30 January 2025
EMA/280465/2025
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Dazluma

International non-proprietary name: troriluzole

Procedure No. EMEA/H/C/006068/0000

Note

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

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List of abbreviations

AD	Alzheimer's disease
ADCOMS	Alzheimer's Disease Composite Score
ADL	Activities of daily living
AE(s)	Adverse event(s)
ALP	Alkaline phosphatase
ALS	Amyotrophic lateral sclerosis
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BE	Bioequivalence
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BID	Twice daily
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CGI-I	Clinical Global Impression of Improvement
C_{max}	Maximum concentration
CMC	Chemistry, Manufacturing, and Controls
CO	Clinical Overview
COAs	Clinical outcome assessments
COVID-19	Coronavirus disease 2019
CRC-SCA	Clinical Research Consortium for the Study of Spinocerebellar Ataxia
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Technical Criteria for Adverse Events
CTD	Common Technical Document
DB	Double-blind
DKP	N-methyl diketopiperazine
ECG	Electrocardiogram
eDISH	Evaluation of Drug-induced Serious Hepatotoxicity
EU	European Union
EUROSCA	European Integrated Project on Spinocerebellar Ataxias
FARS-ADL	Activities of Daily Living Scale from the Friedreich's Ataxia Rating Scale
FARS-FUNC	Functional Staging for Ataxia Scale from the Friedreich's Ataxia Rating Scale
FDA	Food and Drug Administration

f-SARA	Functional Scale for the Assessment and Rating of Ataxia
GAD	Generalised Anxiety Disorder
GCP	Good Clinical Practice
HPMC	Hydroxypropyl methylcellulose
ICH	International Conference on Harmonisation
ID	Identification
IR	Immediate release
LFT	Liver function test
LS	Least squares
LSM	Least squares mean
MAA	Marketing Authorisation Application
MAIC	Matching Adjusted Indirect Comparison
MedDRA	Medical Dictionary of Regulatory Activities
mITT	Modified Intent to Treat
MMRM	Mixed model for repeated measures
MMSE	Mini Mental State Exam
MOA	Mechanism of Action
Neuro-QOL-Lower	Neurology Quality of Life Lower Extremity Scale
Neuro-QOL-Upper	Neurology Quality of Life Upper Extremity Scale
Neuro-QOL-Fatigue	Neurology Quality of Life Fatigue Scale
OCD	Obsessive compulsive disorder
OL	Open-label
OLE	Open-label extension
PO	Per os (by mouth)
PepT1	Peptide transporter 1
PGI-C	Patient Global Impression of Change
PIFAS	Patient Impression of Function and Activities of Daily Living Scale
PK	Pharmacokinetic
PT	Preferred term
QD	Once daily
RCT	Randomised Clinical Trial
SAD	Single ascending dose
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SARA	Scale for the Assessment and Rating of Ataxia (standard scale)
SCA	Spinocerebellar ataxia
SCACOMS	SCA Composite Scale
SCACOMS-CRC-SCA-SCA3	SCACOMS Clinical Research Consortium for the Study of Cerebellar Ataxia (All SCA populations and SCA genotype 3)
SCA1	Spinocerebellar ataxia genotype 1

SCA2	Spinocerebellar ataxia genotype 2
SCA3	Spinocerebellar ataxia genotype 3
SCA6	Spinocerebellar ataxia genotype 6
SCA7	Spinocerebellar ataxia genotype 7
SCA8	Spinocerebellar ataxia genotype 8
SCA10	Spinocerebellar ataxia genotype 10
SCE	Summary of Clinical Efficacy
SD	Standard deviation
SE	Standard error
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SOC	Standard of care
SSRI	Selective serotonin reuptake inhibitor
S-STS	Sheehan Suicidality Tracking Scale
TEAE(s)	Treatment-emergent adverse event(s)
TESAE(s)	Treatment-emergent serious adverse event(s)
T_{max}	Time of maximum concentration
ULN	Upper limit of normal
URPL	Urzad Rejestracji Produktow Leczniczych
US	United States
UTI	Urinary tract infection
WHO	World Health Organization

1. CHMP's Recommendations

Based on the review of the data on quality, safety, efficacy, the application for Dazluma, an orphan medicinal product in the treatment of adult patients with spinocerebellar ataxia genotype 3 (SCA3), is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the list of questions (REDACTED).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the list of questions (REDACTED).

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Quality:

- Conclusions of risk assessment on potential presence of nitrosamine impurities in the active substance and finished product are still not supported.

Clinical efficacy

- Efficacy has not been demonstrated in the proposed indication.

1.1. Questions to be posed to additional experts

Not applicable.

1.2. Inspection issues

1.2.1. GMP inspection(s)

Not applicable.

1.2.2. GCP inspection(s)

At this stage, a request for GCP inspection is not required.

1.3. New active substance status

Based on the review of the data, it is considered that the active substance troriluzole contained in the medicinal product Dazluma is not qualified as a new active substance.

1.4. Additional data exclusivity /Marketing protection

Not Applicable

1.5. Similarity with authorised orphan medicinal products

Not applicable

1.6. Derogation(s) from market exclusivity

Not Applicable

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

Ataxia is the absence of voluntary muscle coordination and loss control of movement that affects gait stability, eye movement and speech. Spinocerebellar ataxia (SCA) is a progressive neurodegenerative inherited (autosomal dominant) heterogeneous disease that mainly affects the cerebellum.

Spinocerebellar ataxias (SCA) are a group of ultra-rare, dominantly inherited neurodegenerative disorders predominantly characterised by atrophy of the cerebellum. Spinocerebellar ataxias are characterised clinically by relentlessly progressive ataxia. SCA has hallmark symptoms related to loss of control and coordination of voluntary body movements. The disease course of SCA is one of progression over years and inevitably leading to clinical deterioration of motor function, gait imbalance with frequent falling, and a shortened life expectancy by 6 to 29 years. SCAs are thought to be pathogenetically related but disease course and brain region involvement are known to vary between the different genotypes. Currently, there are no approved symptomatic or neuroprotective treatments for SCA.

In SCA3, the clinical presentation includes progressive ataxia along with vestibular dysfunction, ophthalmoplegia, extrapyramidal signs (i.e., Parkinsonism and dystonia), pyramidal/motor neuron degeneration (i.e., spasticity, hyperreflexia, and amyotrophy), and autonomic dysfunction, with symptom onset typically occurring between the 2nd and 5th decade. Disability increases over time, resulting in an inability to perform activities of daily living, decreased quality of life, and ultimately death. Patients with SCA3 have been shown to have an almost five-fold increase in the risk of death when compared with their unaffected relatives; these patients usually survive only 10 to 20 years after symptoms first appear.

Falls directly due to gait abnormalities occur commonly in SCA, particularly SCA3. Falls frequently result in serious injuries, including fractures, joint dislocations, head trauma, and even mortality. Additionally, falls may also result in social self-isolation and decreased ambulation due to a fear of recurrent falling, and consequent diminishing independence. It has been estimated that approximately 85% of patients with SCA reported at least one fall in the prior year. New therapies are therefore urgently needed to treat the underlying pathophysiology of SCA, reduce gait impairment and other functional deficits, and decrease the morbidity associated with falls. According to results from an externally led, patient-focused drug development meeting held by the US National Ataxia Foundation, patients with SCA report that "the most meaningful outcome in a future treatment is the slowing or stopping of disease progression."

2.1.2. Epidemiology and risk factors, screening tools/prevention

SCA is a subset of hereditary cerebellar ataxia and is a rare disease. Approximately 50 distinct genetic subtypes of SCA have been identified to date.

The global prevalence of spinocerebellar ataxia is 1 to 5 per 100000 and overall European prevalence is 0.9 to 3 per 100000 with some geographical variation i.e. 2/100000 in Italy to 4/100000 in Norway and 5/100000 in Portugal. In the EU, the prevalence of SCA has been estimated to be 1 to 4 (average 2.7) individuals per 100,000.

For USA, in 2013, in a 12-center study of 345 patients it was found that SCA3 accounted for 40%, followed by SCA2 in 21.7%, SCA6 in 21%, and SCA1 in 17.4% patients (Teive et al 2019). In the US

and Canada, SCA3 is one of several SCAs comprising the most common autosomal dominant ataxias, with SCA3 accounting for 21%-25% of families [Klockgether et al 2019 and references therein in Paulson and Shakkottai 1998 updated 2020].

According to recently published data, none or few cases were described in Italy, Russia, Poland, Serbia, Finland, and Norway. SCA1 and SCA2 globally displayed similar frequencies, and are more prevalent in Italy, United Kingdom, Poland, Serbia, and France. SCA3 is the most common dominant cerebellar ataxia in Europe, with a ratio between frequency of each specific SCA and the overall frequency of all SCAs detected (RF) of 32-33%. These ratios (RF) present a variability depending on the country. More recent studies confirmed SCA3 as the most common SCA subtype in Portugal, with RFs of 57.4% and 51.2%, respectively. Outside of Portugal, SCA3 has the highest RF among SCAs only in Germany, France and the Netherlands, accounting for 42%, 30-35% and 28.2% of patients with Spinocerebellar ataxias (SCAs) or autosomal dominant ataxias (ADCAs), respectively. In Spain, SCA2 and SCA3 have similar RF of approximately 15% (De Mattei et al 2023).

SCA3 (25 to 50%) is most prevalent followed by descending prevalence SCA2 (13 to 18%), SCA6 (13-15%), and SCA7. The frequency of different types varies from region to region. Asian countries have limited published data; however, studies have been performed in India, China, Singapore, Japan, and Korea. Despite SCA3 being most common worldwide, it was found that SCA2 is most common in South Korea and India. SCA genotype 3 (SCA3), also known as Machado-Joseph disease, is the most common genotype in the EU and accounts for approximately 30% to 50% of SCAs worldwide.

2.1.3. Biologic features and Aetiology and pathogenesis

The main disease mechanisms of these SCAs include toxic RNA gain-of-function, mitochondrial dysfunction, channelopathies, autophagy and transcription dysregulation. Recent studies have also demonstrated the importance of DNA repair pathways in modifying SCA with CAG expansions. [https://link.springer.com/article/10.1007/s00415-018-9076-4] CAG repeat expansion occurs in SCA1, 2, 3, 6, 7, 8, 12, and 17. Similarly, SCA 10 is caused by the expansion of ATTCT (pentanucleotide), SCA 31, 36, 37 involve amplification of TGGAA (pentanucleotide), GGCCTG (hexanucleotide), and ATTTT (pentanucleotide) respectively.

The exact pathogenesis of spinocerebellar ataxia is still not known. But many study series promulgated that common mechanisms of SCA are genetic mutations causing abnormal protein products, transcriptional dysregulation, dysfunction of autophagy, channelopathies, mitochondrial dysfunction, toxic RNA gain of function.

Six forms of SCA involve CAG repeat amplification encoding glutamine, which gets assembled into ataxins that alters the protein configuration into the beta-pleated structure and toxic gain of function with autosomal inheritance. Ataxins are misfolded proteins from the expansion of a polyglutamine (more than 40 glutamines), which is abnormally translocated and accumulated in nuclei that interact with other proteins and oligomerise forming intranuclear inclusions in Purkinje cells. Normally, ataxins are present in CNS, which regulates normal protein homeostasis and cytoskeleton regulation. Biochemical studies have shown cytoplasmic aggregations in SCA2, the nucleus in SCA1, SCA3, and SCA7 and nucleolar in SCA7. Ataxins are targeted by ubiquitin-proteasome proteolytic complex in an attempt to degrade a remove and form the aggregations. Also, cellular interactions with abnormal ataxins have some role in pathogenesis. Ataxins bind to other proteins, including the TATA-binding transcription protein and the CREB-binding protein, impairing their functions disrupt the normal transcription regulation, which leads to abnormal and uncontrolled transcription. Some hypothesis declares that intranuclear inclusions are not supposed to be the sole cause of cellular dysfunction. In SCA subtype 1, Ataxin-1 is an uninterrupted expansion of polyglutamine. The polyglutamine tract interrupted by histidines are not affected and does not show any pathological effects. In addition to

ataxin-1, the immune response against the 1C2 monoclonal antibody has some role in the pathogenesis of SCA type 1. A protein, 14-3-3, binds and stabilises the ataxin-1 regulated by Akt phosphorylation decreases normal proteolysis of ataxin-1 that increases neurotoxicity.

The principal cells involved in degeneration are Purkinje cells, and other cells, such as granule cells, astrocytes, Golgi cells, and oligodendrocytes are not involved. Purkinje cells regulate fine movement and muscle coordination. So, the degeneration of Purkinje cells is highly associated with ataxia. [https://www.ncbi.nlm.nih.gov/books/NBK557816/]

2.1.4. Clinical presentation, diagnosis and stage/prognosis

SCAs are a group of hereditary ataxias that often do not begin until adulthood, affecting people from the age of 25 up to 80, depending on the type of SCA. Occasionally, some types of SCA begin in childhood.

The symptoms vary depending on the type of SCA. They can include:

- problems with balance and co-ordination – many people find walking difficult and need to use a wheelchair after a few years
- increasingly slurred, slow and unclear speech (dysarthria)
- difficulty swallowing (dysphagia)
- muscle stiffness and cramps
- loss of sensation in the hands and feet (peripheral neuropathy)
- memory loss and difficulties with spoken language
- slow eye movement, which means people have to move their head to compensate
- reduced bladder control (urinary urgency or incontinence) [https://www.nhs.uk/conditions/ataxia/symptoms/]

Although SCAs are symptomatically heterogeneous disorders, they share ataxia as a core symptom. Other symptoms may include extrapyramidal and pyramidal signs, although at least one SCA, SCA6, solely involves the cerebellum. Cognitive impairment can also be observed among patients with SCA, such as impaired executive dysfunction, verbal fluency and memory. Depression might also occur. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9048095/]

2.1.5. Management

A number of symptomatic therapies are being used for the management of SCAs.

Riluzole, a drug used to treat amyotrophic lateral sclerosis (ALS), improved cerebellar symptoms in patients with various types of degenerative ataxia in two small clinical trials [15,16]. The proposed mechanism of action for riluzole is to open calcium-activated potassium channels that regulate the firing of deep cerebellar neurons and/or Purkinje cells, thus decreasing neuronal hyperexcitability. It also appears to interrupt glutamatergic transmission, thus offering potential protection against excitotoxic neurodegeneration.

Thyrotropin-releasing hormone (TRH) TRH promotes thyroid-stimulating hormone in the pituitary and promotes prolactin release. Several case reports in the 1980s found anecdotal improvement of ataxia with TRH use.

Varenicline (Chantix; Pfizer, New York, NY) is used as a smoking cessation drug that acts as a partial agonist at α4β2 nicotinic acetylcholine receptors. Case reports have noted that varenicline improved cerebellar symptoms in various types of ataxia.

Buspirone is a 5-HT1A and dopamine D2 agonist anxiolytic that has been evaluated as treatment for ataxia with mixed results. The use of buspirone in ataxia was based on evidence of extensive cerebellar serotonergic innervation.

Valproic acid (VPA) is an anticonvulsant and histone deacetylase (HDAC) inhibitor used to treat both seizures and bipolar disorder, that demonstrated positive results in a randomised, double-blind, placebo-controlled study in 12 SCA3 patients.

While there has been interest regarding lithium as treatment for ataxia, at least one double-blind, randomised, placebo-controlled, study in 62 patients with genetically confirmed SCA3 failed to note improvement in cerebellar function. The study took place over 48 weeks with subjects randomised into either lithium group (300 mg tablets) or placebo group.

Amantadine is a noncompetitive N-methyl-D-aspartate agonist that has been shown to be beneficial in treatment of parkinsonian features and degenerative ataxias.

Acetazolamide is a carbonic anhydrase inhibitor that is used in the treatment of epilepsy, congestive heart failure, and glaucoma. Acetazolamide was first demonstrated to be useful in the treatment of ataxia by Griggs et al. (1978).

Trehalose is a disaccharide that has shown promising effects in stabilizing the progression of SCA17 in mice model. One open-label trial of 14 SCA3 patients showed trehalose administration to be safe and tolerable, as well as effective in stabilizing SARA scores.

A number of disease-modifying treatments are currently being developed: gene editing technology-like CRISPR/Cas9, antisense oligonucleotides (ASOs) (short, synthetic oligonucleotides that are gaining increasing popularity in treatment of neurodegenerative conditions), adeno-associated virus (AAV)-mediated gene therapy, DNA mismatch repair (MMR) [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9048095/].

2.2. About the product

Troriluzole is a prodrug of riluzole (Rilutek). As such, the applicant is submitting this full-mixed MAA under Article 8(3) of Directive 2001/83/EC for troriluzole for the treatment of SCA3 in adults. Biohaven Bioscience Ireland Limited ("Biohaven" or "applicant") has developed troriluzole (BHV-4157) as a potential therapy for the treatment of SCA.

Troriluzole is a novel, rationally designed, third-generation tripeptide prodrug of the glutamate modulating agent riluzole. Troriluzole was designed to increase oral bioavailability, deliver consistent drug exposures, bypass first-pass metabolism, allow for QD dosing, and avoid the negative food hypothesised to address the widely documented glutamatergic dysregulation that underlies neurodegeneration and Purkinje cell dysfunction in patients with SCA.

The synaptic glutamate modulating activity of troriluzole is hypothesised to address the widely documented glutamatergic dysregulation that underlies neurodegeneration and Purkinje cell dysfunction in patients with SCA.

The proposed indication is:

DAZLUMA is indicated for the treatment of adult patients with spinocerebellar ataxia genotype 3 (SCA3).

The proposed posology is:

The starting dose is 125 mg (one 125 mg capsules) once daily for the first four weeks of treatment. The dose should then be increased to the recommended dose of 178 mg (two 89 mg capsules) once daily.

2.3. The development programme/compliance with guidance/scientific advice

Biohaven Therapeutics, Ltd. (Biohaven) has developed a prodrug of riluzole, troriluzole (BHV-4157, formerly FC-4157), as a treatment for adult patients with spinocerebellar ataxia genotype 3 (SCA3).

The selection of the starting materials was discussed in the EMA scientific advice on 23 June 2022 (EMA/SA/0000086653). According to CHMP advice all three proposed starting materials qualify as starting materials, the same starting materials are proposed in MAA. In general, scientific advice is followed, meanwhile additional data regarding control strategy of starting materials that should be submitted in MAA was specified. Not all additional data mentioned in scientific advice is submitted in MAA, questions were raised regarding this matter.

Eligibility to the centralised procedure was confirmed on 27 January 2022. A letter of intent was submitted on 26 October 2022 and the rapporteurs were confirmed as appointed on 15 December 2022. Changes to the appointed rapporteurs were confirmed on 8 March 2023.

A large clinical programme was conducted to assess the pharmacokinetics, efficacy, and safety of troriluzole in 17 studies. The initial disease indications selected for assessment in Phase 2 proof-of-concept studies included disorders with glutamatergic dysfunction thought to contribute to underlying disease pathology (SCA, OCD, AD, GAD). Of the 4 Phase 2 proof-of-concept studies completed with troriluzole, a signal for efficacy was observed in the long-term treatment of SCA patients and the OCD study; thus, SCA and OCD were the two indications selected for advancement into well-powered Phase 3 trials.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

A valid MA issued by an EU competent authority covering the proposed activities is provided for manufacturing sites located in EU and is considered sufficient proof of GMP compliance.

For manufacturing site located in the United States of America EU-US MRA is in operation. Screenshots of the FDA drug establishment registration site and FDA's inspection dashboard are provided and are accepted as a MIA equivalent and valid proof of GMP compliance (EMA has been consulted and in accordance with FDA's COMSTAT database the site has an acceptable GMP status).

The QP declaration for EU GMP compliance is provided by (batch release site). Declaration is based on on-site audits performed in June 2023 and September 2023 in all four manufacturing sites.

GLP

All safety pharmacology, and pivotal toxicology studies were performed in compliance with GLP regulations. In addition, method validation for pharmacokinetic studies was claimed to be performed according to GLP. However, the GLP compliance statements for those studies have not been provided The applicant should provide GLP compliance statements (**OC**).

GCP

According to the applicant, the studies presented in the dossier were conducted in accordance with Good Clinical Practice (GCP) guidelines, as defined by the International Conference on Harmonisation (ICH) and the US Code of Federal Regulations, Title 21, Part 50 (21CFR50).

No issues requiring a GCP inspection have been identified.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The applicant has submitted a full-mixed marketing authorisation under Article 8(3) of Directive 2001/83/EC.

2.5.2. PRIME

Not Applicable

2.5.3. Accelerated assessment

On 12th May 2023, the applicant, Biohaven Biosciences Ireland Ltd, submitted a request for accelerated assessment pursuant to Article 14 (9) of Regulation (EC) No 726/2004, for an application for marketing authorisation to the Agency for troriluzole, for the treatment of spinocerebellar ataxia genotype 3 (SCA3) in adults.

The CHMP did not agree to the applicant's request for an accelerated assessment.

Based on the assessment of the request provided by the applicant and the CHMP guideline on the procedure for accelerated assessment pursuant to Article 14 (9) of Regulation (EC) no 726/2004, **it is not** recommended to grant the accelerated assessment procedure pursuant to Article 14 (9) of Regulation (EC) No 726/2004 for troriluzole hydrochloride Biohaven Pharmaceutical Ireland Limited.

The claim for an unmet medical need for the SCA3 patient population can be supported based on the absence of therapies to modify the disease course of SCA3, which is a rare neurodegenerative disease that dramatically affect the lives of affected individuals and their families.

The claim that troriluzole has the potential to address the unmet medical need in patients with SCA3 is not currently supported based on the concerns about the strength of the efficacy evidence and concerns about the size of the safety database and its update during the procedure.

In particular, efficacy results for an enriched SCA population focusing only on the SCA3 subgroup come from a post hoc analysis and hence it can be considered as exploratory. Further, it is questionable whether the therapeutic effect observed using a newly developed scale, f-SARA can be considered as statistically and clinically compelling [EMA guideline points to consider on applications with 1. Meta-analyses and 2. One pivotal study (CPMP/EWP/2330/99)]. The applicant´s claims that this benefit has been confirmed through the application of the new SCACOMS composite score or through the MAIC comparisons with external natural history cohorts cannot be agreed.

[Briefing Note and Recommendations on a Request for Accelerated Assessment Pursuant to Article 14 (9) of Regulation (EC) No 726/2004, dated 22 June 2023]

2.5.4. Conditional marketing authorisation

Not applicable.

2.5.5. Marketing authorisation under exceptional circumstances

The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of the above mentioned Regulation based on the following points.

Given that it is not possible to provide comprehensive clinical data on the efficacy and safety of troriluzole for SCA3, an ultra-rare disease, the applicant feels that an application under exceptional circumstances, in accordance with the European Medicines Agency (EMA) Guideline for Procedures for the Granting of a Market Authorisation Under Exceptional Circumstances, Pursuant to Article 14 (8) of Regulation (EC) No. 726/2004 is justified for this MAA.

According to the applicant, this application meets the following criteria for marketing authorisation under Exceptional Circumstances:

- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- in the present state of scientific knowledge, comprehensive information cannot be provided, or
- it would be contrary to generally accepted principles of medical ethics to collect such information.

A summary of their position is presented below.

<u>The indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence.</u>

SCA3 is an ultra-rare disease with high unmet need.

Approximately 50 distinct genetic subtypes of SCA have been identified to date. In the EU, the prevalence of SCA has been estimated to be 1 to 4 (average 2.7) individuals per 100,000. SCA Type 3 (SCA3), also known as Machado-Joseph disease, is the most common genotype in the EU and accounts for approximately 30% to 50% of SCAs worldwide.

The ability to conduct clinical trials in ultra-rare diseases, such as SCA3, is limited by significant practical challenges.

Developing clinical trials in the rare and ultra-rare disease space poses unique challenges, in terms of study design, patient recruitment, and execution. Despite these obstacles, Biohaven has conducted the first registrational trial in SCA and has accrued the largest interventional trial database of SCA patients across genotypes, from two randomised clinical studies of troriluzole in subjects with SCA, which has taken over 6 years to complete.

Given the ultra-rare nature of each individual SCA genotype, completing a registrational trial recruiting only a single genotype (i.e., SCA3 only) would be lengthy and subject to other practical challenges that would limit the feasibility of conducting such a trial. Based on the data from Study BHV4157-206, another trial in SCA3 subjects would require randomizing approximately 314 subjects and is estimated to take more than 7 years to complete. The requirement for 314 subjects is based on 90% power, a treatment effect of –0.50 points, standard deviations of 1.0 and 1.5, and a 12% drop out rate. The estimated timeline assumes standard operational timelines for regulatory approvals in the EU from national competent authorities and ethics committees (i.e., 1 year), 5 additional years to randomise 314 subjects with SCA3 who meet study entry criteria, and 1 year of treatment to collect the 1-year

endpoint. No appropriately powered, registrational trials has ever been conducted in SCA3, highlighting the potential difficulties associated with conducting this type of a trial.

In the present state of scientific knowledge, comprehensive information cannot be provided.

Because troriluzole is a prodrug of the marketed drug riluzole, and because of the available data showing a therapeutic benefit of troriluzole in SCA3, another evaluation of troriluzole in a randomised, double-blind, placebo-controlled trial for SCA3 is not possible, given the likelihood that off-label usage of riluzole will impact recruitment and retention and/or potentially confound the data analysis and the interpretability of the study.

It would be contrary to generally accepted principles of medical ethics to collect such information.

The applicant asserts that obtaining comprehensive information through further evaluation of troriluzole in another randomised, double-blind, placebo-controlled trial for SCA3 would be contrary to generally accepted principles of medical ethics because troriluzole 200 mg administered once daily for the treatment of SCA3 has a favourable benefit/risk profile, with an improved pharmacological and safety profile compared to riluzole; and, even if conducting another trial were to be feasible, patients with SCA3 without access to troriluzole during the relatively long timeframe (i.e., many years) it would take to complete another trial would experience irreversible progression of their disease, including neuronal cell death and neurodegeneration, accrual of functional deficits and disability, decreased quality of life, and even death.

Even if such a trial was possible, conducting another trial in this indication would be extremely protracted and take many years for the reasons outlined above, including the ultra-rare nature of SCA3 and associated feasibility challenges. During the years it would take to complete another trial, patients with SCA3 would continue to progress in their disease course, sustaining further neuronal cell death and, ultimately, irreversible functional deficits and disability, and mounting burden to the patients and caregivers of families living with SCA.

According to the applicant the potential advantages of troriluzole compared to riluzole present an ethical challenge with respect to delaying approval of troriluzole, and potentially substituting it with off-label use of riluzole, while conducting another randomised, double-blind, placebo-controlled trial for SCA3.

2.5.6. Additional data exclusivity/ marketing protection

Not Applicable

2.5.7. New active substance status

The applicant requested the active substance *troriluzole* contained in the above medicinal product to be considered as a new active substance in comparison to riluzole previously authorised in the European Union as *Rilutek*, as the applicant claimed that *troriluzole* differs significantly in properties with regard to pharmacokinetic and safety from the already authorised active substance.

A NAS claim cannot be supported with the justification provided. It is not justified that troriluzole differs significantly in properties with regard to safety and/or efficacy from the already authorised riluzole. The NAS claim is not supported either from a quality and nonclinical perspective.

2.5.8. Orphan designation

Dazluma (troriluzole hydrochloride) was granted an EU Orphan Drug Designation (ODD) on 10 December 2021, indicated for the treatment of spinocerebellar ataxia, in accordance with Article 3(1)

of the Regulation (EC) No. 141/2000 (Community Register no. EU/3/21/2553). The ODD was transferred from Biohaven Pharmaceutical Ireland DAC to Biohaven Bioscience Ireland Limited on 4 May 2023.

2.5.9. Similarity with orphan medicinal products

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.

2.5.10. Derogation(s) from orphan market exclusivity

Not Applicable

2.5.11. Information on paediatric requirements

An application for a product specific Paediatric Investigation Plan (PIP) waiver was submitted on 5 August 2021 and the applicant chose to withdraw this application on 29 October 2021 following receipt of the Day 30 report. Subsequently, an application for a PIP, including a waiver in children from birth to less than 11 years of age was issued an EMA decision (P/0044/2023) on 31 January 2023. A copy of this decision is presented in Module 1.10.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as hard capsules containing 89 mg and 125 mg of troriluzole (in form of troriluzole hydrochloride monohydrate) as active substance.

Other ingredients are:

Capsule content: calcium phosphate, colloidal anhydrous silica, crospovidone, hydroxypropyl cellulose, magnesium stearate, mannitol, microcrystalline cellulose.

Capsule shell (89 mg strength):

Capsule cap: gelatin, titanium dioxide (E171), FD&C blue (E133), yellow iron oxide (E172), sodium lauryl sulfate, white ink TEK SW 0012.

Capsule body: gelatin, titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172), sodium lauryl sulfate, black ink TEK SW 9008.

Capsule shell (125 mg strength):

Capsule cap and body: gelatin, titanium dioxide (E171) black ink S-1-17822/S-1-17823.

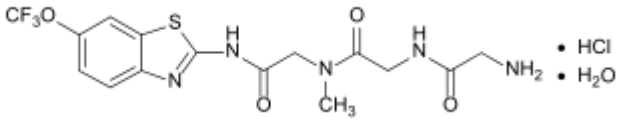
The product is available in white high-density polyethylene (HDPE) bottles with white child-resistant polypropylene cap and incorporated induction-seal. Each bottle (89 mg strength) contains 60 hard capsules. Each bottle (125 mg strength) contains 30 hard capsules.

3.1.2. Active Substance

3.1.2.1. General Information

The drug substance is troriluzole (INN) as hydrochloride monohydrate. It is not subject of an official compendium. Full information on the drug substance is given in the dossier.

Structural formula:



Molecular formula: $C_{15}H_{16}F_3N_5O_4S \bullet HCl \bullet H_2O$

Relative molecular mass: 473.85

General Properties:

The drug substance is a white to off-white solid, slightly hygroscopic.

Active substance is freely soluble in DMF and dimethyl sulfoxide, slightly soluble in ethanol and water and very slightly soluble in acetonitrile, isopropyl alcohol and 1-propanol. It's solubility in water is pH dependent.

Troriluzole hydrochloride does not contain any chiral centres. The drug substance exhibits polymorphism. The monohydrochloride monohydrate polymorphic form is the thermodynamically stable form and is consistently produced by the synthetic process and does not change during storage.

Drug substance particle size is routinely controlled.

3.1.2.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls:

A reaction scheme including all starting materials, reagents, catalysts, solvents, intermediates and the drug substance is provided. A detailed narrative description is given for each step. Input quantities, process parameters and IPCs are stated. All numerical values are expressed as target quantities, operation space for manufacturing process of each of intermediates and final active substance are summarised as well with information on nominal conditions (already included in process description), proven acceptable range (PAR), normal operating range (NOR). PAR values are based on experimental data presented in 3.2.S.2.6.

Specifications are provided for each starting material. Relevant parameters like appearance, identity, assay or purity and related substances are specified. Limits for impurities are justified with spike and purge data. Question is raised regarding information in QOS about addition of new starting material suppliers.

Raw materials are controlled according to appropriate specifications.

Specifications are presented for each isolated intermediate. Relevant parameters like identity, assay or purity and related substances are specified. Limits for impurities in intermediates are justified with spike and purge data.

The drug substance is non-sterile. Accordingly, no process validation and/or evaluation data need to be submitted in the course of the MA application.

Development of manufacturing process from process applied at initial manufacturing site to commercial process currently is described in S.2.2 is described, changes made are identified and impact to the quality of intermediates and final active substance briefly discussed.

Characterisation:

Drug substance structure has been elucidated applying standard methods. Batches tested were manufactured according to proposed synthetic process.

A comprehensive discussion on impurities (including mutagenic impurities) of starting materials, isolated intermediates and final DS is provided (including starting materials, solvents, intermediates, by-products and degradations products). Mutagenicity assessment has basically been performed according to principles outlined in ICH M7.

Elemental impurities risk assessment is provided, no metal catalysts are used in manufacturing process, it is demonstrated that no further control of elemental impurities is required in final active substance, information provided is considered sufficient for active substance.

Summary of nitrosamines risk assessment is submitted. All stages of the manufacturing process (including synthesis of starting materials) were evaluated for possibility to generate nitrosamines, or to contain nitrosamines as contaminants.

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

Drug substance specification is provided. Relevant parameters are included in line with ICH Q6A and Ph.Eur. 2034 ('Substances for pharmaceutical use').

Unspecified impurities are controlled in line with ICH Q3A and Ph.Eur. 2034 identification threshold, limits for specified impurities are above qualification threshold, however satisfactory qualification data are submitted in non-clinical part.

Residual solvents are controlled according to ICH Q3C limits.

Analytical procedures

Analytical methods were developed. It seems that the same analytical methods are used by finished product manufacturer. These analytical methods for the test parameters have been described in detail. Methods include the principle of the method, the equipment parameters, the sample and standard preparation, the calculation formula and an adequate System Suitability Test. The applied methods are in accordance with current technical and scientific requirements.

Validation of analytical procedures

Full validation reports for identification, assay, related substances, and purity by HPLC, residual solvents by GC/FID-HS and HCl content by potentiometric titration have been performed in accordance with ICH Q2 (R2) guideline, appropriate data, chromatograms are provided. Stability indicating properties of analytical method used for determination of assay, related substances and purity by HPLC has been evaluated by forced degradation studies including evaluation of mass balance and are included in section 3.2.S.7. The HPLC method is considered as stability indicating and suitable for its intended use. Suitability of methods of microbiological contamination has been demonstrated by appropriate validation data. Overall, validation reports are considered as acceptable.

Reference standards

Full characterisation of reference standard is provided. A batch is designated as the primary and current reference standard for troriluzole hydrochloride. It has been characterised according to

Ph.Eur.5.12. Assign potency has been determined by applying principle of mass balance and it is acceptable. The same reference standard batch is used by the finished product manufacturer for quality control of final API.

Batch analysis

Batch data of 18 batches is provided from proposed manufacturer including batches used in toxicology, clinical studies and registration batches.

Container closure

Primary packaging material is appropriately controlled.

3.1.2.4. Stability

Design of performed long-term and accelerated, and stress studies is in line with ICH Q1A. Photostability has been tested in line with ICH Q1B. All batches were manufactured in 2019. No specific trends have been observed; all data are within established specification. According to results of photostability study active substance is not light sensitive.

The container closure system of stability samples is representative for the commercial container closure system.

Basically, all relevant parameters of the drug substance specification were tested: appearance, assay, related substances, purity, particle size, water content and microbiological purity. Particle size is tested only for batches manufactured by one manufacturer, which is acceptable. Additionally X-ray powder diffraction was tested during stability studies and results were compliant throughout studies, therefore absence of this test in specification is acceptable.

Forced degradation studies are performed, drug substance is sensitive to acidic, basic and oxidative conditions.

No temperature storage conditions are necessary since no OOS results are observed in long term and accelerated storage conditions.

Re-test period of 60 months is stated and is acceptable.

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and pharmaceutical development

The drug product is immediate release solid oral dosage form (hard capsules), containing troriluzole hydrochloride monohydrate (Biohaven code BHV-4157) as active substance. Two strengths are proposed - 100 mg and the 140 mg strengths. The active substance is expressed as troriluzole hydrochloride monohydrate that corresponds to 89 mg or 125 mg of active substance free base respectively.

Primary packaging is white HDPE bottles with child resistant polypropylene screw cap with an induction seal.

Dazluma is proposed in two strengths as hard capsules and is considered standard pharmaceutical form. The 140 mg and the 100 mg strengths correspond to 125 mg or 89 mg of active substance troriluzole as base (stated with a note below the composition table). Dosing in the product information is referred to the free-base strengths 125 mg and 89 mg and is proposed to be used for commercial label.

The composition of filling of the both strengths is the same and differs with fill weight. Capsule shell between strengths (capsule size 1 and size 2) differs by size, colour and imprint, therefore both strengths are considered sufficiently different. Capsule shell composition differs between strengths by colorants and printing inks, in addition capsule size 2 contain sodium lauryl sulphate.

The excipients used in the drug product are well established, commonly used in solid oral dosage forms. Compliance with national pharmacopoeia, Ph.Eur./USP or EU Regulation 231/2012 is declared. No characteristics of excipients related functionality related characteristics (FCF) are discussed nor controlled in the specifications of excipients. The applicant is asked to assess functionality related characteristics of the individual excipients may have an impact on the consistency of the manufacturing process and the quality of the drug product. (**OC**) Capsule shell development from early formulation development, clinical, registration/stability and proposed commercial batches should be further justified. (**OC**)

Initial clinical studies were conducted using drug substance without excipients filled in the size #3 HPMC white opaque capsules (drug in capsule, DIC) to evaluate safety, tolerability and pharmacokinetics in single ascending dose (SAD) and multiple ascending doses (MAD). Further, before Phase 2 and 3 clinical studies has been started a formulation (drug substance with excipients) has been developed. The formulation studies included development of Quality Target Product Profile and identification of the critical quality attributes (CQAs) for drug product (appearance, identity, assay, related substances uniformity of dosage units, water content, microbiological quality).

Before introducing final formula into Phase 2 and 3 clinical studies, bioequivalence (BE) has been performed in human volunteers between the drug in capsule (DIC) formulation used in Phase 1 to the formulation product with excipients. Since initially manufacturing process were performed at the first manufacturer of the drug product) and later at the commercial manufacturer of the drug product analytical data has been provided to demonstrate comparability. Registration and/stability batches are manufactured by the proposed manufacturer.

To ensure robust formulation risk assessment of the formulation variables was performed to evaluate the impact on the drug product critical quality attributes (CQAs). High and medium risk formulation variables were further investigated targeted the two manufacturing steps where the drug substance and excipients are added: intra-granular blending and lubrication, extra-granular blending and lubrication and drug substance particle size impact. Based on experimental studies it is concluded that the formulation of drug product is robust, and the initially identified high or medium risks associated with formulation variables were reduced to low.

Dissolution method development has been described in sufficient detail and is based on standard requirements for dissolution conditions in accordance with EP, drug substance and drug product solubility across the physiological range. The choice of apparatus, agitation speed, dissolution medium and volume selected are in line with EP Recommendations and BE guideline CPMP/EWP/QWP/1401/98.

Dissolution specification limit is proposed and is based on dissolution results for clinical batches tested using QC method. Compliance with the proposed specification limit is demonstrated for clinical batches and for registration batches at release and within proposed shelf-life of the drug product for both strengths.

Dissolution

The discriminatory nature of the dissolution methods has been evaluated using critical formulation attributes and process parameters variables. Tested variations included changes in qualitative composition of excipients, particle size of the drug substance, roller compaction and milling process parameters, changes in lubricant parameters (lubricant concentration and lubrication time) and

tamping force. Dissolution rate was not impacted significantly by any of the variations studied for both dissolution methods at proposed specification time point.

Stability of polymorphic form has been briefly discussed; however, additional justification still is necessary.

Initially, several steps were identified as high risk steps during manufacturing process development. Several steps were identified as medium risk steps. Process parameter ranges for these steps were evaluated in relation to drug product CQA and final risk assessment were updated and risks related to these steps were reduced to low since appropriate control of process parameters can provide drug product with acceptable quality. For roller compaction/milling step proven acceptable ranges (PAR) were investigated and are justified with development data.

No claims for design space have been found throughout MAA.

3.1.3.2. Manufacture of the product and process controls

Manufacturing process consist of raw materials weighing, intra-granular blending and lubrication, roller compaction and milling, extra-granular blending and lubrication, encapsulation, primary packaging in bottles and secondary packaging. The blending process and blend composition is common for both the strengths. Based on manufacturing operations and active substance load per dosage unit, the manufacturing of the drug product is considered standard manufacturing process.

The equipment working capacity is stated in the description of the manufacturing process.

Statement that the shelf life of the finished product is calculated according to "NfG on Start of Shelf-life on the Finished Dosage Form" is provided.

No manufacturing validation data are presented in the MAA. Multiple batches supporting clinical studies as well as proposed commercial scale, has already produced and evaluated on stability. Drug substance from both manufacturers were used for drug product manufacturing. Process parameters with proposed ranges are those concluded in the section 3.2.P.2.3. All batches met the acceptance criteria (refer to Section 3.2.P.5.4 for the results) indicating that the manufacturing process is robust and is capable of producing batches with consistent quality. Based on available data from the batches successfully manufactured thus far, process development studies and performed risk assessments, it is agreed that formal validation at commercial scale can be performed post-approval. The validation protocols (scheme) for the manufacture of the 89 mg and 125 mg hard capsules should be provided in Module 3.2.R (**OC**).

3.1.3.3. Product specification, analytical procedures, batch analysis

Parameters included in the specification of finished product comply with the ICH Q6A.

Shelf-life specification for the finished product is provided, however it is not yet acceptable. Issues are raised concerning the assay limit and the omission of identification testing and uniformity of dosage units testing (OCs). This is marked in red in the above specifications.

The applicant has clearly stated that identification tests and uniformity of dosage units are not performed during stability. Identification tests and test for uniformity of dosage units are not stability indicating parameters; hence omission of these tests form the stability specification is acceptable, however these tests should be included in the shelf-life specification.

Dimensions of the capsule in mm should be part of the description in the drug product specification (**OC**).

Omission of test for water is sufficiently justified and finished product is concluded not hygroscopic and no additional protection from water is needed for the finished product.

Analytical procedures and reference standards

Analytical methods for the test parameters have been described in detail. Methods include the principle of the method, the equipment parameters, the sample and standard preparation, the calculation formula, representative chromatograms, UV spectra's and an adequate System Suitability Test. The applied methods are in accordance with current technical and scientific requirements.

Validations of in-house methods have been performed in accordance with ICH Q2 (R2) guideline, appropriate data, chromatograms are provided. Forced degradation study has been performed for assay and related substances methods. Suitability of method of microbiological purity tests has been demonstrated by appropriate validation data. Overall, results show that both methods are stability indicating. Provided validation reports are considered as acceptable.

Reference standard of troriluzole hydrochloride and reference standards of impurities provided in section 3.2.P.6 has been used for validation of analytical methods. Reference standard of troriluzole hydrochloride has been characterised according to Ph.Eur.5.12. Assign potency has been determined by the principle of mass balance. The analytical procedures and the acceptance criteria set has been provided to establish primary reference and working standards in future.

Batch analysis

Sufficient number of batches including commercial batch size batches have been analysed (4 batches of 89 mg strength and 4 batches of 125 mg strength in different configuration of packaging) and compliance with the proposed specification has been demonstrated.

It is noted that imprints on capsules are different than proposed in the specification of finished product for both strengths i.e. appearance of capsules does not comply with the specification, however it is not expected that different imprint has any impact on quality of finished product.

The dissolution results are obtained using paddle method which is different than the dissolution method proposed for quality control in the section 3.2.P.5.2 basket method. This is not considered an issue since change of dissolution method was made during stability study, therefore results of aged drug product batches demonstrate that compliance with limit is reached.

The provided risk assessment on elemental impurities according to ICH Q3D is considered acceptable. The applicant has provided analytical results for Class 1 and Class 2A elemental impurities in 2 batches of 89 mg strength and 1 batch of 125 mg strength as a supporting information to the risk assessment. It is confirmed that routine testing of elemental impurities is not necessary for the drug product.

Container closure

Compliance of primary packaging materials including cup liner with relevant requirements has been declared (Ph. Eur. and EU regulation No 10/2011).

Bulk capsules are held in fibre drums double lined with PE liners. Specification of bulk packaging is provided and is acceptable. The material is identified by IR and its compliance with EU 10/2011 is declared. Additional information is requested with regards to hold times for bulk product.

3.1.3.4. Stability of the product

The claimed shelf-life/storage for the finished product:

The proposed storage conditions: This medicinal product does not require any special storage conditions.

Stability studies in line with ICH guidelines have been performed for the finished product at accelerated and long-term storage conditions.

Post approval commitment has been included in section 3.2.P.8.2, stating that in addition to three initial production batches or PPQ, batches in the proposed container closure system will be placed on stability study (long-term condition). On-going stability study in line with GMP will be performed as well.

Since significant change in assay should be discussed and it should be clarified at which time-point current QC method was used for dissolution testing, no clear conclusion on the proposed shelf-life for the finished product can be made at this state of assessment.

Updated photostability study according to ICH Q1B has been performed using both strengths, however the report was not located in the dossier. In addition, the samples should be examined for any changes in appearance as well in line with ICH Q1B requirements. Additional details on photostability study (details on batches included in the study, study design, presentation of samples, tested parameters, obtained results etc.) should be included in the updated section 3.2.P.8.

Since additional data on photostability study is requested, final conclusions cannot be made on the required storage conditions at this stage of assessment. However, no restrictions for storage temperature are needed since data from accelerated studies are satisfactory.

Freeze thaw study has been performed and conclusion that no difference was noted for the tested quality attributes (assay, related substances, dissolution, and water content) between capsules subjected to freeze thaw cycles and control samples is acknowledged.

No in-use stability study for the finished product has been conducted and this is supported. There is no indication from stability and stress studies that the drug product may be susceptible to deterioration. Therefore, in line with EMA Q/A, in-use stability studies for this finished product do not need to be undertaken and no shelf-life after first opening is necessity to be established for this particular medicinal product.

A shelf-life for both strengths with the storage condition of "This medicinal product does not require any special storage conditions" is requested. No clear conclusions on the requested shelf-life and conditions can be made as unresolved issues remain. See LoQ.

3.1.3.5. Biosimilarity

Not applicable.

3.1.3.6. Post approval change management protocol(s)

The applicant proposes to delete parameters for control of particle size, residue on ignition test and microbiological purity from active substance specification via Post Approval Change Management Protocol (PACMP). The proposed changes are described. The risk assessment of the impact of the change on product quality has been provided, along with evaluation on the appropriateness of the control strategy. It is also justified why these changed are grouped in one PACMP. Present/proposed comparison of 3.2.S.4.1 documentation before/after implementing this PACMP is submitted. However, before final conclusion on acceptability of PACMP, issues identified should be resolved.

With respect to the reporting of the implementation of the change to the relevant competent authorities using the existing variation procedures, a Type IA / IAIN variation (implemented prior to

notification) is proposed. The applicant´s proposal to classify the variations as Type IA is considered acceptable providing that the identified issues are resolved.

3.1.3.7. Adventitious agents

Not applicable

3.1.3.8. GMO

Not applicable

Not applicable

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

A major objection on nitrosamine impurities in API and finished product has been raised. (**MO**)

From a quality perspective the product is not approvable since a major objection and several other concerns regarding Module 3 and SmPC have been raised.

3.2. Non-clinical aspects

3.2.1. Introduction

Troriluzole is a tripeptide prodrug conjugate of riluzole, which is a member of the benzothiazole class and is the active ingredient in Rilutek. Riluzole is currently approved for the treatment of ALS.

Due to widespread clinical use of riluzole globally since its first approval in 1995, the applicant considered that it was not necessary nor would it have been ethical to repeat all non-clinical testing of troriluzole as troriluzole rapidly converts to riluzole, the active moiety.

Troriluzole is intended to provide improved systemic exposure of riluzole by means of reduced pharmacokinetic (PK) variability via diminished first-pass metabolism, improved posology (i.e., avoid negative food effects, potential for once-daily dosing), and diminished liability for transient liver function tests (via diminished first-pass metabolism, reduced portal vein concentrations of riluzole, and reduced molar burden of riluzole as a result of improved bioavailability). As a prodrug, troriluzole is intended to persist long enough in plasma prior to conversion to riluzole to mitigate loss of riluzole by first-pass metabolism. Troriluzole is expected to provide systemic exposure of riluzole that equals or exceeds the expected minimally clinically efficacious exposure of riluzole.

No primary pharmacology studies were conducted using troriluzole as troriluzole rapidly converts to riluzole, the active moiety. In most non-clinical studies, the C_{max} of troriluzole was REDACTED of the riluzole C_{max}. The finding of low to no exposure to troriluzole at therapeutically relevant doses suggests that there is a very low risk for troriluzole-mediated effects on safety pharmacology parameters. Nevertheless, troriluzole was assessed in a battery of safety pharmacology studies including hERG assays, in-vivo cardiovascular assessment in conscious monkeys, respiratory assessment in rats, and neurobehavioral assessment in rats. In addition, a PK programme including investigations on the major metabolite N-methyl diketopiperazine (also known as l-methylpiperazine-2,5-dione; referred to as DKP metabolite), and an adapted toxicology programme were submitted. Specifically, no carcinogenicity and extensive reproductive toxicity studies, juvenile toxicity studies, phototoxicity, local tolerance, antigenicity/immunotoxicity studies and studies on dependence potential were performed with

troriluzole, which was justified by the marginal exposure of animals towards troriluzole and the fast conversion to riluzole with a known toxicity profile and clinical experience.

3.2.2. Pharmacology

3.2.2.1. Primary pharmacodynamic studies

Neither in-vitro nor in-vivo primary pharmacodynamics studies have been conducted for troriluzole nor was literature discussed concerning the claimed mode of action in SCA including SCA3 treatment. The provided rational for SCA treatment remains weak and contentious. Even the cited literature discusses the proposed "multivalent" mode of action for riluzole critically in SCA treatment. Since riluzole is not approved for SCA treatment and clinical efficacy has not been shown for motor function, muscle strength or motor symptoms in the approved indication of ALS treatment, a detailed discussion on the claimed efficacy and pharmacological activity of riluzole in SCA would have been appreciated respecting accessible literature data. For example, several non-clinical SCA models for different SCA genotypes in animals are available. In addition, such data are available for riluzole in the literature (e.g. Nag N. et al. 2013 for SCA1) and the claimed pharmacological activity of riluzole should have been discussed critically by the applicant. It is supported that in-vivo studies conducted with troriluzole are not needed, but a critical discussion of these literature data are expected in general.

