring list as deutetrabenazine is not to be qualified as new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics, and the package leaflet accordingly, should not include the following symbol and statement(s):

SmPC

▼*This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.*

PL

▼*This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.*

5.8. Risk Management Plan

5.8.1. Safety concerns

Table 93 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

5.8.2. Pharmacovigilance plan

The CHMP, having considered data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product and to monitor the effectiveness of the risk minimisation measures (RMMs).

No additional pharmacovigilance activities are deemed necessary.

5.8.3. Risk minimisation measures

The CHMP is of the opinion that the applicant's proposed (routine) RMMs are sufficient to minimise the risks of the product in the agreed indication.

No additional RMMs are deemed necessary.

5.8.4. Conclusion on the RMP

The CHMP considered that the risk management plan version 1.2 is acceptable.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

5.9. Pharmacovigilance

5.9.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

5.9.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Based on the new indication of moderate to severe tardive dyskinesia, the CHMP agreed with the PRAC recommendation that a separate entry in the EURD list for Austedo is needed, as the PSUR cycle cannot follow the already existing entry for tetrabenazine. The requirements for submission of PSURs for this medicinal product are set out in Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The new EURD list entry uses the EURD PSUR data lock point (DLP) with 31 March (DLP for Austedo global PSUR cycle) to determine the forthcoming DLPs. The PSUR cycle for Austedo should follow a yearly cycle.

5.10. Product information

5.10.1. User consultation

Overall, the methodology of the user test was considered satisfactory and the results meet the success criteria for all questions posed. Therefore, the results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

5.10.2. Additional monitoring

As above detailed, pursuant to Article 23(1) of Regulation No (EU) 726/2004, Austedo (deutetrabenazine) is not included in the additional monitoring list as deutetrabenazine is not to be qualified as new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet do not include a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information.

6. Benefit-risk balance following re-examination

EMA note: the applicant's request for re-examination of the CHMP opinion dated 19 June 2025 was limited to the recommendation of the CHMP to refuse Teva NAS status claim. Therefore, with regard to

Austedo benefit-risk balance, the CHMP opinion of June 2025 (and the text in the following sections) is unchanged.

6.1. Therapeutic Context

6.1.1. Disease or condition

Tardive dyskinesia (TD) is a disabling, potentially irreversible, delayed onset, hyperkinetic movement disorder in which predisposed patients experience abnormal involuntary movements (dyskinesias), resulting from chronic or even episodic exposure to dopamine receptor antagonists (DRAs), such as antipsychotics and some antiemetics.

TD is generally not progressive even with continued antipsychotic treatment. It can persist for years after discontinuation of the causative agent, although some patients can experience partial or complete remission of symptoms a few years after discontinuation of the causative agent (Savitt and Jankovic 2018).

Dyskinesias are often bothersome and incapacitating. The impact of the movements is multifactorial, significantly affecting the patient's physical, psychological, social, and professional functioning and overall quality of life.

Moreover, TD affects how patients manage their underlying condition, which can interfere with effective treatment (Jain et al 2023). Thus, management of TD should not be based solely on the severity of movements, but also on the control of the underlying condition (Jackson et al 2021). To minimize TD, the approach of stopping the dopamine receptor antagonist (DRA) (e.g., an antipsychotic) carries the risk of worsened underlying disease (e.g., schizophrenia).

The risk of treatment-emergent TD with newer-generation antipsychotics is lower than with first-generation antipsychotics, in line with the observed global mean prevalence in adults of 30% for first-generation antipsychotics exposure versus 21% for second-generation antipsychotics exposure (Carbon et al 2017). Despite the decreased use of first-generation antipsychotics, the incidence of TD remains high in the antipsychotic-treated population.

6.1.2. Available therapies and unmet medical need

Vesicular monoamine transporter type 2 (VMAT2)-inhibitors are regarded as treatment options for TD.

Several products with similar mechanism of action (MoA) and efficacy have been marketed in the EU, none has (yet) been centrally approved, and their efficacy and tolerability are far from perfect, leading to insufficient treatment, significant AEs, such as depression or Parkinsonism, and interaction with the concomitant psychiatric medication. As such, there is an unmet medical need for new efficacious treatments with a favourable safety profile, including not compromising the stability or control of the underlying disorder.