Further, Schmidt et al. (2016) analysed the long-term treatment of riluzole in a transgenic SCA3 mouse model with surprisingly negative effects on Purkinje cell functionality. To our knowledge, this is the only study evaluating potential effects of riluzole treatment on SCA3 in a non-human in-vivo disease model. The authors of this studies discuss that riluzole might have some detrimental effects on accumulation of insoluble attaxin-3 protein which might have some implications on long-term safety. However, the relevance of each SCA model is limited for humans and would be superseded by the availability of clinical data.

The applicant further implicates that a main in-vivo metabolite of troriluzole, which is not related to riluzole, 1-methylpiperazine-2,5-dione (DKP), is pharmacological non-active. No supporting in-vitro data beside a screening panel for secondary pharmacology effects (TW04-0014561) were provided or respective literature was discussed. However, in a mini-review Cornacchia et al. (2012) discussed the neuroprotective properties of substances with a 2,5-diketopiperazine scaffold. DKP contains only a minimal substitution compared to those substances that were recognised with neuroprotective activity.

3.2.2.2. Secondary pharmacodynamic studies

The applicant conducted an adequate panel of non-GLP in-vitro tests for secondary pharmacology of troriluzole, riluzole and DKP. For troriluzole, a significant inhibition at the analysed maximum concentration was only reached for the norepinephrine transporter (NET), which was also shown for riluzole in the same assay and is therefore clinically known from riluzole treatment in ALS patients. All three assays were conducted at concentrations well in excess of the exposures at the MRHD and provide adequate multiples of exposure.

3.2.2.3. Safety pharmacology programme

A GLP-compliant safety pharmacology battery has been performed with troriluzole in line with ICH S7A/B. No additional data were provided or discussed for riluzole.

High safety margins for hERG inhibition are given for troriluzole due to the low exposure after clinical administration of 200 mg in humans (study no. BHV4157-101: Cmax ss = 3.42 ng/mL (MW = 419.40 g/mol; protein binding not evaluated and therefore not included in the calculation; ~8 nM). But no

available riluzole hERG data were discussed by the applicant. The clinical exposure to riluzole after administration of Rilutek is lower according to the EU-SmPC than those expected for Dazluma, resulting in Cmax of 173 ng/mL and 284 ng/mL respectively. Nevertheless, no signs of arrhythmia are noticed from the GLP in-vivo cardiovascular telemetry study in monkeys and a clinical TQT study (study no. BHV4157-108) did not show potential for QTc prolongation. This issue is therefore not pursued further. Further cardiovascular evaluation in the monkey telemetry study resulted in either a direct, or indirect mild, reversible, dose-related and reversible increase (5.1, 7.7% and 9.9% increases relative to baseline at 3, 10 and 30 mg/kg, respectively compared to 2.7 % in controls) in systolic arterial blood pressures (SABP) between 1.25 and 6.00 hours post dose. Roughly estimated, a safety margin of 6 to the intended clinical efficacious dose is expected at the highest dose of 30 mg/kg (1882 ng/mL). This expected low safety margin was further confirmed by the occurrence of hypertension in clinical studies. SABP elevation and the further shown periods of sedation during 2 and 4 hours after dosing, are related to riluzole exposure. Troriluzole's exposure is low in monkeys and only occurs during the first hour of administration. Hypertension was named as an adverse reaction in the US prescribing information for Rilutek, while not further mentioned in the EU SmPC.

Respiratory effects were evaluated in head-out plethysmographs with restraint rats. No effects were shown on respiration up to 30 mg/kg (nominal 25.5 mg/kg). No exposure was evaluated in this study. However, similar doses were analysed in rats with respect to troriluzole and riluzole exposure for repeat-dose toxicity. From these studies (study no. 2584-001-001 and 3113-059) tmax of troriluzole in rats is expected at ~0.25-1 hours and for riluzole at 4 hours post dose. Although tmax might have been missed for troriluzole as well as for riluzole by the study design, the major effects on core battery are expected by riluzole and a potential lack of non-clinical information is superseded by clinical safety data. DKP tmax is further expected at 2 hours post-dose and potential related effects are covered by repeat-dose toxicity studies.

CNS related effects were analysed as part of a 7-day repeat-dose GLP toxicity study in rats. Troriluzole administration resulted in the known sedative effects of riluzole at the 1 hour-point of evaluation for FOB, since troriluzole was only measured during the first hour post dose and only in the highest dose. The applicant defines the NOAEL of the study for general target organ toxicity at 30 mg/kg/day, which is supported. However, no NOEL was defined for CNS effects, which would be at 3 mg/kg/day. The riluzole exposure of the 10 mg dose in rats, that resulted in first although statistically not significant pharmacodynamics effects, is similar to the human exposure at 200 mg while the multiple of exposure is only 2-fold at 30 mg/kg. However, these detrimental neurological effects are well known and due to an exaggerated pharmacology of riluzole.

3.2.2.4. Pharmacodynamic drug interactions

No analysis of pharmacological drug-drug interaction was provided and is not considered necessary.

3.2.3. Pharmacokinetics

A series of in-vitro ADME studies in a variety of biological matrices and in-vivo PK and TK studies were conducted with troriluzole in mouse, rat, rabbit, and cynomolgus monkey.

In addition to the non-clinical pharmacokinetic information provided for troriluzole, non-clinical pharmacokinetic information for riluzole is well known due to widespread clinical use of the active metabolite riluzole.

Analytical methods have been developed and validated or qualified for troriluzole and riluzole in plasma of rat, mouse, rabbit and cynomolgus monkey and in for troriluzole, riluzole and DKP metabolite in rat and cynomolgus monkey plasma and urine.

Several analytical methods for use in pharmacokinetic studies have been adequately qualified for quantification of troriluzole, riluzole and DKP metabolite in rat and cynomolgus monkey plasma and urine.

Troriluzole, but not riluzole, is a substrate of the intestinal proton-coupled peptide transporter (PepT1). Therefore, it is assumed that troriluzole is actively absorbed in the gut via the PepT1 transporter.

PK and TK studies suggest that troriluzole is rapidly metabolised to riluzole and the DKP metabolite in-vivo in mice, rats, monkeys and rabbits with negligible plasma exposure to troriluzole but significant exposure to riluzole and the DKP metabolite. The ratio of DKP metabolite to riluzole plasma AUC (on a molar basis) was approximately 0.7 in rats and 1.4 in cynomolgus monkeys. After oral doses of troriluzole that provide a therapeutically relevant exposure of riluzole, troriluzole plasma concentrations, if detectable, are only measurable shortly after dosing (1 to 2 hours).

In rats treated with troriluzole, riluzole was rapidly formed after oral administration of troriluzole with t_{max} of 2-8 h. Exposure to riluzole generally increased dose-dependently, but in a more than dose-proportional manner probably due to saturation of one or more riluzole clearance pathways. There were no consistent sex-related differences on exposure to riluzole across the repeat-dose toxicity studies in rats. There was a tendency for riluzole to accumulate after longer-term repeated dosing of troriluzole.

In cynomolgus monkeys dosed orally with troriluzole, riluzole was rapidly formed with a t_{max} of around 2-6 hours and plasma riluzole exposures were measurable at all dose levels and all days of dosing. The mean C_{max} and AUC_{0-t} values of riluzole increased dose-dependently but with no consistent trend for dose-proportionality across the studies. There was no evidence of troriluzole or riluzole accumulation after repeated dosing. There were no apparent sex differences in exposure in cynomolgus monkeys.

Similar pharmacokinetic properties for riluzole were also found in Tg.rasH2 mice and pregnant rats and rabbits after treatment with troriluzole.

A reduced programme of distribution studies has been performed by the applicant. These include distribution studies of troriluzole and riluzole across the blood brain barrier and protein binding studies of the DKP metabolite.

Riluzole but not troriluzole was detected in brain of rats after oral administration of troriluzole. The brain to plasma ratios for riluzole were similar after administration of riluzole and troriluzole.

Low or no protein binding to human plasma, human serum albumin, and human AGP were observed for the DKP metabolite.

Protein binding studies with troriluzole have not been performed as it is not stable in plasma from human and animals and is rapidly converted to riluzole.

Clinical study data (clinical study BHV4157-104) showed that riluzole is 98.4% bound to plasma proteins in healthy subjects and 97.4% bound to plasma proteins in subjects with moderate hepatic impairment.

No whole body tissue distribution studies have been performed after administration of troriluzole and no data have been provided for riluzole and DKP.

No placental transfer studies and studies on excretion into milk of lactating animals of breast-feeding women have been performed with troriluzole and no data have been provided for riluzole.

Troriluzole was not stable in human, rat, dog and monkey plasma. Troriluzole was cleaved by aminopeptidases in human plasma in-vitro but not by carboxy- and endo-peptidases and esterases. In human liver microsomes metabolism of troriluzole occurs via CYP450-independent mechanisms.

In-vitro studies demonstrated that troriluzole disappeared rapidly in human, rat, dog, and monkey hepatocytes, in monkey liver S9, and in human, rat, dog, and monkey plasma but disappeared much more slowly in human, rat, dog, and monkey liver microsomes.

Comparative in-vitro data with troriluzole in human and animal hepatocytes showed that the rat and cynomolgus monkey are relevant species for toxicity studies based on the metabolite profile.

In human and animal hepatocytes the metabolites M1 to M6 were found, but have not been identified and quantified and no comparison between the metabolism of troriluzole and riluzole has been performed. The applicant believes that riluzole-related metabolites are the same after troriluzole and riluzole administration and that the only major troriluzole metabolite is the DKP metabolite. Although this has not been experimentally proven, given the high clinical absolute bioavailability of 80% to 90% of riluzole after troriluzole administration and the peptidic nature of the prodrug moiety the view of the applicant is agreed.

In in-vivo metabolism studies in rats and monkeys troriluzole is rapidly metabolised to riluzole and the DKP metabolite. The ratio of DKP metabolite to riluzole plasma AUC (on a molar basis) was approximately 0.7 in rats and 1.4 in cynomolgus monkeys.

Excretion studies in animals are limited to the quantification of troriluzole, riluzole and DKP in urine of rats and cynomolgus monkeys after 7 day of QD administration of troriluzole. These data suggest that renal excretion is a significant elimination pathway of troriluzole, riluzole and DKP. Human study data with riluzole showed that 90.9% of riluzole-related radioactivity is excreted in urine while only 4.7% was excreted in faeces.

In vitro interaction studies on CYP450 enzymes and transporter systems have been performed with troriluzole, riluzole and DKP metabolite.

Troriluzole did not significantly inhibit the metabolic activity of CYP2A6 CYP2B6 CYP2C8 CYP2C9 CYP2C19 and CYP2E1 in human liver microsomes. Troriluzole may have potential for time-dependent inhibition of CYP2B6, is unlikely a time-dependent inhibitor of CYP2C19 and no time dependent inhibitor for all other CYP450 Isozymes. Troriluzole is unlikely an inducer of CYP3A4, but is an inducer of CYP1A2 and CYP2B6 in human hepatocyte cultures.

Transporter inhibition and substrate studies showed that troriluzole was not a substrate and inhibitor of P-gp or BCRP. Troriluzole was an inhibitor of OATP1B1 and OATP1B3 with IC_{50} values of 142 and 85.9 µM, respectively. Troriluzole was not a substrate for OATP1B1 and was inconclusive for OATP1B3.

In CYP enzymes riluzole directly inhibited CYP2B6 and CYP2C8 with IC_{50} values of 37 µM (8,700 ng/mL) and 16 µM (3,700 ng/mL), respectively and was a metabolism-dependent inhibitor of CYP3A4/5 and CYP2B6. Enzyme induction of CYP1A2, CYP2B6, CYP3A4(/5) were observed in cultures of human hepatocytes at concentrations of ≥ 1.2 µM (280 ng/mL), 4 µM (940 ng/mL) and 12 µM (2820 ng/mL), respectively.

DKP is no inhibitor of CYP450 isoenzymes.

Transporter inhibition and substrate studies showed that riluzole was not a substrate or inhibitor of P-gp. Riluzole was an inhibitor of BCRP, OATP1B1, OAT3, and MATE1 with IC_{50} values of 5.14, 60.2, 6.87, and 76.3 µM (1,200; 14,000; 1,600; and 17,900 ng/mL), respectively. Riluzole was not an inhibitor of OATP1B3, OAT1, or MATE2-K under the conditions examined. Riluzole was not a substrate for BCRP, OATP1B1, OATP1B3, or OAT1 under the conditions examined.

DKP did not inhibit BCRP, BSEP, or MDR1 nor did DKP influence MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2.

3.2.4. Toxicology

All in-vivo toxicology studies involved PO administration, the clinically relevant route of dosing. Troriluzole was tested in single and repeat-dose toxicity studies in rats and monkeys as relevant species which produce all major troriluzole metabolites. Both species were also used in the development programme of riluzole (Rilutek SmPC). In addition, rabbits were used in reproductive toxicity studies. A GLP 28-day repeat-dose toxicity study was also performed in hemizygous Tg.rasH2 mice, which was intended as a dose range-finding study for an eventual carcinogenicity study, which finally was not performed.

The pivotal studies were conducted in compliance with GLP. The only non-GLP studies were the single-dose rat and monkey studies, the dose range finding 7-day rat and monkey studies, and the preliminary Ames and chromosomal aberrations studies. These studies were not required to be conducted in compliance with GLPs as they were dose-ranging and exploratory in nature. The troriluzole drug substance batches used in GLP compliant toxicology studies were manufactured under GMP and, hence, are comparable to the lots produced by the same manufacturer for clinical trials.

3.2.4.1. Single dose toxicity

A non-GLP rat single dose toxicity study to define the maximum tolerated dose (MTD) and a non-GLP single dose range finding study as part of a dose escalation study with a wash out phase in monkeys were performed. Toxicological findings after single dose exposure of rats and monkeys were attributed to the known sedative properties of riluzole (MTD rat: 30 mg/kg, MTD cynomolgus monkey: 100 mg/kg). Sever toxicity including death was only observed at doses in high excess to the clinical exposure, e.g. the AUC-based riluzole exposure of cynomolgus monkeys at the MTD of 100 mg/kg was ~80-fold the exposure of patients at the MRHD of 200 mg/day.

3.2.4.2. Repeat-dose toxicity

GLP-conform repeat-dose studies have been completed in rats up to 26 weeks and in monkeys for up to 39 weeks. A GLP 28-day repeat-dose toxicity study was also performed in hemizygous Tg.rasH2 mice.

The GLP studies included evaluations of clinical signs, body weight, food consumption, ophthalmology, electrocardiography and FOB (monkeys only), clinical pathology (haematology, serum chemistry, coagulation, urinalysis), gross pathology, organ weights, and histopathology. Exposure (TK) was determined for troriluzole and riluzole. Major findings in the pivotal studies are displayed in the table below. As exposure towards troriluzole was very low close to the detection limit in all studies only values for riluzole are displayed in the table.

Table 1: Repeat-dose Toxicity Studies with Troriluzole

Study details / ID	**No:Sex / Group**	**Dose (mg/kg/d)**	**Exposure at NOAEL (riluzole M/F combined)**		**Major findings & NOAEL**
			C_{max} ng/mL	AUC ng·h/mL	
Repeat-dose toxicity studies (NOAELs highlighted)					
Mouse (Tg.rasH2 hemizygous)		0 3 10			No drug-related adverse effects up to 30 mg/kg.

28 days Route: PO GLP Troriluzole batch number: A11601756 73481		**30**	**1815** (Day 28)	**22650** (Day 28)	30 mg/kg (not statistically significant): food consumption (M)↓, body weight gain↓ **NOAEL**: **30 mg/kg/day**
Rat (SD) 7 days Route: PO GLP Troriluzole batch number: A11601756 2622-001	10M/10F	0 3 10 **30**	**2805** (Day 7)	**42600** (Day 7)	No drug-related effects on mortality, physical exams, or ophthalmology. ≥10 mg/kg: recumbency, hypoactivity, abnormal gait 30 mg/kg: lethargy, cold to touch; staggered gait, wider foot splay; food consumption↓, body weight gain↓; reticulocytes↓; cholesterol (M)↑; spleen weight (M)↓, thymus weight (M)↓, small thymus (M); cellularity in splenic white pulp (marginal zone, minimal to mild)↓, cellularity (lymphocytes, minimal to moderate) in thymus (F)↓ **NOAEL**: **30 mg/kg/day**
Rat (SD) 4 weeks Recovery: 4 weeks Route: PO GLP Troriluzole batch number: A11601756 2602-001-002	Main: 10M/10F Recovery: 5M/5F TK satellites: none	0 3 10 **30**	**3688** (Day 28)	**64011** (Day 28)	No drug-related effects on mortality, physical exams, ophthalmology, body weight and food consumption, histopathology. ≥10 mg/kg: recumbency, hypoactivity, abnormal gait 30 mg/kg: cholesterol↑; ALT↑; liver weight↑; urine volume↑, urinary pH↑, refractive index↓, specific gravity↓ **Recovery: all findings reversed** **NOAEL: 3 mg/kg/day** **NOAEL (recovery)**: **30 mg/kg/day**

Rat (SD) 26 weeks Recovery: 4 weeks Route: PO GLP Troriluzole batch number: A11601756 73393	Main (26 weeks): 15M/15F Interim: (13 weeks) 15M/15F Recovery: 5M/5F TK satellites: 8M/8F (4M/4F controls)	0 3 **6 (M)** **20 (F)**	**784** **3150** (Day 182)	**11100** **43500** (Day 182)	No drug-related effects on mortality, clinical signs, ophthalmology, haematology, serum chemistry, coagulation, urinalysis, macroscopic findings. ≥3 mg/kg: body weight gain (M) ↓ ≥6 mg/kg: splenic hemosiderin pigment (F)↑ 20 mg/kg: body weight gain (F) ↓; food consumption↓; liver weight↑ **Recovery: all findings reversed** **NOAEL:** **M: 6 mg/kg/day and 20 mg/kg/day (recovery)** **F: 20 mg/kg/day**
Monkey (Cynomolgus) 13 weeks Recovery: 4 weeks Route: PO GLP Troriluzole batch number: A11601756 2602-001-001	4M/4F Recovery: 2M/2F	0 3 6 **20**	**3418** (Day 91)	**36705** (Day 91)	No troriluzole-related adverse findings. 20 mg/kg: liver weight (M)↑ **NOAEL: 20 mg/kg/day**
Monkey (Cynomolgus) 39 weeks Recovery: 4 weeks Route: PO GLP	4M/4F Recovery: 2M/2F	0 3 6 **20**	**3275** (Day 273)	**35600** (Day 273)	No troriluzole-related adverse findings. Three animals died early on study with cause of death to be incidental to drug, procedure-related, or secondary to handling.

Troriluzole batch number: A11601756 31131					**NOAEL: 20 mg/kg/day**

ND = not determined; F = female; M = male

In rats after repeated exposure toxicity findings were restricted to the known pharmacological effects of riluzole, namely sedation and its sequelae including recumbency, hypoactivity, lethargy abnormal gait and reduced body weight gain and food consumption. At higher doses ≥ 20 mg/kg/day increased liver weights accompanied by increases in serum alanine aminotransferase were observed which could be attributed to increased metabolic activity. All findings reversed after recovery from treatment. No additional toxicities were observed which could be related to troriluzole.

In cynomolgus monkeys troriluzole was well tolerated up to 20 mg/kg/day and caused no adverse effects in long-term studies with the exception of reversible increases in liver to body weight ratios without histological correlate. This increase in liver weight can be considered to be an adaptive response to drug metabolism in line with what was observed in rats and toxicity studies with riluzole. Sedative riluzole-related effects were only observed in short-term studies at doses ≥ 30 mg/kg/day.

The NOAEL doses of troriluzole in rats and cynomolgus monkeys resulted in little to no systemic exposure to troriluzole and provided riluzole exposures in excess (usually >> 10-fold) of clinically efficacious concentrations. However, it has to be noted that riluzole is highly plasma protein-bound in humans but plasma protein binding has not been determined in animal species. Therefore, a final assessment of safety margins can only be made after revision of protein binding data in animals (refer to OC in Pharmacokinetics section for details).

In hemizygous Tg.rasH2 mice, no relevant toxicities were observed at doses up to 30 mg/kg/day.

Overall, no unexpected troriluzole- and riluzole-related adverse effects were observed in repeat-dose toxicity studies in rats and cynomolgus monkeys which warrant further clinical monitoring.

3.2.4.3. Genotoxicity

Troriluzole was negative in GLP-compliant in-vitro Ames tests, chromosome aberration assays in human peripheral blood lymphocytes and in an oral in-vivo Micronucleus test performed in rats. In addition, no genotoxic potential is anticipated from riluzole (Rilutek SmPC) and the tripeptide moiety.

The major metabolite DKP was negative in GLP-conform Ames tests and in-vitro micronucleus assays.

Overall based on the weight of evidence, troriluzole and its major metabolite DKB are not considered to be genotoxic in-vitro and in-vivo.

3.2.4.4. Carcinogenicity

No carcinogenicity studies have been performed with troriluzole. The risk for potential troriluzole mediated carcinogenicity was judged to be low because troriluzole was not mutagenic, oral doses of troriluzole do not provide significant systemic exposure of troriluzole in plasma because troriluzole is short lived in plasma and quickly converts to riluzole. In addition, riluzole is neither mutagenic nor carcinogenic in mice and rats (SmPC RILUTEK®). The major metabolite DKP was also shown to be non-mutagenic in-vitro.

Overall, the lack of carcinogenicity studies was sufficiently justified.

3.2.4.5. Reproductive and developmental toxicity

Troriluzole was tested in dose range-finding embryo-foetal developmental studies in rats and rabbits in compliance with GLP regulations. Furthermore, TK studies were conducted in pregnant rats and rabbits. The applicant was granted a waiver from the obligation to carry out reproduction and development studies for both the fertility and early embryonic development and pre- and postnatal development studies. Therefore, no dedicated fertility studies have been conducted with troriluzole. Fertility has been evaluated in repeat-dose toxicity studies by especially evaluating reproductive organs. No troriluzole-related effects were observed.

In the DRF embryo-foetal development study in pregnant rats, adverse dose-dependent decreased activity (sedation) in all dosing groups, and decreased body weights and food consumption only at the highest dose of 30 mg/kg/day troriluzole were observed. Due to the clinical signs, animals at 30 mg/kg troriluzole were terminated early. Necropsy of these dams showed small spleen, adrenal gland enlargement, and pale liver. There was no evidence of embryo-foetal mortality, fetotoxicity, or dysmorphogenesis at the lower doses of 3 and 10 mg/kg/day troriluzole. The NOAEL for maternal toxicity and for embryo-foetal development was 10 mg/kg/day. At the NOAEL, 10 mg/kg/day, there was little to no systemic troriluzole exposure (C_{max}: 1.2 ng/mL). In contrast, that dose resulted in systemic riluzole exposure of 14,200 ng·h/mL (C_{max}: 1,090 ng/mL) on the last dosing day. The AUC-based safety margin over humans for riluzole is 7.9 for this study.

In the DRF embryo-foetal development study in pregnant rabbits, no adverse effects on maternal parameters, and no evidence of embryo-lethality, fetotoxicity, or teratogenicity was observed up to 45 mg/kg/day. At the NOAEL, 45 mg/kg/day troriluzole, there was little troriluzole exposure (AUC_{last}: 205 ng·h/mL). In contrast, that dose resulted in systemic riluzole exposure of 7,450 ng·h/mL on the last dosing day. The AUC-based safety margin over humans for riluzole is 4.1 for this study.

Troriluzole has not been tested in juvenile animals. Troriluzole is not indicated for the use in children. Therefore, juvenile toxicity studies are not needed.

3.2.4.6. Toxicokinetic data

In pivotal TK studies in rats, rabbits (see section Reproductive Toxicity), and cynomolgus monkeys, troriluzole was barely detectable in animals after PO doses of troriluzole that cause supra-therapeutic doses of riluzole. In animals, troriluzole is typically only detectable for up to 2 hours post oral dose across species at concentrations that rarely exceed 10 ng/mL and were generally less than 1% of riluzole concentrations.

In rats riluzole exposure generally increased greater than proportional to dose with a tendency of accumulation probably related to saturation of clearance pathways. There were no noteworthy sex-related differences (e.g. >2-fold) for any of the measured TK parameters.

In cynomolgus monkeys riluzole exposure generally increased dose-proportional and accumulation was only observed in the non-pivotal dose range-finding study at very high doses in monkeys (100 mg/kg/day). There were no noteworthy sex-related differences (e.g. >2-fold) for any of the measured TK parameters.

Overall, good riluzole exposure was achieved in all relevant animal species yielding sufficiently high exposure margins to the MRHD of 200 mg QD. Exposure to the DKP metabolite of rats and cynomolgus monkeys was higher than the anticipated human exposure. However, it has to be noted that riluzole is highly plasma protein-bound in humans, but plasma protein binding has not been determined in animal

species. Therefore, a final assessment of safety margins can only be made after revision of protein binding data in animals (refer to OC in Pharmacokinetics section for details).

3.2.4.7. Tolerance

Studies specific for local tolerance were not conducted with troriluzole. Local tolerance studies were not warranted for an orally dosed, small molecule drug. The non-GLP and GLP toxicology studies included gross and histopathology evaluations of the gastrointestinal organs and tissues. There were no drug-related findings related to local tolerance in rats dosed at 20 mg/kg for 26 weeks or cynomolgus monkeys dosed at 20 mg/kg for 39 weeks.

3.2.4.8. Other toxicity studies

Antigenicity

Due to the nature of troriluzole as small-molecule prodrug of riluzole antigenicity is not anticipated and no immune system-mediated effects have been observed in animals and patients so far. Therefore, dedicated antigenicity studies are not warranted.

Immunotoxicity

No immune suppression, autoimmune potential and hypersensitivity reactions have been observed in animals and patients after troriluzole exposure so far. Therefore, dedicated immunotoxicity studies are not warranted.

Dependence

No information and discussion on the dependence potential of troriluzole/riluzole has been provided.

Nevertheless, in secondary pharmacodynamic receptor screening studies, no relevant influence of troriluzole or its metabolites on receptors which are involved in drug-dependence was identified. In addition, no obvious withdrawal symptoms have been reported after drug cessation of troriluzole in recovery phases of repeat-dose toxicity studies. Together with the knowledge about the mode of action of riluzole and its long-standing clinical experience, no concern was identified regarding a dependence potential of troriluzole which would warrant further non-clinical testing.

Studies on impurities

In total 38 process impurities were subjected to risk assessment in line with ICH M7(R1) guidance. For eight impurities literature data were retrieved showing that they were non-mutagenic. Although the references have not been provided by the applicant, non-mutagenicity of the impurities is acknowledged by the Assessor as all impurities are well-known compounds and are frequently used as synthesis chemicals and observed in many drug substances.

For acetamide a PDE of REDACTED mg/day was proposed without further justification or reference to literature data. However, a PDE of 7.1 mg/day is proposed in a publication by Bercu et al, 2018 retrieved by the Assessor. The PDE is supported.

Potential mutagenic impurities were subjected to two complementary QSAR methods, namely Leadscope Model Applier Version 1.8.2 and Derek Nexus Version 4.05. However, the used software versions are outdated and all analyses should be repeated with the actual versions of the software. In addition, the QSAR reports including detailed expert reviews for equivocal results could not be located in the documentation and should be provided (**OC**).

Two impurities, Impurity-1 (0.96 RRT) at 0.35% and Impurity-2 (0.95 RRT), exceed the ICH Q3A/B qualification threshold and are controlled at a limit of NMT REDACTED. This limit was toxicologically

justified as batch No. REDACTED was used in relevant toxicity studies containing Impurity-1 (0.96 RRT) at 0.35% and Impurity-2 (0.95 RRT) at 0.44%.

Phototoxicity studies

Phototoxicity assessments were not conducted using troriluzole because troriluzole does not accumulate in animals. In each in-vivo PK and TK assessment for studies ranging from single doses to chronic QD dosing, troriluzole was barely detectable in plasma shortly after dosing. When troriluzole was detectable in plasma of animals, the duration of exposure was short, typically less than 2 hours. Since troriluzole does not persist in-vivo in mice, rats, rabbits or cynomolgus monkeys, troriluzole is unlikely to accumulate in tissues. Therefore, phototoxicity assessment of troriluzole was considered to be not relevant.

3.2.5. Ecotoxicity/environmental risk assessment

The applicant submitted an ERA Phase I for the active substance troriluzole hydrochloride monohydrate.

The environmental risk assessment is complete. The outstanding issues are resolved.

Based on prevalence data taken from the orphan designation EU/3/21/2553 for the treatment of spinocerebellar ataxia the Fpen has been refined and used for calculation of a refined PECsurfacewater resulting in a value of 0.003 µg/l. The literature on prevalence cited by the applicant was provided.

As the PECsurfacewater does not exceed the action limit of 0.01 µg/l it is concluded that a Phase II testing is not triggered. The provided calculation is acceptable and the risk assessment stopped in Phase I of the procedure.

The submitted study report for the experimental determination of the log Kow value of troriluzole hydrochloride monohydrate was performed in accordance with the OECD test guidelines and can be evaluated as valid. The log Kow value is below the trigger of 4.5. A PBT assessment is therefore not required.

Summary of main study results

Substance (INN/Invented Name): troriluzole hydrochloride			
CAS-number (if available): 1289023-67-1 (free base)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log *K*ow	OECD 107	0.04 pH 5.5 1.02 pH 7 1.14 pH 8.8	Potential PBT (N) pending
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PECsurfacewater, refined with prevalence (orphan disease)	0.003	µg/L	< 0.01 threshold (Y)

3.2.6. Discussion on non-clinical aspects

Pharmacology

Although the applicant's presentation of pharmacology elicits major deficiencies, no further concerns are raised. SCA3 is an ultra-rare disease without available therapeutic options so far. A general discussion of riluzole's neuroprotective properties justified the clinical development of troriluzole for SCA treatment without knowledge of the detailed underlying mode of action. Clinical efficacy and safety, if shown, would supersede any lack of in-depth knowledge of pharmacodynamics in SCA or deficiencies in the analysis of core battery related effects anyway.

Pharmacokinetics

A series of in-vitro ADME studies in a variety of biological matrices and in-vivo PK and TK studies were conducted with troriluzole in mouse, rat, rabbit, and cynomolgus monkey. Troriluzole systemic exposure is negligible as it is rapidly converted to riluzole and DKP metabolite in vivo. Therefore pharmacokinetic data for riluzole and DKP metabolite are important.

However, a range of non-clinical pharmacokinetic data for riluzole and DKP metabolite are missing in this MAA. These include data on whole tissue distribution of riluzole and DKP metabolite, protein binding of riluzole, metabolism of riluzole and DKP metabolite. These data are essential for a full assessment of troriluzole pharmacokinetics.

Tissue distribution studies were limited to study on brain distribution of troriluzole and riluzole and protein binding study of DKP metabolite.

Protein binding data for animal species used in non-clinical toxicology studies were provided for riluzole based on the FDA original Rilutek NDA (20-599) filed in 1995. However, the cited report has not been submitted. (**OC**)

No whole body tissue distribution studies have been performed after administration of troriluzole. The peptide prodrug portion of troriluzole is expected to be embedded into endogenous protein metabolism and only tissue distribution of riluzole would be relevant. Data have been provided for riluzole based on the FDA original Rilutek NDA (20-599) filed in 1995. Some difference in transporter systems have been observed between troriluzole and riluzole which may lead to differences in tissue distribution. The data for tissue distribution available for riluzole should be provided. Potential differences in tissue distribution of riluzole when administered as troriluzole instead of riluzole should be discussed. (**OC**)

No placental transfer studies and studies on excretion into milk of lactating animals of breast-feeding women have been performed with troriluzole and no data have been provided for riluzole. It is assumed that due to the rapid conversion of troriluzole to riluzole and DKP in-vivo, no relevant placental or milk transfer of troriluzole occurs. Therefore, data for riluzole may be most relevant. However, such data have not been provided by the applicant.

In human and animal hepatocytes the metabolites M1 to M6 were found (15FOX 19R2) but have not been identified and quantified. Furthermore, no comparison between the metabolism of troriluzole and riluzole has been performed. Given the high clinical absolute bioavailability of 80% to 90% of riluzole after troriluzole administration and the peptidic nature of the prodrug moiety the view of the applicant is agreed.. The applicant believes that riluzole-related metabolites are the same after troriluzole and riluzole administration and that the only major troriluzole metabolite is the DKP metabolite. Although this has not been experimentally proven, given the high clinical absolute bioavailability of 80% to 90% of riluzole after troriluzole administration and the peptidic nature of the prodrug moiety this view is agreed.

In-vivo metabolism studies for troriluzole are limited to detection of riluzole and DKP metabolite in rats and monkeys. It is not known whether and to which amount the metabolites M1 to M6 are also formed in-vivo in human and animal or if there are troriluzole-specific metabolites in-vivo in addition to DKP metabolite.

Before these issues are not resolved, the reference to riluzole data for non-clinical studies is not acceptable. (**OC**)

In-vitro studies showed that troriluzole is cleaved by aminopeptidase in human plasma. Aminopeptidases are also present in gastrointestinal tract and the possibility that some cleavage of troriluzole also occurs in gastrointestinal tract after oral administration cannot be excluded. However, its impact on bioavailability of riluzole dosed as troriluzole is considered low.

Excretion studies in animals are limited to the quantification of troriluzole, riluzole and DKP in urine of rats and cynomolgus monkeys after 7 day of QD administration of troriluzole. These data suggest that renal excretion is a significant elimination pathway of troriluzole, riluzole and DKP.

Since troriluzole rapidly converts to riluzole in plasma, excretion studies of riluzole are also relevant for troriluzole. Although animal excretion data for riluzole have not been provided and discussed by the applicant, human study data with riluzole showed that 90.9% of riluzole-related radioactivity is excreted in urine while only 4.7% was excreted in faeces (Martinet M et al., 1997).

In vitro interaction studies on CYP450 enzymes and transporter systems have been performed with troriluzole, riluzole and DKP metabolite.

Many study reports for in-vitro drug interaction studies performed with troriluzole are of low quality. However, given that troriluzole is a prodrug which is rapidly converted to riluzole in-vivo its exposure is negligible and drug interactions are unlikely.

It is likely that some effects of troriluzole observed in the in-vitro systems used for the interaction studies could be attributed to riluzole, due to conversion of troriluzole to riluzole under the experimental conditions. This has not been considered by the applicant.

The concentrations at which effects of riluzole were observed in in-vitro drug interaction studies were almost well above the maximum concentration of riluzole at the therapeutic troriluzole dose of 200 mg QD (C_{max} 285 ng/mL in clinical study BHV4157-101 after 200 mg dose of troriluzole), except for CYP1A2 induction, were effects on mRNA expression and activity were already observed at ≥ 1.2 µM (280 ng/mL). CYP1A2 is the principal CYP isozyme for riluzole metabolism resulting in N-hydroxylation of riluzole and induction of this enzyme may lead to self-induction of its metabolism. However, the lack of time-dependency in observed PK of riluzole in clinical studies suggests that riluzole does not induce its own metabolism (Please also refer to the clinical AR).

Toxicology

In repeat-dose toxicity studies no unexpected troriluzole- and riluzole-related adverse effects were observed in rats, mice and cynomolgus monkeys which warrant further clinical monitoring. Troriluzole and its metabolites are not genotoxic and carcinogenicity testing was further not considered necessary due to low troriluzole exposure of animals.

Concerning reproductive toxicity, the applicant was granted a waiver from the requirement to conduct reproduction and development studies for both the fertility and early embryonic development and pre- and postnatal development studies. DRF studies on embryo-foetal development were performed in rats and rabbits including toxicokinetic measurements.

The wording of the SmPC section 4.6 and 5.3/Reproductive Toxicity might have to be changed depending on the answer of the applicant to the other concerns raised (**SmPC comment**).

Potential mutagenic impurities were subjected to two complementary QSAR methods, namely Leadscope Model Applier Version 1.8.2 and Derek Nexus Version 4.05. However, the used software versions are outdated and all analyses should be repeated with the actual versions of the software. In addition, the QSAR reports including detailed expert reviews for equivocal results could not be located in the documentation and should be provided (**OC**).The lack of phototoxicity, local tolerance, antigenicity/immunotoxicity studies and studies on dependence potential with troriluzole was justified by the marginal exposure of animals towards troriluzole and the fast conversion to riluzole with a known toxicity profile and clinical experience, which is acceptable.

Considering the above data, troriluzole hydrochloride is not expected to pose a risk to the environment.

Assessment of paediatric data on non-clinical aspects

An application for a product specific paediatric investigation plan (PIP) waiver was submitted on 5 August 2021 and the applicant chose to withdraw this application on 29 October 21 following receipt of the Day 30 report. Subsequently, an application for a PIP, including a waiver in children from birth to less than 11 years of age was issued an EMA decision (P/0044/2023) on 31 January 23.

3.2.7. Conclusion on non-clinical aspects

No pharmacology studies have been performed with troriluzole and no in-depth discussion on riluzole has been provided. Nevertheless, based on the clinical experience with troriluzole and that SCA3 is an ultra-rare diseases the lack of this information is acceptable.

The applicant's non-clinical data of troriluzole's pharmacokinetics are complete, however, there are still missing data on protein binding of riluzole and lack of a discussion on differences in tissue distribution of riluzole and troriluzole.

Overall, the toxicology programme revealed that troriluzole was well tolerated in mice, rats and monkeys. Observed toxicities were related to riluzole and no additional toxicities were observed for troriluzole which would warrant clinical monitoring. Several concerns are still not resolved regarding the lack of data on reproductive toxicity studies and studies on impurities. The lack of phototoxicity, local tolerance, antigenicity/immunotoxicity studies and studies on dependence potential with troriluzole was reasonably justified.

Troriluzole hydrochloride is not expected to pose a risk to the environment.

No major objections were identified which preclude marketing authorisation from a non-clinical point of view. However, several Other concerns were identified which have to be addressed before a final conclusion on the safety profile and SmPC wording of troriluzole can be made.

3.3. Clinical aspects

- **Tabular overview of clinical studies**

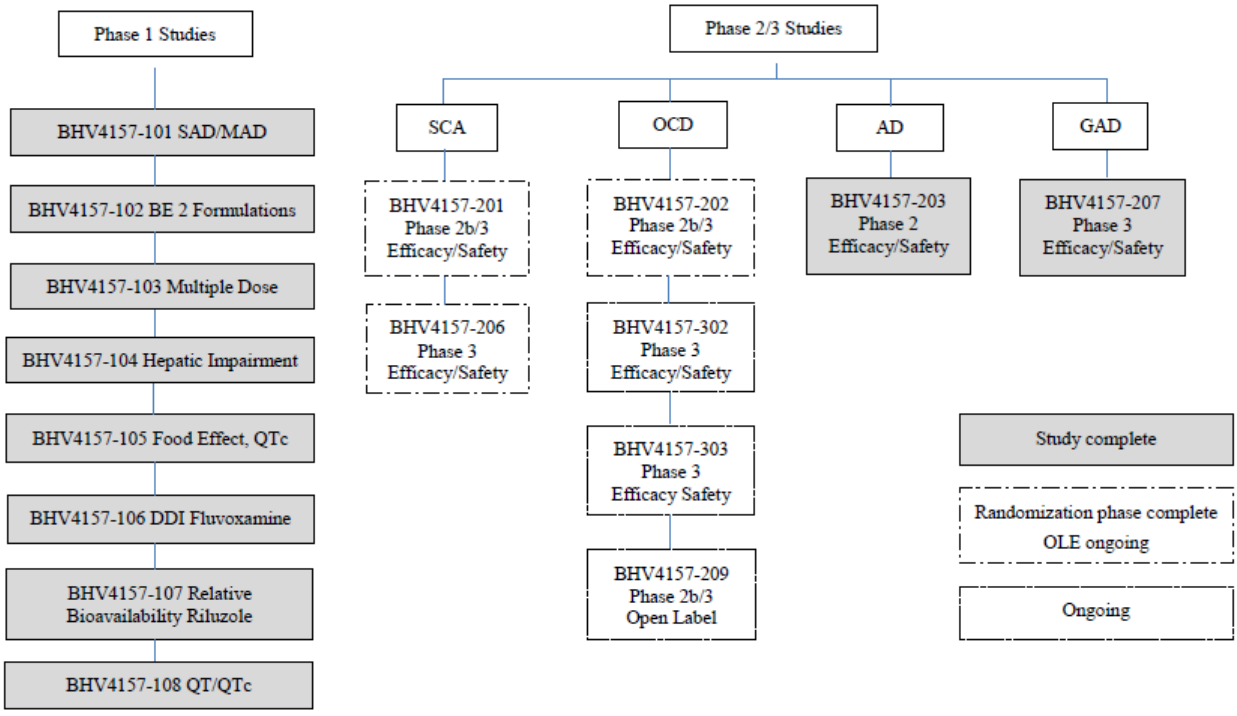
As of 21-Jul-2023, more than 2,000 subjects were administered study drug (troriluzole, placebo, riluzole, fluvoxamine, or moxifloxacin) in 9 Phase 1 studies in healthy subjects (N = 267) or subjects with hepatic impairment (N = 8), and in 8 ongoing or completed Phase 2/3 studies in subjects with spinocerebellar ataxia or SCA (N = 358), obsessive-compulsive disorder or OCD (N = 650), generalised anxiety disorder or GAD (N = 390), or Alzheimer's disease or AD (N = 349).

As of 25-July-2024, 1,998 subjects were administered at least 1 dose of troriluzole across the Phase 1, 2, and 3 studies. The troriluzole doses evaluated ranged from single doses of 17.5 up to 840 mg, and multiple-dose regimens of up to 280 mg QD (140, 200, or 280 mg) or 100 mg BID, including:

- 220 subjects who received troriluzole single or multiple doses ranging from 17.5 through 840 mg in the 10 clinical pharmacology studies (BHV4157-101, BHV4157-102, BHV4157-103, BHV4157-104, BHV4157-105, BHV4157-106, BHV4157-107, BHV4157-108, and BHV4157-110)
- 1,778 subjects who received troriluzole 140, 200, or 280 mg QD, or 100 mg BID in 6 Phase 2/3 studies in subjects with SCA (BHV4157-201, BHV4157-206), OCD (BHV4157-202, and BHV4157-209), GAD (BHV4157-207), or AD (BHV4157-203)
- Subjects with OCD were randomised 1:1 to receive blinded study drug (troriluzole up to 280 mg QD or placebo), in the 2 Phase 3 ongoing and blinded studies BHV4157-302 (N = 369) and BHV4157-303 (N = 488).

A complete list of all clinical studies included in this application is provided in Module 5.2 and displayed in the following Figure.

Figure 1: Clinical Studies in the Troriluzole Clinical Development Programme



3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

The pharmacokinetic profiling of troriluzole focuses on the active moiety riluzole. Following oral administration, troriluzole concentrations in plasma are very low (REDACTED % of riluzole) and transient.

Absorption

Assuming that the absolute BA of riluzole from Rilutek is 60%, the absolute BA of riluzole from troriluzole is estimated to be 80% to 90%. T_{max} of riluzole was comparable at concentrations between 100 and 280 mg of troriluzole.

To compare the BA of riluzole following administration of troriluzole to that of riluzole tablets, healthy subjects under fasting conditions (N = 23) were randomised to receive single doses of troriluzole (Treatment A: 100 and Treatment B 280 mg) and riluzole (Treatment C: 50 mg) in Study BHV4157-107.

Table 2: Ratios (A/C), 90% Geometric Confidence Intervals

Parameter (unit)	Geometric LSM		Ratio A/C[a] (%)	90% Geometric CI[b]		Intrasubject CV (%)[c]	Intersubject CV (%)[d]	p-value
	Treatment A	Treatment C		Lower (%)	Upper (%)			
[redacted]								
$AUC_{0\text{-inf}}$ (h•ng/mL)	798.98	570.83	139.97	130.78	149.80			
C_{max} (ng/mL)	130.19	128.95	100.96	86.25	118.18			

[a] Calculated using LSM according to the formula: $\exp^{(DIFFERENCE)} * 100$
[b] 90% Geometric CI calculated according to the formula: $\exp(DIFFERENCE \pm t_{(dfResidual)} * SE_{DIFFERENCE}) * 100$
[redacted]

Treatment A (Test 1): 1 × 100 mg troriluzole capsule administered orally under fasted conditions
Treatment C (Reference): 1 × 50 mg riluzole tablet administered orally under fasted conditions

Similarly, dose-normalised $AUC_{0\text{-inf}}$ was 50% higher for troriluzole 280 mg than for riluzole 50 mg. Assuming 60% absolute BA of riluzole from oral riluzole, the absolute BA of riluzole from troriluzole is estimated to be 80% to 90%.

Table 3: Ratios (B/C), 90% Geometric Confidence Intervals

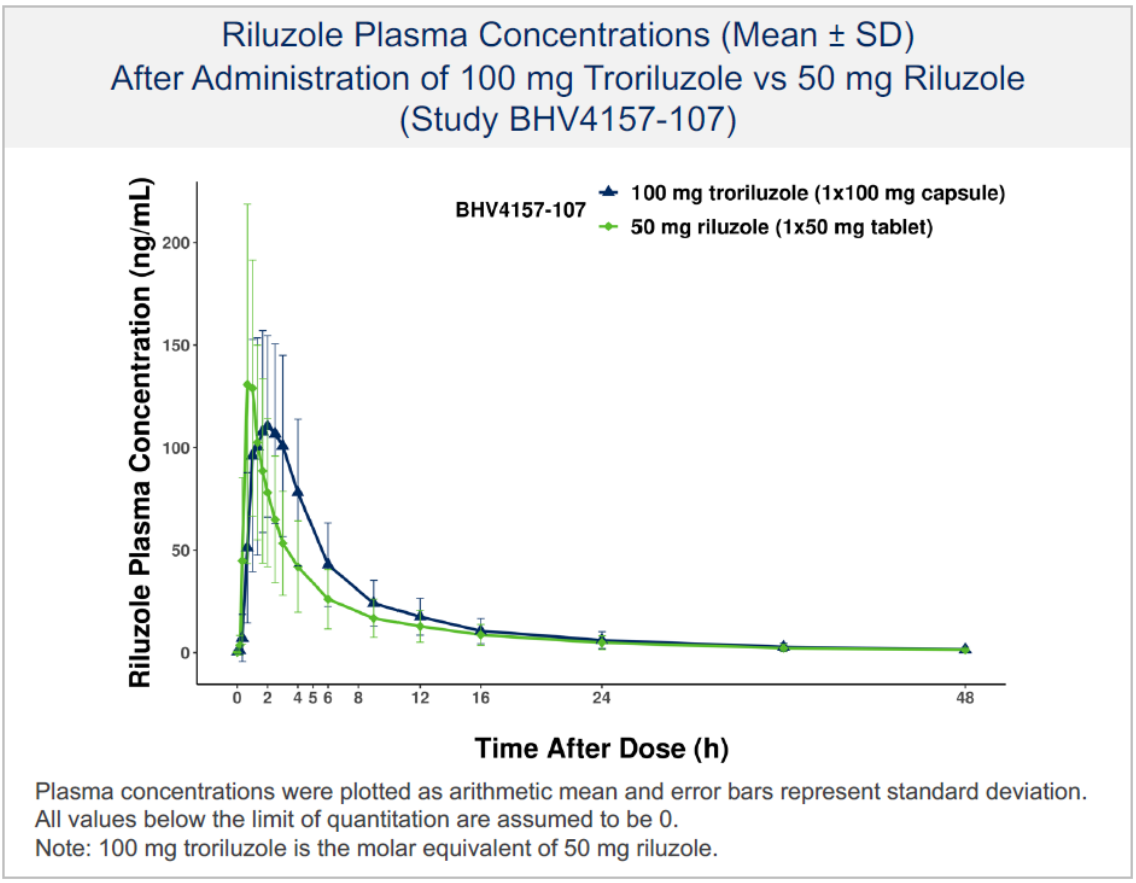
Parameter* (unit)	Geometric LSM		Ratio B/C[a] (%)	90% Geometric CI[b]		Intrasubject CV (%)[c]	Intersubject CV (%)[d]	p-value
	Treatment B	Treatment C		Lower (%)	Upper (%)			
[redacted]								
$AUC_{0\text{-inf}}$ (h•ng/mL/mg)	856.54	570.83	150.05	140.36	160.41			
C_{max} (ng/mL/mg)	131.14	128.95	101.70	87.09	118.76			
[redacted]								

[a] Calculated using LSM according to the formula: $\exp^{(DIFFERENCE)} * 100$
[b] 90% Geometric CI calculated according to the formula: $\exp(DIFFERENCE \pm t_{(dfResidual)} * SE_{DIFFERENCE}) * 100$
[redacted]

Treatment B (Test 2): 2 × 140 mg troriluzole capsule administered orally under fasted conditions
Treatment C (Reference): 1 × 50 mg riluzole tablet administered orally under fasted conditions

While C_{max} was similar between the 3 treatments, riluzole T_{max} was later for troriluzole by 1 hour. The higher extent of riluzole absorption, even when dose-normalised, demonstrates that troriluzole enhances riluzole BA relative to riluzole tablets, likely attributed to bypassing of first pass metabolism, consistent with absorption of troriluzole in the gut via PepT1 and the later T_{max} of riluzole following troriluzole administration.

Figure 2: Mean (± SD) Riluzole Plasma Concentrations (Treatments A(blue) and C (green))



The extent of oral BA of riluzole after oral administration of troriluzole is 40% to 50% higher than after oral riluzole. Bioequivalence has been investigated in study BHV4157-102 between the highest strength of the commercial formulation as stated in module 3 (treatment A) and pure active substance filled in hard gelatine capsules (treatment B; prototype formulation). Cmax and AUC for the main metabolite riluzole in plasma were within conventional acceptance criteria (80-125%), and therefore bioequivalence can be concluded for the active metabolite.