Cessation or reduction of the DRA to the lowest efficacious dose for controlling the underlying condition, or switching to a different DRA (e.g., from first- to second-generation antipsychotic) is the first-line therapeutic approach in TD (Bhidayasiri et al 2018). However, these actions do not guarantee the resolution of TD and they risk compromising the stability of the underlying condition for which the DRA is being used.

Deutetrabenazine (DTBZ) aims at reducing bothersome involuntary movements caused by previous or concomitant treatment with DRA(s) and improve patient’s quality of life. The proposed therapeutic indication of this medicinal product is: treatment of moderate to severe tardive dyskinesia in adults.

6.1.3. Main clinical studies

Two pivotal trials, C-18 with best tolerated ascending dose, and C23 with fixed dose, have been conducted by the applicant. Study treatment maintenance duration was of 6 and 8 weeks, respectively. One long-term, open label extension study in tardive dyskinesia (C-20) and other supportive studies in Huntington's disease were also submitted.

6.2. Favourable effects

Deutetrabenazine showed a statistically significant and clinically meaningful improvement in the Abnormal Involuntary Movement Scale (AIMS) total score from baseline compared to placebo, as detailed thereafter.

The mean AIMS improvement at week 12 for study C18 was -1.6 for placebo and -3.0 for DTBZ, with a treatment effect of -1.4. Similarly, the mean AIMS improvement in study C23 was -1.4 for placebo and -3.3 for the 36 mg arm of DTBZ. The treatment effect did not reach the minimally clinically significant threshold of -2.0 points in the Abnormal Involuntary Movement Scale (AIMS), the identified minimally clinically important difference of 2 points (Stacy et al. 2019) with this primary efficacy tool.

Efficacy at 12 weeks: primary and key secondary endpoint

At week 12 of study C-18, the LS mean change in the total motor AIMS score (primary efficacy endpoint) in the mITT population (N=113) was -3.0 (SE 0.45) in the DTBZ group compared with -1.6 (SE 0.46) in the placebo group, the mean difference was -1.4 (95% CI: -2.6, -0.2, p=0.0188, a multiplicity-adjusted p value for difference from placebo, statistically significant).

In study C-23, the LS mean change in total motor AIMS score at week 12 (primary efficacy endpoint) in the mITT population (N=222) was-3.2 (SE 0.45) for the 24 mg/day arm and -3.3 (SE 0.42) in the DTBZ 36 mg/day group compared with -1.4 (SE 0.41) in the placebo group. The mean difference was -1.9 (95% CI: -3.09, -0.79, p=0.001, a multiplicity-adjusted p-value for difference from placebo, statistically significant) between placebo and DTBZ 36 mg/day group.

In study C-23, because of the hierarchical testing approach, the analysis based on the change in total motor AIMS score at week 12 for the DTBZ 24 mg/day group was exploratory. Nevertheless, the efficacy estimate with DTBZ 24 mg/day is of the same magnitude as with DTBZ 36 mg/day (mean difference -1.8; 95% CI -3.00, -0.63, p=0.003). This supports the claim that the two doses of 24 mg/day and 36 mg/day are efficacious.

Long term efficacy

Consistent improvements across efficacy assessments (AIMS and CGIC - Clinical Global Impression of Change) were observed in study C-20 for up to 3 years. The mean (SE) change in the total motor AIMS score from baseline of study C-20 was -2.0 (0.38) at week 145/158 (min -14, max 9). The mean (SE) change in the total motor AIMS score from baseline of the parent studies C-18 and C-20 was -4.0 (0.37) at week 145/158 (min -14, max 7).

Also, of note, in the clinical development programme, the Phase 3 trials were conducted using a clinical matrix-based gastro erosional formulation for twice daily (BID) dosing. Thereafter, an osmotic drug delivery formulation was developed, resulting in a prolonged release formulation for once daily (QD) dosing, which can be beneficial for patients with TD, who are likely receiving one or more neuropsychiatric medications (e.g. an antipsychotic, an antidepressant, a mood stabilizer, and/or medications to control some drug-induced adverse effects) as treatment adherence and persistence are generally expected to be higher with a long-term treatment taken QD versus a more frequent dosing.

6.3. Uncertainties and limitations about favourable effects

A limitation of trial C-18 is the modest sample size whereas trial C-23 was larger. Both studies had a short treatment duration (12-weeks including dose adjustment), bearing in mind that TD has a spontaneous up and down time course of severity. Nevertheless, the Abnormal Involuntary Movement Scale (AIMS) was evaluated at sufficiently close intervals over the course of the studies which reduces the concern that patients developing signs of TD may have been missed due to the fluctuating nature of the disease.