Troriluzole may be taken regardless of food. Administration of troriluzole with a high-fat meal reduced riluzole Cmax by 22% but did not impact AUC. Although, the results of study BHV-4157-101 are considered supportive only, because it was conducted with a different formulation it can be concluded from the second food effect study BHV-4157-105 that food intake had no significant effect on AUC, although Tmax is slightly increased and Cmax is decreased.

Table 4: *Ratios (B/A), 90% Confidence Intervals*

	Geometric LSM			90% Geometric CIb		p-values		
Parameter (unit)	**Treatment B**	**Treatment A**	**Ratio B/Aa (%)**	**Lower (%)**	**Upper (%)**	**Sequence**	**Period**	**Treatment**
[redacted]								
$AUC_{0\text{-}inf}$ (h•ng/mL)			98.39	91.57	105.72			
C_{max} (ng/mL)			77.56	68.83	87.39			

[a] Calculated using least squares means according to the formula: exp (DIFFERENCE) * 100
[b] 90% Geometric CI calculated according to the formula: exp(DIFFERENCE ± $t_{(dfResidual)}$ * $SE_{DIFFERENCE}$)*100
[redacted]
Treatment A: Troriluzole capsule 280 mg (2 × 140 mg) administered under fasted conditions.
Treatment B: Troriluzole capsule 280 mg (2 × 140 mg) administered under fed conditions.

The proposed wording that the troriluzole can be administered regardless of food is considered justified.

Distribution

The levels of unbound riluzole after troriluzole administration are negligible for the proposed dose range and values are comparable to oral riluzole.

A distribution volume of riluzole as main metabolite of troriluzole is reported to be 500 -3000 l.

Elimination

Troriluzole is a tripeptide prodrug of riluzole. It is actively absorbed in the gut and cleaved by aminopeptidases.

It is assumed that the subsequent metabolism of troriluzole after cleavage is comparable to orally administered riluzole.

Riluzole $T_{1/2}$ (9 – 15 h) of riluzole after administration of troriluzole seems to be comparable to results reported for oral riluzole.

The DKP metabolite (N-methyl diketopiperazine) concentrations were greater than those of riluzole and troriluzole through 24 hours, and the mean t½ for the DKP metabolite was similar or less than the mean t½ of riluzole.

Figure 3: Formation of Riluzole and DKP Metabolite from Troriluzole

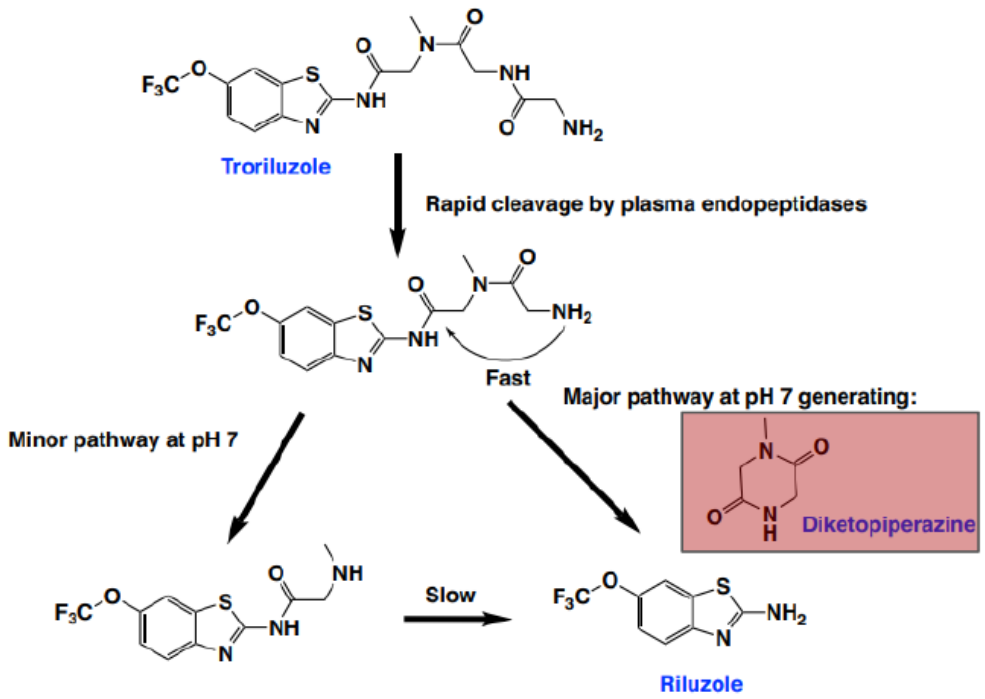
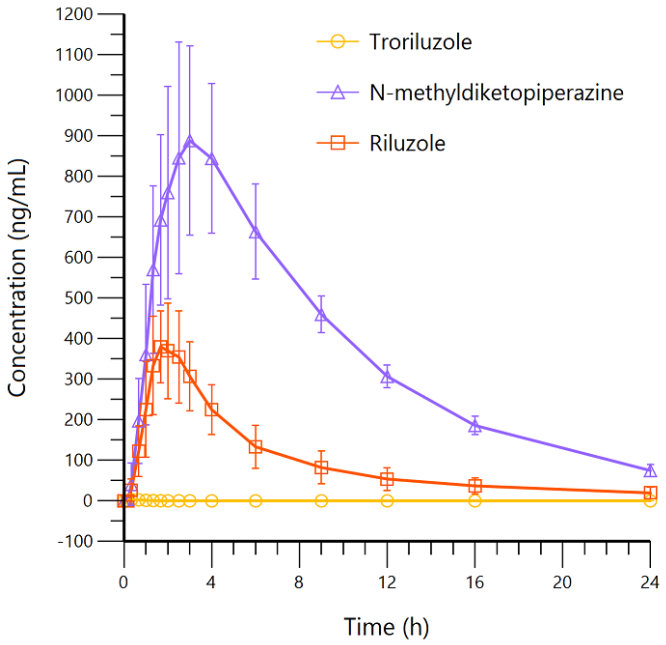


Figure 4: Mean (± SD) Plasma Concentration versus Time Plot of Troriluzole, DKP Metabolite, and Riluzole following Administration of 280 mg Troriluzole (Linear and Semi-log) (Study BHV4157-105)



Dose proportionality and time dependencies

Time dependency of troriluzole has not been investigated in vivo. The active moiety Riluzole is mainly metabolised by CYP1A2, and the lack of time-dependency in observed PK of riluzole suggests that riluzole does not induce its own metabolism.

Dose proportionality has been investigated in studies BHV4157-102 and -108. Following administration of troriluzole, riluzole exposures increase in a dose proportional manner from 17.5 mg to 840 mg.

Table 5: Power Model Results for Dose Proportionality Assessment of Riluzole following Administration of Troriluzole (BHV4157-101)

		90% Confidence Interval	
Parameter (unit)	**Slope (b)**	**Lower**	**Upper**
AUC_{0-t} (h•ng/mL)	1.07	0.92	1.23
AUC_{0-inf} (h•ng/mL)	1.06	0.90	1.21
C_{max} (ng/mL)	1.05	0.91	1.18

Table 6: Power Model Results for Dose Proportionality Assessment of Riluzole following Administration of Troriluzole (BHV4157-108)

		90% Confidence Interval	
Parameter (unit)	**Slope (b)**	**Lower**	**Upper**
AUC_{0-t} (h•ng/mL)	1.21	0.98	1.43
AUC_{0-inf} (h•ng/mL)	1.21	0.98	1.43
C_{max} (ng/mL)	1.05	0.87	1.24

Special populations

Elderly

In study BHV4157-103 only 5 subjects above 65 years and no individual above 75 have been evaluated. The results indicated no significant age effect. However, the age effect has been evaluated in more detail by popPK analysis. Riluzole $AUC_{0-\tau}$ and C_{max} increased 41% and 6%, respectively, in subjects ≥ 65 years compared to the reference 46-year-old male, which is not considered clinically meaningful. Limited data were provided in concern of the age effect.

Hepatic impairment

The effect of hepatic impairment has been investigated in Study BHV4157-104 for moderately impaired subjects only and the results indicate that the increase of AUC and C_{max} of riluzole after administration of troriluzole is less pronounced if compared to oral riluzole. Consequently, moderate hepatic impairment did not have a clinically meaningful impact on total riluzole exposures.

Figure 5: Ratios (Moderate/Normal), 90% Geometric Confidence Intervals, Intersubject CV (%), and P-values for Riluzole

	Geometric LSM		Ratio	90% Geometric CI[b]		Intersubject CV (%)[c]	p-value
Parameter (unit)	**Moderate Hepatic Impairment**	**Normal Hepatic Function**	**Moderate/ Normal[a] (%)**	**Lower (%)**	**Upper (%)**		**Group**
AUC_{0-t} (h•ng/mL)	796.72	717.24	111.08	80.06	154.13	38.52	0.5809
AUC_{0-inf} (h•ng/mL)	814.29	731.40	111.33	80.45	154.08	38.19	0.5698
C_{max} (ng/mL)	112.31	122.43	91.74	63.88	131.74	42.89	0.6811

[a] Calculated using least squares means according to the formula: $\exp^{(DIFFERENCE)} * 100$
[b] 90% Geometric CI calculated according to the formula: $\exp(DIFFERENCE \pm t_{(dfResidual)} * SE_{DIFFERENCE}) * 100$
[c] Calculated according to formula: SQRT (exp (MSE) - 1) * 100
Probability (p) values are derived from Type III sums of squares

Unbound riluzole exposure increased by approximately 70%.

Mean troriluzole exposure (AUC0-inf, Cmax) was approximately 2.5-fold greater for AUC0-inf and 2.1-fold greater for Cmax in subjects with moderate hepatic impairment compared to those with normal hepatic function.

However, the exposure to unbound riluzole and troriluzole is still very low in comparison to riluzole. The results can be extrapolated to subjects with mild hepatic impairment.

Renal impairment

No studies in in patients with renal impairment have been conducted and respective dose recommendations and warnings are derived by published data obtained with oral riluzole.

Pharmacokinetic interaction studies

Only one DDI study (Study BHV4157-106) has been conducted aiming at CYP1A2, which is the main metabolisation route of riluzole. Coadministration of troriluzole with the strong CYP1A2 inhibitor fluvoxamine resulted in a 2.9-fold and 3.3-fold increase in riluzole C_{max} and AUC, respectively.

Figure 6: Ratios ([F+R]/R), 90% Geometric Confidence Intervals, Intra- and Inter-Subject CV (%) and P-values for Riluzole

	Geometric LSM			90% Geometric C.I.[2]				p-values
Parameter (unit)	Treatment F+R	Treatment R	Ratio (F+R)/R[1] (%)	Lower (%)	Upper (%)	Intra-Subject CV (%)[3]	Inter-Subject CV (%)[4]	Treatment
AUC_{0-t} (h*ng/mL)	2555.84	762.09	335.37	280.05	401.63	29.72	20.55	<0.0001
AUC_{0-inf} (h*ng/mL)	2593.56	780.81	332.16	275.99	399.77	30.57	20.21	<0.0001
C_{max} (ng/mL)	212.03	73.09	290.09	250.63	335.75	23.92	25.57	<0.0001

[1]Calculated using least-square means according to the formula: $\exp^{(DIFFERENCE)} * 100$.
[2]90% Geometric Confidence Interval (CI) calculated according to the formula: $\exp(DIFFERENCE \pm t_{(dfResidual)} * SE_{DIFFERENCE}) * 100$.
[3]Calculated according to formula: SQRT (exp (MSE) - 1) * 100.
[4]Calculated according to formula: SQRT (exp ($(MS_{SUBJECT}$ - MSE)/2) - 1) * 100.
C.I.: confidence interval; CV: coefficient of variation; LSM: Least Square Mean; Probability (p) values are derived from Type III sums of squares.
Treatment R: Troriluzole Capsule 100 mg administered alone (administered on Day 1).
Treatment F+R: Fluvoxamine 100 mg ER Capsule from Day 12 to Day 16+Troriluzole 100 mg capsule on Day 12

The proposed dose reduction in the informative texts is considered adequate: For SCA patients taking a strong CYP1A2 inhibitor who initiate dosing with troriluzole, the recommended dose of troriluzole is 89 mg once daily (free base equivalent of 100 mg HCl monohydrate salt) with no increase in dose after 4 weeks. In patients who are on stable troriluzole therapy and initiate treatment with a strong CYP1A2 inhibitor, it is recommended that the dose of troriluzole be reduced to 89 mg once daily (free base equivalent of 100 mg HCl monohydrate salt).

Population pharmacokinetic analysis

A population Pk analysis was conducted based on 8 Phase 1 studies in healthy subjects, 5 Phase 2 or 3 studies in SCA, Obsessive-Compulsive Disorder, Alzheimer's Disease or General Anxiety Disorder patients receiving troriluzole, and 1 Phase 1 study in healthy subjects receiving riluzole. The dataset included data from 169 healthy subjects and 810 patients.

The final popPK model of riluzole was a two-compartment model with linear elimination. Absorption was described by a separate zero order release followed by first order absorption of troriluzole and riluzole and estimated relative bioavailability between troriluzole and riluzole.

Several covariates (body weight, age, sex, fed state or evening dose, concomitant medication with CYP1A2 inhibitors) and were found to influence exposure:

Low weight (39-63.5 kg) resulted in 41% higher AUC, age ≥ 65 years resulted in 40% higher AUC, females had 25% higher AUC compared to males, fed state or evening dose increased AUC by 10% and concomitant administration of fluvoxamine increased AUC by 100% (2-fold).

Pharmacokinetics using human biomaterials

Please see preclinical assessment

3.3.1.2. Pharmacodynamics

Mechanism of action

The mechanism of action has not been discussed by the applicant. However, as troriluzole is a prodrug of riluzole analogy to ALS can be assumed:

Riluzole is proposed to act by inhibiting glutamate processes, the primary excitatory neurotransmitter in the central nervous system. The exact mode of action is unclear.

Primary and Secondary pharmacology

No primary pharmacodynamic studies with troriluzole have been conducted.

The therapeutic window has been discussed on high level and in general, reference is made to riluzole. In the Phase 1 studies of troriluzole in healthy adult subjects (BHV4157-101 study], BHV4157-103 [5 consecutive daily doses], and BHV4157-110 [single, and 5 consecutive daily doses in Chinese subjects]), single and multiple daily doses of 17.5, 35, 70, 100, 140, 200, and 280 mg QD were well tolerated. A MTD (maximum tolerated dose) of troriluzole was not identified in any Phase 1 study.

There are no explicit studies investigating the influence of genetic differences on pharmacodynamic response; however, the indication has been restricted to treatment of SCA with genotype 3.

Troriluzole at supratherapeutic doses did not significantly alter ECG parameters of conduction, rate, or repolarisation as described in the ICH E14 guidance.

As troriluzole plasma exposure is very low and as riluzole is the main active component in plasma, evaluation of the QTc effects of troriluzole based on riluzole exposure is endorsed.

Although hERG assay data for riluzole in module 2 were not discussed, non-clinical secondary pharmacodynamic studies included a limited hERG evaluation which did not result in a relevant inhibition. Please see also non-clinical assessment for further details.

Based the on these data there is no indication, that troriluzole at the intended dose of 200 mg OD causes clinically relevant QTc interval prolongations.

3.3.2. Discussion on clinical pharmacology

Troriluzole is an orally administered third-generation tripeptide prodrug of riluzole. Riluzole has been marketed globally for over 20 years and is considered safe and well tolerated. The primary mode of action of riluzole is reduction of glutamate synaptic levels. Glutamatergic dysfunction has been implicated in the pathophysiology of a broad range of disorders, including SCA, ALS, AD and other forms of dementia, OCD, chronic pain, and a variety of cancers.

Riluzole was the analyte determined in most studies and this assessment report describes the pharmacokinetic profile of riluzole after cleavage from troriluzole in the relevant seconds, whereas only limited data for the parent compound were provided.

Bioanalytical & Statistical methods

In general, the bioanalytical methods have been validated for relevant analytes (e.g. (bound/unbound) riluzole, troriluzole and DKP) in accordance with the Guideline on Bioanalytical Method Validation. All studies have been conducted before ICH M10 came into operation. The sample storage was always covered by relevant long term stability data for the specific storage conditions, except for the inactive DKP metabolite. Unless updated stability data are provided respective study results should be considered with caution, as that they are reliable (yet). The applicant should commit to continue the stability study and report any OOS results (**OC**).

Absorption

A short description of the absorption step of troriluzole has been provided. Conclusions are based on relative bioavailability studies.

Bioavailability

Troriluzole is rapidly transformed to riluzole and can be therefore considered as derivative. Troriluzole was quantifiable in several studies.

For troriluzole quantifiable plasma profiles were also reported in the bioequivalence study and this should be the primary endpoint in accordance with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). Although the variability of data were high for the parameters C_{max} and AUC, it can be concluded that bioinequivalence between the formulations has been demonstrated, as point estimates and 90% CI were outside conventional acceptance criteria. Due to the low exposure to troriluzole and the fact that the prototype formulation was only used in early development, this is considered acceptable.

Only two very different formulations (pure drug substance in capsules and the to be marketed formulation) have been described which differ qualitatively

There are slight discrepancies in the quantity of excipients as stated in module 3 and module 2.7 which can be explained with rounding errors.

Distribution

The levels of unbound riluzole after troriluzole administration are negligible for the proposed dose range.

No mass balance studies with troriluzole have been conducted and the applicant refers to a study with orally administered riluzole due to the fact the troriluzole is quantitatively metabolised to riluzole. This is considered acceptable.

Metabolism

The metabolism of troriluzole has been not thoroughly investigated in humans. The conclusions made by the applicant are mainly derived of data obtained with riluzole and in vitro data.

The metabolites formed in humans are not considered fully elucidated. It is not known whether and to which amount the metabolites M1 to M6 are also formed in vivo or if there are troriluzole-specific metabolites in vivo in addition to DKP metabolite and sarcosyl metabolites.

The applicant postulates that by a diminished first-pass hepatic metabolism, the concentration of riluzole metabolites from dosing with troriluzole are anticipated to be lower than that observed after dosing with oral riluzole at doses that yield similar riluzole exposures, however no data were generated. The posology proposes equimolar dosage for riluzole and troriluzole, so that with increased

exposure of riluzole (as metabolite of troriluzole) an increase of its subsequent metabolites can be expected as equimolar amounts of troriluzole lead to higher exposure.

Overall, the initial conclusion remains that the pharmacokinetic profile is partially altered. However, there are only limited benefits like less food effect and once a day dosing.

Special Populations

Renal impairment

The exposure to DKP metabolite is ~4 fold higher than for riluzole. Approximately 25-50% of the DKP metabolite is excreted in urine in rats and non-human primates, and the applicant anticipates a similar range of renal excretion in humans.

The applicant has provided a brief discussion of the effect of renal of impairment on the exposure of the metabolite DKP. Although no pharmacokinetic data were obtained in this population, the risk of accumulation and corresponding adverse effects appear to be negligible. This is supported by preclinical data.

Hepatic impairment

Mean troriluzole and unbound riluzole exposure is significantly increased for hepatic impaired subjects, whereas the levels for riluzole (as metabolite of troriluzole) showed slight increase. The applicant has proposed a warning advice, which is not considered sufficient in regard to hepatotoxic effects. It should be specified in SmPC section 4.2, that use of troriluzole is contraindicated in patients with moderate hepatic impairment (according to Child-Pugh B classification). The wording of the contraindication relating to hepatic disease (and related information to SmPC sections 4.2 and 4.4) should be further amended (see attached documents) (OC).

Elderly

In particular in study BHV4157-103 included elderly patients (65-74 years n=10 and 75-84 years n=2) . The results indicated no significant age effect. Moreover, the age effect has been evaluated in more detail by popPK analysis.

Children

No PK data have been generated in paediatric population. This is acceptable due to the rarity of the condition and the typical age of onset.

Other demographic factors

Regarding demographic factors, females exhibited a 22.3% lower CL/F, resulting in a 25% increase in AUC0-τThe observed exposure increase in females is considered to have no clinical significance.. The safety of doses up to 280 mg QD has been documented, with no safety issues identified over more than five years and the absence of new safety signals across various doses and indications support the claim that the observed exposure increase in females does not have clinical significance.

Interaction

The applicant provided a brief discussion on possible aminopeptidase inhibitor-based drug interactions. Although not supported by formal interaction studies the theoretical considerations are considered comprehensible and the risk of respective DDIs is considered negligible.

Population pharmacokinetic analysis

The DDI study with the strong CYP1A2 inhibitor fluvoxamine had been conducted in healthy volunteers. The popPK analysis revealed that interindividual variability (IIV) of clearance in healthy volunteers was

19.2%, whereas in patients IIV of clearance was much higher (64.6%). The higher variability in clearance in patients might at least in part be explained by higher variability in influencing covariates (see above). Thus, much higher exposure can be expected in some patients regrouping several covariates leading to higher AUC (e.g. a female patient, aged 65 years with low body weight, taking a CYP1A2 inhibitor). In addition, in the DDI study conducted with the strong CYP1A2 inhibitor fluvoxamine, increase in AUC was larger than predicted by the popPK model (3.3-fold increase in AUC, 2.9-fold increase in Cmax in the DDI study versus 2-fold increased AUC in popPK analysis). In the popPK dataset only 14% of patients had concomitant medication with a CYP1A2 inhibitor. Therefore, the effect of CYP1A2 inhibition appears to be underpredicted by the model The applicant clarified that the popPK dataset already included the DDI study (106). Provided popPK evaluation of the DDI study revealed that the study data were separately adequately described by the model and resulted in an AUC increase of 3.2-fold, which is comparable to that from NCA analysis (3.3-fold). Reported pcVPCs revealed that in the overall dataset, interaction with fluvoxamine was not adequately captured by the model, but was highly underpredicted, which explained the discrepancy between NCA and overall model results mentioned above. Since the model underpredicts the impact of interaction with CYP1A2 inhibitors, the adequacy of the proposed dose reduction is doubted and should be adjusted and justified with respect to safety and efficacy. **(LoOI)**

Different worst case scenarios have been conducted and revealed that exposures were in the range of exposures with doses given in the studies, including the 280 mg dose. Scenarios including interaction with CYP1A2 inhibitors need to be redone, when underprediction of interaction effects are solved. **(LoOI)**

In addition, simulations with the proposed dose reduction when a CYP1A2 inhibitor is given concomitantly should be conducted and the adequacy of the dosing schedule should be discussed. The provided simulations are not yet acceptable due to the above mentioned underprediction of the interaction effects. **(LoOI)**

The concentrations achieved with simulations of the scenario with combination of all covariates that lead to increased exposure were compared to the concentrations evaluated in the C-QT study. This comparison revealed that sufficiently high exposures have been evaluated in the C-QT study.

Initial model performance was not optimal and at least in part difficult to interpret. Additional plots have been provided and show that overall model performance was acceptable, except of the interaction with fluvoxamine, see above.

Secondary Pharmacology

There were no treatment related findings for vital signs; however, one subject with increased HR (from 81 bpm pre-dose to > 100 bpm) 6 hours after 280 mg troriluzole was reported, that was designated as a mild and possibly treatment related TEAE. Blood pressure was within normal in this subject during the timeframe concerned. Tachycardia is a known ADR of riluzole.

Using C-QTc analysis, a QTcF effect exceeding 10 msec can be excluded for riluzole concentrations observed up to approximately 1364 ng/mL. Sufficiently high enough concentrations have been included into the C-QT analysis, even when taking into account the underprediction of Cmax and the underestimation of interaction effect with CYP1A2 inhibitors.

3.3.3. Conclusions on clinical pharmacology

A reduced clinical pharmacology programme has been conducted. In summary, the clinical PK programme seems adequate, some other issues need to be clarified.

Limited pharmacokinetic data for troriluzole as parent compound have been provided and a comprehensive summary and evaluation across the studies is missing. The applicant argues that troriluzole plasma concentrations are very low highly variable and transient.

Focus on the pharmacokinetic evaluation was therefore set on riluzole which is the active moiety of troriluzole and formed after cleavage by aminopeptidases in vivo. In some cases, direct reference is made to studies with oral riluzole, although the overall results indicate a partially altered pharmacokinetic profile. Some of these differences might be beneficial to patients:

- Riluzole plasma levels appear to have a later t_{max} but increased exposure (40-50%) if compared to directly administered riluzole.
- The food effect has been investigated and studies showed no clinically relevant food effect.
- Intersubject variability seems to be lower for riluzole plasma levels after administration of troriluzole.

Dose proportionality has been shown for a broad dose range, including the proposed dose regimen.

The analytical methods seem to be properly validated, however one point concerning long-term stability data should be addressed via commitment.

The PD data do not substantiate the proof-of-concept for use of troriluzole in SCA. The overall concept of troriluzole's action in SCA appears unclear.

3.3.4. Clinical efficacy

In the troriluzole clinical programme there were 17 studies for disorders with glutamatergic dysfunction thought to contribute to underlying disease pathology (SCA, OCD, AD, GAD). Of the 4 Phase 2 proof-of-concept studies completed with troriluzole, a signal for efficacy was observed in the long-term treatment of SCA patients and the OCD study; thus, SCA and OCD were the two indications selected for advancement into well-powered Phase 3 trials.

The 2 randomised clinical studies in SCA (BHV4157-206 and BHV4157-201) represent, according to the applicant, the largest, multicentre, placebo-controlled dataset for SCA (N = 358), in which 340 subjects received at least one dose of troriluzole, in either the double-blind or OLE phase. Of those 340 subjects, 202 subjects received the recommended dose of 200 mg QD either in the double-blind (N = 108) or OLE phase (N= 94) of pivotal study BHV4157-206 in subjects with SCA.

In the two SCA studies (BHV4157-201 and BHV4157-206), the open-label extension phase remains ongoing with a total of 303 subjects received troriluzole 140, 200 or 280 mg QD for > 6 months (> 24 weeks) and 271 subjects received troriluzole for > 1 year (> 48 weeks).

In the pivotal SCA study (BHV4157-206), 190 subjects received troriluzole 200 mg QD for > 6 months (> 24 weeks), and 177 subjects received troriluzole 200 mg QD for > 1 year (> 48 weeks).

A total of 232 subjects, including 186 subjects with SCA, have received troriluzole for > 2 years (> 96 weeks).

3.4. Clinical development

Table 7: Clinical studies

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
BHV4157-201 Phase 2b/3 Efficacy/Safety	Randomisation phase completed; Date first subject enrolled: 15-Dec-2016 Database lock date for the report: 31-Jul-2020 OLE phase ongoing CSR available (Week 8; primary endpoint) Addendum 01 available (Week 96)	Randomised, double-blind, placebo-controlled, parallel group study (**total N=141**)	Randomisation phase (8 weeks): **Troriluzole orally 140 mg QD (N=71)** **Placebo (N=70)** Open-label extension phase (288 weeks): Troriluzole 140 mg to 280 mg for up to 240 weeks (N=131) Randomisation + open-label troriluzole (N=138)	Ambulatory (able to ambulate 8 meters without assistance) male and female subjects 18 to 75 years of age with known or suspected diagnosis of specific hereditary ataxias (SCA genotypes: SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, and SCA10); screening total SARA score ≥ 8, a score of ≥ 2 on gait subsection of the SARA.
BHV4157-206 Phase 3 Efficacy/Safety	Randomisation phase completed; Date first subject enrolled: 08-Mar-2019 Date LSLV for Extension Week 48: 23-Jan-2023 Database lock for the report: 21-Jul-2023 OLE phase ongoing CSR available (Week 48; primary endpoint) Addendum 01 available	Randomised, double-blind, placebo-controlled, parallel group study (**total N=217**)	Randomisation phase (48 weeks): Troriluzole 140 mg QD for 4 weeks titration then **Troriluzole 200 mg QD for 44 weeks (N=108)** **Placebo (N=109)** Open-label extension phase (192 weeks): Troriluzole 200 mg QD (N=188) Randomisation + open-label troriluzole (N=202)	Ambulatory (able to ambulate 8 meters without human assistance) male and female subjects 18 to 75 years of age with known or suspected diagnosis of specific hereditary ataxias (SCA genotypes: SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, and SCA10); and SCA was to be confirmed; screening f-SARA total SARA score ≥ 3, a score of ≥ 1 on gait subsection of the f-SARA.

SCA is an ultra-rare disease with different genotypes that may carry a similar pathophysiology over time. The following genotypes were studied: SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, and SCA10 and all genotypes together referred to as All SCA.

Following the double-blind, randomisation phase for each of these studies, patients had the opportunity to enter into an open label phase, during which all patients are administered troriluzole. Confirmatory evidence from the 3-year, long-term, OLE phases of both of these trials is presented below in section 3.3.1.5.6. Ancillary analyses. These analyses compared efficacy results from the OLE phases of each trial to an external control pooled from 2 independent natural history studies (US and Europe) using a Matched Adjusted Indirect Comparison (MAIC) analysis.

The open label phases of both of these studies (201 and 206) remain ongoing in order to gather additional long-term data for the safety and efficacy of troriluzole in adult SCA patients.

Consistent with the methods described by Wang et al, distinct composite measures were developed (SCACOMS), from 2 independent landmark natural history data sets, CRC-SCA (US subjects) and EUROSCA (European subjects) with each composite measure intending to be more sensitive than any of the individual items/scales employed. Each model was cross-validated by assessing performance in the other independent natural history data set. According to the applicant, the consistency of item selection derived from 2 disparate natural history datasets further confirmed the validity of this approach. The totality of the methods employed served to minimise bias for analysis conducted in a post-hoc setting.

3.4.1.1. Dose-response studies

The recommended starting dose of troriluzole for the treatment of SCA in adult patients with SCA3 is 125 mg troriluzole (corresponding to 140 mg of troriluzole as the HCL monohydrate salt) QD for the first 4 weeks of treatment. The dose should then be increased to the recommended dose of 178 mg (two, 89 mg capsules [corresponding to a total dose of 200 mg as the HCl monohydrate salt]) QD.

IR formulations were developed at 60 mg (equivalent to 53.4 mg free base), 100 mg (equivalent to 89 mg free base), and 140 mg (equivalent to 125 mg free base) strengths.

In the Phase 1 studies of troriluzole in healthy subjects (BHV4157-101 and BHV4157-103), doses of up to 80 mg administered QD were well tolerated with single- and multiple-dose administration. In all Phase 1 studies, a maximum tolerated dose was not identified. Troriluzole doses of 200 mg QD were well tolerated.

The composition of the formulation qualitatively and quantitatively remained the same between Phase 2 and Phase 3 clinical studies. This composition without any modification is proposed for commercial use.

In Phase 2/3 clinical studies, the 60 mg capsule (equivalent to 53 mg free base) was used in studies BHV4157-202, and BHV4157-206; the 100 mg capsule (equivalent to 89 mg free base) was used in BHV4157-207, BHV4157-209, and BHV4157-303; and the 140 mg capsule (equivalent to 125 mg free base) was used in BHV4157-201, BHV4157-202, BHV4157-203, BHV4157-206, BHV4157-209, BHV4157-302, and BHV4157-303.

A dedicated relative BA study subsequently compared riluzole BA following administration of troriluzole 100 mg and 280 mg versus the Rilutek 50 mg tablet (BHV4157-107).

The dose selected for BHV4157-206 was 200 mg of troriluzole administered QD.

Assuming 60% absolute BA of riluzole from Rilutek, the absolute BA of riluzole from troriluzole is estimated to be 80% to 90%. Little accumulation of troriluzole or its active metabolite is expected, as concentrations of troriluzole were unmeasurable 3 hours after a 140-mg oral dose, and the mean riluzole concentration at 24 hours after dosing was approximately 3% of the Cmax.

On the basis of this PK profile, troriluzole is expected to deliver therapeutic exposures of riluzole with QD dosing that have been demonstrated to be well tolerated safely administered with less pharmacokinetic variability. This target riluzole exposure is achieved with QD dosing. At these target exposures, troriluzole is likely to diminish hepatic burden and is associated with a lower risk of increased alanine aminotransferase or aspartate aminotransferase. The delayed Tmax compared to oral riluzole adds support to QD dosing with troriluzole. There was no noteworthy exposure-response relationship between model-predicted riluzole steady state exposure following troriluzole administration and increased serum markers of liver injury. Preclinical studies and affinity for gastroenteric transporters (PEPT1) suggest a low likelihood for a food effect that would require fasting, as is required with oral riluzole. In addition, a high-fat meal did not have a clinically meaningful impact on exposures to riluzole when administered as troriluzole. This is consistent with troriluzole's affinity for gastroenteric transporters (PepT1) and represents an advantage over oral riluzole. These features serve safety, tolerability, and patient convenience that will support treatment adherence for a medication that is anticipated to require chronic administration in patients with SCA3.

An exposure-response relationship was not evident in the SCA3 subgroup between model-predicted riluzole steady-state exposure following troriluzole 200 mg QD and SCA efficacy endpoints in pivotal study BHV4157-206, suggesting similar efficacy across the range of clinical dose exposures.

3.4.1.2. Main study

There is one phase 3 pivotal study, and one phase 2/3 supportive study described below. Both these studies are double blind and placebo controlled.

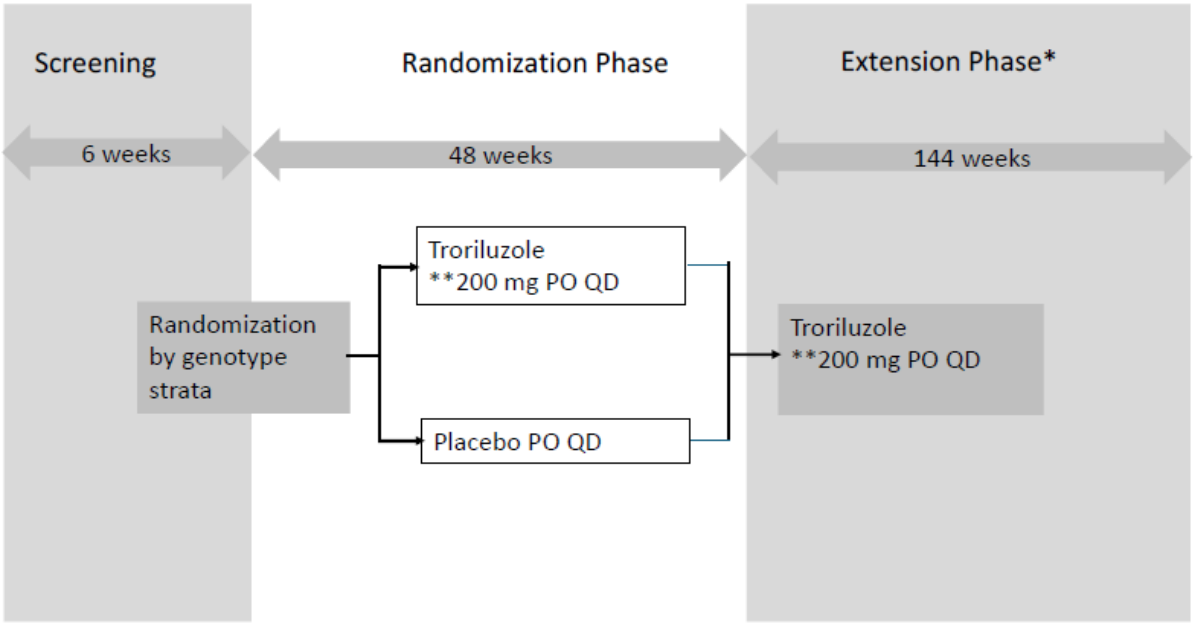
BHV4157-206: A Phase 3, Long-term, Randomized, Double-blind, Placebo-controlled Trial of Troriluzole in Adult Subjects with Spinocerebellar Ataxia

Methods

BHV4157-206 (study 206) is a Phase 3, multicentre, randomised, double-blind, 2-arm, placebo-controlled, parallel-group study conducted to assess the safety, tolerability, and efficacy of troriluzole in subjects with SCA after 48 weeks.

Subjects who completed the randomisation phase were given the option to receive up to an additional 144 weeks of treatment with troriluzole during the OLE phase, provided the primary investigator believed open-label treatment offered an acceptable risk-benefit profile. Subjects entering the OLE phase had their first extension visit 4 weeks after the Week 48 randomisation phase visit. Thereafter, assessment visits occurred every 4 to 8 weeks through extension Week 24, and every 12 weeks through the end of the OLE phase at Week 144. All subjects were to complete a termination visit 2 weeks after the last dose of study drug.

Figure 7: Study schema



Abbreviations: OLE = open-label extension; PO = orally; QD = once daily
*Eligible subjects for the OLE phase included those for whom the investigator believed extended treatment with troriluzole would offer an acceptable risk-benefit profile.
**Subjects received 140 mg for the first 4 weeks and then the dose was increased to 200 mg for the duration of the study. Down titration was temporarily allowed only to address tolerability issues.
***Troriluzole subjects who entered the OLE phase continued with the same dose taken at the end of the randomisation phase. Subjects on placebo in the randomisation phase were switched in a blinded manner to 140 mg QD for the first 4 weeks and then the dose was increased to 200 mg QD for the duration of the study. Down titration after the first 4 weeks of the OLE phase was allowed only for tolerability purposes. All visits after OLE phase Week 4 are open label. Source: Appendix 16.1.1

Study Participants

Approximately 210 subjects were to be randomised into the study. Subjects with SCA1, SCA2, and SCA3 genotypes were to comprise approximately 80% to 90% of the total randomised subjects. Subjects with SCA6, SCA7, SCA8, and SCA10 genotypes were to comprise approximately 10% of the total randomised subjects.

Overall, 299 adult subjects were enrolled at 23 sites in two countries (21 sites in the US and 2 sites in China).

Inclusion Criteria

Key inclusion criteria were the following:

- Male and female outpatients 18 to 75 years of age inclusive with a known or suspected diagnosis of the following specific hereditary ataxias: SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, and SCA10. SCA was to be confirmed based on one of the following:
    - The subject had a confirmed genotypic diagnosis from a CLIA certified laboratory (can produce test results); or,
    - The subject had a family member that had a confirmed genotypic diagnosis from a CLIA certified laboratory (can produce test results) and was willing to undergo genetic testing to confirm underlying SCA diagnosis; or,

- The subject had a confirmed genotypic diagnosis from a laboratory that was not CLIA certified and was willing to undergo genetic testing to confirm underlying SCA diagnosis; or,
- The subject had clinical evidence that supported diagnosis of one of the aforementioned SCA genotypes but did not have producible test results from a CLIA certified laboratory from either a family member or for himself or herself, and the subject was willing to undergo such testing to confirm the SCA diagnosis (in this case, site must wait for results of genotypic testing prior to randomisation)

- Ability to ambulate 8 meters without human assistance (canes and other devices allowed)
- Screening f-SARA total score ≥ 3
- Score of ≥ 1 on the Gait subsection of the f-SARA
- Determined by the investigator to be medically stable at baseline/randomisation as assessed by medical history, physical examination, laboratory test results, and ECG testing. Subjects must be physically able and expected to complete the trial as designed.

Refer to Section 5.2 of the protocol (Appendix 16.1.1) for a full list of inclusion criteria.

Exclusion Criteria

Key exclusion criteria included

- A ≥ 2-point difference on the f-SARA score between screening and baseline
- MMSE score ≥ 24
- Any medical condition other than one of the hereditary ataxias specified in the inclusion criteria that could predominantly explain or contribute significantly to the subjects' symptoms of ataxia (for example, alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, tumours, paraneoplastic disease, head injury, idiopathic late onset ataxia, multisystem atrophy) or that can confound assessment of ataxia symptoms (for example, stroke, arthritis)
- A prominent spasticity or dystonia that, in the opinion of the investigator, would compromise the ability of the f-SARA instrument to assess underlying ataxia severity
- A score of 4 on any individual item (Items 1-4) of the f-SARA
- Subjects were to be excluded at screening or baseline if medical conditions had arisen or there was a change in disease status that could confound the ability of the f-SARA to accurately reflect changes in ataxia severity
- Active liver disease or a history of hepatic intolerance to medications that in the investigator’s judgment was medically significant
- A history of not tolerating treatment with riluzole for any reason
- Treatment with riluzole in the 60 days prior to randomisation and throughout the duration of the study

Treatments

Subjects received troriluzole 140 mg QD or matching placebo for the first 4 weeks of the randomisation phase; the dose was increased to 200 mg QD or matching placebo for the remaining 44 weeks of the 48-week randomisation phase. Temporary down titration to 140 mg QD was allowed, with medical monitor approval, to address tolerability issues.

Subjects who agreed to enter the OLE phase received treatment with troriluzole. If subjects received placebo in the randomisation phase, they were switched in a blinded manner to troriluzole 140 mg for the first 4 weeks of the OLE phase. If subjects received troriluzole in the randomisation phase, they started the OLE phase on the same dose they received at Week 48 of the randomisation phase. After OLE Week 4, all subjects received open-label troriluzole 200 mg. In order to maintain the blind of the randomisation phase and to safely increase all subjects to 200 mg after OLE phase Week 4, the first 4 weeks of open-label treatment remained blinded for all subjects. The total duration of the OLE phase was 144 weeks. Down titration during the OLE phase was allowed only to address tolerability issues. Subjects who entered the OLE phase on 140 mg due to tolerability issues could be rechallenged to increase to 200 mg beginning at OLE phase Week 4 at the investigator's discretion.

Note that for all troriluzole dosing summarised and presented in this report, troriluzole refers to troriluzole monohydrate hydrochloride; 140 mg troriluzole monohydrate hydrochloride is equivalent to troriluzole 125 mg free base; 60 mg troriluzole monohydrate hydrochloride is equivalent to troriluzole 53 mg free base; the total daily dose of 200 mg troriluzole monohydrate hydrochloride is equivalent to troriluzole 178 mg free base.

Concomitant and rescue therapies

Treatment with riluzole in the 60 days prior to randomisation and during the study was prohibited. In addition, subjects with prior use of riluzole who discontinued due to tolerability issues or lack of clinical benefit (in the opinion of the investigator) were not eligible for this study

The following medications were prohibited in the 30 days prior to randomisation and during the entire course of the randomisation phase:

- Chlorzoxazone, aminopyridine, acetylcholinesterase inhibitors, memantine; topiramate, lamotrigine, N-acetylcysteine, ketamine, sodium valproate, varenicline, tricyclic antidepressants and monoamine oxidase inhibitors; the start of an anxiolytic or sleep medication within 30 days prior to randomisation (baseline) (but such medications may be permitted if at a stable dose for longer than 30 days before randomisation [baseline]); and medical marijuana (and subjects were expected to refrain from medical marijuana use during the entire study period)

The following medications were prohibited at least 5 half-lives prior to randomisation and during the study:

- Strong to moderate CYP1A2 inhibitors, which may increase the risk of riluzole-associated AEs
- Strong to moderate CYP1A2 inducers, which may result in decreased efficacy
- Hepatotoxic drugs (e.g., allopurinol, methyldopa, sulfasalazine), which may increase the risk for hepatotoxicity

Herbal medication use was permitted, provided the subject had been on stable doses for a minimum of 30 days prior to screening and with consent from the medical monitor.

Objectives

Primary: To compare the efficacy of troriluzole 200 mg once daily (QD) versus placebo on ataxia symptoms in subjects with spinocerebellar ataxia (SCA) after 48 weeks of treatment, as measured by the total score on the Modified Functional Scale for the Assessment and Rating of Ataxia (f-SARA)

Secondary:

- To compare the efficacy of troriluzole versus placebo on patient impression of benefit as measured by the Patient Impression of Function and Activities of Daily Living Scale (PIFAS), an internally developed 12-item instrument modelled after the Functional Assessment of Chronic Illness Therapy - Fatigue Scale
- To compare the efficacy of troriluzole versus placebo on activities of daily living as measured by the Friedreich's Ataxia Rating Scale - Activities of Daily Living (FARS-ADL) scale
- To compare the efficacy of troriluzole versus placebo on daily functioning as measured by the Friedreich's Ataxia Rating Scale – Functional Staging of Ataxia (FARS-FUNC) scale
- To assess the safety and tolerability of troriluzole in subjects with SCA during the randomisation and open-label extension (OLE) phases

Outcomes/endpoints

The pivotal study evaluated both efficacy and safety of troriluzole in SCA

Efficacy Assessments

The primary efficacy endpoint was the change from baseline on the f-SARA at Week 48.

The secondary efficacy endpoints were: PIFAS; FARS-ADL; and FARS-FUNC.

The exploratory efficacy endpoints were: CGI-I; PGI-C; Neuro-QOL Lower Extremity Mobility Scale; Neuro-QOL Upper Extremity Mobility Scale; and Neuro-QOL Fatigue Scale.

f-SARA

The f-SARA is a modified version of the standard SARA, designed to create new response categories that reflect clinically meaningful changes in patient function.

The standard SARA is an 8-item performance-based scale, yielding a total score of 0 (no ataxia) to 40 (most severe ataxia). The 8-item scale measures performance related to (1) gait, (2) stance, (3) sitting, (4) speech disturbance, (5) finger chase, (6) nose-finger test, (7) fast alternating hand movements, and (8) heel-shin slide.

The f-SARA includes only the axial items of the SARA, that is, items 1 through 4. The appendicular items (items 5 through 8) are not included in the f-SARA, as they are not sensitive to change over a period of time during which there is a clear decline on other measures. This finding was determined in a population of SCA patients that administered the SARA approximately every 6 months for up to 2 years and assessed in a population described by Ashizawa in 2013.

Based on a series of FDA correspondences (FDA communication, 01-Feb-2019 Reference ID 4384512), response categories for the axial items of the f-SARA are rated to reflect a meaningful change in function as follows:

0. Normal (no impairment)
1. Mildly impaired function, but no assistance required
2. Moderately impaired function, but needs assistance for certain parts of the task
3. Severely impaired function to the degree that assistance is needed for all parts of the task
4. Unable to perform function

The total score (maximum = 16) is derived as the sum of the individual items, which include gait, stance, sitting, and speech disturbance.

All f-SARA raters participated in training on both administration of the f-SARA and rating of the f-SARA. Additionally, raters were required to be certified in both administration and rating prior to beginning the study at 3 months, and every 6 months thereafter until all subjects completed OLE Week 48.

PIFAS

The PIFAS is an internally developed multi-item instrument modelled after the FACIT-fatigue Scale, and designed to assess level of functional disability. The scale is rater administered (i.e., questions are asked to the patient and the rater fills them in, as opposed to handing the patient the form to complete) and the items were selected primarily to encompass domains of relevance to SCA (i.e., mobility, speech/swallowing, fatigue), and to capture function and activities of daily living within these domains. Statements are rated on a 5-point Likert-like Scale ranging from "0" reflecting "not at all" to "4" reflecting "very much." A high total score indicates a more severe condition.

FARS-ADL

The FARS-ADL is a multicomponent scale designed to assess neurological domains affected in Friedreich's Ataxia, another hereditary cerebellar ataxia disorder. It assesses 9 areas of activities of daily living with response categories rated on a 5-point scale with "0" reflecting "normal" and "4" reflecting an inability to perform the specific function. The FARS-ADL is rater administered.

FARS-FUNC

The FARS-FUNC is a subscale of the FARS designed to provide functional staging for ataxia in which clinicians are asked to assess function on a 6-stage staging system, with "0" reflecting "normal" and "6" reflecting a stage in which the patient is "total disabled." The FARS-FUNC is rater-administered.

Neuro-QOL Lower Extremity Scale (long form)

The Neuro-QOL-Lower Extremity Scale is designed to assess fine motor skills of the lower extremities by asking specific questions about activities of daily living. This is a 19-item scale with questions rated on a 5-point Likert Scale, with "5" reflecting "no difficulty" and "1" reflecting "unable to do" said activity.

Neuro-QOL Upper Extremity Scale (long form)

The Neuro-QOL-Upper Extremity Scale is designed to assess fine motor skills of the upper extremities by asking specific questions about activities of daily living. This is a 20-item scale with questions rated on a 5-point Likert Scale, with "5" reflecting "no difficulty" and "1" reflecting "unable to do" said activity.

Neuro-QOL Fatigue Scale (long form)

The Neuro-QOL Fatigue Scale is designed to assess level of fatigue in patients with neurologic disorders. This is a 19-item, patient-rated scale designed to rate a patient's fatigue over the past 7 days. Patients are asked to rate answers to these items on a 5-point Likert scale, with "1" reflecting "never" and "5" reflecting "always." A high total score indicates a more severe condition.

CGI-I Scale

The CGI-I requires the clinician to assess how much the subject's illness has improved or worsened relative to the baseline visit and is rated on a 7-point scale, with "1" reflecting "very much improved" and "7" reflecting "very much worse."

PGI-C

The PGI-C is a patient self-reported, Likert-based scale used to assess the response of a condition to a therapy. The response categories of the scale range from "no change" to "a great deal better." For the secondary and exploratory endpoints, raters were trained on how to properly administer and record the results.

Pharmacokinetic Assessments

PK assessments were conducted on the treated subjects. A PK sample was collected at Weeks 4, 8, 12, 24, 36, and 48 of the randomisation phase. Time of last dose and time of last meal prior to PK assessment was also collected. Per protocol, additional PK samples could be drawn if there were any SAEs that could possibly be drug related, or severe AEs that could be drug related.

Pharmacogenetic Assessments

A pharmacogenetic sample was collected at screening in all subjects for possible exploratory genotype analysis. A pharmacogenetic sample was collected at screening for subjects who had not previously undergone genotype testing or who did not have documentation to verify genotype.

Sample size

The sample size for this study was approximately 210 randomised subjects to accommodate for dropouts and was determined based on the following rationale.