In individual studies and in the pooled analysis, the effect size was borderline compared to the minimal clinically important difference (MCID) of 2 points reported in the literature (Stacy et al. 2019). Therefore, further analyses were provided to confirm that the patients who managed to fine tune their treatment achieved a reasonable improvement.

The key secondary efficacy endpoint for both C-18 and C-23 was the proportion of patients rated by the investigator as treatment success based on the Clinical Global Impression of Change (CGIC) at Week 12. In C-18, the results only showed a favourable trend of DTBZ over placebo (48.2% and 40.4% respectively, p=0.4001). In C-23, although a greater proportion of patients were considered a treatment success at week 12 after treatment with DTBZ 36 mg/day versus placebo, the result was not statistically significant (44% vs 26% respectively, odds ratio=2.11, p=0.059). The results of the CGIC analysis at 24-mg/day dose were similar to those at 36 mg/day (49% vs 26% respectively, odds ratio=2.71, p=0.014) although considered exploratory because of the hierarchical testing approach.

The point estimate of the primary endpoint was -1.4 and -1.9 in trials C-18 and C-23 respectively. It was -1.8 in the pooled analysis from trial C-18 and the efficacious doses from trial C-23 (36 mg/day and 24 mg/day). Therefore, the effect size was lower or borderline compared to the MCID of 2 points reported in the literature (Stacy et al. 2019). This issue remained not solved until the applicant provided further data including an analysis of AIMS response anchored to the Patient Global Impression of Change (PGIC), together with the class improvement of 2, 3, 4, 5, 6 or more AIMS points. These have shown that most patients who improved 3 points or more sensed "very much" or "much improved". Likewise, patients who scored "very much improved" in PGIC had a mean 5 points improvement in AIMS.

DTBZ proposed therapeutic indication initially included all patients irrespective of disease severity and without mentioning that symptoms must be bothersome to the patient and/or cause functional impairment.

The claim was based on a pooled post-hoc subgroup analysis of the primary endpoint, that compared patients with a centrally read total motor AIMS score ≤6 (mild TD) at baseline of studies C18 and C23 to those with a centrally read total motor AIMS score >6 (moderate to severe TD) at baseline. However, the treatment effect in the subgroup of patients with mild TD was not statistically significant. Also considering the exploratory nature of the presented pooled post-hoc analysis on the one hand, and the unconvincing treatment effect in the mild TD subgroup on the other hand, the therapeutic indication was ultimately restricted to "treatment of moderate to severe TD in adults", as requested by CHMP.

DTBZ should only be used in patients who had their underlying psychiatric condition stable for some time as unstable patients may have higher suffering with treatment-related adverse events such as depression or worsening psychiatric condition. It is at the clinician's discretion to decide if the patient is sufficiently stable to endure a treatment with DTBZ.

6.4. Unfavourable effects

The safety data from the TD development programme demonstrated that DTBZ was generally well tolerated for up to ~4 years. In the placebo-controlled trials, the overall safety profile was similar between DTBZ and placebo, with similar numbers of participants experiencing 1 or more adverse event

(AE), serious AE (SAE), or severe AEs in the treatment groups. The discontinuation rate due to AEs for DTBZ was low and comparable to that of placebo.

The most common side effects of DTBZ, identified in clinic trials and post-marketing use are: urinary tract infection, nasopharyngitis, anxiety, insomnia, restlessness, somnolence, akathisia, Parkinsonism, diarrhoea, constipation, dry mouth, fatigue, and depression. Other (potential) risks carefully considered were: neuroleptic malignant syndrome and QTc prolongation. These are adequately characterised and managed via routine risk minimisation measures (RMMs).

There were no new safety findings resulting from the post-marketing experience besides several reports of parkinsonism. While review of the clinical trial data did not identify parkinsonism as an ADR, evaluation of post-marketing reports resulted in the classification of parkinsonism as an ADR.

6.5. Uncertainties and limitations about unfavourable effects

QT prolongation

DTBZ may prolong the QTc interval, but the degree of QTc prolongation is not clinically significant when DTBZ is administered within the recommended dose range. Overall, no safety signals were observed in ECG parameters in clinical trials.