As the f-SARA is a modified version of the standard SARA, a new scale with no data to estimate changes and variance in this patient population, an mSARA scale from study BHV4157-201 was used as a proxy. Both scales have the same structure, consisting of 4 items with 5 points/item. The mean changes from randomised baseline using an SARA were -0.3 (SD = 1.35) and 0.00 (SD = 1.44) at OLE phase Weeks 24 and 48, respectively, for all genotypes. Because this study expects an increase on the f-SARA for the non-treated patients, the Week 48 difference in the change from baseline in f-SARA between treatment groups (troriluzole – placebo) is estimated to be -0.75. For a single fixed test, on the primary endpoint, 210 mITT subjects will provide 90% power, based on a 2-sample t-test, assuming a two-sided alpha of 0.05, SD of 1.44, a delta of 0.75, and 25% dropout.

Randomisation and blinding (masking)

Subjects were randomised 1:1 to receive troriluzole or placebo during the randomisation phase. Randomisation was stratified by genotype for 3 subgroups: SCA1 and 2; SCA3; and SCA6, 7, 8, and 10.

Blinding was critical to the integrity of this clinical study.

Statistical methods

Target of estimation (estimand)

To compare the efficacy of troriluzole versus placebo on ataxia symptoms in subjects with SCA after 48 weeks of treatment as measured by the total score on the f-SARA in the hypothetical scenario of no discontinuation, regardless of modest treatment non-compliance, protocol allowed dose adjustments, or initiation or adjustment of concomitant medications related to other symptoms, based on difference in mean change from baseline in f-SARA scores between treatment groups at randomisation Week 48.

Since the primary intent of this trial was to evaluate the effect of the drug when taken as intended in the protocol, a hypothetical strategy was employed for the intercurrent event of treatment/study discontinuation (due to any reason).

Statistical analysis

Analysis sets:

Treated subjects/Safety: Enrolled subjects who received at least one dose of study therapy (blinded or open label troriluzole, or blinded placebo)

Troriluzole Safety: Enrolled subjects who received at least one dose of double-blind or open-label troriluzole

mITT subjects in the randomisation phase: All randomised subjects who received at least one dose of double-blind study medication (troriluzole or placebo) during the randomisation phase, and provided a non-missing baseline measurement and at least one non-missing post-baseline efficacy assessment during the randomisation phase.

mITT subjects in the OLE phase: Randomised subjects who received at least one dose of open-label study troriluzole during the OLE phase and provided a non-missing baseline measurement and at least one non-missing efficacy assessment during the OLE phase.

Principal analyses

The primary endpoint was the change from baseline in the f-SARA total score at Week 48 of the randomisation phase in mITT subjects. The treatment comparison of troriluzole versus placebo used a two-sided alpha level of 0.05 and a mixed model for repeated measures (MMRM) model that included fixed effects for treatment group, randomisation stratum (SCA1 & 2; SCA3; SCA6, 7, 8, 10), visit week, treatment group-by visit week interaction, country (US; China), and baseline f-SARA score as a covariate. MMRM-based estimates (i.e., least squares mean [LSM] with corresponding standard error [SE] and 95% confidence interval [CI]) of values and changes from baseline were presented by treatment group and visit week. In addition, the LSM difference in change from baseline between treatment groups (troriluzole – placebo) at Week 48 with corresponding SE, 95% CI, and p-value from MMRM were also presented. The covariance structure for within subject error ("R" matrix in SAS proc mixed) was initially specified as unstructured.

LSMs of the change from baseline for each treatment group were derived for Week 4, Week 8, Week 12, Week 24, Week 36, and Week 48. These estimates were presented together with df, SE, and 2-sided 95% CIs. The difference in the change from baseline between treatment groups (troriluzole – placebo) was also derived for the same visits, and presented with df, SE, 2-sided 95% CIs, and p-values.

Continuous secondary, change-from-baseline endpoints (i.e., PIFAS, FARS-ADL, FARS-FUNC) were analysed for mITT subjects using the same methodology described above.

The principal analysis of the total f-SARA score, based on a MMRM analysis model, assumed data are MAR, and subjects who discontinue study medication prematurely have a response profile for the remainder of the randomisation phase similar to subjects who completed the 48 weeks of the randomisation phase (in line with the hypothetical strategy for treatment discontinuation). In order to explore the impact of these assumptions, a sensitivity analysis was conducted where subjects who discontinued troriluzole prematurely had a response profile similar to those subjects on placebo using both a jump to reference and copy increment reference approach. These analyses were based on the methods described in Carpenter et al. and implemented in the SAS Macros provided by the DIA

Working Group section of the missingdata.org.uk website, and can be considered to be aligned to the treatment policy strategy for treatment discontinuation.

Type I error was controlled for the primary and secondary efficacy endpoints by testing these endpoints with a gate-keeping procedure. The primary endpoint, f-SARA on all SCA subjects, was tested at a two-sided alpha level of 0.05. If this test was significant (i.e., $p < 0.05$), then the secondary efficacy endpoints were tested using Hochberg's procedure. If the test of the primary endpoint was not significant, then the unadjusted p-values for the secondary endpoints were presented only for descriptive purposes, and no conclusions could be drawn from these results. No attempt was made to adjust for multiplicity when testing the exploratory endpoints.

Changes from protocol-specified analyses

Efficacy analyses in this clinical study report (CSR) are presented for 3 populations:

- All SCA subjects
- SCA3 subjects
- Ambulatory SCA3 subjects (defined as baseline Gait Item score = 1 or 2 indicating mild or moderate impairment, respectively, on the f-SARA scale)

Analyses for the All SCA population were prespecified. Analyses for both the SCA3 subjects and Ambulatory SCA3 subjects were added to the prespecified analyses in 2, post-unblinding, SAP amendments.

The SCA3 analyses are post hoc and since a statistical model was not prespecified for the SCA3 subjects, the additional analyses included a search for a model for SCA3. The best model was found to be one with no covariates and with fixed effects for treatment, visit, and the visit-by-treatment interaction. Generally, results presented for the SCA3 group are based on this model and p-values are used for descriptive purposes.

"Ambulatory SCA3 subjects" is a new subgroup introduced in the SAP amendments.

In general, the SAP amendments documented a number of post-hoc analyses conducted in subgroups. This included multiple parametric models that were fit in the SCA3 and other genetically defined populations. Responder analyses for groups defined by SCA genotype and ambulatory status were included for the primary endpoint, secondary endpoints, CGI-I, and PGI-C. In addition, the risk of falls, as recorded on AE CRFs, was analysed using two methods. The first method used unique subjects as the unit of analysis in contingency tables to compute relative risk of falls. Second, a generalised linear model was fit to the number of falls per subject using a Poisson family model with a log link function.

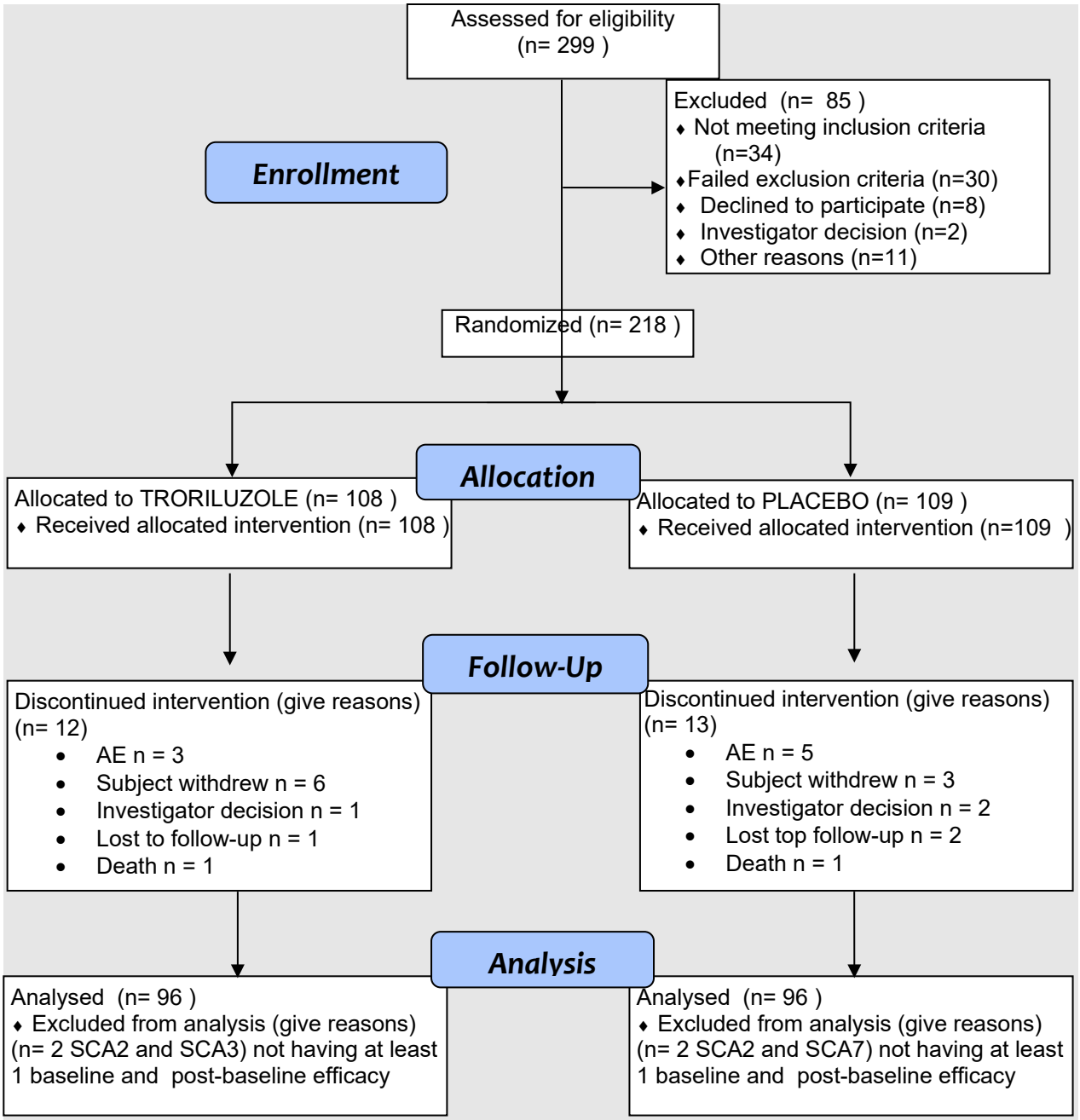
Results

Participant flow

All SCAs group

The majority of patients (~93%) were enrolled in 21 sites in USA and the rest in 2 sites in China. There were no sites from Europe. Most subjects (58.9%) were ≥ 40 and < 65 years of age; 28.1% subjects were < 40 years of age; and 13.0% subjects were ≥ 65 years of age.

Figure 8: Participant flow

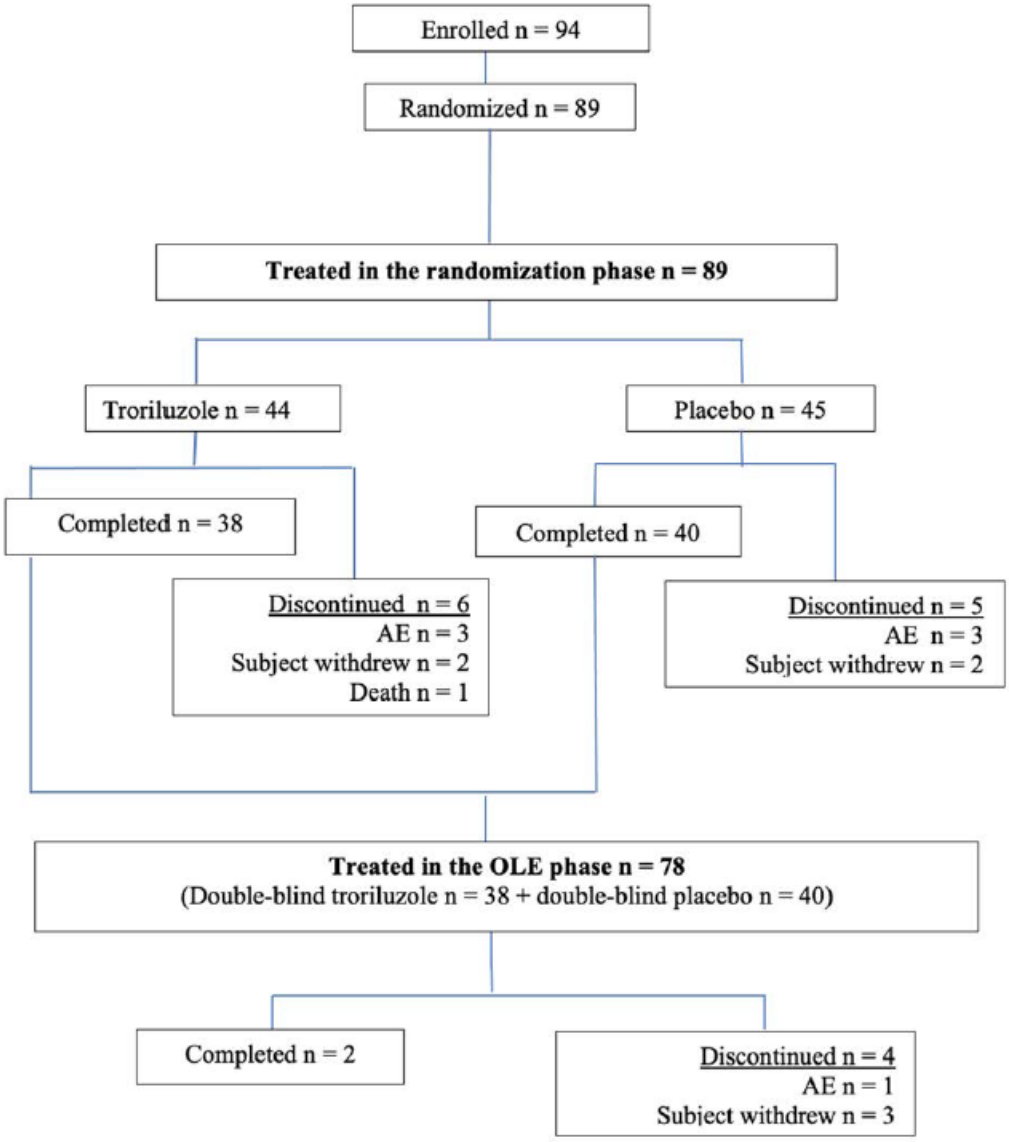


SCA3 genotype subgroup: Participants and flow

Overall, 94 SCA3 subjects were enrolled at 22 sites in 2 countries (20 sites in the US and 2 sites in China) (Table 14.1.4AA and Table 14.1.4CA). The majority of subjects were enrolled at sites in the US (83.0%).

A total of 5 subjects were screen failures (Table 14.1.5AA). The only reason for screen failure was other (100.0%). Overall, 89 subjects were randomised to double-blind treatment (44 subjects to troriluzole 200 mg QD and 45 subjects to matching placebo), and all were treated.

Figure 9 (from Figure 10-2 of the BHV4157-206 CSR): Subject Disposition – SCA3 Genotype



Source: Tables 14.1.5AA and 14.1.5BA

Recruitment

All SCAs group

First subject enrolled (first subject, first visit): 08-Mar-2019

Last subject completed (last subject, last visit) for the current analysis: 18-Feb-2022

Overall, 299 adult subjects were enrolled at 23 sites in 2 countries (21 sites in the US and 2 sites in China) (Table 14.1.4A and Table 14.1.4C). The majority of subjects were enrolled at sites in the US (92.6%). Most subjects (58.9%) were ≥ 40 and < 65 years of age; 28.1% subjects were < 40 years of age; and 13.0% subjects were ≥ 65 years of age.

Overall, 218 subjects were randomised to double-blind treatment (109 subjects to troriluzole 200 mg QD and 109 subjects to matching placebo). A total of 186 subjects who completed the randomisation phase, including 94 subjects who had been randomised to the troriluzole group and 92 subjects who had been randomised to the placebo group, continued in the OLE phase.

Conduct of the study

Some changes from protocol-specified analyses have been described above.

Baseline data

All SCAs group

The details of the demographic and disease baseline characteristics are presented in the Tables in Annex I of the Clinical Assessment report.

Results of baseline eligibility assessments showed no clinically relevant treatment differences in medical history (Table 14.1.7.2A), smoking history (Table 14.1.7.2B), or in baseline cognition as measured by the MMSE total score, or individual scores for orientation, attention, memory, language, and visual-spatial skills (Table 14.1.7.3).

Baseline disease characteristics for All SCA genotypes were also balanced between the troriluzole and placebo groups based on f-SARA scores, which suggested similar levels of progression at baseline, while the time since SCA diagnosis was also similar in the two treatment groups (Table 10-6 of the BHV4157-206 CSR).

Table 8 (from Table 10-6 of the BHV4157-206 CSR): Baseline SCA Disease Characteristics – All SCA Genotypes – Treated Subjects

	Troriluzole	**Placebo**	**Overall**
	(N = 108)	**(N = 109)**	**(N = 217)**
f-SARA			
N	108	109	217
Mean (SD)	**4.9 (1.59)**	**4.9 (1.96)**	**4.9 (1.78)**
Median	4.0	4.0	4.0
Min, Max	2, 10	2, 11	2, 11
Time since onset of symptoms (years)			
N	108	109	217
Mean (SD)	9.8 (7.89)	8.8 (6.66)	9.3 (7.30)
Median	7.0	7.0	7.0
Min, Max	1, 46	0, 43	0, 46
Time since diagnosis (years)			
N	108	109	217
Mean (SD)	5.5 (5.55)	5.2 (5.15)	5.3 (5.34)
Median	3.6	3.8	3.6
Min, Max	-1*, 23	0, 22	-1[a], 23
SCA Genotype, n (%)			
SCA1	15 (13.9)	11 (10.1)	26 (**12.0**)
SCA2	32 (29.6)	35 (32.1)	67 (**30.9**)
SCA3	44 (40.7)	45 (41.3)	89 (**41.0**)
SCA6	6 (5.6)	6 (5.5)	12 (5.5)
SCA7	5 (4.6)	5 (4.6)	10 (4.6)

	Troriluzole	Placebo	Overall
SCA8	3 (2.8)	2 (1.8)	5 (2.3)
SCA10	3 (2.8)	5 (4.6)	8 (3.7)

a Two subjects had confirmatory genetic testing after randomisation because they were unable to obtain the genetic testing confirmation. Source: Table 14.1.7.1A

* One subject had confirmatory genetic testing after randomisation because they were unable to obtain the genetic testing confirmation. Source: Table 14.1.7.1AA

SCA3 genotype subgroup - Baseline

For subjects with the SCA3 genotype, results of baseline eligibility assessments showed no clinically relevant treatment differences in medical history (Table 14.1.7.2AA), smoking history (Table 14.1.7.2BA), or in baseline cognition as measured by the MMSE total score, or individual scores for orientation, attention, memory, language, and visual-spatial skills (Table 14.1.7.3A).

Baseline disease characteristics were also balanced between the troriluzole and placebo groups based on f-SARA scores, which suggested similar levels of progression at baseline, while the time since SCA diagnosis was also similar in the two treatment groups (Table 10-7).

SCA3-treated subjects had a shorter time since onset of symptoms (overall median 6.0 years) than the All SCA-treated population (overall median 7.0 years, Table 10-6).

Among the 71 treated subjects with the SCA3 genotype and baseline Gait 1 or 2, baseline characteristic variables were also balanced between the troriluzole and placebo groups and were similar to the SCA3 genotype population.

*Table 9 (from Table 10-7 of the BHV4157-206 CSR): Baseline SCA Disease Characteristics – **SCA3 Genotype** – Treated Subjects*

	Troriluzole	Placebo	Overall
	(N = 44)	**(N = 45)**	**(N = 89)**
f-SARA			
N	44	45	89
Mean (SD)	5.0 (1.55)	4.8 (1.99)	4.9 (1.78)
Median	4.5	4.0	4.0
Min, Max	3, 10	2, 9	2, 10
Time since onset of symptoms (years)			
N	44	45	89
Mean (SD)	8.1 (6.89)	7.0 (4.55)	7.6 (5.82)
Median	6.0	6.0	6.0
Min, Max	1, 33	0, 24	0, 33
Time since diagnosis (years)			
N	44	45	89
Mean (SD)	5.1 (5.30)	4.6 (4.27)	4.9 (4.78)
Median	3.7	3.4	3.6
Min, Max	-1*, 19	0, 17	-1*, 19

* One subject had confirmatory genetic testing after randomisation because they were unable to obtain the genetic testing confirmation. Source: Table 14.1.7.1AA

Numbers analysed

A 192-week OLE phase in which subjects in the troriluzole group continued the same dose taken at the end of the randomisation phase. Subjects in the placebo group in the randomisation phase were switched in a blinded manner to troriluzole 140 mg QD for the first 4 weeks and then 200 mg QD for the duration of the study. All extension visits after Week 4 were open label.

Subjects returned to the clinic 2 weeks after discontinuing study medication for a follow-up safety visit.

Unless otherwise specified, all efficacy analyses in BHV4157-206 were performed on mITT analysis sets (from Table 2 of Module 2.5 Clinical Overview).

Table 10: (from Table 2 of Module 2.5 Clinical Overview): Analysis Sets for BHV4157-206

Number of Subjects (%) – All SCA Genotypes	**Troriluzole Randomised (N = 109)**	**Placebo Randomised (N = 109)**	**Overall Randomised (N = 218)**
Treated Subjects / Safety	**108 (99.1)**	**109 (100.0)**	**217 (99.5)**
mITT Subjects in the Randomisation Phase	106 (97.2)	107 (98.2)	213 (97.7)
mITT Subjects in the Open Label Extension Phase	94 (86.2)	92 (84.4)	186 (85.3)
Number of Subjects (%) – SCA3 Genotype	**Troriluzole Randomised (N = 44)**	**Placebo Randomised (N = 45)**	**Overall Randomised (N = 89)**
Treated Subjects / Safety	44 (100.0)	45 (100.0)	89 (100.0)
mITT Subjects in the Randomisation Phase	43 (97.7)	45 (100.0)	88 (98.9)
mITT Subjects in the Open Label Extension Phase	38 (86.4)	40 (88.9)	78 (87.6)

Treated Subjects: Enrolled subjects who received at least one dose of study therapy (blinded or OL troriluzole, or blinded placebo
mITT Subjects in the Randomisation Phase: Randomised subjects who received at least one dose of DB study medication (troriluzole or placebo) during the randomisation phase and provided a non-missing baseline measurement and at least one non-missing post-baseline efficacy measurement during the randomisation phase.
mITT Subjects in the OLE Phase: Randomised subjects who received at least one dose of OLE study medication (troriluzole) during the OLE phase and provided a non-missing baseline measurement and at least one non-missing efficacy assessment during the OLE phase.

Outcomes and estimation

All SCAs group

In the All SCA population across genotypes, both groups, troriluzole and placebo, showed an increase in the f-SARA endpoint, with a small numeric improvement for troriluzole compared to placebo. According to the applicant, an overall absence of disease progression in the placebo group of the All SCA genotype population precluded meaningful assessment of the treatment response on the f-SARA scale.

Disease progression on placebo, as measured by an increase in f-SARA at Week 48 and by a decline in f-SARA scores in the SCA3 genotype led to a difference between troriluzole and placebo [-0.56 (95% CI = -1.11, -0.01; p = 0.0450)].

Greater treatment benefit in the total f-SARA score for troriluzole relative to placebo was observed in the analysis of the change from baseline at Week 48 in SCA3 subjects with mild or moderate (Gait 1 or 2) baseline disease. The treatment difference in the LS mean change from baseline at Week 48 was -0.91 (95% CI: -1.48, -0.34; p = 0.0024).

No improvement for troriluzole relative to placebo on the f-SARA endpoint was observed in the combined Non-SCA3 genotypes. Non-SCA3 genotype population was driven by the SCA2 genotype, where no change was observed in the f-SARA score from baseline to Week 48.

Table 11: (from Table 9 f-SARA from Module 2.7.3. Summary of Clinical Efficacy): Summary Results at Week 48 of the Randomisation Phase – mITT Subjects

Change from Baseline	**Troriluzole**	**Placebo**	**Difference from Placebo**
All SCA[a]			
N	94	95	---
Change from Baseline LS Mean (SE)	**0.20** (0.19)	**0.27** (0.18)	**-0.06** (0.20)
95% CI	-0.17, 0.58	-0.09, 0.63	-0.47, 0.34
p-value	---	---	0.7581
SCA3 [b]			
N	38	40	---
Change from Baseline LS Mean (SE)	**-0.03** (0.20)	**0.53** (0.19)	**-0.56** (0.28)
95% CI	-0.43, 0.37	0.15, 0.92	-1.11, -0.01
p-value	---	----	0.0450
SCA3 Gait 1 or 2 [b]			
N	30	32	---
Change from Baseline LS Mean (SE)	**-0.28** (0.21)	**0.63** (0.20)	**-0.91** (0.29)
95% CI	-0.70, 0.13	0.23, 1.03	-1.48, -0.34
p-value	---	---	0.0024
Non-SCA3 [b]			
N	56	55	---
Change from Baseline LS Mean (SE)	**0.25** (0.20)	**-0.02** (0.21)	**0.27** (0.28)
95% CI	-0.15, 0.66	-0.43. 0.39	-0.29, 0.84
p-value	---	---	0.3368

Abbreviations: f-SARA = Functional Scale for the Assessment and Rating of Ataxia
a Pre-specified analysis using baseline score as a covariate.
b For SCA3 and Non-SCA3, a no covariate analysis was used.
Source: Tables 14.2.1A (All SCA), 14.2.1AAN (SCA3), 14.2.1ACN (SCA3 bl Gait 1-2), and 14.2.8AN (Non-SCA3) of the BHV4157-206 CSR

A lack of progression over 1 year of treatment in the Non-SCA3 group, with minimal increases in f-SARA scores from baseline was observed at Week 48. According to the applicant, high variability between genotypes in the rate of progression, and small sample sizes in the less common subtypes, were factors leading to less than 1-point overall rate of progression at Week 48 in the placebo group

across genotypes. A meaningful change from baseline in f-SARA scores was observed only in the SCA3 genotype (see Table below).

Table 12: (from Table 10 of Module 2.7.3. Summary of Clinical Efficacy): Placebo Group f-SARA Change from Baseline at Week 48 of the Randomisation Phase by Genotype - mITT Subjects (N = 107)

Genotype	**N**	**Descriptive Statistics Mean (SD)**
All SCA Placebo	95	0.2 (1.32)
SCA3 Placebo	40	**0.5** (0.96)
Non-SCA3 Placebo	55	**0.0** (1.5)
SCA1	10	0.4 (2.22)
SCA2	31	**-0.3** (1.27)
SCA6	4	0.0 (1.15)
SCA7	3	0.3 (0.58)
SCA8	2	1.5 (0.71)
SCA10	5	-0.2 (1.92)

Source: Table 14.2.1A (All SCA), Table 14.2.1AA (SCA3 covariate), Table 14.2.1AAN (SCA3 no covariate), Table 14.2.8A2 (SCA1, 2, 6, 7, 8, 10, and Non-SCA3 covariate), Table 14.2.8AN (SCA1, 2, 6, 7, 8, 10, and Non-SCA3 no covariate) of the BHV4157-206 CSR

All SCAs group: Change from baseline in the f-SARA endpoint

BHV4157-206 study did not show separation from placebo on the prespecified primary endpoint, i.e. the change from baseline f-SARA at Week 48 in the population of All SCA subjects (SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, and SCA10) (LS mean between group treatment difference = -0.06; p = 0.7581).

An overall absence of disease progression in the placebo group of the All SCA genotype population precluded meaningful assessment of the treatment response on the f-SARA scale. Results for secondary and exploratory efficacy endpoints in the All SCA genotypes population also did not generally differentiate troriluzole from placebo (please see the following Tables and Figure).

Table 13: (from Table 11-1 of the BHV4157-206 CSR): Summary of Primary and Secondary Endpoints at Week 48 During the Randomisation Phase – All SCA mITT Subjects

Week 48 Endpoints [a]	**LS Mean Change Difference from Placebo (95% CI)**	**p-value**
Primary Endpoint		
f-SARA total score change from baseline	**-0.063** (-0.465, 0.339)	**0.7581**
Secondary Endpoints		
PIFAS total score change from baseline	-1.959 (-5.089, 1.170)	0.2184
FARS-ADL total score change from baseline	0.470 (-0.544, 1.485)	0.3620
FARS-FUNC total score change from baseline	0.040 (-0.114, 0.193)	0.6092

f-SARA = Modified Functional Scale for the Assessment and Rating of Ataxia; PIFAS = Patient Impression of Function and Activities of Daily Living Scale; FARS-ADL = Friedreich's Ataxia Rating Scale – Activities of Daily Living; FARS-FUNC = Friedreich's Ataxia Rating Scale – Functional Staging.

a Model based summary statistics are from a mixed model with repeated measures, including fixed effects for treatment, randomisation stratum (SCA genotype group), visit, treatment-by-visit interaction, and country; baseline score as a covariate. Source: Table 14.2A

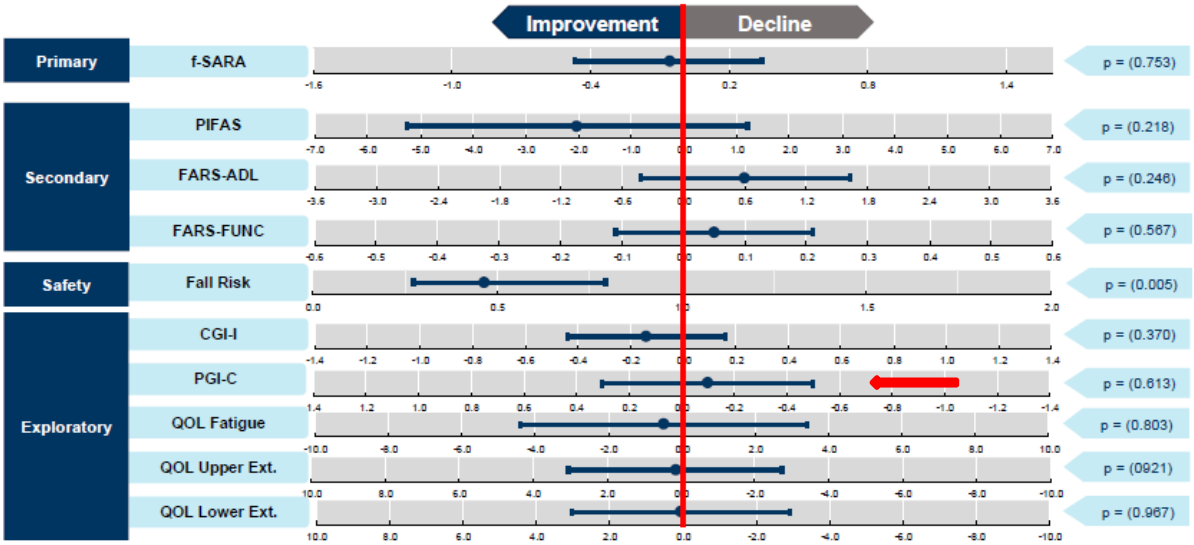
The troriluzole and placebo groups each had mean baseline scores of 4.9 on the f-SARA and the two groups showed minimal change in f-SARA scores at the 48-week endpoint.

Table 14: (from Table 11-4 of the BHV4157-206 CSR): f-SARA: Change from Baseline in Total Score by Visit During the Randomisation Phase – All SCA mITT Subjects

	Troriluzole	**Placebo**	**Difference from Placebo** [a]
Total Score / Visit	**(N = [redacted])**	**(N = [redacted])**	
Baseline			
N	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 12 Change from Baseline			
N	[redacted]	[redacted]	
LS Mean (SE)	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
p-value			[redacted]
Week 24 Change from Baseline			
N	[redacted]	[redacted]	
LS Mean (SE)	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
p-value			[redacted]
Week 36 Change from Baseline			
N	[redacted]	[redacted]	
LS Mean (SE)	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
p-value			[redacted]
Week 48 Change from Baseline			
N	94	95	
LS Mean (SE)	0.20 (0.19)	0.27 (0.18)	**-0.06** [redacted]
95% CI	[redacted]	[redacted]	[redacted]
p-value			**0.7581**

Abbreviations: f-SARA – Modified Functional Scale for the Assessment and Rating of Ataxia a Model based summary statistics are from a mixed model with repeated measures, including fixed effects for treatment, randomisation stratum (SCA genotype group), visit, treatment-by-visit interaction, and country; baseline score as a covariate. Source: Table 14.2.1A

Figure 10: (from Figure 11-1 of the BHV4157-206 CSR): Efficacy Endpoints at Week 48 – All SCA Genotypes



PGI-C, QOL-UE, and QOL-LE scales reversed on x-axis.
Fall risk: incidence rate ratio based on number of fall events
Abbreviations: f-SARA = Modified Functional Scale for the Assessment and Rating of Ataxia; PIFAS = Patient Impression of Function and Activities of Daily Living Scale; FARS-ADL = Friedreich's Ataxia Rating Scale – Activities of Daily Living; FARS-FUNC = Friedreich's Ataxia Rating Scale – Functional Staging; CGI-I – Clinical Global Impression – Global Improvement Scale; PGI-C – Patient Global Impression of Change; QOL – Quality of Life Source: Tables 14.2.1A (f-SARA); 14.2.9A (PIFAS); 14.2.14A (FARS-ADL); 14.2.19A (FARS-FUNC); 14.3.2.8A (Falls); 14.2.26A (CGI-I); 14.2.27A (PGI-C); 14.2.25A (QOL-fatigue); 14.2.24A (QOL-Upper Extremity); 14.2.23A (QOL-Lower Extremity)

SCA3 genotype subgroup: Efficacy Results

SCA3 Efficacy Results – f-SARA [applying the same statistical model (besides not adjusting for genotype) as used for primary analysis in all SCA patients but restricted to SCA3 mITT)]

Table 15: (from Table 14.2AA of the BHV4157-206 Section 14 Tables and Figures): Overall Summary of Primary and Key Secondary Endpoints during the Randomisation Phase, adjusting by Baseline Scale Score and Country SCA3 mITT Subjects

	Difference from Placebo			
Endpoint [1]	LS Mean Change (95% CI)	P-Value	Rank	Critical P-Value
Primary Endpoint				
f-SARA total score change from baseline at Week 48	-0.535 (-1.104, 0.034)	0.0649		
Secondary Endpoints				
PIFAS total score change from baseline at Week 48	-2.395 (-6.916, 2.125)	0.2945	1	0.0167
FARS-ADL total score change from baseline at Week 48	-0.441 (-1.923, 1.041)	0.5552	3	0.0500
FARS-FUNC total score change from baseline at Week 48	-0.108 (-0.324, 0.108)	0.3212	2	0.0250

According to the applicant, descriptive statistics from the first analyses indicated efficacy in the SCA3 group. Since there was no prespecified statistical model for the SCA3 population, it was necessary to select a post-hoc model. This led to additional efficacy analyses that are documented in two post-unblinding SAPs (SAP version 3.0 Amendment version 1.0 and version 2.0). These amendments document post-hoc analyses that were largely focused on the SCA3 subgroup. All of the analyses for the SCA3 population are post-hoc and hence, the p-values are nominal.

SCA3 Efficacy Results – f-SARA (post-hoc model)

According to the applicant, analysis by the prespecified genotype strata revealed consistent treatment effects of troriluzole in SCA3, the most common genotype, which represented 41% of study participants. In SCA3 subjects, troriluzole 200 mg QD demonstrated benefit on the f-SARA compared with placebo at 48 weeks (LS mean treatment difference = -0.56; 95% CI = -1.11, -0.01; p = 0.0450). The Figure below shows the treatment effect in the SCA3 population over the 48 weeks of the treatment period.

Table 16: (from Table 11-2 of the BHV4157-206 CSR): Summary of Primary and Secondary Endpoints at Week 48 During the Randomisation Phase (post-hoc selected model) – SCA3 mITT Subjects

Week 48 Endpoints [a]	**LS Mean Change Difference from Placebo (95% CI)**	**p-value**
Primary Endpoint		
f-SARA total score change from baseline	**-0.563** (-1.113, -0.013)	**0.0450**
Secondary Endpoints		
PIFAS total score change from baseline	-2.400 (-7.071, 2.271)	**0.3092**
FARS-ADL total score change from baseline	-0.212 (-1.660, 1.236)	**0.7716**
FARS-FUNC total score change from baseline	-0.112 (-0.331, 0.107)	**0.3114**

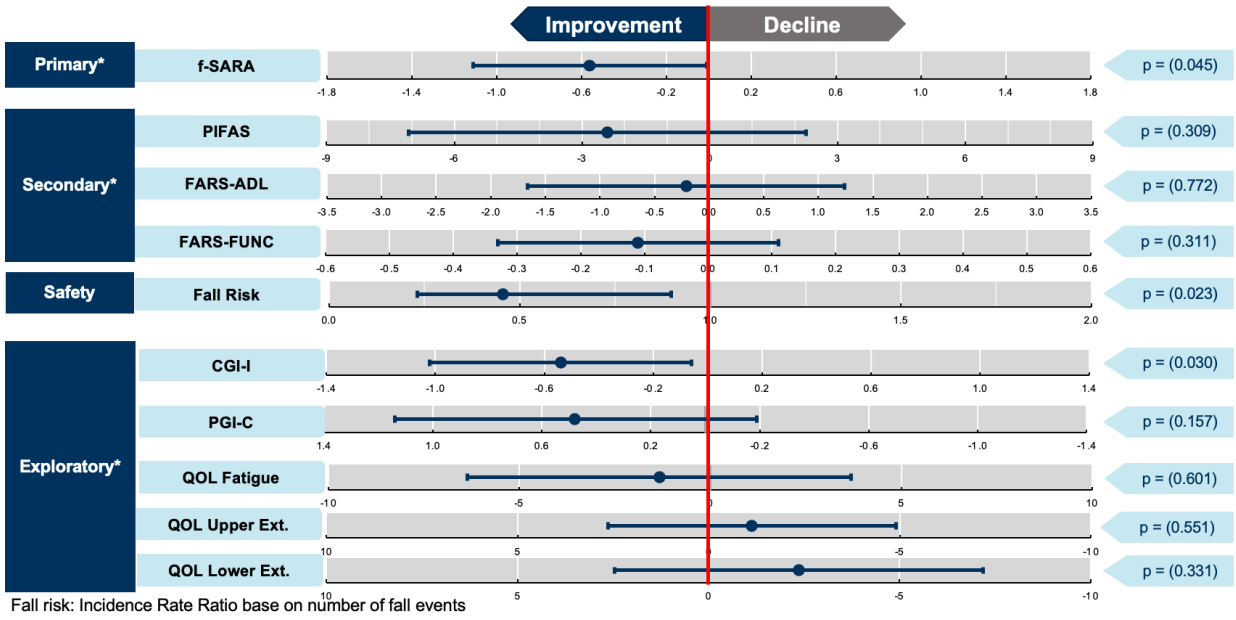
f-SARA = Modified Functional Scale for the Assessment and Rating of Ataxia; PIFAS = Patient Impression of Function and Activities of Daily Living Scale; FARS-ADL = Friedreich's Ataxia Rating Scale – Activities of Daily Living; FARS-FUNC = Friedreich's Ataxia Rating Scale – Functional Staging.
a Model based summary statistics are from a mixed model with repeated measures, including fixed effects for treatment, randomisation stratum (SCA genotype group), visit, treatment-by-visit interaction, and country; baseline score as a covariate. Source: Table 14.2A

Alternative methods for analysing the data for the SCA3 genotype subgroup have been employed:

SCA3 genotype subgroup: Efficacy Results – Primary and secondary endpoints

In addition to the effects observed on the f-SARA and the CGI-I, the applicant is of the opinion that the forest plot below demonstrates a consistent treatment benefit of troriluzole in SCA3 genotype subjects across multiple prespecified primary, secondary, and exploratory study outcome measures. The SCA3 genotype analysis of the clinician- and patient-rated endpoints in the Table 11-2 of the BHV4157-206 CSR represent all of the prespecified endpoints in the study protocol.

Figure 11: (from Figure 6 of Module 2.5 Clinical Overview): Efficacy Endpoints at Week 48– Subjects with the SCA3 Genotype in BHV4157-206



* Genotype analysis was post-hoc as the All SCA study population (SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA 10) was the mITT population for the primary analysis.
f-SARA, PIFAS, FARS-ADL, FARS-FUNC, QOL Fatigue, QOL Upper Extremity, and QOL Lower Extremity display treatment difference in the LS mean change from baseline at Week 48 and 95% CI; Fall Risk displays relative incidence rate reduction and 95% CI; CGI-I and PGI-C display treatment difference in LS Means at Week 48 and 95% CI.
PGI-C, QOL-UE, and QOL-LE scales reversed on x-axis
Abbreviations: f-SARA = Modified Functional Scale for the Assessment and Rating of Ataxia; PIFAS = Patient Impression of Function and Activities of Daily Living Scale; FARS-ADL = Friedreich's Ataxia Rating Scale – Activities of Daily Living; FARS-FUNC = Friedreich's Ataxia Rating Scale – Functional Staging; CGI-I – Clinical Global Impression- Global Improvement Scale; PGI-C – Patient Global Impression of Change; QOL – Quality of Life. Source: Figure 3 in Module 2.7.3

SCA3 genotype subgroup: Baseline disease mild or moderate (Gait 1 or 2)

Notably, the treatment benefits of troriluzole in the SCA3 genotype described above were generally greater in SCA3 subjects with earlier disease who were ambulatory at baseline (defined as baseline Gait 1 or 2 on the f-SARA scale). According to the applicant, this analysis showed that subjects who were more ambulatory with less severe disease at baseline were more likely to benefit from troriluzole, which is consistent with the early treatment paradigm in other neurodegenerative diseases. Baseline Gait 1 or 2 correlates with early, less severe disease stages where change in phenotypic progression is more easily measured, likely due to a higher sensitivity to change. Treatment benefits with troriluzole across the prespecified primary, secondary, and exploratory study measures in ambulatory SCA3 subjects are presented in detail within Module 2.7.3 Summary of Clinical Efficacy.

Table 17: (from Table 11-7 of the BHV4157-206 CSR): f-SARA: Change from Baseline in Total Score by Visit During the Randomisation Phase – SCA3 and Baseline Gait 1 or 2 mITT Subjects

	Troriluzole	**Placebo**	**Difference from**
Total Score / Visit	**(N = 34)**	**(N = 36)**	**Placebo [a]**
Baseline			
N	34	36	---

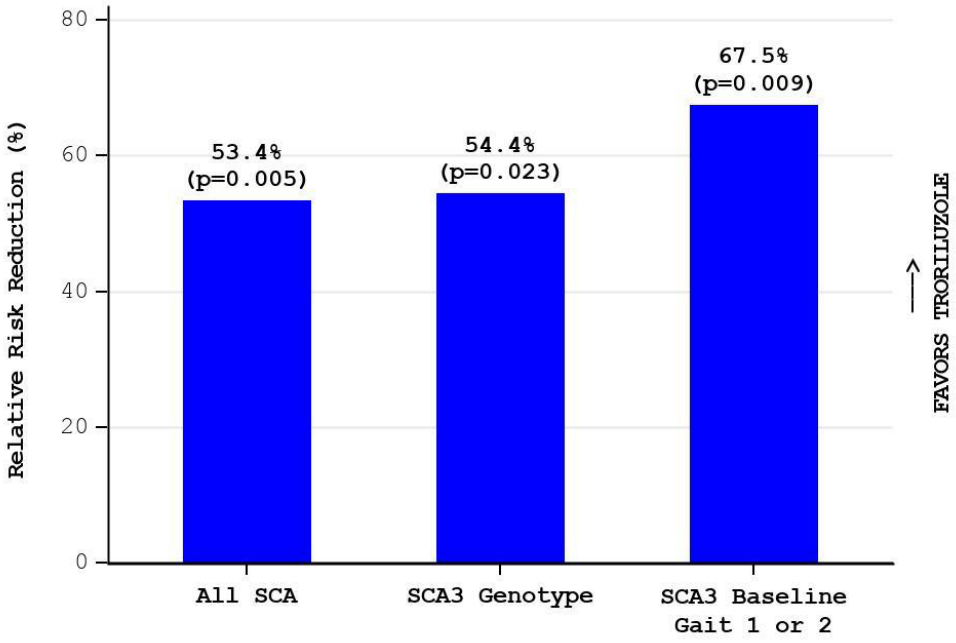
Mean (SD)	4.4 (1.02)	3.9 (1.02)	---
Week 48 Change from Baseline			
N	30	32	---
LS Mean (SE)	-0.28 (0.21)	0.63 (0.20)	**-0.91 (0.29)**
95% CI	-0.70, 0.13	0.23, 1.03	-1.48, -0.34
p-value	---	---	**0.0024**

Abbreviations: f-SARA – Modified Functional Scale for the Assessment and Rating of Ataxia
a Model based summary statistics are from a mixed model with repeated measures, including fixed effects for treatment, visit, and treatment-by-visit interaction. Source: Table 14.2.1ACN

All SCAs group and SCA3 genotype subgroup; Risk of Falls

The risk of falls was used in the analyses as a proxy efficacy endpoint as it is a potential indicator for disease progression. Falls are one of the most common mechanisms of injury and endure as a persistent risk to morbidity and mortality across all ages. Safety data from Study BHV4157-206 showed that troriluzole-treated subjects had a substantial risk reduction in falls (see Figure below) in the SCA3 genotype, as well as in the All SCA study population. The applicant presented results by which treatment with troriluzole for 48 weeks is thought to reduce the risk of fall events by 53.4% in subjects in the All SCA population (108 troriluzole subjects, 109 placebo subjects; p = 0.005), by 54.4% in subjects in the SCA3 population (44 troriluzole subjects, 45 placebo subjects; p = 0.023), and by 67.5% in subjects with SCA3 who were ambulatory (i.e., baseline Gait 1 or 2) (35 troriluzole subjects, 36 placebo subjects; p = 0.009). These data may suggest troriluzole is the first agent to confer a benefit in reducing the risk of falls and the potential morbidity and loss of function commonly associated with SCA. The reduction in falls associated with troriluzole represents an important clinical and functional benefit to patients who currently have no treatment options.

Figure 12: (from Figure 7 of Module 2.5 Clinical Overview): Relative Incidence Rate Reduction in Treatment-Emergent 'Fall' Events defined by Preferred Term during the Randomisation Phase – Treated Subjects in BHV4157-206



Source: Figure 4 in Module 2.7.3

Ancillary analyses

SCA Composite Scale (SCACOMS) Analysis of Study BHV4157-206 using Two Independent Natural History Datasets

Evidence of efficacy in SCA3 from a composite scale analysis of Study BHV4157-206 at Week 48.

A SCA composite scale, defined herein as SCACOMS, was developed by an objective selection process (partial Least Squares Regression) from items most responsive to disease progression (in untreated SCA patients) among the rating scales employed in two independent, landmark natural history SCA patient data sets: Clinical Research Consortium for the Study of Cerebellar Ataxia, CRC-SCA (US patients) and European Integrated Project on Spinocerebellar Ataxias, EUROSCA (European patients).

The SCACOMS analysis was developed utilizing these two independent natural history cohorts and then applied to the Study BHV4157-206 data to validate the study's efficacy findings in SCA3.

There were 4 study populations used to derive SCACOMS. The primary populations of interest were those with the SCA3 genotype:

SCA3 patients from the CRC-SCA natural history database

SCA3 patients from the EUROSCA natural history database

Additional populations examined were those with any SCA genotype (termed All SCA):

All SCA patients from the CRC-SCA natural history database

All SCA patients from the EUROSCA natural history database

From several candidate scales, the items that matched measures in BHV4157-206 are the f-SARA, FARS-ADL, FARS-FUNC, and CGI-C. In both natural history databases, the f-SARA that was utilised in BHV4157-206 was mapped from the SARA.

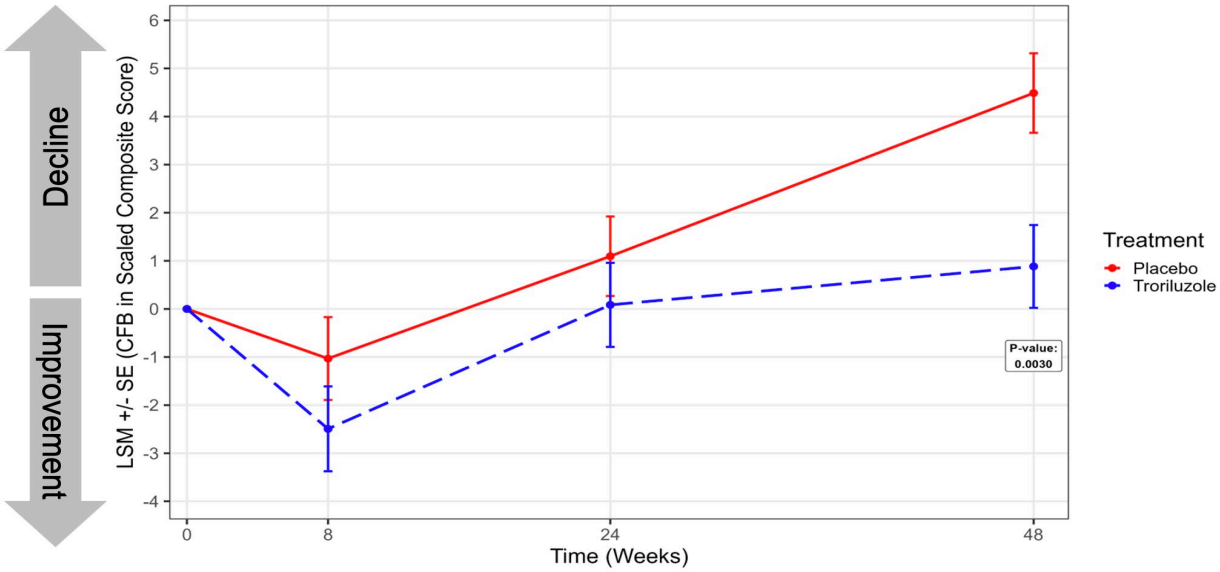
The MSDRs, VIP scores, PLS coefficients (weights) and percent contribution to the total composite score for the linear clinical decline models fitted to the CRC-SCA and EUROSCA natural history datasets and resulted in N=77 and N=106 subjects as the CRS-SCA-SCA3 and EUROSCA-SCA3 natural history populations, respectively.