In an *in vitro* study, deuterated α-HTBZ and β-HTBZ inhibited the human ether-à-go-go-related gene (hERG) potassium channel. The corresponding safety margins, calculated as ratio of 50% inhibitory effect and the predicted unbound $C_{max,ss}$ of deuterated α-HTBZ and β-HTBZ at the maximum recommended doses were 216- and 242-fold, respectively, in EM and 172- and 52-fold, respectively, in PM.

Despite these observations, a risk cannot be excluded when DTBZ is used in combination with other products that prolong the QTc interval and in patients with congenital long QTc syndrome, a history of cardiac arrhythmias, bradycardia, hypokalaemia or hypomagnesaemia. Risk minimisation measures include (routine risk management activities): a warning in SmPC Sections 4.4 and PL (accordingly) and the legal status of "medicinal product subject to restricted medical prescription".

Further details about the potential interaction with medicines known to prolong the QTc interval are included in SmPC section 4.5 together with specific examples of such medicines. These RMMs are sufficient to address the concern of potential clinically insignificant QTc interval prolongations and therefore ECG records (e.g. a normal ECG [QTc< 450 ms] when starting treatment and tapering the dose) are not deemed required for all patients when starting DTBZ treatment or tapering the dose.

Dose Recommendations

The dose selection for DTBZ in the Phase 3 programme in TD was based on targeting similar exposure (AUC) for the deuterated active metabolites of DTBZ as for the nondeuterated active metabolites of TBZ following TBZ administration. In early PK trials, this was achieved with approximately 50% lower DTBZ doses compared to TBZ. The therapeutic benefit of these doses was confirmed in the Phase 3 efficacy trials in participants with TD.

The TD Phase 3 programme, using the DTBZ matrix formulation BID, supports a treatment initiation and titration scheme ranging from 12 to 48 mg/day and demonstrated the efficacy of DTBZ treatment at the efficacious dose range of 24 to 48 mg/day in adult patients with TD. The titration to effect in 6 mg/day steps showed that, although a considerable portion of participants were titrated up to 48 mg/day, for other participants treatment effect was achieved at dose levels below 48 mg/day starting from 24 mg/day.

The initiation phase is important to allow monitoring of safety and tolerability in each patient while they reach their efficacious dose level. However, as supported by US market research and real-world experience with DTBZ, the duration of initiation and titration phases can be a driver for lack of treatment

adherence or even drop-out of patients from the therapy before clinical efficacy is reached (Caffrey and Borrelli 2020). An integrated safety analysis and subsequent modelling analyses supports treatment initiation by increasing the dose from 12 mg/day in the first week to 24 mg/day in the second week and thereby skipping the 18 mg/day dosing step applied in the TD Phase 3 programme. This allows patients to reach the efficacious dose range of 24 to 48 mg/day sooner and potentially increase adherence and persistence to treatment without adversely affecting the safety profile. This approach is expected to have a positive impact on patients' outcomes and ultimately in controlling the highly debilitating symptoms of TD.

The osmotic drug delivery formulation for QD dosing was shown to match PK exposures to that of the clinical matrix formulation BID, and thereby generate an equivalent therapeutic effect in TD. Based on matched PK exposures, dose proportionality established for both formulations over the full clinical dose range, and modelling and simulations, the dosing recommendation for the commercial osmotic PR tablet QD is the same as for the clinical matrix tablet BID.

In summary, DTBZ dosing should be determined individually for each patient, based on adequate reduction of TD symptoms and tolerability. The applicant did not plan to register the 18 mg dose (i.e. 12 mg, 24 mg, 30 mg, 36 mg, 42 mg and 48 mg). Thus, the first increment in the titration phase will be an increment of 12 mg/day, instead of 6 mg/day in the clinical program. Therapy should be initiated at 12 mg QD for one week, and the dose then increased to 24 mg QD for another week. After the second week, the dose should be titrated at weekly intervals in increments of 6 mg QD, based on reduction of TD symptoms and tolerability. The efficacious dose range is considered to be 24 mg to 48 mg. The maximum recommended daily dose is 48 mg.

As higher exposures are observed in patients receiving strong CYP2D6 inhibitors or who are known poor CYP2D6 metabolisers, the total daily dose of DTBZ should not exceed 36 mg in these patients. This recommendation is in line with the maximum daily dose of 36 mg used in the Phase 3 efficacy trials in TD patients who received concomitant treatment with strong CYP2D6 inhibitors.