According to the applicant, Analysis of the SCACOMS change from baseline show the efficacy of troriluzole in SCA3 at Week 48. Applying each of the composite scales (SCACOMS-CRC-SCA-SCA3 and SCACOMS-EUROSCA-SCA3) to the BHV4157-206 SCA3 study population demonstrated a significant difference for troriluzole compared to placebo at 48 weeks ($p = 0.0030$ and $p = 0.0041$, respectively).

In the applicant's view, the magnitude of treatment effect on the SCACOMS resulted in an 80% to 87% delay in disease progression for subjects treated with troriluzole compared to placebo. Results of troriluzole vs placebo, based on the natural history cohorts from the US and Europe, are presented in the Figures below.

The SCACOMS composite score derived from the US natural history CRC-SCA study in the BHV4157-206 SCA3 study population demonstrated a statistically significant LS mean treatment difference of 3.61 favouring troriluzole over placebo at 48 weeks, $p = 0.0030$.

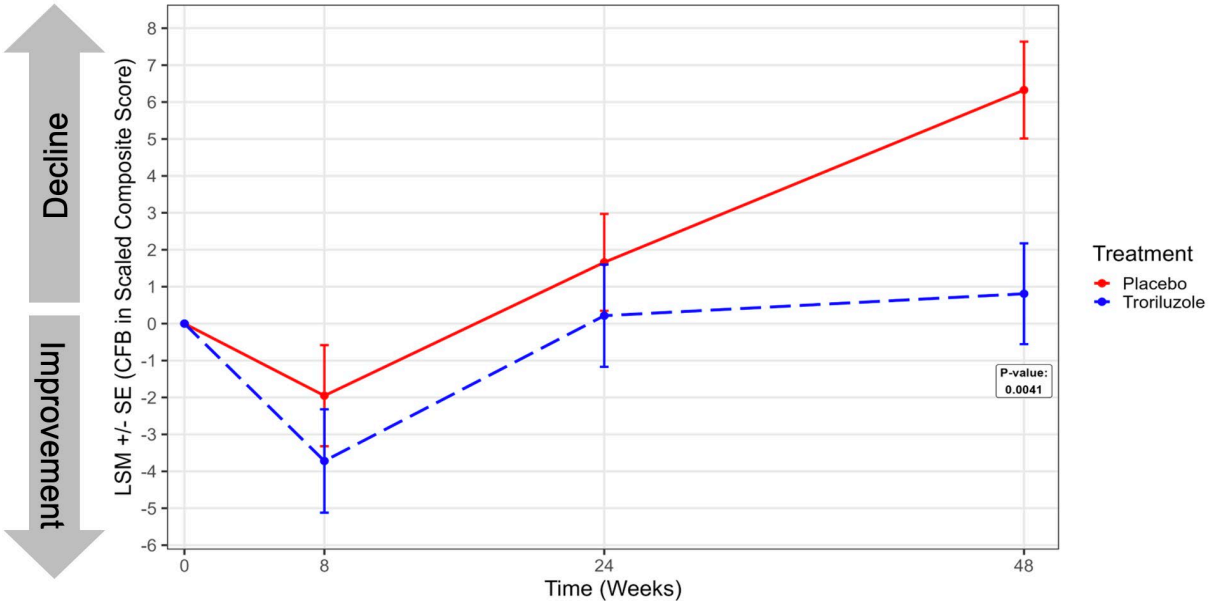
Figure 13 (from Figure 8 in Module 2.5 Clinical Overview): SCACOMS Treatment Effect Estimate for Placebo vs Troriluzole in BHV4157-206 SCA3 Cohort (CRC-SCA SCA3 Model)



US Natural History Dataset (SCACOMS-CRC-SCA-SCA3)
Source: Figure 8 of the Clinical Overview, and Figure 14 of Module 2.7.3 SCE[41]

A second composite analysis from the European natural history dataset applied to the BHV4157-206 SCA3 study population (SCACOMS-EUROSCA-SCA3 composite score) also yielded comparable findings, with a statistically significant treatment difference of 5.52 favouring troriluzole over placebo at 48 weeks, p = 0.0041.

Figure 14 (from Figure 9 in Module 2.5 Clinical Overview): SCACOMS Treatment Effect Estimate for Placebo vs. Troriluzole in BHV4157-206 SCA3 Cohort (EUROSCA-SCA3 Model)



European Natural History Dataset (EUROSCA-SCA3)
Source: Figure 9 of the Clinical Overview, and Figure 15 of Module 2.7.3 SCE[41]

The difference in the SCACOMS score in troriluzole- versus placebo-treated subjects corresponds to an 80% to 87% slowing of disease progression approximately equivalent to a 7-month delay during the 48-week trial period.

To address the potential limitations that may have been introduced by the limited sample size of the SCA3 patients in both the CRC-SCA (n=77) and EUROSCA (n=106) natural history studies, composite models were derived by the applicant in the All SCA sample as a sensitivity analysis. The MSDRs, VIP scores, PLS coefficients (weights) and percent contribution to the total composite score for the linear clinical decline models fitted to the CRC-SCA natural history dataset (=214).

Applying SCACOMS-CRC-SCA-ALL composite score to the BHV4157-206 SCA3 study population demonstrated a statistically significant difference at 48-weeks (difference in least squared mean for PBO-TRO: 2.73, SE:0.95, p=0.0046).

Applying SCACOMS-EUROSCA-ALL composite score to the BHV4157-206 SCA3 study population demonstrated a statistically significant difference at 48-weeks (difference in least squared mean for PBO-TRO: 5.59, SE: 2.03, p=0.0064).

3-Year Long-Term Treatment from Study BHV4157-206 Comparison to External Control: Treatment Effects of Troriluzole in All SCA and SCA3 Genotypes using Matching Adjusted Indirect Comparison (MAIC)

According to the applicant, natural history cohorts can serve as an appropriate external control to assess potential therapeutic effects when studying investigational drugs in ultra-rare diseases.

The applicant undertook, an external control comparative analysis, based in part on work described by Lynch et al, comparing the combined CRC-SCA and EUROSCA data sources to the original troriluzole-treated BHV4157-206 subjects with up to 3 years of data (48-week randomisation phase with troriluzole and up to 2 years of additional OLE). The CRC-SCA and EUROSCA natural history datasets were combined (to increase sample size out to 3 years of measurement) and then compared in an analysis to the original troriluzole treatment arm of BHV4157-206. A Matching Adjusted Indirect Comparison (MAIC) was performed to match natural history subjects to subjects in BHV4157-206. MAIC is a statistical technique that allows for weighting individual patient data (IPD) of one population to match aggregate baseline characteristics reported for a comparable population. Individuals in the IPD population are weighted to balance the covariate distribution with that of the target aggregate population (i.e., BHV4157-206).

The MAIC was conducted using data from BHV4157-206 SCA3 and All SCA subjects. Patients who did not provide post-baseline data were excluded (i.e. all patients who dropped out during year 1). Data from the pooled natural history datasets (CRC-SCA and EUROSCA) were matched to baseline characteristics from target population BHV4157-206 including f-SARA score, genotype, gender, age, and age of symptoms onset, and weighted accordingly. The MAIC was conducted in accordance with recommendations made by the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU).

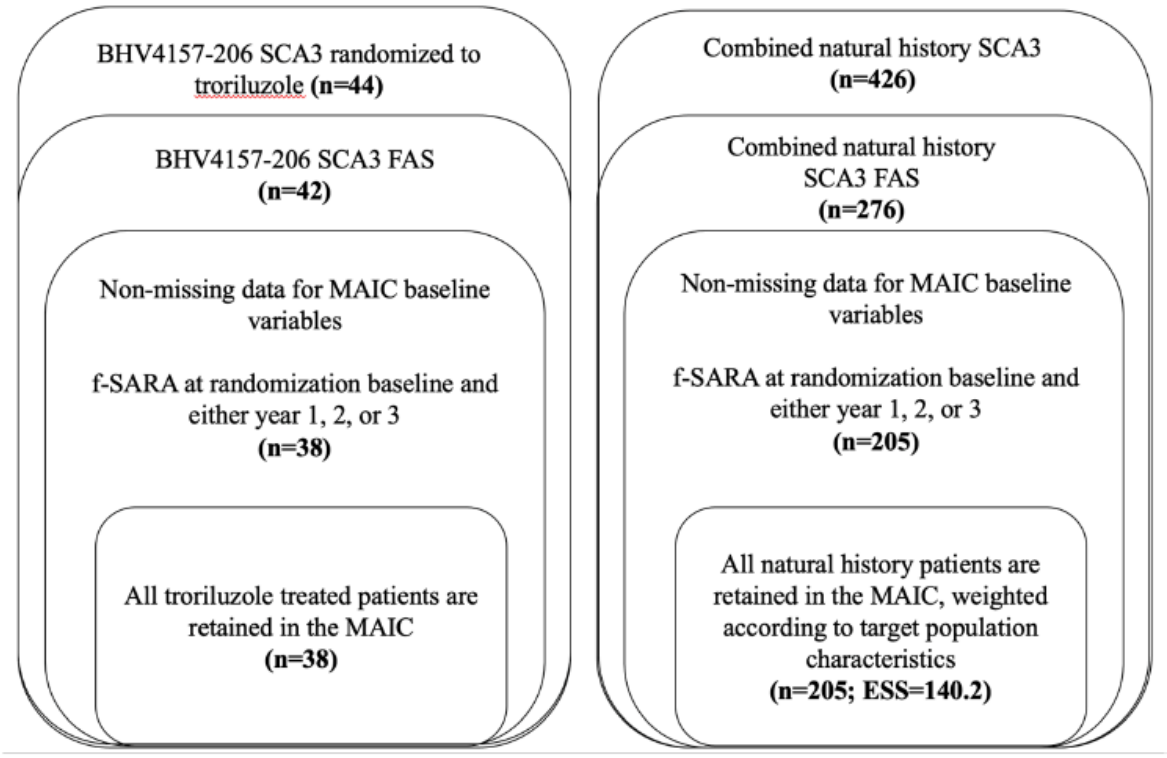
Mixed models for repeated measures (MMRM) were evaluated, and least-squared means were computed at 1, 2, and 3 years. The linear regression models included fixed effect covariates for cohort (troriluzole treated vs natural history), year (1, 2, or 3), cohort by year interaction, and baseline SARA and/or f-SARA scores. The model was fit using restricted maximum likelihood with a covariance structure informed by model fit.

Comparing the baseline characteristics for SCA3 and All SCA genotypes between Study BHV4157-206 subjects and the combined natural history patients, only the SCA genotype distributions differed, likely as a result of a higher proportion of SCA6 patients in the natural history datasets. For the SCA3 only analyses, there were no statistical differences between any of the defined baseline characteristics, including age, gender, age at onset of symptoms, and f-SARA total and gait scores.

The outcome of interest was the change from baseline in f-SARA scores at 1, 2, and 3 years. A mapping of SARA (natural history datasets) to f-SARA scores (study BHV4157-206) was performed for the analysis.

Subjects from BHV4157-206 were weighted using a logistic propensity score model, which is a method used to attempt to mimic randomisation between the 2 treatment arms in a comparison. Natural history subjects were each weighted by matching baseline characteristics to the pooled subject characteristics from BHV4157-206, such that the distributions of characteristics were equivalent across both. The approach for SCA3 is presented below.

Figure 15 (from Figure 1 of the Analysis of BHV4157-201 and BHV4157-206 Subjects with SCA treated BHV4157 compared to a Natural History Cohort report): Populations in IAS206-SCA3-DB&OLE, MAIC



FAS=full analysis set, MAIC=matching adjusted indirect comparison, f-SARA=modified functional scale for the assessment and rating of ataxia. Source: BHV4157-206 CSR Table 14.1.5AA and Appendix Table 1

For the timing of the results, the 1-year, 2-year, and 3-year values for CRC-SCA were taken as the visit variable equal to "12-months", "24-months", and "36-months", respectively. The 1-year, 2-year, and 3-year values for EUROSCA were estimated by employing the following visit windows: Year 1 included 274-456 days from baseline, Year 2 included 640-821 days from baseline, and Year 3 included 1,005-1,187 days from baseline. If a patient had multiple values within a window, the value occurring closer to the middle of the window was used (i.e., Year 1 = 365 days, Year 2 = 731 days, Years 3 = 1096 days).

The Tables below from Table 11 and 10 of Module 2.5 Clinical Overview describe the LSM change from baseline and MMRM results for SCA3 and All SCA genotypes, respectively, among combined natural history and original troriluzole-treated subjects at years 1, 2, and 3. All subjects were included in the analysis who were originally assigned to troriluzole (i.e., not limited to 3 year completers). MMRM models were adjusted for baseline f-SARA score.

Treatment differences of -0.64, -1.16, and -1.34 were observed at years 1, 2, and 3, favouring troriluzole (p = 0.0008, < 0.0001, and < 0.0001, respectively), in the All SCA MAIC analysis.

Table 18: (from Table 11 of Module 2.5 Clinical Overview): LSM & MMRM treatment effects – All SCA (MAIC Results)*

All SCA Genotypes – Original Troriluzole only from BHV4157-206 – LSM Change from Baseline and LSM of Difference of f-SARA by Year and Source (MAIC results)

	f-SARA	BHV4157-206 (n = 96)	Combined natural history (n = 611)	Difference from combined natural history
Year-1	n	94	568	--
	LS Mean	0.14	**0.79**	**-0.64**
	SE	0.174	0.079	0.190
	95% CI	-0.20, 0.48	0.63, 0.94	-1.02, -0.27
	p-value	--	--	**0.0008**
Year-2	n	79	384	--
	LS Mean	0.35	1.51	**-1.16**
	SE	0.182	0.087	0.202
	95% CI	-0.01, 0.71	1.34, 1.68	-1.56, -0.77
	p-value	--	--	**<0.0001**
Year-3	n	35	273	--
	LS Mean	0.81	2.15	**-1.34**
	SE	0.242	0.099	0.261
	95% CI	0.33, 1.28	1.96, 2.34	-1.85, -0.83
	p-value	--	--	**<0.0001**

*adjusted for baseline f-SARA
Source: Table 35 in Module 2.7.3

Treatment differences of -0.75, -1.11, and -1.92 were observed at years 1, 2, and 3, favouring troriluzole (p = 0.0181, 0.0009, and < 0.0001, respectively), in the SCA3 MAIC analysis.

Table 19: (from Table 10 of Module 2.5 Clinical Overview): LSM & MMRM treatment effects – SCA3 (MAIC Results)*

SCA3 Only – Original Troriluzole Only from BHV4157-206 – LSM Change from Baseline and LSM of Differences of f-SARA by Year and Source (MAIC results)

	f-SARA	BHV4157-206 (n = 38)	Combined natural history (n = 193)	Difference from combined natural history
Year-1	n	38	193	--
	LS Mean	-0.05	**0.70**	**-0.75**
	SE	0.282	0.137	0.314
	95% CI	-0.60, 0.51	0.43, 0.97	-1.36, -0.13
	p-value	--	--	**0.0181**
Year-2	n	34	121	--
	LS Mean	0.16	1.27	**-1.11**
	SE	0.290	0.157	0.330
	95% CI	-0.41, 0.73	0.96, 1.58	-1.76, -0.46
	p-value	--	--	**0.0009**
Year-3	n	14	76	--
	LS Mean	0.15	2.07	**-1.92**
	SE	0.386	0.192	0.431

	f-SARA	BHV4157-206 (n = 38)	Combined natural history (n = 193)	Difference from combined natural history
	95% CI	-0.61, 0.91	1.70, 2.45	-2.77, -1.08
	p-value	--	--	**<0.0001**

*adjusted for baseline f-SARA. Source: Table 34 in Module 2.7.3

Evidence from the 3-year, long-term, were collected from Open Label Extension MAIC-analyses from BHV4157-206 compared to an external control pooled from two independent, natural history studies (US and Europe). Troriluzole-treated SCA3 and All SCA subjects showed some effect compared to expected progression from the external control at 1 year, 2 years, and 3 years in the f-SARA.

According to the applicant meaningful treatment effects were observed when troriluzole-treated subjects were compared to natural history patients from two independent SCA datasets. These results potentially add some evidence that treatment with troriluzole could lead to a clinically relevant delay in SCA disease progression that is sustained up to 3 years.

Natural History Comparison as External Control Especially Relevant in Rare Disease Research

As SCA comprises multiple ultra-rare genotypes, the power to detect a signal was low in most SCA genotypes enrolled in Study BHV4157-206. Expected placebo worsening only convincingly occurred in the SCA3 subjects. In fact, there were only 10 or fewer subjects in the placebo arm of each of the following genotypes: SCA1, SCA6, SCA7, SCA8, and SCA10. Given the low number of subjects enrolled in these other genotypes, it is difficult to expect to detect a treatment signal in them. The Table below (from the Table 12 of the Clinical Overview) shows the f-SARA change from baseline at Week 48 and number of subjects by genotype in the placebo arm of Study BHV4157-206.

Since SCA3 subjects are readily identified by genetic testing and the BHV4157-206 study was stratified by genotype groupings, a rigorous assessment of treatment effects in SCA3 was possible as it represents the most common genotype. However, the finding of a treatment effect in the Study BHV4157-206 SCA3 genotype does not rule out a potential therapeutic effect of troriluzole in other less common SCAs.

As SCA comprises multiple ultra-rare genotypes, the power to detect a signal was low in most SCA genotypes enrolled in Study BHV4157-206. Expected placebo worsening only convincingly occurred in the SCA3 subjects. In fact, there were only 10 or fewer subjects in the placebo arm of each of the following genotypes: SCA1, SCA6, SCA7, SCA8, and SCA10. Given the low number of subjects enrolled in these other genotypes, it is difficult to expect to detect a treatment signal in them. The Table below shows the f-SARA change from baseline at Week 48 and number of subjects by genotype in the placebo arm of Study BHV4157-206.

Table 20: Placebo Group f-SARA Change from Baseline at Week 48 of the Randomisation Phase by Genotype – mITT Subjects (N = 107)

Genotype	N	Descriptive Mean (SD)	Statistics
All SCA Placebo	95	0.2 (1.32)	
SCA3 Placebo	40	0.5 (0.96)	
Non-SCA3 Placebo	55	0.0 (1.5)	
SCA1	10	0.4 (2.22)	
SCA2	31	-0.3 (1.27)	
SCA6	4	0.0 (1.15)	
SCA7	3	0.3 (0.58)	
SCA8	2	1.5 (0.71)	
SCA10	5	-0.2 (1.92)	

Source: Table 10 in Module 2.7.3

The placebo arm of the Non-SCA3 genotypes did not progress as expected compared to information from available natural history cohorts. Whether the lack of progression in the Non-SCA3 genotypes was due to small sample size, higher variability, or another factor is unknown. In these situations when enrolment is limited by a rare disease and placebo did not progress during the study period as anticipated by natural history databases, the use of a well characterised external control can provide important comparator data to analyse potential treatment effects in longer-term clinical outcomes.

Quantitative and Objective Video Analysis of Gait in BHV4157-206 Shows Improvement in Troriluzole-treated SCA Subjects

A novel exploratory kinematic (video) gait analysis from BHV4157-206 provided post-hoc additional evidence regarding the potential benefit of troriluzole on gait in All SCA.

As per the original study protocol, the subject was asked to walk 10 meters, followed by a half turn, without pausing, and then return to the starting point. This activity is referred to as the "normal walk" assessment throughout the applicant's documentation. If the patient had completed the normal walk without needing access an assistive device, then he/she was asked to complete 10 additional steps with both feet in one line and with no spaces between heel and toe, e.g., a "tandem walk" assessment. For subjects attempting the tandem walk assessment, scoring of the gait was based on the initial 10-step gait attempt and more than 1 misstep was scored as a failure.

The adjusted mixed linear model for tandem walk Pose Dispersion Index is a metric used to assess how balanced and stable a person's movements are during a given task such as walking and represents a quantitative assessment of gait ataxia. The metric is calculated using video recordings of the given task, taking into account the position and movement of key body parts, such as the feet and chest. The index encompasses 2 discrete parts describing key parameters of movement. The first part quantifies the dispersion of the person's gait asymmetry index, a quantitative measure of how much the person's movements differ between their right and left sides - this is a measure of gait imbalance indicated by differences between the two sides. The second part evaluates the dispersion of the person's base support index, a measure of how much their feet are apart from each other - this is a measure of the wideness of the base of gait. The Pose Dispersion Index is an objective way to quantify a person's movement during tandem walk that was video recorded during the BHV4157-206 study.

While this analysis was performed post hoc, an exploratory analysis in videos captured during Study BHV4157-206 f-SARA assessment, the machine learning methodology was pre-specified, post database lock, in a project-specific SAP. This emerging technology has the potential to be particularly impactful

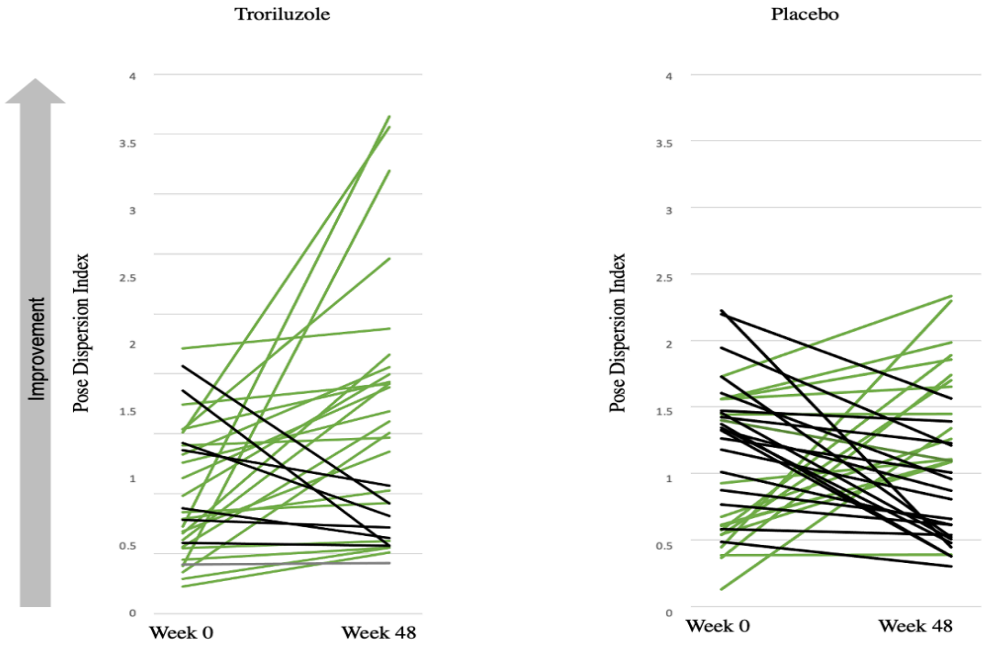
in diseases where mobility is impaired and where impacts to mobility can be subtle and/or present differently among patients.

Out of the 218 subjects who underwent successful randomisation in the parent study, n=67 subjects had available videos of a tandem walk attempt at both screening/week 0 and week 48, and n=56 subjects had available videos of a normal walk attempt at both timepoints. The baseline demographic and clinical characteristics for the original study subjects were compared to the subjects with available video assessments. No significant differences were seen in the age distribution, random treatment assignment, genotype distribution or time since diagnosis between included and excluded subjects. There were numerically lower gait item scores in the video assessed subpopulation compared to the overall sample.

The video analysis of tandem walk for All SCA subjects in BHV4157-206 illustrated the sensitivity of the Pose Dispersion Index to change with troriluzole treatment over 48 weeks, which was statistically significant (p = 0.010) compared to placebo treatment. The sample comprised 36 placebo- and 31 troriluzole-treated subjects with videos available at the screening and Week 48 timepoints. The video analysis suggested improvement on tandem walk and in gait quality associated with the troriluzole group, compared to the placebo-treated group. A significant increase in the Pose Dispersion Index (denoting both improvement and less frame-to-frame variability), independent of age, sex, baseline f-SARA score and/or time since diagnosis.

The figure below displays the scatter plots of the individuals participating in this video gait assessment. This further demonstrates that over a period of 48 weeks, the majority of individuals assigned to treatment with troriluzole exhibited improvement in the kinetic pose of their gait, detected through the video-based analysis of a during a tandem walk attempt. Of note, a consistent trend was observed when analysing paired videos of individuals attempting a normal walk.

Figure 16 (from Figure 13 of Module 2.5 Clinical Overview): Change in Pose Dispersion Index During Tandem Walk – Treated and Placebo in BHV4157-206



Green line indicates change in the Pose Dispersion Index > 0 between Week 0 and Week 48; black line indicates change in the Pose Dispersion Index < 0 between Week 0 and Week 48. Source: Figure 22 Module 2.7.3

According to the applicant, assignment to the troriluzole versus placebo arm was associated with a numerical improvement in the Pose Dispersion Index, though this did not meet statistical significance.

Further, a statistically significant relationship between normal walk-derived Pose Dispersion Index and number of falls (p = 0.041) was shown, with a higher index observed amongst subjects with fewer falls. However, for the tandem walk-derived Pose Dispersion Index nominal statistical significance was not met (p=0.231), though the association was directionally consistent in both tasks, independent of baseline age, sex, baseline f-SARA scores, and the time since diagnosis or the treatment received.

Table 21: (from Table 5 of the Automated Video Assessment Report): Adjusted Poisson Regression Models of Fall Counts During the Randomisation Double-blind Phase (Weeks 0 through 48)

	Coefficient	Std. Err.	z	P>|z|	95% LCI	95% UCI
During tandem walk (n=67)						
Pose Dispersion Index (per unit increase)	-0.7442	0.622	-1.197	0.231	-1.963	0.475
During normal walk (n=56)						
Pose Dispersion Index (per unit increase)	-0.3555	0.174	-2.039	0.041	-0.697	-0.014

All models further adjusted for age, sex, baseline f-SARA score, time since diagnosis and treatment arm with offset term for each subject's follow-up time.

These findings, according to the applicant, suggest that troriluzole treatment confers improvement in cerebellar and motor function, as defined by the machine-learning video assessed metrics captured in the pose dispersion index.

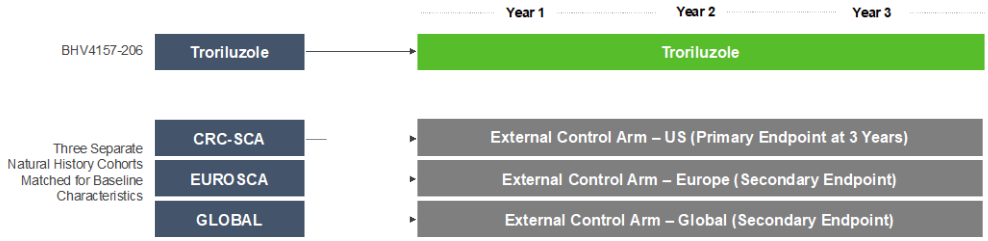
3.4.1.3. Real World Evidence (3-year) – BHV4157-206-RWE

Results from a real-world evidence (RWE) study (BHV4157-206-RWE) have been submitted with the Responses to the Day 120 LoQ. Study BHV4157-206-RWE was designed based on extensive dialogue with the FDA, to assess the benefit of long-term troriluzole treatment in SCA patients.

Study design

BHV4157-206-RWE was a 3-year study using RWE that incorporated all of FDA's feedback on the Sponsor's initially proposed study design and statistical analysis plan to maximise the scientific rigor, reliability and interpretability of the RWE study results as well as address potential sources of bias. The primary analysis compared clinical trial data collected prospectively over 3 years in troriluzole-treated subjects from BHV4157-206 compared to an external control of rigorously matched, untreated SCA patients from the US Clinical Research Consortium for the Study of Cerebellar Ataxia (CRC-SCA) natural history study in accordance with the principles outlined in FDA guidance on the use of RWE in regulatory decision-making. A second external control was added to the prespecified outcome measures from a European natural history cohort (EUROSCA) to provide additional data for the EMA filing.

Figure 17 (from Figure 6 of the updated Module 2.5 Clinical Overview): BHV4157-206-RWE Study Design Schematic



DESIGN	3-Year Real-World Evidence Protocol with external control using Propensity Score Matching
PRIMARY ENDPOINT	**Total f-SARA Scale** Change from baseline at 3 years in troriluzole-treated subjects vs untreated subjects from US Natural History control (CRC-SCA)
SECONDARY ENDPOINTS INCLUDE	• f-SARA change from baseline at 1 and 2 years vs US Natural History external control (CRC-SCA) • f-SARA change from baseline at 1, 2, and 3 years vs EU Natural History external control (EUROSCA) • f-SARA change from baseline at 1, 2, and 3 years vs global US and EU Natural History external control (independently matched CRC-SCA and EUROSCA)

Inclusion and exclusion criteria for BHV4157-206-RWE

BHV4157-206

Eligible subjects were male and female between the ages of 18 to 75, with genetic confirmation of the following specific hereditary ataxias: SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, and SCA10, with screening f-SARA total score of ≥ 3 and score of ≥ 1 on gait item of the f SARA. The full set of inclusion and exclusion criteria can be found in the BHV4157-206 protocol. The study consists of a 48-week randomisation phase and a 192-week OLE phase. Subjects received blinded troriluzole or placebo for 48 weeks during the randomisation phase. Subjects who completed the randomisation phase had the option to receive troriluzole in an OLE phase, as long as the investigator believed open-label treatment offered an acceptable risk-benefit profile.

Only subjects initially randomised to troriluzole were included in this analysis.

CRC-SCA

Eligible subjects for this BHV4157-206-RWE study were age 18 years and above, with a genetic confirmation of SCA in themselves, had baseline f-SARA ≥ 1, and lacked evidence of treatment with troriluzole (as noted in the registry mediation capture fields). Any patient from the CRC SCA study treated with troriluzole was eliminated from the analysis (N=6).

EUROSCA

Participants were recruited across approximately 17 centres, and evaluations were conducted at 12-month intervals. Data on 418 subjects with SCA genotypes 1, 2, and 3 were available for the current analysis. While the EUROSCA study enrolled subjects with SCA6 genotype, the data cut provided by the EUROSCA study group did not include data for the SCA6 subjects, prohibiting the inclusion of these subjects in the analyses. All patients were age 18 or older and had baseline f-SARA ≥ 1. Since Study BHV4157-206 was conducted entirely in the USA and EUROSCA was conducted entirely in Europe, we do not believe any EUROSCA study patients were enrolled in BHV4157-206.

Endpoints

The primary endpoint was the change from baseline in the f-SARA at Year 3 in troriluzole-treated subjects compared to the change from baseline in the mapped f-SARA at Year 3 in natural history subjects from CRC SCA.

All endpoints in BHV4157-206-RWE were prespecified, but with knowledge of the results of study 206, and both the study protocol and statistical analysis plan were submitted to EMA, and reviewed by FDA prior to database lock and analysis. As per instructions from FDA on the study design and statistical analysis plan, Propensity Score Matching (PSM) was used to ensure that untreated subjects from the external controls were rigorously matched to treated subjects from the troriluzole arm of Study BHV4157-206 on multiple prognostic, demographic, and baseline characteristics. The following covariates were used in the PSM: age (continuous), sex (male female), genotype (SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10), f-SARA baseline score (continuous), Age at symptom onset and CAG trinucleotide repeat, expanded allele length (continuous). As also instructed by the FDA, the external control for the primary endpoint was derived from the US natural history population (CRC-SCA). A second and confirmatory independent external control was derived from the European natural history population (EUROSCA), and a third external control was derived from a separately matched global natural history population (CRC-SCA and EUROSCA).

Also, per FDA direction, the modified functional Scale for the Assessment and Rating of Ataxia (f-SARA) was selected as the primary outcome measure for this study. Importantly, the f-SARA is a validated scale that reliably measures clinically meaningful change in SCA disease progression, designed based on FDA input. It is an objective examination of cerebellar function performed by a certified neurologist that minimises effort dependence. The f-SARA focuses on core functional aspects of the disease - gait, stance, sitting, and speech-with clearly distinguishable response categories that reflect clinically meaningful changes in patient function.

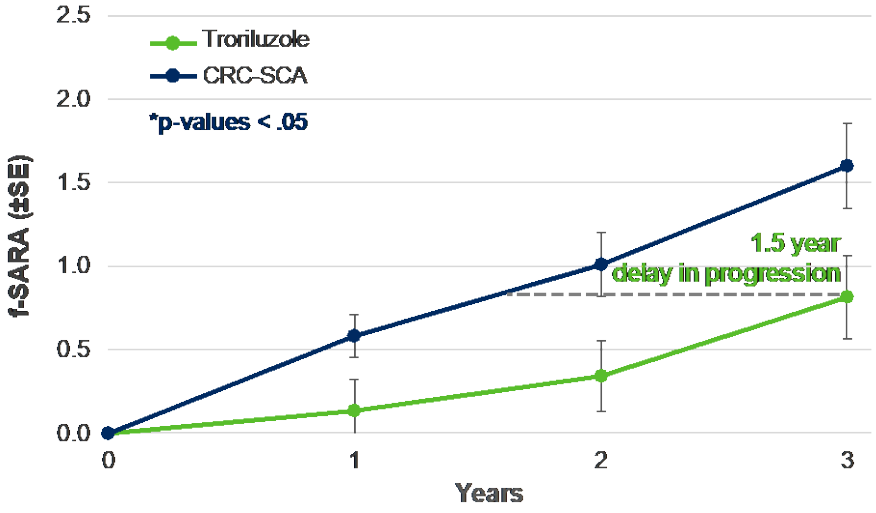
Compared to untreated matched external controls, troriluzole 200 mg dosed orally, once daily, in subjects with SCA (all study genotypes) achieved statistical significance on 9 consecutive, prespecified primary and secondary endpoints. A summary of the results from BHV4157-206-RWE is highlighted below.

According to the applicant, troriluzole met the study's primary endpoint on the change from baseline in f-SARA at 3 years. Troriluzole also showed statistically significant superiority after both 1 and 2 years of treatment. SCA subjects treated with troriluzole experienced a 50% slowing of disease progression relative to an external control from the natural history US population (CRC-SCA), representing 1.5 years delay in disease progression over the 3-year study period (Figure with CRC-SCA below).

A separate, matched, external control from the natural history EU population (EUROSCA) replicated the results from the primary analyses of the US natural history population. SCA subjects treated with troriluzole experienced a 70% slowing of disease progression relative to an external control natural history EU population, representing 2.2 years delay in disease progression over the 3-year study period (Figure with EUROSCA below).

A third, matched, external control from the combined, global natural history population also replicated the study results across all timepoints from the primary analyses. The global external control was derived from CRC-SCA and EUROSCA but represents a third distinct population because PSM was applied to identify a different set of patients comprising the external control. SCA subjects treated with troriluzole experienced approximately 60% slowing of disease progression relative to the global external control, representing 1.9 years delay in disease progression over the 3-year study period (Figure with Global below).

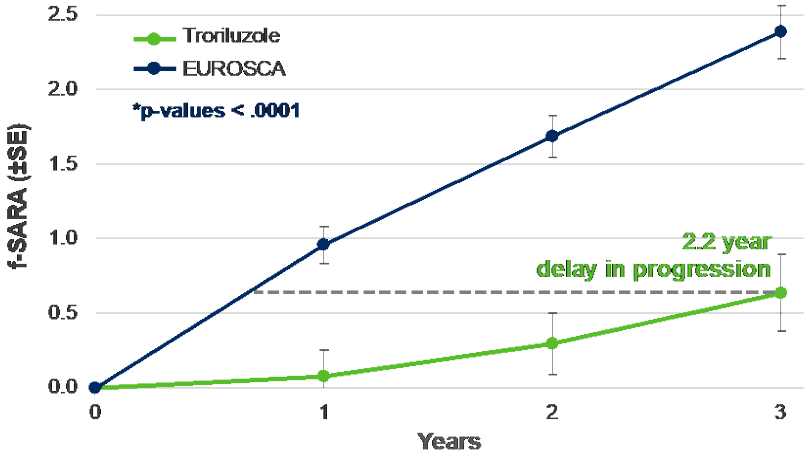
Figure 18 (from Figure 1 of the updated Module 2.5 Clinical Overview): Change from Baseline in f-SARA Total Score at 1-, 2-, and 3-years in Troriluzole-treated Subjects vs Untreated US External Control (Natural History Cohort: CRC-SCA)



TRO	101	90	75	61
US	202	177	65	43

Figure shows approximately 50% slowing of disease progression in troriluzole-treated subjects.
Source: BHV4157-206-RWE study report

Figure 19 (from Figure 2 of the updated Module 2.5 Clinical Overview): Change from Baseline in f-SARA Total Score at 1-, 2-, and 3-years in Troriluzole-treated Subjects vs Untreated EU External Control (Natural History Cohort: EUROSCA)



TRO	85	78	65	54
EU	170	157	146	112

Figure shows approximately 70% slowing of disease progression in troriluzole-treated subjects.
Source: BHV4157-206-RWE study report

Figure 20 (from Figure 1 of the updated Module 2.5 Clinical Overview): Change from Baseline in f-SARA Total Score at 1-, 2-, and 3-years vs in Troriluzole-treated Subjects vs Untreated Global External Control (Natural History Cohorts: CRC-SCA and EUROSCA)

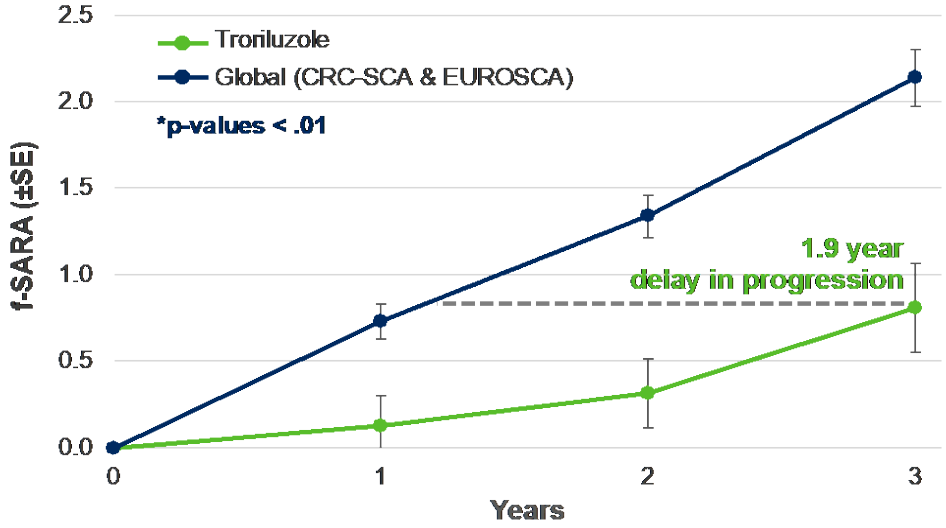


Figure shows approximately 60% slowing of disease progression in troriluzole-treated subjects.
Source: BHV4157-206-RWE study report

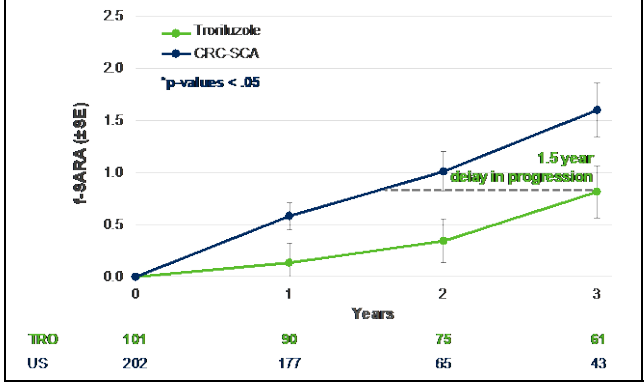
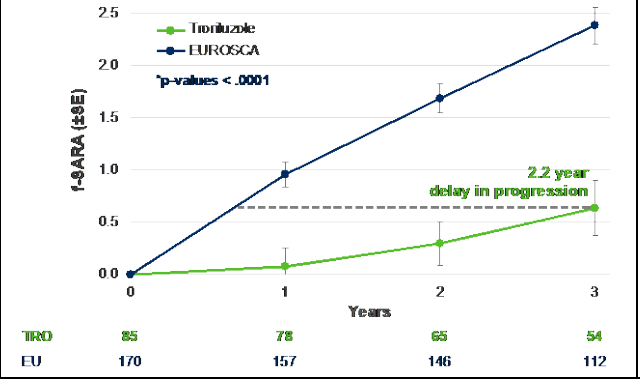
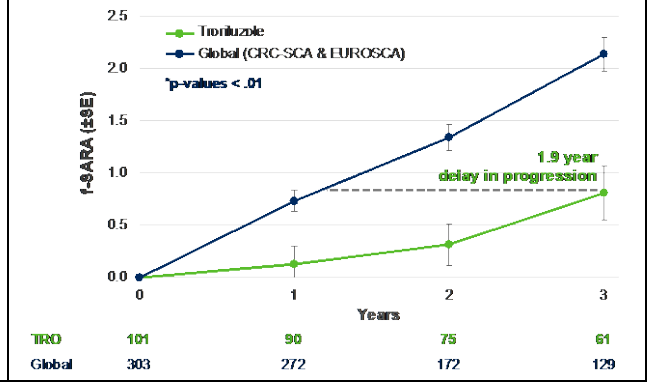
According to the applicant, BHV4157-206-RWE was of sufficient duration to demonstrate the treatment effect of troriluzole across all genotypes studied. Notably, the results of the real-world evidence study were consistent with the previous data from the troriluzole development programme. In Study BHV4157-206, the relatively short treatment period of 1-year, small sample size of most genotypes included and different disease progression rates for the multiple SCA genotypes precluded demonstrating an effect of troriluzole across different SCAs. The lack of progression on the f-SARA over 1 year in non-SCA3 genotypes made it impossible to assess the presence of a treatment effect in the overall study population. By contrast, evidence of efficacy was observed in the SCA3 genotype on the f-SARA primary outcome ($p<0.05$), as the SCA3 placebo group progressed over the 1- year treatment period and provided an appropriate signal detection of efficacy in the troriluzole SCA3 treated group. Importantly, the prespecified SCA3 randomisation stratum represented 40% of the sample size in Study BHV4157-206 and was sufficiently powered to show a meaningful treatment effect. In addition, in Study BHV4157-206 troriluzole-treated subjects had a risk reduction for AEs of falls in both the overall SCA population and SCA3 genotype group compared to the placebo arm. Falling is a core functional manifestation of the cerebellar dysfunction in SCA and likely represents an even more sensitive measure than psychometric scales.

The applicant is of the view that the results from Study BHV4157-206-RWE demonstrate a clear treatment benefit in troriluzole-treated subjects versus rigorously matched, external control natural history comparators and establish that long-term once daily dosing of troriluzole provides a highly clinically meaningful attenuation of disease progression. According to the applicant the study provides primary evidence of effectiveness of troriluzole as a treatment for SCA. Evidence of effectiveness is claimed to be provided also from the 2 additional independently matched, external control natural history cohorts (EUROSCA and global) compared to troriluzole-treated subjects. In addition, the applicant is of the opinion that supportive evidence are also provided by Study BHV4157-206 and Study BHV4157-201, which demonstrated benefits in troriluzole-treated SCA subjects across multiple different analyses including: reduction in falls in All SCA compared to placebo over 48 weeks (Study

BHV4157-206); improvement in multiple clinical outcomes (f-SARA, CGI-I, and fall risk) in SCA3 genotype compared to placebo at 48 weeks (Study BHV4157-206); improvement in f-SARA in All SCA vs pooled US & EU external control using MAIC analysis (Study BHV4157-206); improvement in SARA in All SCA over 3 years vs pooled US & EU external control using MAIC analysis (Study BHV4157 201).

The following Table is showing in a comparative view the different results from the external comparisons to natural history controls: CRC-SCA, EUROSCA and Global.

Table 22: A Comparative View of the Results from the Comparisons with Natural History Cohorts

Change from Baseline in f-SARA Total Score at 1-, 2-, and 3-years in Troriluzole-treated Subjects vs Untreated US External Control (Natural History Cohort: CRC-SCA)	Change from Baseline in f-SARA Total Score at 1-, 2-, and 3-years in Troriluzole-treated Subjects vs Untreated EU External Control (Natural History Cohort: EUROSCA)	Change from Baseline in f-SARA Total Score at 1-, 2-, and 3-years vs in Troriluzole-treated Subjects vs Untreated Global External Control (Natural History Cohorts: CRC-SCA and EUROSCA)
		

The best explanation offered by the applicant for the differences between natural history cohorts is that the US dataset also included genotypes SCA 6, 7, 8 and 10, where progression rates are known to be slower. The larger effect size in the EUROSCA cohort is predominantly driven by SCA1, SCA2, and SCA3 (2nd clarification meeting minutes). It was also mentioned that SCA2 patients are 1.6 times more likely to be non-progressors.

Table 23: Baseline Covariates Adjusted to Achieve Equipoise Between Cohorts in PSM Analysis - f-SARA Analysis Set (CRC-SCA) Matching BHV4157-206 Troriluzole-treated Subjects

Matching Variable	**Troriluzole N = 101**	**Untreated CRC-SCA after PSM N = 202**	**p-value**
Baseline f-SARA, mean (SD)	5.0 (1.61)	4.6 (3.27)	0.2827
Male sex, n (%)	44 (43.6)	88 (43.6)	1.0000
Baseline age, mean (SD)	47.9 (12.92)	48.8 (11.29)	0.5068
Age at symptom onset, mean (SD)	37.9 (12.39)	38.6 (12.37)	0.6183
Genotype, n (%)			0.5778
SCA1	15 (14.9)	33 (16.3)	
SCA2	**30 (29.7)**	**57 (28.2)**	
SCA3	40 (39.6)	85 (42.1)	
Subtotal SCA1, 2 and 3	**85 (84.2)**	**175 (86.6)**	
SCA6	5 (5.0)	10 (5.0)	
SCA7	5 (5.0)	4 (2.0)	
SCA8	3 (3.0)	11 (5.4)	
SCA10	3 (3.0)	2 (1.0)	
Subtotal SCA6, 7, 8 and 10	**16 (16.0)**	**27 (13.4)**	

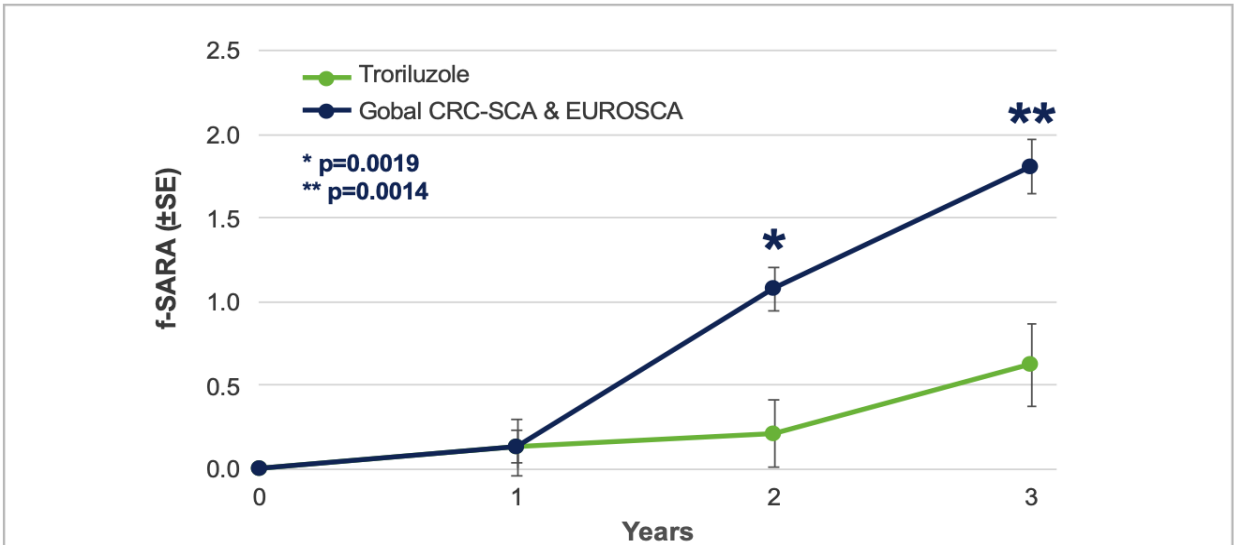
Table 24: Baseline Covariates Adjusted to Achieve Equipoise Between Cohorts in PSM Analysis - f-SARA Analysis Set (EUROSCA) Matching BHV4157-206 Troriluzole-treated Subjects

Matching Variable	**Troriluzole N = 85**	**Untreated EUROSCA after PSM N = 170**	**p-value**
Baseline f-SARA, mean (SD)	5.0 (redacted to 2)	5.0 (redacted to 4)	[redacted]
Male sex, n (%)	35 (redacted to 41)	80 (redacted to 47)	[redacted]
Baseline age, mean (SD)	Redacted to 48 (redacted to 13)	Redacted to 48(redacted to 14)	[redacted]
Age at symptom onset, mean (SD)	Redacted to 38 (redacted to 12)	38.0 (redated to 12)	[redacted]
Genotype, n (%)			[redacted]
SCA1	15 (redacted to 18)	39 (redacted to 23)	
SCA2	**30 (redacted to 35)**	**62 (redacted to 36)**	
SCA3	40 (redacted to 47)	69 (redacted to 41)	
Subtotal SCA1, 2 and 3	**85 (100.0)**	**170 (100.0)**	
SCA6	0	0	
SCA7	0	0	
SCA8	0	0	
SCA10	0	0	
Subtotal SCA6, 7, 8 and 10	**0 (0)**	**0 (0)**	

As to the applicant, a potential source of bias with regard to the matched analysis can be a lack of anchoring of 1-year progression rates between the BHV4157-206 subjects randomised to placebo and the patients enrolled in the NH cohort. The applicant attempted to address this issue by selecting NH

controls from the global cohort that have comparable 1-year progression rates with the BHV4157-206 placebo group. While the progression at Year 1 in these patients was comparable to the troriluzole-treated patient as expected by the design, a separation was observed after Year 1.

Figure 21: Change from Baseline in f-SARA Total Score at 1-, 2-, and 3-years Troriluzole vs Matched External Control Anchored to Year 1 Progression Rate - Matched BHV4157-206-PBO Subjects



Source: BHV4157-206-RWE report (Figure 11-15)

The applicant claims that Study BHV4157-206-RWE analyses were pre-specified. However, the study was planned when data from Study BHV4157-206 were already known.

The primary analysis method was MMRM. Sensitivity analyses were provided using jump-to-reference imputation method (please see Table below).

3.4.1.4. Summary of main efficacy results

Table 25: Summary of efficacy for trial BHV4157-206

Title: A Phase 3, Long-term, Randomized, Double-blind, Placebo-controlled Trial of Troriluzole in Adult Subjects with Spinocerebellar Ataxia	
Study identifier	BHV4157-206
Design	BHV4157-206 is a Phase 3, multicentre, randomised, double-blind, 2-arm, placebo-controlled, parallel-group study conducted to assess the safety, tolerability, and efficacy of troriluzole in subjects with SCA. Subjects with SCA1, SCA2, and SCA3 genotypes were to comprise approximately 80% to 90% of the total randomised subjects. Subjects with SCA6, SCA7, SCA8, and SCA10 genotypes were to comprise approximately 10% of the total randomised subjects. Randomisation was stratified by genotype for 3 subgroups: SCA1 and 2; SCA3; and SCA 6, 7, 8, and 10. Subjects were randomised to receive troriluzole (QD) or placebo (QD) for 48 weeks during the double-blind randomisation phase. Subjects received either troriluzole 140 mg or matching placebo for the first 4 weeks of the randomisation phase, and then the dose was increased to 200 mg QD (or matching placebo) for the duration of the 48-week randomisation phase. Down titration during the randomisation phase was temporarily allowed only for tolerability purposes. The placebo-controlled randomisation phase of this study is complete. Subjects who completed the randomisation phase were given the option to receive up to 192 weeks of treatment with troriluzole during the OLE phase,

	provided the primary investigator believed open-label treatment offered an acceptable risk-benefit profile. Subjects entering the OLE phase had their first extension visit 4 weeks after the Week 48 randomisation phase visit. Thereafter, assessment visits occurred every 4 to 8 weeks through extension Week 24, and every 12 weeks through the end of the OLE at extension Week 192. All subjects were to complete a termination visit 2 weeks after the last dose of study drug. The OLE phase is ongoing.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 weeks not applicable 192 weeks
Hypothesis	Superiority		
Treatments groups SCA3 genotype	Troriluzole randomisation phase		140 mg QD for 4 weeks/200 mg QD for 44 weeks, 44 randomised
	Placebo randomisation phase		Placebo QD for 48 weeks, 45 randomised
	Troriluzole OLE phase		200 mg QD for 192 weeks, 78 treated
Treatments groups All SCA genotypes	Troriluzole randomisation phase		140 mg QD for 4 weeks/200 mg QD for 44 weeks, 109 randomised
	Placebo randomisation phase		Placebo QD for 48 weeks, 109 randomised
	Troriluzole OLE phase		200 mg QD for 192 weeks, 186 treated
Endpoints and definitions	Primary endpoint	f-SARA	Change from baseline in the f-SARA total score at Week 48 of the randomisation phase in Modified Intent-to-Treat (mITT) subjects.
	Secondary endpoint	PIFAS	Change from baseline in the PIFAS total score at Week 48 of the randomisation phase in mITT subjects.
	Secondary endpoint	FARS-ADL	Change from baseline in the FARS-ADL total score at Week 48 of the randomisation phase in mITT subjects.
	Secondary endpoint	FARS-FUNC	Change from baseline in the FARS-FUNC total score at Week 48 of the randomisation phase in mITT subjects.
	Secondary safety endpoint as a proxy efficacy endpoint (post hoc)	Fall risk	Relative incidence rate reduction in falls, as recorded on AE CRFs, through Week 48 of the randomisation phase in treated subjects (safety population)
Database lock	29-Apr-2022		
Results and Analysis			
Analysis description	**Primary Analysis (Prespecified SCA3 genotype stratum; post hoc)**		
Analysis population and time point description	SCA3 mITT subjects: randomised SCA3 subjects who received at least one dose of double-blind study medication (troriluzole or placebo) during the randomisation phase, and provided a non-missing baseline measurement and		

	at least one non-missing post-baseline efficacy assessment during the randomisation phase.		
Descriptive statistics and estimate variability	Treatment group	Troriluzole	Placebo
	Number of subjects	N = 43	N = 45
	f-SARA change from baseline in total score at 48 weeks LS Mean (SE) 95% CI	(n = 38) -0.03 (0.20) -0.43, 0.37	(n = 40) 0.53 (0.19) 0.15, 0.92
Effect estimate per comparison	f-SARA change from baseline in total score at 48 weeks	Comparison groups Treatment difference (troriluzole – placebo) in the LSM change from baseline (SE) 95% CI P-value	Difference from Placebo -0.56 (0.28) -1.11, -0.01 0.0450
Notes	Statistics are from a mixed model with repeated measures, including fixed effects for treatment, visit, and treatment-by-visit interaction.		
Analysis description	**Secondary analysis (Prespecified SCA3 genotype stratum; post hoc)**		
Analysis population and time point description	SCA3 Modified Intent-to-Treat (mITT) subjects: randomised SCA3 subjects who received at least one dose of double-blind study medication (troriluzole or placebo) during the randomisation phase, and provided a non-missing baseline measurement and at least one non-missing post-baseline efficacy assessment during the randomisation phase.		
Descriptive statistics and estimate variability	Treatment group	Troriluzole	Placebo
	Number of subjects	43	45
	PIFAS change from baseline in total score at 48 weeks LS Mean (SE) 95% CI	(n = 38) 0.56 (1.65) -2.73, 3.85	(n = 37) 2.96 (1.67) -0.36, 6.28
	FARS-ADL change from baseline in total score at 48 weeks LS Mean (SE) 95% CI	(n = 37) 0.918 (0.523) -0.124, 1.959	(n = 39) 1.130 (0.506) 0.124, 2.136
	FARS-FUNC change from baseline in total score at 48 weeks LS Mean (SE) 95% CI	(n = 37) 0.216 (0.079) 0.059, 0.374	(n = 39) 0.328 (0.077) 0.176, 0.481
Effect estimate per comparison	PIFAS change from baseline in total score at 48 weeks	Comparison groups Treatment difference (troriluzole – placebo) in the LSM change from baseline (SE) 95% CI P-value	Difference from Placebo -2.40 (2.34) -7.07, 2.27 0.3092

	FARS-ADL change from baseline in total score at 48 weeks	Comparison groups Treatment difference (troriluzole – placebo) in the LSM change from baseline (SE) 95% CI P-value	Difference from Placebo -0.212 (0.728) -1.660, 1.236 0.7716
	FARS-FUNC change from baseline in total score at 48 weeks	Comparison groups Treatment difference (troriluzole – placebo) in the LSM change from baseline (SE) 95% CI P-value	Difference from Placebo -0.112 (0.110) -0.331, 0.107 0.3114
Notes	Statistics are from a mixed model with repeated measures, including fixed effects for treatment, visit, and treatment-by-visit interaction.		
Analysis description	**Secondary analysis (Prespecified SCA3 genotype stratum; post hoc)**		
Analysis population and time point description	SCA3 treated subjects (safety population): randomised subjects who received at least one dose of double-blind study medication (troriluzole or placebo) during the randomisation phase		
Descriptive statistics and estimate variability	Treatment group	Troriluzole	Placebo
	Number of subjects	44	45
	Falls (by events), as recorded on AE CRFs	12	28
Effect estimate per comparison	Risk reduction in falls	Relative incidence rate reduction (troriluzole:placebo) P-value	54.4% 0.023
Notes	The risk of falls was used in the analyses as a proxy efficacy endpoint as it is a potential indicator for disease progression and a major cause or morbidity and mortality in this patient population. During the 48-week randomisation phase, an AE of fall was recorded if there was a worsening of frequency of falls or if a fall was associated with an injury. The risk reduction of falls was analysed using a generalised linear model where the model was fit using a Poisson family model with a log link function.		
Analysis description	**Primary Analysis (All SCA Genotypes; prespecified)**		
Analysis population and time point description	All SCA Modified Intent-to-Treat (mITT) subjects: randomised subjects who received at least one dose of double-blind study medication (troriluzole or placebo) during the randomisation phase, and provided a non-missing baseline measurement and at least one non-missing post-baseline efficacy assessment during the randomisation phase.		
Descriptive statistics and estimate variability	Treatment group	Troriluzole	Placebo
	Number of subjects	106	107
	f-SARA change from baseline in total score at 48 weeks LS Mean (SE) 95% CI	(n= 94) 0.20 (0.19) -0.17, 0.58	(n = 95) 0.27 (0.18) -0.09, 0.63

Effect estimate per comparison	f-SARA change from baseline in total score at 48 weeks	Comparison groups Treatment difference (troriluzole – placebo) in the LSM change from baseline (SE) 95% CI P-value	Difference from Placebo -0.06 (0.20) -0.47, 0.34 0.7581
Notes	Statistics are from a mixed model with repeated measures, including fixed effects for treatment, randomisation stratum (SCA genotype group), visit, treatment-by-visit interaction, and country; baseline score as a covariate.		
Analysis description	**Secondary analysis (All SCA genotypes; prespecified)**		
Analysis population and time point description	All SCA Modified Intent-to-Treat (mITT) subjects: randomised subjects who received at least one dose of double-blind study medication (troriluzole or placebo) during the randomisation phase, and provided a non-missing baseline measurement and at least one non-missing post-baseline efficacy assessment during the randomisation phase.		
Descriptive statistics and estimate variability	Treatment group	Troriluzole	Placebo
	Number of subjects	106	107
	PIFAS change from baseline in total score at 48 weeks LS Mean (SE) 95% CI	(n = 94) -0.93 (1.49) -3.86, 1.99	(n = 90) 1.03 (1.43) -1.79, 3.85
	FARS-ADL change from baseline in total score at 48 weeks LS Mean (SE) 95% CI	(n = 94) 0.453 (0.502) -0.535, 1.440	(n = 95) -0.017 (0.480) -0.962, 0.927
	FARS-FUNC change from baseline in total score at 48 weeks LS Mean (SE) 95% CI	(n =93) 0.266 (0.075) 0.118, 0.414	(n = 94) 0.226 (0.072) 0.084, 0.368
Effect estimate per comparison	PIFAS change from baseline in total score at 48 weeks	Comparison groups Treatment difference (troriluzole – placebo) in the LSM change from baseline (SE) 95% CI P-value	Difference from Placebo -1.96 (1.59) -5.09, 1.17 0.2184
	FARS-ADL change from baseline in total score at 48 weeks	Comparison groups Treatment difference (troriluzole – placebo) in the LSM change from baseline (SE) 95% CI P-value	Difference from Placebo 0.470 (0.514) -0.544, 1.485 0.3620
	FARS-FUNC change from baseline in	Comparison groups Treatment difference (troriluzole – placebo) in	Difference from Placebo

	total score at 48 weeks	the LSM change from baseline (SE) 95% CI P-value	0.040 (0.078) -0.114, 0.193 0.6092
Notes	Statistics are from a mixed model with repeated measures, including fixed effects for treatment, randomisation stratum (SCA genotype group), visit, treatment-by-visit interaction, and country; baseline score as a covariate.		

Analysis description	**Secondary analysis (All SCA genotypes)**		
Analysis population and time point description	All SCA treated subjects (safety population): randomised subjects who received at least one dose of double-blind study medication (troriluzole or placebo) during the randomisation phase		
Descriptive statistics and estimate variability	Treatment group	Troriluzole	Placebo
	Number of subjects	108	109
	Falls (by events), as recorded on AE CRFs	20	42
Effect estimate per comparison	Risk reduction in falls	Relative incidence rate reduction (troriluzole:placebo) P-value	53.4% 0.005
Notes	The risk of falls was used in the analyses as a proxy efficacy endpoint as it is a potential indicator for disease progression and a major cause or morbidity and mortality in this patient population. During the 48-week randomisation phase, an AE of fall was recorded if there was a worsening of frequency of falls or if a fall was associated with an injury. The risk reduction of falls was analysed using a generalised linear model where the model was fit using a Poisson family model with a log link function.		

3.4.1.5. Clinical studies in special populations

Specific studies in special populations such as patients with renal or hepatic impairment, paediatric patients or older patients >65 years of age were not performed. Subgroups with these characteristics in a very rare disease such as SCA could have only included very small numbers of patients. From very small numbers, the conclusions could not have been meaningful.

3.4.1.6. In vitro biomarker test for patient selection for efficacy

There was no biomarker used for patient selection. There was neither an investigation for a biomarker during the studies.

3.4.1.7. Supportive studies

Supportive Study BHV4157-201, Intersection Analyses and 201-OLE

BHV4157-201 was a Phase 2b/3, multicentre, randomised, double-blind, placebo-controlled, parallel-group hypothesis generating study conducted to assess the safety, tolerability, and efficacy of troriluzole in subjects with SCA, with an ongoing OLE phase.

Subjects received troriluzole or placebo for 8 weeks during the randomisation phase. Subjects who completed the randomisation phase had the option to receive troriluzole in an open-label extension phase, as long as the investigator believed open-label treatment offered an acceptable risk-benefit profile. The originally planned duration of the extension phase was 48 weeks but the duration was expanded to 192 weeks in a series of protocol amendments: Amendment 04 (Version 05, dated 22-Jun-2018), Amendment 06 (Version 07, dated 8-Jul-2019), and Amendment 07 (Version 08, dated 17-Apr-2020).

A total of 181 subjects were screened for the study, of which 141 subjects were randomised at 18 sites in the United States (US). Subjects were male and female adults 18 to 75 years of age with a known or suspected diagnosis of specific hereditary ataxias: SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, or SCA10. Subjects had a moderate level of symptoms and were excluded based on presence of neurologic and medical conditions that could confound assessment of efficacy and safety.

Male and female outpatient subjects between the ages of 18 and 75 years, inclusive, with a known or suspected diagnosis of the following specific hereditary ataxias: SCA1, SCA2, SCA3, SCA6, SCA7, SCA8 and SCA10. Subjects were required to have a screening total SARA score ≥ 8 points and a score of ≥ 2 points on the gait subsection of the SARA.

Subjects who completed the randomisation phase could continue in the OLE phase:

- 131 subjects entered the open-label extension phase. 104 subjects completed the first 48 weeks of the extension phase and 27 subjects discontinued, including 16 subjects who withdrew, 5 subjects who discontinued due to AEs, and 6 subjects who discontinued for other reasons.
- 73 subjects continued in the extension phase after the first 48 weeks of open-label treatment. As of database lock, 16 subjects had discontinued due to withdrawing (7 subjects), AE (1 subject), death (1 subject) or other reason (7 subjects).

Participant flow and numbers analysed

One hundred and forty one (141) subjects were randomised into the double-blind randomisation phase> 71 subjects in the troriluzole group and 70 subjects in the placebo group). The most common reasons for not being randomised in the study were inability to confirm a known or suspected SCA diagnosis (3 subjects) and hypothyroidism (2 subjects); however, reasons for screen failure were not reported for 70% of the subjects who failed screening. During the double-blind randomisation phase, the rate of discontinuation for any reason was 9.9% in the troriluzole group and 2.9% in the placebo group, with the difference driven predominantly by discontinuations for AEs. Adverse events were the most frequently reported reason for discontinuation in the troriluzole group. More than 90% of subjects in each treatment group completed the randomisation phase.

One hundred and thirty one (131) subjects entered the open-label extension phase. 104 subjects completed the first 48 weeks of the extension phase and 27 subjects discontinued, including 16 subjects who withdrew, 5 subjects who discontinued due to AEs, and 6 subjects who discontinued for other reasons.

Seventy three (73) subjects continued in the extension phase after the first 48 weeks of open-label treatment. As of database lock, 16 subjects had discontinued due to withdrawing (7 subjects), AE (1 subject), death (1 subject) or other reason (7 subjects).

Baseline data study BHV4157-201

Demographic variables were well-balanced between the troriluzole and placebo groups. The median age was 54.1 years; 23.4% of subjects were ≥ 65 years of age. Subjects were evenly distributed by sex (51.1% female) and the majority of subjects were white (77.3%) and not Hispanic or Latino (91.5%). The median weight of the study population was 76.4 kg. The most common genotypes of randomised subjects were SCA2 (26.2%), SCA1 (24.8%) and SCA6 (22.0%).

Overall, subjects had SCA for a median of 7 years (range: 0.08 to 38 years) before enrolment into the study. At the time of enrolment, the diagnosis had been confirmed for 79.4% of subjects; 10.6% of subjects had a confirmed diagnosis of a family member and 6.4% had clinical evidence of disease (Table 14.1.4). Subjects without a confirmed diagnosis at enrolment were all subsequently confirmed by genetic testing during the study. Baseline measures of disease characteristics were generally similar between the troriluzole and placebo groups as measured by multiple scales assessing ataxia symptoms, non-ataxia symptoms, physical task performance, emotional status, cognitive function, and quality of life.

Efficacy results from study BHV4157-201

During the randomisation phase, troriluzole administered at 140 mg QD for 8 weeks to subjects with SCA did not show statistically significant differences from placebo on the primary and key secondary endpoints. While the troriluzole group showed a similar improvement in SARA scores to 2 academic trials assessing the effects of riluzole in a diverse set of ataxia patients (Ristori et al, 2010; Romano et al, 2015), there was an unexpectedly high placebo response at 8 weeks. During open-label treatment over the 48-week extension phase, however, troriluzole did show slowing of disease progression in troriluzole-treated subjects, in contrast to measurable decline expected for a cohort of untreated subjects based on the natural history of the disease (Ashizawa, 2013).

For the protocol-defined primary endpoint of change from rBaseline to Week 8, the total SARA score decreased in both treatment groups between rBaseline and Week 8. Mean baseline values for total SARA score were 14.0 points in the troriluzole group and 14.7 points in the placebo group. At Week 8, the mean values for total SARA score were 13.1 points (LS mean change of -0.8 points) in the troriluzole group and 13.5 points (LS mean change of -1.0 points) in the placebo group. The LS mean difference between the troriluzole and placebo groups was 0.2 points (95% CI: -0.5, 0.9; p = 0.519).

Among the subjects treated with open-label troriluzole in the extension phase, a decrease from rBaseline in total SARA score of approximately 1 point was maintained through Week 24. The change from rBaseline to Week 48 was -0.42 points.

Troriluzole-treated subjects reported similar global impression of benefit scores after 8 weeks of treatment as compared to placebo-treated subjects, based on results from the 7-point patient-reported PGI-C health outcome measure (p = 0.2808). At Week 8, the majority of subjects in each treatment group indicated no noticeable improvement in their condition based on the PGI-C (84.1% [53/63 subjects] in the troriluzole group and 80.3% [53/66 subjects] in the placebo group).

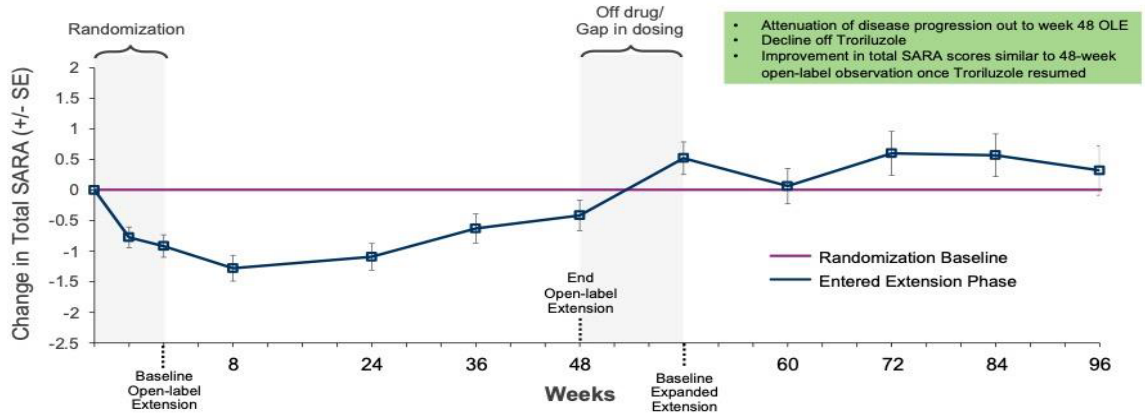
Further data analysis indicated a high placebo response rate with the total SARA score and suggested that the modified SARA score based on the axial items of the SARA was more likely to capture a clinically significant change in ataxia symptoms. Therefore, post hoc analyses were performed using the modified SARA score.

201- Extension Phase

Among the subjects treated with open-label troriluzole in the extension phase, the modified SARA score mean change from rBaseline was -0.3 points at Week 24 and 0 at Week 48.

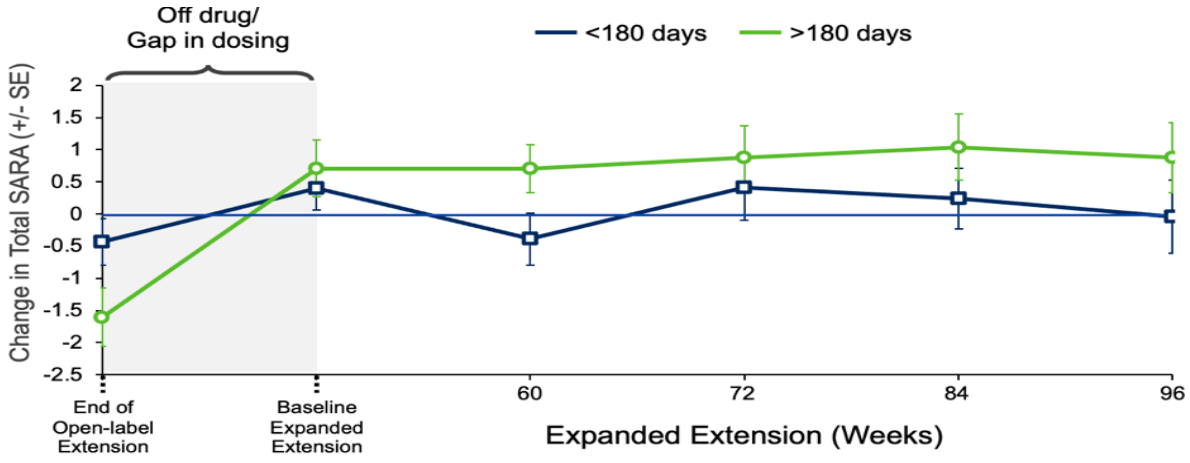
The following Figure (Figure 25) plots the mean change in total SARA score from randomisation for subjects who received troriluzole through 96 weeks of open-label treatment. The increase in scores after OLE Week 48 reflects the gaps in dosing, with increased SARA scores indicating worsening disease. However, when the subjects continuing in the expanded extension resumed open-label troriluzole, SARA scores again stabilised, suggesting further attenuation of disease progression. The observed changes suggest an attenuation of disease progression in subjects treated with troriluzole for up to 3 years, including up to a 1-year gap in dosing during which subjects declined, versus the expected rate of decline in the SARA in untreated subjects.

Figure 22: (from Figure 25 of Module 2.7.3 Summary of Clinical Efficacy): Long-term Extension Data through Open-label Week 96 (BHV4157-201)



As described above, during the administrative dosing gaps which occurred between the end of the Week 48 OLE phase and initiation of the subsequent OLE expansion SARA scores showed a greater than 1-point worsening during the off-treatment period. As shown in the following Figure, this worsening increased with longer duration off troriluzole (<180 days and >180 days gap in troriluzole dosing). Treatment benefits in total SARA scores were observed after re-initiation of troriluzole treatment.

Figure 23: (from Figure 26 of Module 2.7.3 Summary of Clinical Efficacy): Worsening in SARA Scores During Gap in Dosing Correlates with Duration off Troriluzole Treatment (BHV4157-201)



Only 14 subjects in BHV4157-201 had the SCA3 genotype and only twelve of them continued in the OLE phase.

BHV4157-201 One-year Data Matched to Natural History

A formal analysis was conducted to compare data from BHV4157-201 subjects treated with troriluzole for 48 weeks (140 mg or 200 mg QD) with data obtained from the cohort of untreated subjects in a natural history study. The intersection analysis set included 85 troriluzole-treated subjects in BHV4157-201 and 163 untreated subjects in the natural history cohort.

Based on the linear regression model, the LS mean change from baseline on the SARA after 1 year was -0.27 (95% CI: -0.86, 0.31) in troriluzole-treated subjects, representing a numeric improvement, versus +1.18 points (95% CI: 0.76, 1.61) in the natural history cohort, representing a numeric decline. The LS mean difference between cohorts was -1.46 (95% CI: -2.20, -0.72) (p = 0.0001).

According to the applicant, these findings indicate that SCA subjects treated with troriluzole over 1-year in BHV4157-201 demonstrated stability on the SARA as compared to a matched natural history cohort, which experienced notable decline. The difference in SARA scores across cohorts was statistically significant, suggesting that 1 year of treatment with troriluzole is associated with a slowing of the functional decline in patients with SCA as compared to the natural progression of this disease.

Natural History Cohort Comparison to Long-term 3-year Data in BHV4157-201

Analogous to the external control comparative analysis of the natural history data sources to the original troriluzole-treated BHV4157-206 subjects with up to 3 years of OLE data (48-week randomisation phase with troriluzole and up to 2 years of additional OLE), an additional comparative study was conducted utilizing subjects from BHV4157-201. Due to sample size limitations of the SCA3 genotype in BHV4157-201, this analysis examined the entire All SCA population only.

Treatment differences of -0.87, -0.65, and -1.00 were observed at Years 1, 2, and 3, favouring troriluzole (p = < 0.0001, 0.0007, and 0.0006 respectively), among subjects all SCA genotypes MAIC analysis.

Supportive study – BHV4157-206-OLE

Subjects were randomised to receive troriluzole (QD) or placebo (QD) for 48 weeks during the double-blind randomisation phase of study BHV4157-206.

Subjects who completed the randomisation phase were given the option to receive up to 192 weeks of treatment with troriluzole during the OLE phase, provided the primary investigator believed open-label treatment offered an acceptable risk-benefit profile. Subjects and sites remained blinded to the double-blind treatment assignments. Subjects entering the OLE phase had their first extension visit 4 weeks after the Week 48 randomisation phase visit. Thereafter, subject visits occurred every four weeks up through Week 12 of the Extension Phase. Subjects then had visits every 12 weeks up to Week 144 of the Extension phase. All subjects were to complete a termination visit two weeks after the last dose of study drug.

The primary endpoint CSR (referred to as the final CSR) presented results of efficacy and safety assessments through completion of the 48-week double-blind randomisation phase, and efficacy and cumulative safety through the OLE phase through database lock (29Apr2022). The results did not show separation from placebo on the prespecified primary endpoint or secondary endpoints in the population of All SCA subjects. However, analysis of the SCA3 genotype (one of the prespecified randomisation strata) revealed consistent treatment effects of troriluzole across prespecified primary, secondary, and exploratory outcome measures. The OLE phase was ongoing at the time of this report.

The Addendum 01 to the final CSR presents efficacy and safety results on a database lock date of 21-Jul-2023, and includes data for subjects who had the opportunity to complete OLE Week 60. Efficacy data up to OLE Week 48 and all available safety data are presented. The OLE phase of the study remains ongoing.

Results

Disposition of subjects

Of the 190 subjects who were randomised into the OLE phase, 115 subjects (60.5%) completed 48 weeks of the OLE phase and are continuing treatment, and 71 subjects (37.4%) had discontinued early. Reasons for early discontinuation included subject requested withdrawal (49 subjects, 25.8%), adverse event (8 subjects, 4.2%), investigator decision (6 subjects, 3.2%), lost to follow-up (4 subjects, 2.1%), and other (3 subjects, 1.6%). Four subjects (2.1%) completed Week 48 of the OLE phase but did not have the option to continue treatment because their site was closing, and they did not want to transfer to a new site; they are categorised as "Completed the Extension Phase." (Table 14.1.5B and Figure 10-1).

Efficacy

Overall, in the OLE phase, subjects treated with open-label troriluzole showed relative disease stability as measured by change on the f-SARA from Week 48 to OLE Extension Week 48 (0.3 in SCA3 subjects and 0.2 in All SCA subjects).

In the SCA3 population, subjects who received troriluzole in the randomised phase showed a mean improvement from randomisation baseline to Week 48 on the f-SARA of -0.1, and mean change from Week 48 to Extension Week 48 on the f-SARA of 0.2. For SCA3 subjects randomised to troriluzole, the mean change from randomisation baseline in f-SARA scores at Extension Week 48 (Week 96 total) was 0.1. SCA3 subjects who received placebo during the randomised phase showed a greater worsening from randomisation baseline to Week 48 on the f-SARA of 0.5. After placebo subjects were started on OLE troriluzole, the change from Week 48 to Extension Week 48 on the f-SARA was 0.3. For SCA3 subjects randomised to placebo, the mean change from randomisation baseline in f-SARA scores at Extension Week 48 (Week 96 total) was 0.6. According to the applicant, these observations demonstrate that SCA3 subjects randomised to troriluzole during the double-blind phase and then continued on OLE demonstrated relative stability of disease as measured by the minimal change in f-SARA scores for 2 years. SCA3 subjects randomised to placebo during the double-blind phase worsened while on placebo; and after these subjects began troriluzole during the OLE phase, their disease subsequently stabilised. Overall, these results suggest that troriluzole treatment stabilises disease progression in SCA3 subjects.

*Table 26: (from Table 11-1 of the BHV4157-206 Addendum01 CSR): f-SARA Observed and Change from Randomisation Baseline in Total Score during Randomisation and Open-label Extension Phases - **mITT Subjects** in the Open-label Extension Phase*

Total f-SARA Score / Visit	**Troriluzole/ Troriluzole**	**Placebo/ Troriluzole**
SCA3	**N = 43**	**N = 45**
r-Baseline		
N	43	45
Mean (SD)	5.0 (1.57)	4.8 (1.99)
SE	0.24	0.30
Randomisation Week 48 Change from r-Baseline		
N	38	40
Mean (SD)	**-0.1** (1.45)	**0.5** (0.96)
SE	0.24	0.15
Extension Week 48 Change from Ext Baseline		

Total f-SARA Score / Visit	**Troriluzole/ Troriluzole**	**Placebo/ Troriluzole**
N	34	33
Mean (SD)	**0.2** (1.09)	**0.3** (1.26)
SE	0.19	0.22
Extension Week 48 Change from r-Baseline		
N	34	33
Mean (SD)	**0.1** (1.97)	**0.6** (1.22)
SE	0.34	0.21
All SCA	**N = 106**	**N = 107**
r-Baseline		
N	106	107
Mean (SD)	4.9 (1.60)	4.9 (1.95)
SE	0.16	0.19
Randomisation Week 48 Change from r-Baseline		
N	94	95
Mean (SD)	0.1 (1.51)	0.2 (1.32)
SE	0.16	0.14
Extension Week 48 Change from Ext Baseline		
N	79	76
Mean (SD)	0.3 (1.11)	0.2 (1.24)
SE	0.13	0.14
Extension Week 48 Change from r-Baseline		
N	79	76
Mean (SD)	0.2 (1.63)	0.3 (1.34)
SE	0.18	0.15

The applicant is of the opinion that all SCA subjects randomised to placebo during the double-blind phase progressed less than expected based on natural history studies, but after these subjects began troriluzole during the OLE phase, their disease continued to remain stable. Given that SCAs are known to be relentlessly progressive, these results also suggest a treatment benefit of troriluzole in All SCA subjects.

Table 27: (from Table 14.2.1CA of the BHV4157-206 Addendum01 CSR): f-SARA: Observed and Change from Baseline in Total Score by Visit during the O-L Extension Phase SCA3 mITT Subjects in the O-L Extension Phase

	Troriluzole-Troriluzole (N=38)	**Placebo-Troriluzole (N=40)**
Extension baseline n	38	40
Mean (SD)	**4.8** (2.32)	**5.2** (2.02)
Median	4	5
Min, Max	0, 10	2, 10
Extension Week 156 n	5	5
Mean (SD)	**5.6** (2.70)	**8.0** (2.24)
Median	6	8
Min, Max	2, 9	5, 11
Change from Baseline n	5	5
Mean (SD)	**1.6** (2.07)	**2.6** (1.52)
Median	1	3
Min, Max	0, 5	1, 4

Studies in other indications

Study – BHV4157-202 in OCD

A randomised, double-blind, placebo-controlled trial of adjunctive troriluzole was conducted in 248 overall patients with Obsessive Compulsive Disorder (OCD). The primary endpoint was the change from baseline in the Y-BOCS total score troriluzole relative to placebo at Week 12 of the randomisation phase.

Troriluzole administered for a total of 12 weeks (140 mg QD for 4 weeks, followed by 200 mg QD for 8 weeks) as adjunctive therapy with SOC resulted in a numerically greater improvement versus placebo in the change from baseline in the total Y-BOCS score during all efficacy assessment study visits (Weeks 4, 8, and 12) during the randomisation phase. The treatment difference was greatest at Week 8 (1.5 points [95% confidence interval (CI): 3.02, 0.06] with a nominal p-value of 0.0410). At Week 12 the primary endpoint of change from baseline on the Y-BOCS total score did not reach statistical significance -1.00 (95% CI -2.59, 0.60) (p = 0.2202).

Study – BHV4157-203 in Alzheimer's disease

A Phase 2 randomised double-blind placebo-controlled trial to evaluate the efficacy and safety of troriluzole (BHV-4157) in patients with mild to moderate Alzheimer's Disease was conducted in overall 350 patients. The primary analyses used the within-participant change in ADAS-Cog 11 and in CDR-Sob as the outcome in two separate similar mixed effects repeated measures models, including all available in-clinic outcomes during the double blind phase in the mITT population. Fixed effects in the models are apolipoprotein E (APOE) status (e4 carrier versus e4 noncarrier), MMSE (mild versus moderate) status, site, baseline ADAS-Cog 11 or CDR-Sob score, respectively, treatment group (active versus placebo), visit, visit x baseline score interaction, and visit x treatment group interaction. Visit was treated as a categorical variable. Sites with only one participant were pooled together.

Troriluzole 280 mg, administered once daily as adjunctive therapy on a background of AchEI and/or memantine medication for up to 48 weeks in participants with probable AD did not statistically differentiate from placebo on the study's co-primary endpoints, the Week-48 change from baseline in the ADAS-Cog and the CDR-Sob.

Study – BHV4157-203 in GAD

A multicentre, randomised, double-blind, placebo-controlled trial of troriluzole in Generalised Anxiety Disorder (GAD) was conducted in overall 402 patients. The primary endpoint was the change from baseline in the total HAM-A score for troriluzole relative to placebo at Week 8 of the randomisation phase. The change from baseline in the total HAM-A score through Week 8 was analysed using a Mixed Model for Repeated Measures (MMRM) that included treatment, visit (Weeks 2, 4, 6, and 8), and the treatment-by-visit interaction as fixed effects, and baseline total HAM-A score and baseline-by-visit interaction as covariates.

No statistically significant difference was observed between troriluzole relative to placebo in the mean change from baseline for the primary efficacy endpoint, the total HAM-A score at Week 8. No statistically significant treatment differences for troriluzole relative to placebo were observed in the change from baseline to Week 8 results for the 2 secondary efficacy endpoints, the SDS total score (p = 0.745) and the CGI-S total score (p = 0.834).

3.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Clinical development of troriluzole in SCA and other diseases

In the troriluzole clinical programme there were 17 studies for disorders with glutamatergic dysfunction thought to contribute to underlying disease pathology (SCA, OCD, AD, GAD). Of the 4 Phase 2 proof-of-concept studies completed with troriluzole, a signal for efficacy was observed in the long-term treatment of SCA patients and the OCD study; thus, SCA and OCD were the two indications selected for advancement into well-powered Phase 3 trials.

The applicant performed 2 clinical studies to support this MAA. Study BHV4157-206 is considered a pivotal study and Study BHV4157-201 is considered supportive. The 2 randomised clinical studies in SCA (BHV4157-206 and BHV4157-201) represent, according to the applicant, the largest, multicentre, placebo-controlled dataset for SCA (N = 358), in which 340 subjects received at least one dose of troriluzole, in either the double-blind or OLE phase. The applicant has also conducted an external comparison of the troriluzole data with natural history cohorts, study BHV4157-206-RWE (206-RWE from now on) and submitted the results with the responses to Day 120 LoQ. The applicant is of the view that the primary evidence of effectiveness of troriluzole is based upon results from this real-world evidence (RWE) study, designed based on extensive dialogue with the FDA, to assess the benefit of long-term troriluzole treatment in SCA patients.

SCA is an ultra-rare disease with different genotypes that may carry a similar pathophysiology over time. The following genotypes were studied: SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, and SCA10 and all genotypes together referred to as All SCA.

Study BHV4157-201 (201 from now on) is a Phase 2b/3 randomised, double-blind, placebo-controlled, parallel group study conducted as proof of concept. The dose administered was 140 mg QD and the double-blind period had 8 weeks. Study population included subjects between 18 and 75 years of age with a known or suspected diagnosis of SCA. Randomisation was not stratified. The primary objective of the randomisation phase was to compare the efficacy of troriluzole (140 mg QD) versus placebo on ataxia symptoms after 8 weeks of treatment as measured by the total score on the SARA scale.

Study BHV4157-206 (206 from now on) is the pivotal Phase 3 randomised, double-blind, placebo-controlled, parallel group study in Adult Subjects with Spinocerebellar Ataxia conducted to support an indication in these patients. The design of the phase 3 pivotal trial is appropriate. Since the development concerns an ultra-rare disease, one pivotal study (without the need for repetition of the results) could have been sufficient, providing that the results from this study are compelling.

Of the subjects included in the studies, 202 subjects with SCA received the recommended dose of 200 mg QD either in the double-blind (N = 108) or OLE phase (N= 94) of pivotal study 206.

In the two SCA studies (201 and 206), the open-label extension phase remains ongoing up to 192 weeks, with a total of 303 subjects having received troriluzole 140, 200 or 280 mg QD for > 6 months (> 24 weeks) and 271 subjects troriluzole 200 mg for > 1 year (200mg after 48 weeks).

Dose response

The dose of troriluzole was based on the "required" exposure for riluzole. Rilutek recommended dosing is 50mg every 12 hours. The aim was to have the same or very similar therapeutic exposure of riluzole using troriluzole as prodrug. Troriluzole dosed at 200 mg contains a comparable molar amount of riluzole as found in a 100 mg dose of oral riluzole and an overall exposure (AUC0 24, steady-state of

1,804 ng•h/mL) comparable to approximately 150 mg of oral riluzole. The therapeutic levels achieved for riluzole appeared to be well tolerated at the doses administered.

Randomised placebo controlled study design and characteristics

The 206 study included male and female outpatients 18 to 75 years of age inclusive with a known or suspected diagnosis of the following specific hereditary ataxias: SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, and SCA10. SCA was to be confirmed genotypically. SCA3 genotype was the most common genotype in the study and corresponded to 41% of the total study population. Patients had to have an f-SARA total score ≥ 3 and a score of ≥ 1 on the Gait subsection of the f-SARA at screening.

Subjects received troriluzole 140 mg QD or matching placebo for the first 4 weeks of the randomisation phase; the dose was increased to 200 mg QD or matching placebo for the remaining 44 weeks of the 48-week randomisation phase. Temporary down titration to 140 mg QD was allowed, with medical monitor approval, to address tolerability issues.

The primary efficacy endpoint was the change from baseline on the f-SARA at Week 48. The secondary efficacy endpoints were: PIFAS; FARS-ADL; and FARS-FUNC. A number of exploratory endpoints have also been used: CGI-I; PGI-C; Neuro-QOL Lower Extremity Mobility Scale; Neuro-QOL Upper Extremity Mobility Scale; and Neuro-QOL Fatigue Scale. The selection of endpoints is considered adequate.

The number of patients on troriluzole treatment (N=108) is more than adequate, taking into consideration the rarity of the disease. The planned population was representative of the most common genotypes of SCA, with SCA1, SCA2 and SCA3, accounting for the majority (84%) of the randomised patients. SCA3 accounted for 41.0%, SCA2 for 30.9% and SCA1 for 12.0% of the randomised patients (please see baseline data in Annex I). It is important that for such a rare disease the randomisation was 1:1.

The majority of patients (~93%) were enrolled in 21 sites in USA and the rest in 2 sites in China. It is noted that there were no sites from Europe. Specific PK data from European patients are lacking. It cannot be excluded that SCA patients in Europe with different genotypes and disease characteristics (one of them being different progression rates) behave differently. This would explain that the results present obvious differences in the comparisons of troriluzole with the external natural history cohorts.

Selecting placebo for the comparison was the only appropriate option, since there is no other product approved for the management of SCA. The duration of 1 year of the study was reasonable.

Three strata based on the genotype were pre-defined: SCA1 & SCA2, SCA3 and SCA6, SCA7, SCA8 & SCA10. SCA9 has not been assigned to a clinical disorder. The choice of a stratum, which comprised of SCA6, SCA7, SCA8 & SCA10 is reasonable due to the low prevalence and small numbers. According to the applicant, the prespecified SCA3 randomisation stratum represented 40% of the sample size in Study BHV4157-206 and was sufficiently powered to show a meaningful treatment effect.

It is recognised that upon FDA recommendations SARA was modified to f-SARA by removing the appendicular items and changing the score to 0-4 leading to a total score of 16 compared to the score 40 of SARA. However, it has been reported that after removing the four last items and rescaling all items from 0 to 4, variability increased, and progression was slower and thus would require a larger sample size in a future therapeutic trial (Moulaire et al 2023). It has been also reported in the literature that removing these items worsens the performance of the new scale by decreasing granularity, increasing variability, and slowing the rate of progression.

Main study analyses

For the intercurrent event treatment discontinuation, a hypothetical strategy was employed, which was justified by the applicant with the aim of the trial to evaluate the effect of the drug when taken as

intended in the protocol (study discontinuation is also mentioned by the applicant but is not an intercurrent event). However, from a regulatory point of view, the effect that can be expected in clinical practice is of primary interest. Treatment discontinuation will also occur in clinical practice such that the effect regardless of discontinuation (treatment policy) is considered most relevant and should be the basis for B/R assessment.

Estimands

The estimand proposed by the applicant is not considered appropriate from a regulatory point of view.

In the estimand definition, for the intercurrent event treatment discontinuation, a hypothetical strategy was employed (i.e. the treatment effect if no patient had discontinued treatment was the target of estimation), which was justified by the applicant with the aim of the trial to evaluate the effect of the drug when taken as intended in the protocol. However, from a regulatory point of view, the effect that can be expected in clinical practice is of primary interest. Treatment discontinuation will also occur in clinical practice such that the effect regardless of discontinuation (treatment policy) is considered most relevant and should be the basis for B/R assessment.

Statistical issues

The primary analysis was based on the mITT analysis set, which excluded all patients without post-baseline data. However, all treated patients should be included in the primary analysis to avoid any selection bias. An analysis including these patients could have been provided (whereby all data after treatment discontinuation should be replaced by J2R or CIR). However, it is not to be expected that extensive or additional analyses will significantly influence the B/R decision.

Randomisation was stratified by SCA genotype, which was appropriately taken into account by considering it as covariate in the analysis.

The primary analysis was aligned to the hypothetical effect if all patients had completed treatment under the missing-at-random assumption (i.e. assuming patients who discontinue study medication prematurely have a response profile for the remainder of the randomisation phase similar to subjects who completed the 48 weeks of the randomisation phase). However, as highlighted above, not this hypothetical effect but the effect regardless of treatment discontinuation is of primary interest from a regulatory view. As patients were not followed after treatment discontinuation, missing data needed to be replaced. The sensitivity analyses using both a jump to reference (J2R) and copy increment reference approach (CIR) are more appropriately aligned to this effect, as these assume that patients who discontinued troriluzole prematurely do no longer benefit from treatment after discontinuation. Thereby, J2R assumes that the patient 'jumps' to the mean reference profile after discontinuation, i.e. all potential effects are immediately lost after discontinuation as if patient had never been treated. CIR assumes that, after the patient discontinues, the patient's post-discontinuation mean increments copy those from the reference group, i.e. potential effects before discontinuation are maintained. Therefore, these should be the primary basis for B/R assessment.

Post-hoc analyses are generally likely to be data-driven and can be considered only hypothesis generating. Particularly, this applies for post-hoc defined analysis populations such as the "Ambulatory SCA3 subjects" and analysis of falls, which was a safety endpoint that was originally planned to be analysed descriptively only. After database lock and unblinding of the pivotal study 206, two amendments were added to the SAP to include post-hoc analyses in the SCA3 subgroup. However, as the decision was made after unblinding, this analysis is clearly considered hypothesis generating.

In the study protocol, only descriptive analyses for the subgroups of interest were pre-specified. Post-hoc, a subgroup analysis was conducted in SCA3 patients. The additional analyses included a search for a model for SCA3 and selection of the model with the best fit, which was justified by the applicant

by no statistical model being pre-specified. However, a data-driven model selection is generally not appropriate (see EMA Guideline on adjustment for baseline covariates in clinical trials), even more in this case where no method for model selection was pre-specified. Although no statistical model was specifically pre-specified for SCA3, it would have appeared natural to use the pre-specified model for the primary analysis of the overall population, either restricted to the subgroup without the stratification factor, or the model including treatment-by-covariate interaction.

Of note, the applicant proposed further analysis (included as the post-unblinding amendment to the SAP) identifying mITT subjects with SCA3 and mild or moderate gait impairment at baseline as a group of interest.

Efficacy data and additional analyses

There were no imbalances between the troriluzole group and placebo that could have had an impact on the results of the study.

The natural history of disease progression, as measured by an increase on the f-SARA score, has been estimated at approximately 0.7 points per year (Moulaire 2023 and Appendix S1 - Supplemental Information to Moulaire 2023) and correlates with the expected 1-2 points of progression per year in the standard SARA (or between 0.4 and 0.8 in the f-SARA after transformation). Progression or decline in the condition of the patients is translated as an increase of the score of the two scales.

At week 48 the change from baseline in the f-SARA for All SCA who received troriluzole (+0.20) showed the same degree of deterioration as that for the placebo group (+0.27). The results for the initially intended population ALL SCA genotypes randomised (SCA1, SCA2, SCA3, SCA 6, 7, 8 and 10) were not in favour of troriluzole compared to placebo. No statistically significant difference in the change from baseline of f-SARA score at Week 48 in the pre-specified population of all SCA subjects was demonstrated compared to placebo (95% CI: -0.47, 0.34; p=0.76). Therefore, no confirmatory conclusions can be drawn from the 206 study, which failed to meet its primary objective. Disease did not progress as expected in the placebo group of the All SCA genotype population. A worsening of only +0.23 and +0.27 points in the f-SARA was observed for the placebo group at week 36 and week 48, respectively. Even minor improvements in f-SARA score of -0.17 and -0.06 were observed at week 12 and 24, respectively in the placebo group.

Furthermore, the difference of troriluzole from placebo at week 48 was 0.06 (p=0.7581).

The applicant has generated separately a body of evidence to support the use of the f-SARA, PIFAS and FARS-ADL as primary and secondary endpoints in the 206 study. The evidence reflects a combination of qualitative (Qualitative validation study report and the European clinician interviews addendum) and quantitative (MGH psychometrics report, BHV4157-206 psychometrics report, and BHV4157-201 psychometrics report) research and analysis methods. Based on the evidence generated by the applicant an f-SARA quantitatively meaningful change threshold ranges between 0.89 (using the Standard deviation method) and 1.19 (using Random Error methods). This can suggest that a change of 1 point is supported as a meaningful responder threshold for the f-SARA total score (see BHV4157-206 psychometrics report). In the interviews, the majority of clinicians indicated that a minus 1-point minimum change would be a meaningful improvement, with only a minority recommending larger thresholds such as 2-points decrease. Hence, the effect sizes observed for the ALL SCA population are too small to be considered clinically meaningful.

Moreover, no statistically significant difference was observed between both groups in any of the secondary efficacy endpoints.

Any analysis after the failure of the primary analysis can only be interpreted with caution. The analysis for the SCA3 group showed at week 48 a very small difference of -0.56 between troriluzole and placebo in the f-SARA change from baseline, (p=0.0450). Notably, for the model corresponding to the one used for primary analysis in the overall population, the difference was slightly smaller (-0.53; p=0.065). However, whether the p-value is slightly above or below 0.05 is finally not important for the strength of evidence from a non-confirmatory post-hoc analysis. Furthermore, a difference of 0.56 is very small and corresponds to only 3.5% of the highest score in f-SARA. According to the evidence generated by the applicant for the validation of the measurement tools used in their studies, 1-point minimum change in f-SARA would be a meaningful improvement.