6.6. Effects table

Table 94: Effects table for deutetrabenazine

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Change in total AIMS score (Items 1 through 7) during the 12-week treatment period	AIMS	Point scale	-3.0	-1.6	Treatment effect below the minimal clinically significant difference of 2 points Key secondary endpoints not aligned with primary and not statistically significant	Study C18
Change in total AIMS score (Items 1 through 7) during the 12-week treatment period	AIMS	Point scale	-0,7 (12 mg dose) -3.0 (24 mg dose) -3.3 (36 mg dose)	-1.4	Treatment effect below the minimal clinically significant difference of 2 points Key secondary endpoints not aligned with primary and not statistically significant	Study C23
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Depression	Incidence of depression	%	8.0	N/A*		X1. Data from open label maintenance Study C-20 part A
Anxiety	Incidence of anxiety	%	9.8	N/A*		X1. Data from open label maintenance Study C-20 part A
Somnolence	Incidence of somnolence	%	11.3***	6.9**	more frequent during the titration/dose escalation period	X1
Urinary tract infection	Incidence of Urinary tract infection	%	7.1	N/A*		X1 Data from open label maintenance Study C-20 part A
Nasopharyngitis	Incidence of Nasopharyngitis	%	4.5	N/A*		X1 Data from open label maintenance Study C-20 part A
Insomnia	Incidence of Insomnia	%	4.2	N/A		X3
Agitation / Akathisia / Restlessness	Incidence of Agitation / Akathisia / Restlessness	%	1.8	0.8		X4
Diarrhoea	Incidence of Diarrhoea	%	6.2	N/A*		X1 Data from open label maintenance Study C-20 part A
Constipation	Incidence of Constipation	%	4.4	2.2		X5

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Dry mouth	Incidence of Dry mouth	%	8.9	6.7		X5
Fatigue	Incidence of Fatigue	%	4.4	8.9		X5
Parkinsonism	Incidence of Parkinsonism	%	0.4 / UNK	0 / N/A		**** Pooled data from C18 and C23/Post marketing
Weight decreased	Incidence of Weight decreased	%	7.7	N/A		X1 Data from open label maintenance Study C-20 part A
QT prolongation					DTBZ may prolong the QT interval, but the degree of QT prolongation seems to be not clinically significant when DTBZ is administered within the recommended dose range; a risk cannot be excluded when DTBZ is used in combination with other products that prolong the QT interval and in patients with congenital long QT syndrome, a history of cardiac arrhythmias, bradycardia, hypokalaemia or hypomagnesaemia	X6
Neuroleptic Malignant Syndrome					The risk is associated with products that reduce dopaminergic transmission	X6

Abbreviations: AIMS (Abnormal Involuntary Movement Scale), DTBZ (deutetrabenazine)

Notes:
X1 - Table: Adverse Events Occurring in ≥4% of Tardive Dyskinesia Participants in the Titration/Dose-Escalation or Maintenance Period in Any Participant Group (Safety Population in Trials C-18, C-23, and C-20)
X2 - Table: Exposure-Adjusted Incidence Rate for Adverse Events That Occurred in ≥4% in Any Tardive Dyskinesia Participant Group in the Overall Treatment Period by Participant Group (Safety Population in Trials C-18, C-23, and C-20)
X3 - Table: Adverse Events in ≥4% of Participants in Long-Term Trial C-20 Overall Treatment Period (Safety Population)
X4 – Pooled analysis for the 2 double-blind trials in TD patients

X5 - Adverse Reactions Occurring in >4% in Participants with Huntington's Disease from Trial C-15
X6 – Summary of clinical safety

*- Study C20 Part A maintenance did not run a placebo arm.

**- Placebo values are from C-18 and C-23 titration period and the adverse event value is for the C-20 Part A open label maintenance period.

***- Pooled titration data from C18 and Part A C20.

****- Pooled data from C18 and C23

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

There is no centrally approved therapy for the treatment of tardive dyskinesia (TD) in the EU, although tetrabenazine is marketed in some EU member states.

There is an improvement in the severity of abnormal involuntary movements based on the primary efficacy endpoint, the total motor AIMS score, in the pivotal studies of DTBZ (C-18 and C-23). The primary analysis was statistically significant and was supported by the key secondary endpoint of treatment success based on CGIC where a trend favoured DTBZ over placebo. Both the total motor AIMS score and the CGIC are rated by the clinician and can therefore be considered objective. It is also noteworthy that the total motor AIMS score was centrally rated by experts in movements disorders. PGIC failed to demonstrate benefit. However, AIMS improvement when anchored to PGIC showed that the two endpoint tools were related, and most patients with 4 or more points improvement in AIMS scored improved "much" or "very much". Although a higher response was identified in patients not treated with dopamine receptor antagonists (DRA), the very low number of patients as compared to those recently treated with DRA precludes a restriction to patients not currently treated with DRAs.