Furthermore, the Model based summary statistics, used for the analysis of the SCA3 group, are from a mixed model with repeated measures (MMRM), that is based on a missing at random assumption, which can be considered to be aligned with a hypothetical strategy for the intercurrent event treatment discontinuation that is not appropriate from a regulatory point of view (see above). Using alternative methods of replacing missing data that are more plausibly aligned with the appropriate treatment policy strategy, provided even lower differences between troriluzole and placebo with even less significant/larger p values. By applying jump-to-reference (J2R) analysis, the difference of troriluzole from placebo in the change from baseline in the f-SARA was -0.05 (p=0.8077) for the mITT subjects and -0.5 (p=0.0827) for the SCA3 genotype subgroup. By applying Copy Increment Reference (CIR) analysis, the difference of troriluzole from placebo in the change from baseline in the f-SARA was -0.06 (p=0.7536) for the mITT subjects and -0.53 (p=0.0625) for the SCA3 genotype subgroup. Both analysis led to very small effect sizes and statistically insignificant results. Using the Copy Increment Reference (CIR) analysis is considered the most relevant analysis.

It is difficult to understand why in the randomised controlled trial troriluzole did not differentiate from placebo in the case of SCA1 and SCA2 genotypes, but a marginally nominally statistically significant difference was observed only for SCA3. A mechanistic rationale supporting this type of specificity is lacking and the post-hoc analyses initially done by the applicant was considered as hypothesis generating.

Furthermore, the secondary endpoints did not support the f-SARA results in the All SCA population or in the SCA3 genotype subgroup.

The key Secondary Endpoints at Week 48 during the Randomisation Phase for the mITT subjects were not statistically significant: PIFAS total score change from baseline -1.959 (95% CI:-5.089, 1.170) p=0.2184, FARS-ADL total score change from baseline 0.470 (95% CI:-0.544, 1.485) p=0.3620 and FARS-FUNC total score change from baseline at Week 48 0.040 (95% CI:-0.114, 0.193) p=0.6092.

For the SCA3 genotype subgroup, CGI-I showed some nominally statistically significant difference between troriluzole and placebo of 0.54 which is small and corresponds to 7.7% of the highest score of the scale. The results in PIFAS, FARS-ADL, FARS-FUNC and PGI-C for the SCA3 group were not statistically significant with large 95% confidence intervals and nominal p-values at week 48 of 0.3092, 0.7716, 0.3114 and 0.1568, respectively. CGI-I and Fall Risk were nominally statistically significant. The results for the FARS-ADL (with a large p-value of 0.77) showed borderline improvement, whilst the results for the QOL Upper and QOL Lower Extremities were declining (decreasing scores indicating worsening in the ability to do). The results for the SCA3 genotype subgroup do not all point in the same direction and in favour of troriluzole treatment. This adds to the doubts as to whether the observed effect is a true treatment effect.

With respect to "falls", this was not a pre-specified efficacy endpoint (consequently, no statistical analysis was pre-specified). However, the applicant characterises "*the risk of falls as a proxy efficacy endpoint as it is a potential indicator for disease progression*". Falls were not a pre-defined safety measurement, either. Falls were recorded just on AE CRFs and they were part of the safety analysis.

Furthermore, with the revised protocol version 2 "*Falls diary was removed from Exploratory Objectives*" and "*Falls Diary was removed from Schedule of Assessments*". It is unclear how the applicant ended up using results from "falls" as an efficacy measurement. One could argue that the applicant selected a convenient safety event in the SCA3 subgroup (probably the only positive one) and transformed it "arbitrarily" into an "efficacy advantage". According to the applicant an independent expert panel of SCA clinicians experienced that data from "falls diaries" were highly variable and difficult to interpret and consequently strongly advised against use of a "falls diary" in the protocol. The main concerns regarding falls, however, are related to data quality and the post-hoc nature of the analysis rather than the analysis method.

The lack of consistency in the post-hoc analyses of falls and Pose Dispersion Index is also of concern. Analysis of the falls data and performance of normal walk showed a so-called "statistically significant relationship between PDI during normal walk and number of falls ($p = 0.041$)". However, this was not the case with PDI during tandem walk and number of falls, where no statistically significant relationship could be shown ($p = 0.231$). The so-called "statistically significant treatment relationship between PDI during normal and number of falls of $p = 0.041$" is also questionable, since the video analysis of gait was performed post-hoc and was an additional endpoint, when the primary endpoint f-SARA of the RCT failed to reach statistical significance.

At the extension week 156 of the Open label extension of study 206, the mean change in f-SARA from extension baseline is +1.6 for the troriluzole-troriluzole (N=5) and +2.6 for the placebo-troriluzole group (N=5). The mean change of +1.6 points corresponds to approximately 30% of the mean extension baseline value. One could argue that a 30% deterioration in the condition of the participants after 3 years as measured by an increase in the f-SARA score is an expected decline in the patients' condition and can be attributed to the natural history of the disease. Furthermore, from the 38 subjects with values at the extension baseline only 5 reached week 156. A clear, consistent and meaningful benefit by slowing disease progression from troriluzole treatment cannot be identified from the study BHV4157-206 open-label extension (OLE) phase (BHV4157-206 Addendum01 CSR). The highest level of credible evidence is expected from an RCT and not from its OLE and other indirect comparisons with natural history registries (see below). The fact that different scales SARA and f-SARA were used adds to making results even more difficult to interpret.

In summary, the unmet medical need in SCAs is clearly acknowledged. However, the pre-specified primary analysis using the f-SARA scale failed such that no confirmatory conclusions can be drawn from the study and all post-hoc analyses are considered exploratory and result-driven.

SCA is comprised of different genotypes resulting in similar clinical pictures. Troriluzole is hypothesised to address the glutamatergic dysregulation in SCA. Taking into consideration the unspecific mechanism of action of troriluzole and the clinical similarities between all SCAs, especially SCA1, 2 and 3, no rationale has been provided why troriluzole reached an effect only in one specific SCA subtype.

Development of SCACOMS

Two natural history datasets were used to develop the SCACOMS (one from US CRC-SCA and one from EUROSCA) which were then applied to estimate treatment effects in the pivotal study BHV4157-206. The SCACOMS is a composite endpoint created to combine more sensitive items from the f-SARA [Gait Score, Stance Score, Speech disturbance, Sitting Score (the latte only for EUROSCA)], CGI and Functional Stage (the latter only for CCR-SCA) and thus assumed to be more sensitive to change in a slowly progressive disease in comparison to the originally used scales. According to the SCACOMS, the expected magnitude of treatment effect would be an 80% to 87% delay in disease progression for subjects treated with troriluzole compared to placebo. However, predictive relevance of this analysis remains uncertain, should be treated with caution and cannot replace results of the double blind study. Despite the effort put by the applicant, the enrichment of patients, the limitations with the

scales/endpoints part of the SCACOMS (even differences in SCACOMS between the two natural history registries) and the number of assumptions needed render the interpretation of the SCACOMs results when used for the study BHV4157-206 findings very difficult.

Long term 3-year comparison of All SCA and SCA3 Data in BHV4157-206 with natural history cohort using MAIC

A formal analysis was conducted to compare data from BHV4157-206 subjects treated with troriluzole for up to 3 years with a selected group from the combined natural history datasets. The f-SARA was the endpoint used for the comparison. According to the applicant, these results add further evidence to this submission that treatment with troriluzole leads to a clinically relevant delay in SCA disease progression that is sustained out to 3 years. This is not agreed.

Only patients with at least one follow-up measure after 1,2 or 3 years were included in the analysis, which may have led to selection and bias. A Matching Adjusted Indirect Comparison (MAIC) was performed to match natural history subjects from the registries to subjects in BHV4157-206 to account for potential baseline confounding. It is not understood why MAIC was used, as it is a technique when no individual patient data (IPD) but only aggregate data are available from the external data source that is intended to be used for the comparison, which is not the case here where IPD are available from the registries.

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Automated Video Analysis Study

It is interesting that the post hoc analysis of videos suggests improvement on tandem walk associated with troriluzole. According to the applicant, the sensitivity of the Pose Dispersion Index to change with troriluzole treatment over 48 weeks, was statistically significant ($p = 0.010$) compared to placebo treatment only for the tandem walk. However, the numbers are small, since the sample comprised of 36 placebo- and 31 troriluzole-treated subjects (N=67 in total out of 218) with videos available at the screening and Week 48 timepoints. Furthermore, the finding for the tandem walk becomes less convincing, as the results for the normal walk-derived Pose Dispersion Index (N=56) were less compelling and did not reach statistical significance ($p=0.30$). This lack of consistency is of concern for the reliability of the method.

Another point of inconsistency arose with the analysis attempting to correlate Baseline Pose Dispersion Index distributions with the risk of subsequent falls. In this analysis the reverse situation from the one above was observed. The results for the normal walk were more positive and had a nominal statistical p value of 0.041, whilst the results for the tandem walk had a value of 0.231.

Some examples of stick figure videos (from which the Pose Dispersion Index is calculated) in MP3 format were received from the applicant in an effort to examine whether simple visual observations of these videos can be helpful or whether achieved milestones, which have not been seen before in SCAs, can be detected. However, by simple visual observation no striking differences between baseline and follow-up at 48 weeks could be detected. The applicant was requested to discuss the reliability of the Video Assessment method when the results for the risk of falls from the tandem walk were not consistent with the ones for the normal walk-derived Pose Dispersion Index. The Video analysis of gait method is under development. As stated by the applicant, it is an emerging technology which could serve as a tool to assess a patient's ambulation and an important supplement to traditional clinical assessment of gait using structured ratings scales. Several video analyses are being currently developed (https://pmc.ncbi.nlm.nih.gov/articles/PMC8736327/) as useful addition to clinical trial assessments. None of these video assessments has been validated and established as evidence or tools for demonstration of efficacy. These preliminary post-hoc findings could be used supportively for the design of another confirmatory study.

In conclusion, these results, which were obtained after analyses based on several assumptions, cannot be considered consistent and hence reliable or contribute towards a favourable benefit risk discussion.

BHV4157-206-RWE

Topline data from this RWE study was sent to the EMA and Rapporteurs, updating them on the positive topline study results (Eudralink submission of 23-Sep-2024) that was in parallel also announced with a press release (https://ir.biohaven.com/news-releases/news-release-details/biohaven-achieves-positive-topline-results-pivotal-study). The applicant claims that the data from Study BHV4157-206-RWE provide robust and clinically meaningful results demonstrating a clear treatment benefit in troriluzole-treated SCA subjects versus a rigorously matched natural history (NH) comparator. As to the applicant, these data provide primary evidence of effectiveness that serves as the basis for approval.

A major concern that impacts the credibility of these data is the observation that in the randomised controlled study 206 statistically significant results were not achieved in 1 year. The difference for f-SARA total score change from baseline at 1 year (48 weeks) for the All SCA population was only -0.06 (0.20) [95% CI: -0.47, 0.34] in favour of troriluzole treatment with a p=0.7581. However, in the external comparison of troriluzole treatment group from study 206 with the US natural history cohort CRC-SCA, at the same time period, the difference for f-SARA total score change from baseline was -0.45 (0.22) and marginally statistically significant [95% CI: -0.88, -0.01] p= 0.0464. This discrepancy after 1 year makes the results of the external comparisons to natural history cohorts less credible.

Furthermore, while a comparison to NH controls may contribute to the totality of evidence, it cannot be the only basis for approval here, particularly as results are inconsistent to the results from the randomised controlled study. This is due to the general limitations of comparisons to external controls with several potential sources for bias. Notably, the concern for a relevant bias is strongly supported by the separation between troriluzole treated subjects and NH controls that is observed at Year 1, while no such separation is seen to placebo patients at Week 48. In addition, the comparison of the study data to CRC-SCA (US-based) showed different results than the comparison of study data to EUROSCA (EU-based).

Particularly, there is a concern that selection mechanisms for a study are different than for a registry, leading to a selected set of patients that may not be comparable to NH controls even after matching. For example, for the randomised controlled study BHV4157-206, an inclusion criterion was ”Determined by the investigator to be medically stable at baseline/randomisation as assessed by medical history, physical examination, laboratory test results, and ECG testing. Subjects must be physically able and expected to complete the trial as designed”. This is not possible to reconstruct when selecting patients from a registry and may lead to difference in prognostic factors that cannot be accounted for by matching.

To account for potential confounding, Propensity Score Matching (PSM) was used to match untreated subjects from the external controls to treated subjects from the troriluzole arm of Study BHV4157-206 with regard to age, sex, genotype, baseline f-SARA, age at symptom onset, and CAG trinucleotide repeat length. However, matching may provide an unbiased comparison only if the assumption of no unmeasured confounding is fulfilled, i.e. when all prognostic covariates are taken into account for matching. This is a strong and unverifiable assumption that is unlikely to be fulfilled. Indeed, the separation between troriluzole-treated patients and matched NH controls in Year 1 implies also a separation between NH controls and placebo patients in Year 1, which strongly suggests that the set of matching variables may not include all prognostic factors.

In addition, two cohorts (CRC-SCA, EUROSCA) were used for selection of matched controls, resulting in two sets of matched NH controls, one for every region. However, although the same covariates were

used for matching, the sample sizes and the sizes of difference between troriluzole-treated patients and the respective NH controls were different for the two sets of NH controls. This may also point to the existence of additional underlying prognostic factors that were not included in the set of matching variables.

For the comparison of troriluzole (N=101) to CRC-SCA (N=202) a so called 1.5 years delay in progression was observed. Whilst, for the comparison of troriluzole (N=85) to EUROSCA (N=170) the effect was 2.2 years. The comparison of troriluzole (N=101) to the Global Cohort (CRC-SCA+ EUROSCA; N=303) led to an effect of 1.9 years as the so called "delay in progression".

The best explanation of the applicant for these differences is that the US dataset also included genotypes SCA 6, 7, 8 and 10, where progression rates are known to be slower. However, this can be corroborated by publications. It has been reported that progression was fastest in SCA1 followed by SCA2 and SCA3, which took a similar course, and SCA6, which had the slowest progression (Jacobi et al., 2022 and 2023). REDACTED

Supportive study BHV4157-201 and its OLE

In the supportive study 201 post hoc analyses performed using the modified SARA score (calculated from the SARA score that was used as endpoint in this study) showed minor decreases in both the troriluzole (-0.4) and in the placebo group (-0.3). The supportive study BHV4157-201 did not meet the prespecified primary endpoint (PEP). No statistically significant difference in the change from baseline of the total score of the standard SARA score at Week 8 in the population of all SCA subjects was demonstrated. Moreover, the secondary endpoints were not supportive either. In the case of SCA3 genotype a very small difference between troriluzole and placebo could be detected. In the extension phase at week 48 and from the subgroup analysis very small differences were detected -0.46, 0.31, -0.81, -0.24, -2.70, -1.50, -0.5 for SCA1, SCA2, SCA3, SCA6, SCA7, SCA8 and SCA10, respectively. Despite the small subgroups the results are lacking consistency since for SCA2 there was a minor deterioration at week 48 and a relatively large improvement for SCA7 (-2.70) compared to randomisation baseline. This improvement for SCA7 at week 48 became very small at week 96. Also at week 96 minor deterioration in the patients' condition for SCA1, SCA2, SCA3 and SCA10 was observed, probably indicating a lack of sustainability of any potential treatment effect. These results are not supportive of a clear and consistent troriluzole treatment effect.

Post-hoc analyses or comparisons to natural history data cannot override the negative results of adequately designed and conducted randomised, double-blind, placebo controlled studies. Therefore, the available efficacy data are not considered sufficient to support the current MAA.

Efficacy of troriluzole in patients with all genotypes of SCA has not been demonstrated. (**MO**)

Studies in other indications

Statistically significant results in the primary endpoints in Alzheimer's disease and GAD and in the pivotal trial for OCD were not obtained with troriluzole. The reasons for these failures are unclear. They create, however, a negative impression for the potential treatment capabilities of troriluzole in various diseases/conditions. The unspecific mechanism of action is noted.

Assessment of paediatric data on clinical efficacy

Not Available

Additional efficacy data needed in the context of a MA under exceptional circumstances (MAUEC)

The applicant has also submitted proposals for detailed information on the specific procedures / obligations to be conducted.

Safety Procedures/Pharmacovigilance plan

At this time, no post-approval safety obligations are foreseen. However, adverse events will be carefully monitored, and yearly updates will be provided on any new safety information as part of ongoing pharmacovigilance.

Programme of Studies

Biohaven's SCA programme consists of two registrational trials, proof of concept Study BHV4157-201 and pivotal Study BHV4157-206. The open label phases of both of these studies remain ongoing in order to gather additional long-term data for the safety and efficacy of troriluzole in adult SCA patients. In order to ensure adequate monitoring of safety and efficacy of troriluzole in adults with spinocerebellar ataxia genotype 3 (SCA3), the marketing authorisation holder shall provide yearly updates on any new information concerning the safety and efficacy of troriluzole within the Periodic Benefit Risk Evaluation Report (PBRER).

Prescription or conditions of use

SCAs are a group of ultra-rare neurodegenerative disorders. As such, these disorders are diagnosed and treated by neurologists specializing in movement disorders such as SCA. The proposed indication for troriluzole is for adult patients with a genetically confirmed diagnosis of SCA3. Troriluzole would be supplied to this patient population by a neurologist via a restricted medical prescription.

Applicant's conclusion

Considering (1) the serious, progressive, and ultimately fatal nature of SCA3 and the high unmet medical need and lack of approved treatments, (2) the robust safety database for troriluzole and compelling efficacy data in SCA3, and (3) limited feasibility and long potential duration associated with conducting another trial, it would be medically unethical to delay approval of a potential treatment while conducting another randomised, double-blind, placebo-controlled trial for SCA3. Given the burden of SCA across generations, the progressive decline in functional ability, the absence of treatment options for these patients, and the years it would take to conduct another clinical trial in a single genotype, the applicant is of the view that the evidence from the efficacy and safety data presented is compelling and strongly supports exceptional circumstances for the approval for troriluzole in the treatment of adult patients with SCA3.

The applicant's request for a MA under exceptional circumstances cannot be accepted since a positive benefit/risk ratio in the target population was not established.

3.4.3. Conclusions on clinical efficacy

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3.4.4. Clinical safety

The clinical safety data of troriluzole are drawn from 8 phase 2/3 studies across different indications (see Table 28) and 10 completed Phase I studies. Studies in the SCA indication comprise two completed randomised-controlled studies of 48 weeks duration (pivotal study 206) and 8 weeks

duration, (supportive study 201), respectively with ongoing open-label (OLE) phases each. Two phase III studies in the OCD indication are still blinded.

Table 28: Status and cut-off dates for safety of Phase 2 and 3 studies (applied for the submitted Summary of Clinical Safety, SCS)

Protocol No.	Indication	Status Randomisation Phase	Status Troriluzole OLE Phase	Data Cut Date for SCS
BHV4157-206	SCA	Complete	Ongoing	21-Jul-2023
BHV4157-201	SCA	Complete	Ongoing	20-Mar-2023
BHV4157-202	OCD	Complete	Ongoing	17-Mar-2023
BHV4157-302	OCD	Ongoing/Blinded	NA	14-Mar-2023*
BHV4157-303	OCD	Ongoing/Blinded	NA	14-Mar-2023*
BHV4157-209	OCD	NA	Ongoing	14-Mar-2023*
BHV4157-203	AD	Complete	Complete/Terminated	04-Feb-2022
BHV4157-207	GAD	Complete	Complete/Terminated	18-Jun-2020

*Clinical database cutoff date was 14-Mar-2023, central lab data transfer date was 21-Mar-2023.

AD= Alzheimer's disease; GAD= Generalised anxiety disorder; OCD= Obsessive compulsive disorder;

Table 29: Updated cut-off dates for ongoing in OLE Phase studies (provided with Day 120 Response)

Protocol No.	Indication	Data Cut Date
BHV4157-206[1,2,3]	SCA	25-Jul-2024
BHV4157-201[4,5]	SCA	28-Jun-2024
BHV4157-202[6]	OCD	28-Jun-2024
BHV4157-209[7]	OCD	28-Jun-2024

The troriluzole dose evaluated in pivotal study 206 was 140 mg QD for the first 4 weeks, increased to 200 mg QD thereafter (continuation with same dose in OLE with titration in former placebo patients). The dose could be decreased for tolerability issues. In study 201 a standard dose of 140 mg QD was used, that could be increased to 280 mg (via protocol amendment) during later parts of the OLE phase. Across the phase 2/3 studies patients received troriluzole doses ranging from 140 mg QD to 280 mg QD.

The applicant primarily focused the troriluzole safety evaluation on SCA patients treated with the troriluzole dose recommended in the proposed SmPC, i.e., predominantly on the pivotal study (206).

In addition to safety data presented for the individual randomised clinical studies, pooled safety data for all patients who received at least one dose of troriluzole during the randomisation or OLE phases of the phase II/III studies in the SCA indication (including 340 patients) as well as across indications (including 1,778 patients) were provided.

3.4.4.1. Patient exposure

As of 25-Jul-2024, in the clinical development programme, 1,998 subjects were administered at least one dose of troriluzole across the Phase 1, 2, and 3 studies (excluding the still blinded studies 302 and 303). A total of 1,778 patients across indications received at least one dose of troriluzole 140, 200, or 280 mg QD, or 100 mg BID in the randomised or OLE phases of the Phase 2/3 studies with a mean (SD) treatment duration of 396.4 (460.67) days. Of these, 340 SCA patients received at least one dose

of troriluzole with a mean (SD) treatment duration of 976.5 (664.3) days. A number of 303 SCA patients received troriluzole 140, 200 or 280 mg QD for > 6 months, 271 SCA patients received troriluzole for > 1 year and 58 SCA patients received troriluzole for > 5 years.

During the randomised phases of both SCA studies, a total of 52 troriluzole and 51 placebo treated patients had SCA3. Some updated information on exposure in this subgroup has been provided with the Response to the Day 120 LoQ, however as the applicant no longer seeks an indication restricted to the SCA3 subpopulation, this is of minor relevance.

Overall, 202 SCA patients received the recommended dose of 200 mg QD (either in the double-blind [N = 108] or OLE phase [N = 94] of pivotal study 206; this was not a scheduled dose in study 201).

In addition, the FDA requested an expanded access programme (protocol submitted on 27-Feb-2024; Study BHV4157-401. This open-label SCA study in enrols subjects previously enrolled in BH4157-201 or BHV4157- 206 or troriluzole-naïve subjects. There were no data available for this study at the time of the data cut for this report.

3.4.4.2. Adverse events

An overview of adverse events reported during the placebo controlled studies in the SCA indication is presented in Table 30.

Table 30: Overview of safety during randomisation phase of study 206 and study 201

	BHV4157-206		**BHV4157-201**	
Any TEAE: n (%) [a]	**Troriluzole 200 mg N = 108**	**Placebo N = 109**	**Troriluzole 140 mg N = 71**	**Placebo N = 70**
TEAE leading to death	1 (0.9)	1 (0.9)	0	0
TESAE	6 (5.6)	8 (7.3)	4 (5.6)	1 (1.4)
TESAE related to study drug [b]	1 (0.9)	0 (0.0)	1 (1.4)	1 (1.4)
TEAE leading to study drug discontinuation	5 (4.6)	5 (4.6)	7 (9.9)	0
Severe TEAE	3 (2.8)	8 (7.3)	3 (4.2)	0
TEAE related to study drug [b]	37 (34.3)	29 (26.6)	26 (36.6)	10 (14.3)
TEAE	88 (81.5)	92 (84.4)	43 (60.6)	34 (48.6)

Percentages are based on the number of subjects treated in the randomisation phase of the study.

a. TEAEs are AEs with start date on or after the first dose of randomised study drug and up to (1) the earliest of the day before the first day of dosing of OLE study drug or the last dosing day of randomisation phase study drug + 30, for subjects continuing in the OLE phase or (2) 30 days after the last dose of randomisation phase study drug, for subjects not continuing into the OLE phase.

b. An AE is considered related to study drug if the relationship reported is possibly related or related.

Source: Table 14.3.1A of BHV4157-206 CSR,21 and Appendices 2.2.3.8, 2.3.3.8, 2.1.5.1D, and 2.1.4.1B; Source: Appendices 2.1.1.1 and 2.1.4.1A

The most common TEAEs by PT (occurring in at least 2% of patients in the troriluzole group) of pivotal study 206 are given in the following table.

Table 31: TEAEs reported in at least 2% of subjects in the troriluzole group during the 48 week randomisation phase – study 206

PT: n (%)	Troriluzole 200 mg N = 108	Placebo N = 109
Any TEAE	88 (81.5)	92 (84.4)
Fall [a]	14 (13.0)	24 (22.0)
Headache	12 (11.1)	8 (7.3)
Dizziness	10 (9.3)	11 (10.1)
Fatigue	10 (9.3)	9 (8.3)
Contusion	7 (6.5)	7 (6.4)
COVID-19	7 (6.5)	3 (2.8)
Nausea	7 (6.5)	1 (0.9)
Muscle spasms	6 (5.6)	10 (9.2)
Urinary tract infection	6 (5.6)	7 (6.4)
Upper respiratory tract infection	5 (4.6)	7 (6.4)
Insomnia	5 (4.6)	2 (1.8)
Abdominal discomfort	5 (4.6)	1 (0.9)
Arthralgia	4 (3.7)	7 (6.4)
Cough	4 (3.7)	5 (4.6)
Abdominal pain upper	4 (3.7)	2 (1.8)
Influenza	4 (3.7)	2 (1.8)
Hypertension	4 (3.7)	1 (0.9)
Syncope	4 (3.7)	1 (0.9)
Nasopharyngitis	4 (3.7)	0
Skin laceration	3 (2.8)	4 (3.7)
Back pain	3 (2.8)	3 (2.8)
Myalgia	3 (2.8)	3 (2.8)
Diarrhoea	3 (2.8)	2 (1.8)
Alanine aminotransferase increased	3 (2.8)	1 (0.9)
Neuropathy peripheral	3 (2.8)	1 (0.9)
Sinus congestion	3 (2.8)	1 (0.9)
Vomiting	3 (2.8)	1 (0.9)
Liver function test increased	3 (2.8)	0

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AEs are listed in descending order of troriluzole frequency within PT.

Percentages are based on the number of subjects treated in the randomisation phase of the study.

a. During the 48-week randomisation phase, an AE of fall was recorded if there was a worsening of frequency of falls or if a fall was associated with an injury.

Source: Appendix 2.1.4.1B2

In study 206, most TEAEs reported during the randomisation phase were mild in severity for both treatment groups. TEAEs of moderate severity were reported for 32 (29.6%) subjects in the troriluzole group and 23 (21.1%) subjects in the placebo group; severe TEAEs were reported in 3 (2.8%) subjects in the troriluzole group and 8 (7.3%) subjects in the placebo group.

Common TEAEs (reported in ≥ 5% of subjects in either treatment group) during the 8-week randomisation phase of study 201 are presented in the following table.

Table 32: TEAEs reported in at least 5% of subjects (in any group) during the 8 week randomisation phase – study 201

PT: n (%)	Troriluzole 140 mg N = 71	Placebo N = 70
Any TEAE	43 (60.6)	34 (48.6)
Dizziness	8 (11.3)	1 (1.4)
Fall [a]	7 (9.9)	2 (2.9)
Fatigue	6 (8.5)	3 (4.3)
Headache	5 (7.0)	4 (5.7)
Nausea	4 (5.6)	3 (4.3)
Muscle spasms	4 (5.6)	2 (2.9)

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AEs are listed in descending order of troriluzole frequency within PT.

a. During the 8-week randomisation phase, an AE of fall was recorded for each report of a fall rather than worsening.

Source: Appendix 2.1.4.1A

In study 201, somnolence was reported in 2 (2.8%) troriluzole vs. no placebo patients, considered related in both cases.

TEAEs considered treatment related by the investigator

In study 206, related TEAEs were reported in 37 (34.3%) troriluzole and 29 (26.6%) placebo patients during the randomisation phase. None of the severe TEAEs in the troriluzole group was considered related to study drug. According to CSR table 14.3.2.2.A, related TEAEs by PT that were reported in ≥ 2 patients in the troriluzole group and with a (numerically) higher incidence in the troriluzole vs. the placebo group in study 206 concerned: fatigue (9.3% vs. 4.6%), nausea (4.6% vs. 0.9%), abdominal discomfort (1.9% vs. 0.9%), and ALT increased, AST increased, liver function test increased as well as insomnia, respectively (1.9% vs. 0% each).

In study 201, related TEAEs were reported with a higher frequency in the troriluzole group compared with the placebo group during the randomisation phase (36.6% versus 14.3%, respectively). Dizziness and fatigue were the only TEAEs considered by the investigator to be related to study drug that occurred at an incidence ≥ 5%, and both TEAEs were more common in the troriluzole group than in the placebo group (dizziness: 11.3% versus 1.4%, respectively; fatigue: 7.0% versus 2.9%, respectively).

In the Pooled All troriluzole exposure subjects across indications, related TEAEs (by PT) were reported for < 5% of total subjects each. Related TEAEs reported for ≥ 4% of total subjects in the pooled data were fatigue (78/1,778 [4.4%]) and dizziness (72/1,778 [4.0%]).

The applicant's initial approach to identify ADRs for inclusion in SmPC section 4.8 was based on the comparative incidence of TEAEs reported in during the randomised phase of pivotal study 206. Criteria used by the applicant to select the troriluzole ADRs include:

- Troriluzole arm having a PT with an incidence of 2% or greater, and the incidence is at least 1% higher than the placebo arm.
- Inclusion of PTs if the relative risk ratio (RRR) comparison of the study arms is 2 or greater. The RRR compares the risk of a health event (disease, injury, risk factor, or death) among one group with the risk among another group. The RRR is the incidence of an AE/PT in the troriluzole arm divided by the incidence of the same AE/PT in the placebo arm.
    - The PTs of headache, fatigue, and diarrhoea were excluded from the list of troriluzole ADRs because the RRR comparison was less than 2, indicating there was little difference between the troriluzole and placebo arms of the study. Additionally, the PTs of headache and fatigue are very common in this patient population.
- Exclusion of PTs based on medical judgement, mainly:
    - The background rate of syncope is up to >30% increasing with age, in the general adult population. Individual case narratives for syncope have been reviewed, and there are not causal relationships. And, autonomic dysfunction is a known symptom of SCA, including SCA3 (reviewed by Moro et al., 2019).
    - Peripheral neuropathy is a common feature in SCA, including 55% of subjects with SCA3 (Linnemann et al., 2016). With the Day 120 response the applicant further provided the information that only one event peripheral neuropathy in the troriluzole group of pivotal study 206 was considered treatment related by the investigator. No event of peripheral neuropathy was reported in troriluzole treated patients during the randomised parts of SCA study 201, or the non-SCA studies 202 (OCD), 207 (GAD), or 203 (AD).
    - The PTs of COVID-19, nasopharyngitis, influenza, and sinus congestion were excluded from the list of troriluzole ADRs because these PTs are generally associated with immune response and/or environmental factors. Immune system issues can be ruled out because the data revealed an increased incidence in only 4 immune-related PTs. During the study, the majority of the immune-related PTs observed in the troriluzole arm had a lower incidence than the placebo arm or an incidence that failed to meet the threshold for consideration.

With the response to the Day 120 RSI the applicant provided the results of a different approach to identify ARDs based on TEAEs related to study drug in the double-blind phase of study 206, reported in ≥ 2 patients in the troriluzole group and reported with a numerically higher incidence in the troriluzole vs. placebo group. This led to identification of the following ADRs by the applicant.

Table 33: ADRs proposed for inclusion in the SmPC with the Day 120 Response (deletions compared to the initial proposal are given in strikethrough, additions are underlined and bold)

Psychiatric disorders		**Link to data***
Common	Insomnia	
~~**Vascular disorders**~~		
~~**Common**~~	~~Hypertension~~	
Gastrointestinal disorders		**Link to data***
Common	Nausea, abdominal discomfort~~, abdominal pain upper, vomiting~~	
General disorders and administration site conditions		
Common	Fatigue	
Investigations		Link to data*

Common	~~Alanine aminotransferase increased~~ **Abnormal liver function tests[a]**	

[a] Abnormal liver function tests included alanine aminotransferase increased, aspartate aminotransferase increased, liver function test increased, gamma-glutamyl transferase increased.

Adverse events of special interest (AESI):

Liver impairment, neutropenia, and interstitial lung disease are listed in the special warnings and precautions for use section of the Rilutek SmPC.

According to the SCS, events of special interest in the clinical programme for troriluzole were:

- Neutropenia based on laboratory results and defined as minimum absolute neutrophil count < 500 per mm3
- Liver function test (LFT) Abnormalities:
  - ALT or AST > 3x ULN
  - ALT or AST > 3x ULN concurrent with serum total bilirubin > 2x ULN (concurrent is defined as elevations on the same collection date)
- Interstitial lung disease based on interstitial lung disease Narrow SMQ

Neither cases of neutropenia (based on neutrophil count < 500 per mm³), nor cases of interstitial lung disease (based on interstitial lung disease Narrow SMQ), have been reported in Phase 2/3 studies of troriluzole (as of the).

There was also no apparent imbalance in the incidence or severity of abnormal neutrophil counts within the completed phase 2/3 studies. However, according to the table provided in SCS Appendix 3.2.1.1 (pg. 9), one of 1402 patients in the pooled all troriluzole exposure subjects population across indications had a shift from normal at baseline to worst abnormality of grade 3 on treatment.

LFT Abnormalities

Cumulative elevations of LFT abnormalities reported during the randomisation phase of pivotal study 206 are presented in Table 34. Subsequently, LFT abnormalities derived from the other phase 2/3 studies are summarised.

Table 34: Liver Function Test Elevations in the Randomisation Phase – Study 206

Elevation Type Parameter Category: n (%)	**Troriluzole 200 mg N = 108**	**Placebo N = 109**
n with liver function test data	107	108
Cumulative elevations		
ALT		
> ULN	26 (24.3)	8 (7.4)
> 3x ULN	2 (1.9)	0
> 5x ULN	1 (0.9)	0
AST		
> ULN	19 (17.8)	5 (4.6)
> 3x ULN	1 (0.9)	0
> 5x ULN	0	0

ALT or AST			
> ULN		30 (28.0)	8 (7.4)
> 3x ULN		2 (1.9)	0
> 5x ULN		1 (0.9)	0
TBL			
> ULN		10 (9.3)	7 (6.5)
> 1.5x ULN	0		2 (1.9)
> 2x ULN	0		0
ALP			
> ULN		11 (10.3)	10 (9.3)
> 1.5x ULN	0		2 (1.9)
> 2x ULN	0		0

Study 201, randomisation phase:

All baseline ALT and AST values were ≤ 3x ULN. No shifts in ALT or AST from normal at baseline to > 3x ULN were observed, no shifts in total bilirubin from normal at baseline to > 2x ULN.

Study 202 (OCD), randomisation phase:

2 (1.8%) subjects in the troriluzole group and no subjects in the placebo group with ALT >3x ULN; 2 (1.8%) subjects in the troriluzole group and no subjects in the placebo group with AST > 5x ULN; no subjects in either treatment group had on-treatment abnormalities of total bilirubin > 2x ULN

Study 203 (AD), randomisation phase:

4/171 (2.3%) subjects with ALT > 3x ULN and 1 (0.58%) subject with ALT > 5x ULN in the troriluzole group, and no subjects in the placebo group with ALT > 3x ULN; 1 (0.58%) subject in the troriluzole group and no subjects in the placebo group with AST > 3x ULN; 1/176 (0.57%) subject in the troriluzole group and 2/171 (1.2%) subjects in the placebo group with total bilirubin > 2x ULN

Study 207 (GAD), randomisation phase:

7/194 (3.6%) subjects with ALT > 3x ULN and 1/194 (0.52%) subject with ALT > 5x ULN in the troriluzole group, and 1/178 (0.56%) subject in the placebo group with ALT > 3x ULN; 2 (1.1%) subjects in the troriluzole group with AST > 5x ULN and 1 (0.6%) subject in the placebo group with AST > 3x ULN; no subjects in the troriluzole group and 1/178 (0.56%) subject in the placebo group with total bilirubin > 2x ULN.

Pooled All Troriluzole Exposure Subjects Across Indications (as of the SCS cut-off dates)

Cumulative LFT elevations indications identified

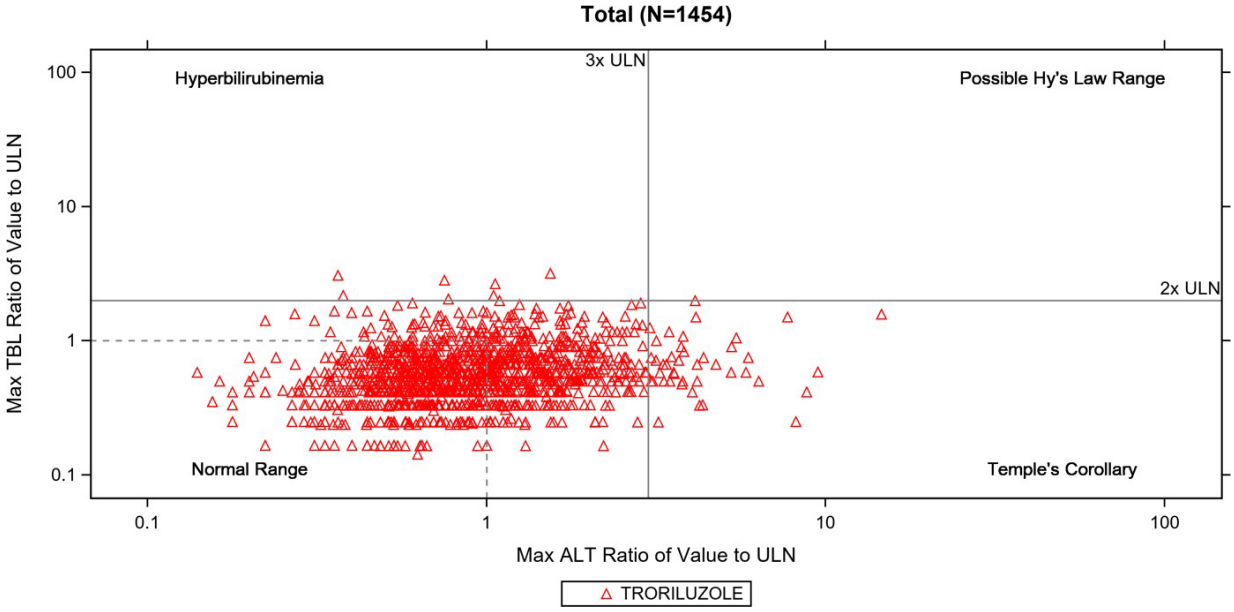
- 49 (3.5%) subjects with ALT or AST > 3x ULN, 15 (1.1%) subjects with ALT or AST > 5x ULN, and 3 (0.2%) subjects with ALT or AST > 10x ULN
- 42 (3.0%) subjects with ALT > 3x ULN, 11 (0.8%) subjects with ALT > 5x ULN, and 1 (0.1%) subject with ALT > 10x ULN
- 23 (1.6%) subjects with AST > 3x ULN, 9 (0.6%) subjects with AST > 5x ULN, and 2 (0.1%) subjects with AST > 10x ULN
- 7 (0.5%) subjects with total bilirubin > 2x ULN

Assessment of worst elevation on treatment for alkaline phosphatase did not identify any subjects with shifts from normal at baseline to > 2.5x ULN across indications. Assessment of worst elevation on treatment for GGT identified 25 (1.8%) subjects with shifts from normal at baseline to > 2.5 x ULN across indications.

As of the updated (Jun/Jul 2024) safety cut-off date, across indications there were 56/1,778 (3.2%) subjects with ALT > 3x ULN, 16 (0.9%) subjects with ALT > 5x ULN, and 3 (0.2%) subjects with ALT > 10x ULN and one (0.1%) subject with ALT > 10x ULN.

A scatter plot for evaluation of drug-induced serious hepatotoxicity (eDISH) displaying maximum ALT ratio of value to ULN against the maximum total bilirubin ratio of value to ULN for All Troriluzole Exposure Subjects across indications is presented in Figure 24.

Figure 24: Evaluation of Drug-induced Serious hepatotoxicity – Pooled All Troriluzole Exposure Subjects across indications (as of the SCS cut-off dates, Jun 2020 – Jul 2023)



Ratios to ULN < 0.1 are set to 0.1.

Note: Laboratory values obtained locally in association with hospitalisation for SAEs (Epstein-Barr virus infection and LFT increased) in Subject reported ALT and AST > 10x ULN that were not included in the clinical database and are therefore not included in this figure.

Note: Subject had maximum ALT of 4.1x ULN and maximum TBL of 2.0x ULN that were not concurrent (SCS Appendix 3.6.5).

Source: SCS Appendix 3.6.6

As of the updated safety cut-off dates (Jun/Jul 2024), in most subjects, time to first onset of ALT increase > ULN and >3× ULN occurred within 4 to < 8 weeks and 8 to < 12 weeks, respectively. Time to first onset of ALT increase >5× ULN occurred later in treatment (12 to < 24 weeks [n = 3] and > 48 weeks [n = 3]). In 19 out of 30 patients with ALT increase > 3 ULN, ALT increase was transient with a mean (SD) time to ALT normalisation < ULN from of 18.5 (30.88) weeks. Out of 11 out or 30 patients who have not reached normalisation, no subject is still ongoing in a study.

Hepatotoxicity related AEs

Table 35: Liver function text TEAEs related to study drug during randomised phase of study 206

PT: n (%)	Troriluzole 200 mg N = 108	Placebo N = 109
Alanine aminotransferase increased	2 (1.9)[a]	0
Liver function test increased	2 (1.9)	0
Aspartate aminotransferase increased	2 (1.9) [a]	0
Gamma-Glutamyltransferase increased	1 (0.9) [a]	0
Liver Function test abnormal	0	0
Hepatic Enzyme increased	0	1 (0.9)
Hepatic enzyme abnormal	0	0

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In the pooled all troriluzole exposure subject population across indications (as of the Jun/Jul 2024 cut-off dates), the following hepatotoxicity-related TEAEs were considered treatment related by the investigator but are not labelled as ADR so far: blood bilirubin increased (in 5 [3%] patients), international normalised ratio and prothrombin time prolonged (in one [0.1%] patient each), hepatic failure (in 2 [0.1%] patients), and hepatic lesion, hyperbilirubinaemia and ocular icterus (in one [0.1%] patients each); three hepatotoxicity related SAEs were considered treatment related by the investigator with PTs liver function test increased, liver function test abnormal and hepatic lesion in one case each.

Across the troriluzole clinical development programme, there were no events of severe DILI or Hy's Law cases (ALT or AST elevation >3x ULN concurrent with total bilirubin > 2xULN; as of the SCS cut-off dates).

As of the SCS safety cut-off dates (Jun 2020 – Jul 2023), the applicant also performed an evaluation of TEAEs relating to Potential Torsade de Pointes/QT Prolongation/Seizure Adverse Events. In the Phase 2/3 studies, no cases of torsade de pointes or polymorphic ventricular tachycardia were reported as a PT. Potential events captured under the torsade de pointes/QT prolongation SMQ and other specified PT are described below:

• Syncope was reported during the completed randomised studies across indications in 9 troriluzole treated subjects and 6 placebo subjects, i.e., in 4 (3.7%) troriluzole and 1 (0.9%) placebo subject in study 206 (SCA; in the placebo subject the event was reported as SAE), in 1 (0.8%) troriluzole and no placebo subject in study 202 (OCD), and in 4 (2.2%) troriluzole 5 (2.9%) placebo subjects in study 203 (AD). No syncope was reported in the randomised parts of studies 201 (SCA) and 207 (GAD). Syncope was considered not related to treatment except for 1 (0.6%) troriluzole and placebo subject each (in AD study 203).

• Ventricular tachycardia was reported in 1 (0.5%) subject in Study 206 (SCA). Tachycardia was reported in 3 (0.2%) subjects in the All Troriluzole Exposure Subjects population across indications; 1 (0.5%) subject in study 206 (SCA), 1 (0.7%) subject with 201, and 1 (0.2%) subjects with OCD.

• ECG QT prolonged was reported in 2 (0.1%) subjects in the All Troriluzole Exposure Subjects population across indications. In both cases the event was considered not related to Dazluma by the investigator.

In the All Troriluzole Exposure Subjects population one AE of cardiac arrest was reported that resulted in death (unlikely related to troriluzole).

No cases of potential torsade de pointes, polymorphic ventricular tachycardia, or syncope were reported in the Phase 1 studies, including dedicated thorough QT study 108.

3.4.4.3. Serious adverse events, deaths, and other significant events

SAEs:

Treatment emergent SAEs irrespective of causality had a generally similar incidence in the two treatment groups across both SCA studies and were reported in 6 (5.6%) troriluzole vs. 8 (7.3%) placebo patients in pivotal study 206 and in 4 (5.6%) troriluzole vs. 1 (1.4%) placebo patient in study 201. Across both SCA studies, no single TESAE was reported for more than 1 subject in the troriluzole group.

In Study 206, SAEs considered related to study drug by the investigator were reported for 1 subject in the troriluzole group (LFT increased, ALT elevation > 5x ULN concurrent with AST elevation > 4x ULN) and no subjects in the placebo group.

In Study 201, SAEs considered by the investigator to be related to study drug were reported for 1 (1.4%) subject in the troriluzole group (atrial fibrillation and cerebral infarction) and 1 (1.4%) subject in the placebo group (chest discomfort and hypertension). The respective causality assessment of the events in the troriluzole subject (PTs: atrial fibrillation and cerebral infarction) was updated to unlikely related (with IMP) by the investigator after data-cut off "as the subject's atrial fibrillation resulted in cerebral infarction". According to the narrative, the subject's relevant medial history included hypertension and atrial tachycardia, the screening electrocardiogram was "considered abnormal (history of atrial fibrillation controlled with medication), but not clinically significant".

In the pooled All Troriluzole Exposure Subjects across indications, SAEs considered by the investigator to be related to study drug across indications were reported overall for 12 (0.7%) subjects (as of the updated Jun/Jul 2024 safety data cut-off dates). No single TESAE considered by the investigator to be related to study drug was reported for more than 1 subject. The respective PTs included cerebral infarction, syncope, depression, paranoia, suicidal ideation, anaemia, atrial fibrillation, vertigo, pancreatitis acute, asthenia, hepatic lesion, hypersensitivity, sepsis, LFT increased, LFT abnormal and respiratory failure.

Deaths:

As of the SCS cut-off date, overall, 10 subjects who received at least one dose of troriluzole died in the All Troriluzole Exposure Population across indications. No deaths were reported in the Phase I studies.

There was no imbalance of deaths between troriluzole or placebo in any of the individual completed randomised study phases (of any indication): In study 206 one patient in both study groups each died, in study 203 in AD two troriluzole and placebo patients each died. No death occurred during the other randomised study phases.

Five of these deaths were reported in SCA patients and were compatible to have been caused by COVID and metastatic cancer in one case each and by the underlying disease in 3 cases, respectively. PTs reported for these latter 3 cases included one patient with subdural haematoma, one patient with death (verbatim term: aspiration), and one patient with dysphagia, pneumonia aspiration, sepsis and adult failure to thrive, respectively.

One death in study 203 (troriluzole group; AD indication; PT respiratory failure) was considered possibly related to troriluzole by the investigator. However, the applicant evaluated the SAEs reported in this patient before death mostly being secondary to a concurrent infection with pneumonia and its complications. The remaining deaths were considered not related by the investigator (11 cases) or unlikely related (1 case).

Apparently, two additional patients in the All Troriluzole Exposure Population across indications population died as of the updated Jun/Jul 2024 cut-off dates, one case occurred during OLE phase of

study 206 and concerned a fatal myocardial infarction not considered related to study drug by the investigator .

3.4.4.4. Laboratory findings

The information provided in this section generally refers to the cut-off dates applied to the SCS. Most haematology parameters and serum chemistry parameters, respectively remained stable from baseline through the end of treatment in the randomisation phase of Phase 2/3 troriluzole studies. Treatment-emergent Grade 3 to 4 abnormalities were infrequent in all studies across indications and did not suggest a trend.

Haematology

In the randomisation phase of the phase 2/3 studies, low lymphocytes (troriluzole 4 [2.3%], placebo 1 [0.6%] in study 203) was the only Grade 3 to 4 haematology abnormality that was reported with an incidence and a difference > 1% for troriluzole versus placebo. Among All Troriluzole Exposure Subjects, Grade 3 to 4 haematology abnormalities were reported with an incidence ≤ 1% across indications.

With regard to neutropenia, see AESI, in Section 3.3.7.2.

Chemistry

In the randomisation phase of SCA studies 206 and 201, there were no trends, and the incidence of Grade 3 to 4 abnormalities in the troriluzole group were infrequent. No clinically meaningful differences were noted in the frequencies of Grade 3 to 4 clinical laboratory test results for the troriluzole and placebo groups. Results were similar for subjects with SCA3 genotype in study 206.

In the randomisation phase of non-SCA studies 202, 203, and 207, AST (troriluzole 2 [1.7%], placebo 0 in study 202 and troriluzole 2 [1.0%], placebo 0 in study 207), creatine kinase (troriluzole 6 [5.1%], placebo 2 [1.7%] in study 202), and high glucose (troriluzole 4 [2.3%], placebo 2 [1.2%] in study 203) were the only Grade 3 to 4 serum chemistry abnormalities that were reported with an incidence and a difference ≥ 1% for troriluzole versus placebo.

Among All Troriluzole Exposure Subjects across indications, creatine kinase (38/1454 [2.7%]) was the only Grade 3 to 4 serum chemistry abnormality that was reported with an incidence > 2% across indications but was reported more frequently in OCD (4.6%) and GAD (3.6%) subjects compared with SCA (1.5%) subjects. Grade 3 to 4 creatine kinase was not reported in AD subjects.