The applicant agreed to align the intended therapeutic indication of DTBZ with the population in the pivotal clinical trials for TD, as requested by CHMP. Consequently, the indication wording in SmPC section 4.1 was amended to reflect a restriction to "moderate to severe TD".

The safety profile of DTBZ is overall well characterised. This includes among others a risk of depression, somnolence, parkinsonism, and QT prolongation. Overall, the frequencies of serious adverse events remained limited based on the comparative data. Several effects observed with other inhibitors of VMAT2 were not observed with deutetrabenazine.

6.7.2. Balance of benefits and risks

There is no centrally approved therapy for the treatment of tardive dyskinesia (TD) in the EU, although TBZ is marketed in some EU member states.

The applicant provided sufficient evidence of DTBZ statistically significant and clinically meaningful improvement in the AIMS total score from baseline compared to placebo in the trial population of adult patients with moderate to severe tardive dyskinesia.

DTBZ dosing should be determined individually for each patient, based on adequate reduction of TD symptoms and tolerability. The efficacious dose range is considered to be 24 mg to 48 mg (maximum recommended daily dose). The dose can be easily titrated to reach a satisfactory equilibrium between benefit and risk of the treatment.

DTBZ safety profile is well characterised. Data from the TD development programme demonstrated that DTBZ was generally well tolerated for up to ~4 years. In addition, no new safety findings resulted from the post-marketing experience in the United States, besides several reports of Parkinsonism.

6.7.3. Additional considerations on the benefit-risk balance

In the context of the CHMP early contact methodology (process and FAQ at www.ema.europa.eu/en/documents/other/chmp-early-contact-patient-and-healthcare-professional-organisations-process-and-faqs_en.pdf), Austedo (deutetrabenazine) had been identified by the CHMP core group as a procedure that would benefit from input from patient and healthcare professional (HCP) groups.

Input was received from the European Academy of Neurology (EAN) and the European Psychiatric Association (EPA), requested to comment on any aspects of particular importance to HCP, such as information on:

- The standard of care or available treatments and to what extent they cover the intended indication of tardive dyskinesia in adults;
- The treatment duration; and, if in your view, the duration needs to be optimised;
- Any possible therapeutic/unmet medical needs;
- What benefits you would hope for in new medicines; as well as what level of side-effects you would consider manageable for patients;
- Considerations for pregnant people/people of child-bearing potential, where applicable.

Comments from the Assessor:

Both EAN and EPA are European organizations committed to the diagnosis, prevention and treatment of TD. Both encompass the need for adequate therapeutics, as no centrally approved agent is available throughout the EU. Both have been guided in their interpretation with the publicly available data for DTBZ, where the focus was on the maximum effect in the responders, with a broad definition of responder, and the higher doses arms, together with the long-term open-label study with up to 3 years of follow up.

EPA alludes to the Solmi et al meta-analysis, but in this tetrabenazine was excluded since trial was not meta-analysable according to the study criteria. Therefore, their conclusions are only about DTBZ and valbenazine.

In conclusion, the information provided in both responses is in line with the clinical perception of an unmet medical need, with tailored treatment centred in the patient. This point is crucial since most patients will require simultaneous DRA treatment, and down titration of these along with up titration of VMAT2 blockers is the key to success.

6.8. Conclusions

The overall benefit/risk balance of Austedo is positive.

7. Recommendations following re-examination

Outcome

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP concluded by consensus that the benefit-risk balance of Austedo (deutetrabenazine) is favourable in the following indication(s):

- Treatment of moderate to severe tardive dyskinesia in adults

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 1 year following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

  Not applicable

- **Obligation to conduct post-authorisation measures**

  Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable

New Active Substance Status

Based on the review of available data on the active substance, the CHMP considers that deutetrabenazine (DTBZ) is **not** to be qualified as a new active substance in itself.

Based on the review of data on the quality and clinical properties of the active substance, the CHMP considers that DTBZ, in comparison to tetrabenazine (TBZ), previously authorised as a medicinal product in the European Union, is **not** to be qualified as a new active substance as insufficient evidence has been provided to demonstrate that it differs significantly in properties with regard to safety and/or efficacy from the previously authorised substance.