With regard to liver function tests, see AESI, in Section 3.3.7.2.

There were no marked differences in the frequency of abnormalities on urinalysis in the troriluzole and placebo groups in the randomisation phase of Phase 2/3 troriluzole studies or between studies and indications. Most treatment-emergent abnormalities reported for All Troriluzole Exposure Subjects were Grade 1 to 2.

Vital Signs

During the randomisation phase of study 206, systolic blood pressure (SBP) > 140 mmHg was reported for 40 (38.1%) troriluzole subjects and 24 (22.6%) placebo subjects; SBP > 160 mmHg was reported for 4 (3.8%) troriluzole subjects and 5 (4.7%) placebo subjects. Diastolic blood pressure (DBP) > 90 mmHg was reported for 27 (25.7%) troriluzole subjects and 28 (26.4%) placebo subjects; DBP > 100 mmHg was reported for 4 (3.8%) troriluzole subjects and 7 (6.6%) placebo subjects.

The occurrence of abnormalities in heart rate and weight change from baseline were similar in the troriluzole and placebo groups in the placebo-controlled SCA studies and other placebo-controlled Phase 2/3 studies.

ECG

There were no differences between the troriluzole and placebo groups in QTcF abnormalities, or in QTcF interval increase from baseline during the randomisation phase of the Phase 2/3 placebo-controlled studies.

Suicidality

The potential for suicidal thoughts or behaviours in subjects treated with troriluzole was assessed for all Phase 2/3 troriluzole studies using the Sheehan Suicidality Tracking Scale (S-STS), except BHV4157-209 (OCD indication) as it used the Columbia-Suicide Severity Rating Scale (C-SSRS).

In the randomised phase of study 206, changes in the suicide behaviour subscale score > 1 on the S-STS were similar in the troriluzole and placebo groups (in no troriluzole and 1 [0.9%] placebo patients). A maximum observed ≥ 1-point change from baseline in the ideation subscale score of the S-STS was reported for 6/104 (5.8%) subjects in the troriluzole group and 11/104 (10.6%) subjects in the placebo group, changes in the suicide ideation subscale score > 1 were reported in 1.9% troriluzole and 6.5% placebo subjects. In the randomised phase of study 201 , no subjects in either treatment group had changes in the suicide behaviour subscale score > 1 on the S-STS, and changes in the suicide ideation subscale score > 1 occurred in 1 patient (1.9%) in each group; the change in the single troriluzole patients was reported as AE of suicidal ideation). In the completed randomised parts of the non-SCA studies, no changes from baseline in the suicide behaviour subscale score > 1 were reported in either treatment group. Changes from baseline in the suicide ideation subscale score > 1 did not show a consistent trend.

During the randomisation phase of study 206, Suicidality AEs with PTs based on the suicide/self-injury SMQ were assessed. TEAEs of suicidal ideation were reported in one subject each in the troriluzole and placebo group. AEs of suicide attempt were reported in no troriluzole and in 2 placebo treated subjects (one of which led to the subject's death). During the OLE phase, suicidal ideation was reported as an AE in 1 treated subject (originally randomised to placebo) which resulted in study drug being withdrawn. Suicide attempt and suicidal ideation were reported as AEs in 1 other treated subject (originally randomised to placebo); suicide attempt was considered an SAE and suicidal ideation resulted in study drug being withdrawn. Both subjects had changes in the suicide ideation subscale scores > 1 during the OLE phase.

Among the Pooled all troriluzole exposure subjects across indications, TESAEs of suicidal ideation were reported for 3 (0.2%) subjects [i.e., 1 (0.7%) subject with SCA (study 201) and 2 (0.4%) subjects with OCD]; suicide attempt was reported for 2 (0.1%) subjects [i.e., 1 (0.5%) subject with SCA (Study 206) and 1 (0.2%) subject with OCD]; and suicidal behaviour was reported for 1 (0.7%) subject with SCA (study 201).

Overdose

Across studies and indications overdose was reported as an AE in 2 (0.1%) subjects (one moderate event in SCA study 206, one mild event in study GAD study 207) and accidental overdose was reported as an AE in 1 (0.1%) subject (one mild event in OCD study 209). All events were reported during the OLE phase and were resolved. No specific antidote for the treatment of troriluzole overdose is available.

Abuse

The applicant compiled a list of potential drug abuse AEs based on all PTs in the drug abuse, dependence, and withdrawal SMQ and additionally on abuse-related AE search terms based on review of reported AEs as recommended in Section V.B. of the FDA Guidance for Industry Assessment of Abuse Potential of drugs.

In the clinical development programme for SCA, potential drug abuse TEAEs were reported for 21 (19.4%) troriluzole subjects and 24 (22.0%) placebo subjects during the 48-week randomisation phase of study 206; and 14 (19.7%) troriluzole subjects and 5 (7.1%) placebo subjects during the 8-week randomisation phase of study 201. The most common potential drug abuse TEAE (occurring in ≥ 5% of subjects in either treatment group) was fatigue (9.3% in the troriluzole group and 8.3% subjects in the placebo group of 206, and 8.5% subjects in the troriluzole group and 4.3% subjects in the placebo group of study 201). However, fatigue is a common symptom in SCA patients. All other potential drug abuse TEAEs were reported infrequently.

No signal suggestive of misuse, overuse, or abuse of troriluzole with long-term administration in the All Troriluzole Exposure Subjects population was identified by the applicant.

3.4.4.5. In vitro biomarker test for patient selection for safety

N/A

3.4.4.6. Safety in special populations

Intrinsic factors

According to the applicant, data for safety endpoints suggest that there was no subgroup, in which the safety profile of troriluzole relative to placebo was markedly different from that observed overall in troriluzole studies. The rates of safety measures by intrinsic subgroups were consistent with the overall rates and in general were consistent between subgroups; interpretation of the results is hindered by the small size of the subgroups. (For more details regarding intrinsic factors in study 206 and for analyses in the All Troriluzole Exposure population across indications, see also SCS Tables 34 and 35 as well as several Appendices of the SCS supporting the subgroup analyses as listed in SCS Table 32).

Table 36: AEs by age range – BHV4157-206 treated subjects

	Active: Troriluzole 200 mg (N=108)		**Comparator: Placebo (N=109)**	
MedDRA Terms	**Age <65 N=95 n (%)**	**Age 65-74 N=13 n (%)**	**Age <65 N=101 n (%)**	**Age 65-74 N=8 n (%)**
Total AEs	80 (84.2)	8 (61.5)	85 (84.2)	7 (87.5)
Serious AEs – Total	4 (4.2)	2 (15.4)	7 (6.9)	1 (12.5)
- Fatal	0	1 (7.7)	1 (1.0)	0
- Hospitalisation/prolong existing hospitalisation	2 (2.1)	2 (15.4)	6 (5.9)	1 (12.5)
- Life-threatening	0	1 (7.7)	3 (3.0)	0
- Disability/incapacity	0	0	1 (1.0)	0

	Active: Troriluzole 200 mg (N=108)		Comparator: Placebo (N=109)	
MedDRA Terms	**Age <65 N=95 n (%)**	**Age 65-74 N=13 n (%)**	**Age <65 N=101 n (%)**	**Age 65-74 N=8 n (%)**
- Other (medically significant)	2 (2.1)	2 (15.4)	2 (2.0)	0
AE leading to drop-out	3 (3.2)	2 (15.4)	5 (5.0)	0
Psychiatric disorders	11 (11.6)	0	12 (11.9)	0
Nervous system disorders	31 (32.6)	2 (15.4)	30 (29.7)	1 (12.5)
Accidents and injuries	29 (30.5)	3 (23.1)	35 (34.7)	1 (12.5)
Cardiac disorders	2 (2.1)	0	1 (1.0)	0
Vascular disorders	6 (6.3)	0	3 (3.0)	1 (12.5)
Cerebrovascular disorders	--	--	--	--
Infections and infestations	29 (30.5)	2 (15.4)	25 (24.8)	4 (50.0)
Anticholinergic syndrome	18 (18.9)	2 (15.4)	19 (18.8)	0
Quality of life decreased	--	--	--	--
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	24 (25.3)	3 (23.1)	32 (31.7)	2 (25.0)

The on-treatment events in subjects ≥ 65 years old were expected background events (or expected in the patient population) and consistent with those reported in the overall population.

In the supportive study 201 the incidence of SAEs in the older troriluzole subgroup (5.3%) did not exceed that in the younger troriluzole subgroup (5.8%), whereas AEs leading to withdrawals occurred with a higher incidence in the older vs. younger troriluzole subgroup albeit with low subject numbers concerned (in 4/19 [21.1%] troriluzole patients > 65 years vs. 3/52 [5.8%] troriluzole patients ≤ 65 years). In AD study 203 evaluating a 280 mg dose of troriluzole QD vs. placebo, the incidence of TEAES, SAEs and AEs leading to withdrawal was higher each in older compared to younger troriluzole subgroups, also when taking the rates in the respective placebo subgroups into consideration. Across placebo controlled studies of all evaluated indications (206, 201, 202, 203 and 207) there was no apparent imbalance with regard to fatal events by age.

Table 37: Safety Measures by sex and SCA genotype during the randomisation phase – Study 206

	N		TESAE		TEAE Leading to Discontinuation		TEAE	
Subgroup	**Troriluzole**	**Placebo**	**Troriluzole**	**Placebo**	**Troriluzole**	**Placebo**	**Troriluzole**	**Placebo**
Sex								
Female	59	53	3 (5.1)	3 (5.7)	3 (5.1)	3 (5.7)	48 (81.4)	42 (79.2)
Male	49	56	3 (6.1)	5 (8.9)	2 (4.1)	2 (3.6)	40 (81.6)	50 (89.3)
SCA Genotype								

SCA3	44	45	3 (6.8)	1 (2.2)	4 (9.1)	3 (6.7)	40 (90.9)	40 (88.9)
Non-SCA3	64	64	3 (4.7)	7 (10.9)	1 (1.6)	2 (3.1)	48 (75.0)	52 (81.3)

Source: TESAE: Appendices 2.2.3.1C, 2.2.3.2C, 2.2.3.3C, 2.2.3.4C, and 2.2.3.8; TEAE Leading to Discontinuation: Appendices 2.3.3.1C, 2.3.3.2C, 2.3.3.3C, 2.3.3.4C, and 2.3.3.8; TEAE: Appendices 2.1.3.1C, 2.1.3.2C, 2.1.3.3C, 2.1.3.4C, and 2.1.3.8

Meaningful subgroup analyses of study 206 by race or ethnicity were precluded by small numbers across non-white subgroups and as ~90% of study subjects were of *not Hispanic or Latino* ethnicity.

No clinically relevant differences in safety and tolerability profiles were observed by the applicant between SCA3 and non-SCA3 subjects (i.e. patients with other SCA genotypes). The most common related TEAEs reported during randomised part of study 206 by SCA genotype are presented in the following table.

Table 38: TEAEs related to Study Drug in the DB Phase by SOC by SCA Genotype with an incidence of ≥ 5% by SOC in any treatment group - Study 206

	SCA3		**Non-SCA3**	
SOC: n (%) PT: n (%)	Troriluzole N=44	Placebo N=45	Troriluzole N=64	Placebo N=64
Any related TEAE	20 (45.5)	12 (26.7)	17 (26.6)	17 (26.6)
Nervous system disorders	9 (20.5)	6 (13.3)	5 (7.8)	8 (12.5)
Dizziness	5 (11.4)	3 (6.7)	1 (1.6)	4 (6.3)
General disorders and administration site conditions	4 (9.1)	4 (8.9)	7 (10.9)	3 (4.7)
Gastrointestinal disorders	5 (11.4)	2 (4.4)	4 (6.3)	5 (7.8)
Nausea	4 (9.1)	0	1 (1.6)	1 (1.6)
Investigations	5 (11.4)	2 (4.4)	3 (4.7)	1 (1.6)
Musculoskeletal and connective tissue disorders	2 (4.5)	3 (6.7)	2 (3.1)	3 (4.7)

Source: derived by Assessor from SCS Appendix 2.1.5.1D

Extrinsic factors

Although sample sizes were small within some subgroups, according to the applicant, the rates of safety events by extrinsic exposure subgroups were generally consistent regardless of exposure defined both by time on troriluzole (Table 47) and dose of troriluzole.

Table 39: Safety measures by maximum time on troriluzole – Pooled All Troriluzole exposure subjects across indications

Subgroup	N	TESAE	TEAE Leading to Discontinuation	TEAE
Time on Troriluzole				
≤ 12 weeks	328	18 (5.5)	85 (25.9)	196 (59.8)
> 12 – 24 weeks	235	14 (6.0)	18 (7.7)	154 (65.5)
> 24 – 48 weeks	328	12 (3.7)	12 (3.7)	205 (62.5)
> 48 – 96 weeks	331	30 (9.1)	19 (5.7)	252 (76.1)
> 96 – 144 weeks	118	24 (20.3)	2 (1.7)	110 (93.2)
> 144 – 192 weeks	50	8 (16.0)	2 (4.0)	48 (96.0)
> 192 – 240 weeks	22	2 (9.1)	0	22 (100.0)
> 240 weeks	42	8 (19.0)	0	42 (100.0)

Table derived from SCS Table 36

In the All troriluzole Exposure population across indications (as of the SCS cut-off dates), a TEAE incidence of 46.8 % was reported in patients with < 140 mg troriluzole at AE onset, the respective incidences were 40.9% with 140 mg troriluzole, 55.2% with 200 mg troriluzole and 60.6% with 280 mg troriluzole at AE onset. There were no trends suggestive of increased rates of ALT or AST > 3x ULN with increased duration of exposure to troriluzole.

Safety in patients with hepatic impairment:

In the phase I study 104, administration of a single 100 mg dose of troriluzole was well tolerated in subjects with moderate hepatic impairment. Patients with active liver disease or a history of hepatic intolerance to medications that in the investigator's judgment was medically significant, were excluded from pivotal study 206.

Safety in patients with renal impairment:

Renal impairment is not expected to have a relevant effect on PK of troriluzole (see also section 3.3.1 of this Report). Patients with severe renal impairment (eGFR< 30 ml/min/ 1.73m2) were excluded from pivotal troriluzole study (206). A limited number of patients with moderate renal impairment (baseline eGFR ≥ 30 to ≤ 59 mL/min/1.73 m²) was included in the randomised pivotal study 206 (4 troriluzole and 2 placebo patients, respectively) and no safety signals are derived from TEAEs or eGFR values reported in these patients during treatment.

Pregnancy

Across the CDP, 14 pregnancies have been reported as of 21-Jul-2023. According to SCS Appendix 6G, 8 of the 14 pregnancies reported during the CDP concerned females assigned to troriluzole, 1 pregnancy concerned the female partner of a male patient receiving troriluzole (pregnancy outcome in this case: live birth), and 5 pregnancies concerned females receiving placebo. The pregnancy outcomes for the 8 female troriluzole patients with positive pregnancy tests are given in this Appendix as unknown in 3 cases, spontaneous abortion in 2 cases, and live birth, ongoing, and voluntary termination, respectively in one case each. However, in one of the cases with 'unknown' pregnancy outcome, the respective narrative provides information that although this subject was lost to follow-up, her mother informed the site that the pregnancy ended in a first trimester miscarriage. Nevertheless,

this subject took the last troriluzole dose one the first day of the last known menstruation cycle. Regarding the other two troriluzole patients reporting spontaneous abortions, the event occurred in the first trimester in subject, no narrative could be found for subject. No malformations were reported for the two live births.

3.4.4.7. Immunological events

N/A

3.4.4.8. Safety related to drug-drug interactions and other interactions

Due to the low and transient concentrations of troriluzole in systemic circulation, there is a low likelihood of clinically meaningful CYP- or transporter-mediated drug interactions as a result of troriluzole. CYP 1A2 is the principal isoenzyme involved in the metabolism of riluzole. In phase I study 106, an increase in riluzole exposure up to 3-fold was observed following administration of troriluzole 89 mg with fluvoxamine compared to troriluzole 89 mg alone was observed in healthy volunteers. The concomitant use of strong or moderate CYP1A2 inhibitors with troriluzole may increase the risk of riluzole-associated adverse reactions. It is therefore recommended in the SmPC, that patients wo are taking a strong CYP1A2 inhibitor initiate and maintain a troriluzole dose of 100 mg (89 mg troriluzole as anhydrous free base, i.e. half the usual recommended maintenance dose), or reduce the dose respectively.

In pivotal study 206, concomitant treatment with strong CYP 1A2 inhibitors was prohibited.

3.4.4.9. Discontinuation due to adverse events

The incidences of TEAEs leading to discontinuation of study drug in the randomisation phase were similar between treatment groups (reported in 5 [4.6%] patients in both treatment groups) of study 206 but were reported more frequently in the troriluzole group compared with the placebo group (reported in 7 [9.9%] troriluzole vs. no placebo patients) in study 201.

TEAEs (by PT) leading to discontinuation in troriluzole treated patients concerned COVID-19, HCG positive, LFT increased, pregnancy, and nausea in one (0.9%) subject each in study 206, and dizziness (in two [2.8%] patients) as well as anhedonia, asthenia, atrial fibrillation, blood creatine phosphokinase increased, cerebral infarction, decreased appetite, dehydration, gait disturbance, somnolence and suicidal ideation in one (1.4%) subject each in study 201.

3.4.4.10. Post marketing experience

N/A

3.4.5. Discussion on clinical safety

In the clinical development programme (CDP), 1,998 subjects were administered at least one dose of troriluzole so far (excluding the still blinded studies 302 and 303 in patients with OCD). In the 2 randomised studies in SCA, 340 subjects received at least one dose of troriluzole in either the double-blind or OLE phase. Of these, 271 patients received troriluzole for > 1 year and 58 patients have received troriluzole for > 5 years. Overall the safety data base including the length of follow-up could be considered sufficient for a comprehensive safety evaluation of troriluzole in the context of an application of approval under exceptional circumstances and taking into consideration that troriluzole is a prodrug of riluzole which has an established safety profile in another neurodegenerative disorder (ALS). However, as is usually the case at the time of approval, the safety data are not large enough in order to characterise rare events. For the initial submission cut-off dates ranging from different dates

in March 2023 to 21-Jul-2023 were applied to the ongoing clinical studies. Updated safety data with focus on the ongoing OLE studies in the SCA indication and with relevant data mainly relating to SAEs and AESIs reported in the Non-SCA studies have been provided as of appropriate cut-off dates (Jun/Jul 2024) and briefly been discussed in the context of an updated Clinical overview.

Troriluzole posology in randomised or OLE part of pivotal study 206 was generally in line with the proposed posology, i.e. 140 mg QD for four weeks, increased to 200 mg QD afterwards, but with the difference, that the dose could be temporarily reduced for tolerability issues in study 206. Nevertheless, the latter occurred in only three patients each (2.8%) across both treatment groups 2.8%) according to the applicant's response to the Day 120 LoQ. It can further be followed from SCS Table 14.1.8.1.A, that 98.1% of subjects in the troriluzole group received a dose of 200 mg QD at least at some point during week 4-8 of this study.

During the first assessment round, the applicant's methodology for identification of ADRs was mainly based on the comparative incidence of TEAEs (PT) in the troriluzole vs. placebo treated patients of pivotal study 206. The following criteria regarding frequency were applied: at least 2% incidence in troriluzole patients, at least 1% higher absolute incidence in troriluzole vs. placebo patients, and at least twice the incidence in troriluzole vs. placebo treated patients. In particular the latter criterion is not considered conservative and led to exclusion of headache, diarrhoea and fatigue from the ADRs proposed to be labelled for troriluzole. However, e.g., headache (reported as TEAE in 11.1% troriluzole vs. 7.3% placebo patients in study 206) and diarrhoea (reported in 2.8% troriluzole vs. 1.8% placebo patients) are both established ADRs of riluzole.

The applicant further excluded few TEAEs for which the above frequency criteria for identification of ADRs were fulfilled based on medical judgement, which can be agreed based on the overall provided argument.

With the Day 120 response the applicant introduced a different approach for identification of ADRs, i.e. based on TEAEs related to study drug in the double-blind phase of study 206, reported in ≥ 2 patients in the troriluzole group and reported with a numerically higher incidence in the troriluzole vs. placebo group. Based on this latter approach, the following, ARDs are currently proposed to be labelled by the applicant for troriluzole: gastrointestinal events (including vomiting and abdominal discomfort), abnormal liver function tests (including ALT increased, AST increased, liver function test increased and GGT increased), fatigue and insomnia (with common frequency each). Apart from insomnia these would be expected for troriluzole based on the known safety profile of Riluzole.

While TEAEs considered treatment related by the investigator are always of particular interest and constitute an important element of the identification of ADRs, the ADRs identified with the initial approach applied by the applicant cannot be necessarily ignored. Relying the ADR identification only on related TEAEs lead to deletion of abdominal pain upper, vomiting as well as hypertension from the initially proposed SmPC. As abdominal pain and vomiting are established common ADRs of riluzole and because of the imbalance found in the pivotal studies reading TEAEs, deletion of these two ADRs from SmPC 4.8 is not considered justified and these should be reintroduced to the SmPC (OC). In study 206, a somewhat higher incidence of TEAEs of hypertension was reported in the troriluzole (4 [3.7%]) vs. the placebo group (1 [0.9%]). However, all patients concerned had risk factors for hypertension and none of the AEs of hypertension was considered related to study drug by the investigator. Across all randomised troriluzole studies, neither a consistent trend towards increased blood pressure values nor consistent imbalances regarding hypertension AEs was found. Hypertension is also not listed as ADR of in the EMA label of Rilutek. It can therefore be agreed at present, that the overall trial data regarding hypertension do not warrant inclusion of hypertension as an ADR and that no particular blood pressure monitoring needs to be recommended during treatment with troriluzole. However, the FDA label informs about a somewhat higher incidence of hypertension among patients treated with 50

mg riluzole twice daily compared to placebo (5% vs. 4%), and mild systolic hypertension was also found in pre-clinical studies. Therefore, the potential ADR of hypertension should be further followed post marketing.

As requested, the applicant has provided a discussion of established ADRs of riluzole which are not proposed to be labelled for troriluzole so far, with particular focus on anaemia, dizziness and somnolence, and tachycardia, respectively. During the randomised SCA studies, no clear imbalance regarding TEAEs of anaemia was found and no grade 3-4 haemoglobin abnormalities occurred. Although an imbalance with regard to grade 1-2 haemoglobin abnormality was found in study 201 (5.9% in troriluzole patients vs. 0% placebo patients), two of the 4 troriluzole patients concerned had already low haemoglobin values at baseline and one patient had only one single intermittent low haemoglobin value. It can therefore be agreed that the data derived from the SCA studies alone do not warrant inclusion of anaemia as an ADR of troriluzole. However, discussion of one SAE of anaemia that was considered related to troriluzole by the investigator (reported in a troriluzole study in the AD indication) is still requested. An imbalance with regard to TEAEs and ADRs each of dizziness and somnolence was found in study 201 but not in pivotal study 206. From these data, it cannot not be clearly derived, that troriluzole may also cause these events. The applicant proposes to monitor cases of dizziness as part of routine pharmacovigilance. This may be agreed; however, it is noted, that evaluation of one SAE of vertigo that was considered related to troriluzole by the investigator (reported in a troriluzole study in the AD indication) is still requested. In addition, because of the potential relevance for the patients, somnolence should also be further followed post marketing. Tachycardia is a common ADR of riluzole. As of the updated (Jun/Jul 2024) safety cut-off date, TEAEs of tachycardia were infrequently reported in the Pooled All troriluzole exposure population (5/1,778; 0.3%), all of which were considered unlikely or not related to troriluzole. No TEAE of tachycardia was reported during randomised part of study 206. It can therefore be accepted that tachycardia is currently not included in the SmPC, however tachycardia should be further followed post marketing. No new safety signal arose from Potential torsade de Points/QT prolongation/Seizure AEs reported with troriluzole in the phase 2/3 studies. No cardiac safety signals are derived from ECG or AE findings including the thorough QT study 108.

The most relevant safety concern identified for troriluzole relates to hepatotoxicity. Adverse Events of Special Interest regarding hepatotoxicity were defined with regards to specified laboratory test constellations regarding LFT increase (ALT or AST > 3 x ULN; ALT or AST concurrent with serum total bilirubin > 2x ULN). It is endorsed, that in addition, liver-related pre-specified AE terms (i.e., nausea, vomiting, anorexia, fatigue, and those containing "abdominal pain") were assessed if they occurred in conjunction with prespecified ALT elevations, which was not found in any subject. Also, no cases of severe DILI or Hy's law were reported as of the SCS; confirmation is requested, that this still holds true as of the updated safety cut-off dates (Jun/Jun 2024). ALT elevation > 3 ULN (or higher) was reported in 1.9% troriluzole vs. no placebo patients in pivotal study 206 and in 3% of the Pooled All troriluzole exposure subject population - across indications (as of the SCS).

Similar to riluzole, in most subjects in clinical troriluzole phase II/III studies (i.e., in the pooled all troriluzole groups excluding study 209), first onset of any ALT increase > ULN and of ALT increase > 3 x ULN, respectively occurred within the first three months of treatment. Nevertheless, first ALT increase could occur also afterwards and ALT increase > 5 ULN was more frequently reported later in treatment. ALT increase > 3 ULN was usually transient (in patients, in whom study data are available). In patients with ALT increase > 5 ULN troriluzole was usually discontinued with missing experience with re-challenge of troriluzole. However detailed information regarding reversibility including time to reversibility in patients with ALT increase > 5 x ULN still needs to be provided in a comprehensible way (OC). In the pooled all troriluzole exposure subject population across indications (as of the updated cut-off dates applied with the response), any hepatotoxicity-related TEAE considered related to

treatment by the investigator occurred in 4.7% (84/1,778) subjects. According to Appendix 2.1.2.3 – R2 of the Day 120 response (provided in module 5.3.5.3 among "Select updated MAA ISS output"), the respective events also concerned the following PTs, which are not proposed to be labelled so far: blood bilirubin increased (in 5 [3%] patients), international normalised ratio and prothrombin time prolonged (in one [0.1%] patient each), hepatic failure (in 2 [0.1%] patients), and hepatic lesion, hyperbilirubinaemia and ocular icterus (in one [0.1%] patients each). The applicant is requested to thoroughly evaluate these cases and discuss whether any of these PTs needs to be added to SmPC section 4.8 (OC).

Overall 0.2% (3/1,778) hepatotoxicity-related TESAE in the pooled all troriluzole exposure subject population were considered treatment related by the investigator. Of these, one (moderate) SAE of liver function test increased (PT) concerned a patient in the troriluzole group, who experienced ALT elevations > 7 x ULN concurrent with AST elevations > 4 x ULN during the randomised pivotal study 206. Troriluzole was discontinued and the event resolved. According to Appendix 2.1.2.3 – R4 of the response, the other two hepatotoxicity-related SAEs considered treatment related by the investigator concerned hepatic lesion (PT) in a patient in AD study 203 and liver function test abnormal (PT) in a patient participating in one of the OCD studies (202 or 209, respectively). The applicant is requested to provide further information regarding these two latter SAEs and discuss respective labelling consequences as appropriate (OC). The applicant proposes to add the following contraindication: "Severe hepatic disease or baseline transaminases greater than 3 times the upper limit of normal (see section 4.4)". Riluzole is contraindicated in patients with "hepatic disease or baseline transaminases greater than 3 times the upper limit of normal". The contraindication to riluzole of "hepatic disease" is a rather broad term, that appears somewhat contradictory to the respective SmPC section 4.4, where it is stated, that "riluzole should be prescribed with care in patients with a history of abnormal liver function or in patients with slightly elevated serum transaminases […], bilirubin […]". It is therefore generally endorsed, that the contraindication to troriluzole has a different wording. Patients with "active liver disease" were excluded from the pivotal study, therefore, patients with moderate hepatic impairment (according to Child-Pugh B classification) would certainly not have been candidates for evaluation in this study. Furthermore, as troriluzole like riluzole is associated with hepatotoxicity, restriction of the corresponding contraindication to only patients with severe hepatic disease is not justified. The respective contraindication should therefore be worded "Moderate to severe hepatic impairment (Child Pugh B/C) or baseline transaminases greater than 3 times the upper limit of normal (see section 4.4)".

As troriluzole exerts is pharmacodynamic effects nearly exclusively via its active metabolite riluzole and as riluzole exposure with the intended troriluzole dose exceeds the riluzole exposure with the approved dose of Rilutek, it is not immediately obvious, why ADRs established for Rilutek would not occur with Dazluma. This is also true for potentially life-threatening events of severe neutropenia (based on neutrophil count < 500 per mm^3) or interstitial lung disease (ILD; based on the ILD narrow SMQ), which have been evaluated among the Adverse Events of Special Interest but have not been reported during the CDP of troriluzole as of the Jun/Jul 2014 cut-off dates. It is quite possible, that these events have not been reported so far because of their rarity, which is particularly true for neutropenia (the frequency in the Rilutek SmPC is labelled as not known). Of note, one case of grade 3 abnormal neutrophils has been reported in the `all troriluzole exposure subjects´ population across indications (although the details of this case, which is derived from SCS Appendix 3.2.1.1, are unclear to the assessor). Interstitial lung disease (ILD) has only been identified for riluzole post-marketing and is included as an uncommon ADR in the Rilutek SmPC, however, there is debate in literature regarding the incidence. Saitoh et al. (2019) discuss, that the precise incidence of riluzole induced ILD in ALS patients is unknown. The authors further refer information, that a literature survey and web-based search of www.druginformer.com for cases of RZ-ILD indicated that more than half of cases were reported in Japan and suggest that constitutional or environmental factors might be associated with

drug induced ILD. Information regarding the risk of neutropenia as well as interstitial lung disease associated with riluzole should therefore also be included in the SmPC of troriluzole. The applicant is requested to make a proposal (**OC**).

During the randomised part of pivotal study 206, SAEs considered by the investigator to be related to study drug were reported for 1 subject in the troriluzole group (LFT increased, ALT elevation > 5x ULN concurrent with AST elevation > 4x ULN) and no subjects in the placebo group. During the randomised part of study 201, 1 (1.4%) subject each of the troriluzole and placebo group reported an SAE considered related by the investigator, however the respective causality assessment of the events in the troriluzole subject (PTs: atrial fibrillation and cerebral infarction) was updated to unlikely related (with IMP) by the investigator after data-cut off, which is plausible, based on the patient's medical history and the reported baseline ECGs abnormality. As of the updated (Jun/Jul 2024) safety cut-off dates, TESAEs considered by the investigator to be related to study drug were reported infrequently in the Pooled All Troriluzole Exposure Subjects Population across indications (12/1,778 [0.7%]. No event (by PT) was reported in more than 1 subject. However, because of the safety profile established for riluzole, an evaluation and discussion of any labelling consequences which may result from the following related SAEs (PT) still needs to be provided: Anaemia, vertigo, pancreatitis acute, asthenia and respiratory failure (OC). From the data provided regarding hypersensitivity SAEs an association of troriluzole with severe hypersensitivity reactions cannot clearly be concluded at present.

No safety concern arises from the information provided in the SCS regarding death cases reported during the CDP of troriluzole. Overall, 10 subjects who received at least one dose of troriluzole died in the All Troriluzole Exposure Population across indications (as of the as of the respective data cut-off dates for the present submission). Five of these deaths were reported in SCA patients and were compatible to have been caused by the underlying disease in 3 cases, and by COVID and metastatic cancer in one case each. There was no imbalance of deaths between troriluzole or placebo in any of the individual completed randomised study phases (of any indication) and causality assessment of individual cases does not raise clear concerns. Apparently, two additional patients in the All Troriluzole Exposure Population across indications population died as of the updated Jun/Jul 2024 cut-off dates, one case occurred during OLE phase of study 206 and concerned a fatal myocardial infarction not considered related to study drug by the investigator. Appropriate information on both additional death cases that occurred since the initial safety data cut in troriluzole treated patients is requested together with a causality assessment of the applicant (OC).

In particular in the pivotal study using the intended dose for a treatment period of 48 weeks, the incidence of TEAEs leading to discontinuation of the study drug was low (4.6% across both treatment groups). However, some of the TEAEs leading to discontinuation in the SCA studies concerned ADRs established for riluzole but not yet proposed to be labelled for troriluzole, i.e. dizziness, somnolence and asthenia. There is still some discussion regarding labelling of dizziness and asthenia in the context of related SAEs.

Regarding the All Troriluzole Exposure population across indications, TEAEs leading to withdrawal were reported most frequently (in 85 [25.9%]) in patients with an overall time on troriluzole exposure ≤ 12 weeks (as of the data cut-off applied to the SCS). According to the applicant, there was no evidence of an increased frequency of TESAEs, TEAEs leading to discontinuation or TEAEs with longer duration of troriluzole exposure.

The applicant primarily focused the troriluzole safety evaluation on SCA patients treated with the troriluzole dose recommended in the proposed SmPC, i.e., predominantly on the pivotal study (206). In contrast to the initial submission of this procedure, were the applicant sought an indication restricted to the SCA 3 subpopulation, the applicant is now applying for the overall SCA indication. Therefore, previous concerns about a limited database in the former SCA3-target population are no

longer valid. In general no clear differences in the safety profile would be anticipated across SCA genotypes and no clear differences in the safety evaluations of troriluzole have been identified by the applicant in the SCA3 vs. non-SCA3. Nevertheless, it is noted, that the safety profile of troriluzole might be somewhat less favourable in the SCA3 subpopulation compared to the overall SCA population, which appeared to be mainly driven by a higher rate of events of dizziness and nausea, however, no final conclusions could be drawn.

Similarly, in the subgroup of patients ≥ 65 years, a higher placebo subtracted and also overall rate of TESAEs and TEAEs leading to discontinuation in the troriluzole treatment group was found compared to patients < 65 years (study 206). However, the low number of patients >65 years in study 206 (i.e., 13 in the troriluzole and 8 in the placebo treatment group) precludes any firm conclusions, and the incidence of any TEAEs in older troriluzole patients was actually numerically lower than the incidences in the older placebo group. According to the applicants evaluations the on treatment events in patients ≥ 65 years of age were expected background events and consistent with those reported in the overall population. This conclusion is basically compatible with SCS Appendix 2.2.3.1 (A-C), displaying SAEs in study 206 and in the pooled all troriluzole exposure populations (in the SCA indication as well as across indications) by age. No clear safety signals can be derived from the subgroup analyses of the pooled All troriluzole exposure subjects across indications (as of the initial data cut-off); however, due to the open-label nature of these data as well as combination of different underlying diseases and posologies, the informational value of these analyses is limited.

Renal impairment is not expected to have a relevant effect on PK of troriluzole. However, Rilutek is not recommended for use in patients with impaired renal function, as studies at repeated doses have not been conducted in this population. Patients with severe renal impairment were also excluded from pivotal troriluzole study (206). As no data are available, troriluzole should not be recommended in patients with severe renal impairment. Data available from a limited number of patients with moderate renal impairment included in the pivotal troriluzole study (4 troriluzole and 2 placebo patients, respectively) did not give raise to safety concerns. In contrast to riluzole, it is therefore acceptable not to exclude patients with moderate renal impairment from troriluzole treatment, however, due to the limited database, caution should be advised for these latter patients.

No clear suicidality related safety signal for troriluzole arose from the evaluation of the Sheehan Suicidality Tracking Scale (S-STS), which was used to evaluate suicidal ideation and behaviour in the majority of the clinical studies. No imbalance regarding suicidality AEs with PTs based on the suicide/self-injury SMQ to the disadvantage of troriluzole was found during the randomised part of study 206 (with suicide attempts reported in two placebo subjects (one of which was fatal) vs. no troriluzole subjects and suicidal ideation reported in one subject in each group). No detailed evaluation of suicidality AEs has been provided for study 201, however, according to SCS Table 17, providing TESAEs during the randomised SCA studies, one SAE of suicidal ideation (PT) was reported in the troriluzole group (1.4%) vs. none in the placebo group and no SAE of suicide attempt was reported in this study. As of the SCS data cut-off, there was no completed suicide among the "Pooled all troriluzole exposure subjects" as clarified by the applicant.

There is limited clinical experience with troriluzole overdose, reported in 3 patients across the CDP as of the cut-off dates of the present submission (mild in two, moderate in one patient). From the information provided by the applicant, no symptoms of troriluzole overdose can be derived.

Based on the results of phase I interactions study 106 in healthy volunteers, which showed an increase in riluzole exposure up to 3-fold following administration of troriluzole with the CYP 1A2 inhibitor fluvoxamine, a general troriluzole dose of 100 mg (i.e. half the recommended maintenance dose) is proposed. No respective safety data are available from pivotal study 206, as concomitant treatment with strong CYP 1A2 inhibitors was prohibited.

Additional safety data needed in the context of a MA under exceptional circumstances

The following measures are necessary to address the missing safety data in the context of a MA under exceptional circumstances:

Regarding the safety data base, there are limitations with regard to interpretability of safety of troriluzole in older (≥ 65 years) vs. younger SCA patients. In the pivotal study, a higher placebo-subtracted and also overall rate of TESAEs and TEAEs leading to discontinuation in the troriluzole treatment group was found in patients ≥ 65 compared to patients < 65 years. However, the low number of patients ≥ 65 years in this study (i.e., 13 in the troriluzole and 8 in the placebo treatment group) precludes any firm conclusions. In AD study 203 the incidence of TEAES, SAEs and AEs leading to withdrawal was higher each in older compared to younger troriluzole subgroups, also when taking the rates in the respective placebo subgroups into consideration, indicating a worse safety profile by age. It is not clear though, in how far these results derived from a dose of 280 mg troriluzole QD in the AD population would translate into a worse safety profile by age in the SCA indication. A total of 53 SCA patients and 287 subjects across the CDP were ≥ 65 years and received least one dose of troriluzole (according to SCS Appendices 2.1.3.1A and 2.1.3.1B). No clear safety signals are derived from the subgroup analyses of the pooled All troriluzole exposure subjects across indications by age (as of the initial data cut-off); nevertheless, due to the open-label nature of these data as well as combination of different underlying diseases, the informational value of these analyses is limited. There may be some overlap of SCA symptoms with anticholinergic syndrome standardised MedDRA query (SMQ) terms. However, from the provided TEAE tables by age there appears to be a striking trend towards higher incidences of anticholinergic syndrome TEAEs (based on the narrow and broad SMQ) in the troriluzole vs. placebo groups, irrespective of age and across indications. Riluzole is not an anticholinergic substance, however, it is associated e.g. with tachycardia (common), which is also a symptom of anticholinergic syndrome. In contrast, tachycardia is not proposed to be labelled for troriluzole so far. The applicant is requested to evaluate the rather consistent imbalance with regard to anticholinergic syndrome TEAEs across the placebo controlled studies with troriluzole, to explain, which TEAEs (by PT) exactly cause these imbalances and to discuss whether labelling of further ADRs are warranted (OC).

These limitations should be further evaluated post-marketing, e.g. via a PASS, however, from a safety perspective, it does not seem impossible to ever assemble a "full" dossier.

3.4.6. Conclusions on clinical safety

As troriluzole is a prodrug of riluzole, which exerts its pharmacodynamic effect almost exclusively via the active metabolite riluzole, in general a similar safety profile compared to riluzole would be expected for troriluzole. At present, ARDs identified by the applicant for troriluzole are: gastrointestinal events (including vomiting and abdominal discomfort), abnormal liver function tests (including ALT increased, AST increased, liver function test increased, and GGT increased), fatigue and insomnia (all with common frequency). The most relevant safety concern identified for troriluzole relates to hepatotoxicity, regarding which further evaluation and discussion is requested from the applicant. Nevertheless, no severe cases of DILI and Hy's law were reported with troriluzole were reported as of the SCS cut-off dates. The potential ADRs of somnolence, tachycardia and (arterial) hypertension should be further followed post-marketing. Currently, the main shortcoming regarding the safety data-base concerns the limited interpretability of troriluzole safety in elderly (≥ 65 years) vs. younger SCA patients. As the applicant no longer pursues an indication restricted to patients with SCA3 genotype, the limitations regarding the former targeted subpopulation do no longer apply.

Taken altogether, the safety profile of troriluzole could be considered acceptable in case there is adequate proof of a clinically relevant efficacy. Regarding safety, there are still several **OC**s, which need to be adequately addressed.

The following measures are necessary to address the missing safety data in the context of a MA under exceptional circumstances:

Current limitations regarding interpretability of safety in older patients should be further evaluated post-marketing, e.g., via a PASS.

3.5. Risk management plan

3.5.1. Safety Specification

REDACTED

3.5.2. Pharmacovigilance plan

REDACTED

3.5.3. Overall conclusions on the PhV Plan

REDACTED

3.5.4. Plans for post-authorisation efficacy studies

The applicant has not proposed any post-authorisation efficacy studies.

3.5.5. Risk minimisation measures

3.5.5.1. Routine Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

3.5.5.2. Summary of additional risk minimisation measures

REDACTED

3.5.5.3. Overall conclusions on risk minimisation measures

REDACTED

3.5.6. Summary of the risk management plan

The public summary of the RMP requires revision in accordance with the final product information and for consistency with other Parts of RMP.

3.5.7. PRAC Outcome

PRAC endorsed the RMP AR and its conclusions and had the following comments and recommendations.

Regarding the PASS study "Post-authorization safety study of troriluzole in patients with spinocerebellar ataxia", the PRAC rapporteur's position that the study follow-up of 1 year is too short is endorsed. The PRAC Rapporteur has proposed a longer time-period of at least 10 years but PRAC position is that a minimum of 5 years of follow-up should be sufficient.

3.5.8. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.2 DLP 25-Jul-2024 (signed off on 14-Nov-2024) could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed CHMP assessment report and in the list of questions in section 5.

3.6. Pharmacovigilance

3.6.1. Pharmacovigilance system

3.6.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the IBD to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant requested an alignment of the PSUR cycle with the international birth date (IBD).

4. Benefit risk assessment

4.1. Therapeutic Context

4.1.1. Disease or condition

Ataxia is the absence of voluntary muscle coordination and loss control of movement that affects gait stability, eye movement, and speech. Spinocerebellar ataxias (SCA) are a group of ultra-rare, dominantly inherited neurodegenerative disorders predominantly characterised by atrophy of the cerebellum. The disease course of SCA is characterised clinically by relentlessly progressive ataxia over years inevitably leading to clinical deterioration of motor function, gait imbalance with frequent falling, and a shortened life expectancy by 6 to 29 years. SCAs are thought to be pathogenetically related but disease course and brain region involvement are known to vary between the different genotypes.

About 50 distinct genetic subtypes of SCA have been identified to data. The global prevalence of spinocerebellar ataxia is 1 to 5 per 100000 In the EU, the prevalence of SCA has been estimated to be 1 to 4 (average 2.7) individuals per 100,000 with some geographical variation i.e. 2/100000 in Italy to 4/100000 in Norway and 5/100000 in Portugal. SCA genotype 3 (SCA3), also known as Machado-Joseph disease, is the most common genotype in the EU and accounts for approximately 30% to 50% of SCAs worldwide.

SCA is a rare, progressively debilitating and fatal neurodegenerative disease with no available treatment.

Spinocerebellar ataxias (SCA) constitute of a group of degenerative and progressive disorders that can be identified on a molecular and cellular basis. The clinical presentation of SCA differs between subtypes which arise through multiple types of mutation mechanisms. SCAs are categorised into two groups according to their underlying mutation type into repeat expansions and point mutations (Cui et

al., 2024). CAG (polyglutamine) repeats are responsible for SCA genotypes 1, 2, 3, 6, 7, and 17 (Rentiya et al., 2020). The exact pathogenesis and the processes involved for the occurrence of SCAs is unclear. As a result of this lack of clarity, a specific target in the whole cascade and applicable to all SCAs is not yet determined. A medication with unspecific mechanism of action is not expected to yield a favourable treatment effect.

4.1.2. Available therapies and unmet medical need

Currently, there are no approved symptomatic or neuroprotective treatments for SCA and there is a clear unmet medical need for effective treatments. Investigational approaches include interventions to suppress polyglutamine neurotoxicity and genetic therapies to reduce polyglutamine gene products. Treatments with some promise include antisense oligonucleotides, ribonucleic acid (RNA) interference, and stem cell therapies.

Several symptomatic treatments have been reported in the literature (Ghanekar et al 2022).

4.1.3. Main clinical studies

In the troriluzole clinical programme there were 17 studies for disorders with glutamatergic dysfunction thought to contribute to underlying disease pathology (SCA, OCD, AD, GAD). Of the 4 Phase 2 proof-of-concept studies completed with troriluzole, a signal for efficacy was observed in the long-term treatment of SCA patients and the OCD study.

Study BHV4157-201 (201 from now on) is a Phase 2b/3 randomised, double-blind, placebo-controlled, parallel group study conducted as proof of concept. Study BHV4157-206 (206 from now on) is the pivotal Phase 3 randomised, double-blind, placebo-controlled, parallel group study in adult Subjects with Spinocerebellar Ataxia conducted to support an indication in these patients. Three strata based on the genotype were pre-defined: SCA1 & SCA2, SCA3 and SCA6, SCA7, SCA8 together with SCA10. SCA9 has not been assigned to a clinical disorder.

The design of the phase 3 pivotal trial is in principle appropriate. The 2 randomised clinical studies in SCA (206 and 201) represent, according to the applicant, the largest, multicentre, placebo-controlled dataset for SCA (N = 358), in which 340 subjects received at least one dose of troriluzole, in either the double-blind or OLE phase.

In study 206, the primary efficacy endpoint was the change from baseline on the f-SARA at Week 48. f-SARA is a modified scale of the SARA, which is considered the mostly used and best validated rating scale in ataxias. f-SARA was developed based on recommendations from FDA. The majority of patients (~93%) were enrolled in 21 sites in USA and the rest in 2 sites in China. There were no sites from Europe.

BHV4157-206-RWE was a 3-year study using real-world evidence (RWE). Clinical trial data collected prospectively over 3 years in troriluzole-treated subjects from BHV4157-206 were compared to an external control of rigorously matched, untreated SCA patients from the US Clinical Research Consortium for the Study of Cerebellar Ataxia (CRC-SCA) natural history study (primary endpoint) and to a European natural history cohort (EUROSCA).

4.2. Favourable effects

The SCA3 subgroup in contrast to the All SCA population, where no effect was observed, showed minor improvement in f-SARA (-0.03) compared to a deterioration in the placebo group (0.53 resulting in a very small difference of -0.56 between troriluzole and placebo in the f-SARA change from baseline at week 48, (p=0.0450, MMRM analysis).

The following favourable effects are reported by the applicant but they need to be looked at together with the limitations of the analyses and the fact that the primary analysis in the All SCA genotype group failed and all post-hoc analyses are considered exploratory and hypothesis generating.

The applicant also presented results by which treatment with troriluzole for 48 weeks is thought to reduce the risk of fall events by 53.4% in subjects in the All SCA population (108 troriluzole subjects, 109 placebo subjects; p = 0.005), by 54.4% in subjects in the SCA3 population (44 troriluzole subjects, 45 placebo subjects; p = 0.023), and by 67.5% in subjects with SCA3 who were ambulatory (i.e., baseline Gait 1 or 2) (35 troriluzole subjects, 36 placebo subjects; p = 0.009).

In addition, a SCA composite scale, defined herein as SCACOMS, was developed by a selection process (partial Least Squares Regression) from items most responsive to disease progression (in untreated SCA patients) among the rating scales employed in two independent, landmark natural history SCA patient data sets: Clinical Research Consortium for the Study of Cerebellar Ataxia, CRC-SCA (US patients) and European Integrated Project on Spinocerebellar Ataxias, EUROSCA (European patients). Applying the SCACOMS composite score derived from the US natural history CRC-SCA study in the 206 SCA3 study population demonstrated a statistically significant LS mean treatment difference of 3.61 favouring troriluzole over placebo at 48 weeks, p = 0.0030. A second composite analysis from the European natural history dataset applied to the 206 SCA3 study population (SCACOMS-EUROSCA-SCA3 composite score) yielded comparable findings, with a statistically significant treatment difference of 5.52 favouring troriluzole over placebo at 48 weeks, p = 0.0041.

The applicant undertook, an externally controlled comparative analysis, comparing the combined CRC-SCA and EUROSCA data sources to the original troriluzole-treated 206 subjects with up to 3 years of data (48-week randomisation phase with troriluzole and up to 2 years of additional OLE). The CRC-SCA and EUROSCA natural history datasets were combined (to increase sample size up to 3 years of measurement) and then compared in a Matching Adjusted Indirect Comparison (MAIC) analysis to the original troriluzole treatment arm of study 206. Treatment differences of -0.64, -1.16, and -1.34 were observed at years 1, 2, and 3, favouring troriluzole (p = 0.0008, < 0.0001, and < 0.0001, respectively), in the All SCA MAIC analysis.

A video analysis of tandem walk for some All SCA subjects in study 206 (36 placebo- and 31 troriluzole-treated subjects) illustrated the sensitivity of the Pose Dispersion Index to change with troriluzole treatment over 48 weeks, which was statistically significant (p = 0.010) compared to placebo treatment. Further, a statistically significant relationship between normal walk-derived Pose Dispersion Index and number of falls (p = 0.041) was shown, with a higher index observed amongst subjects with fewer falls.

The 9 prespecified, but with knowledge of the outcome of study 206, primary and secondary endpoints in Study BHV4157-206-RWE demonstrated treatment effects on the f-SARA favouring troriluzole-treated subjects versus matched, external control natural history comparators.

4.3. Uncertainties and limitations about favourable effects

The results for the initially intended population ALL SCA genotypes (SCA1, SCA2, SCA3, SCA 6, 7, 8 and 10) were not in favour of troriluzole compared to placebo. Disease did not progress as expected in the placebo group. Since study 206 failed to meet its primary objective in the pre-specified primary 'all SCA' population, no confirmatory conclusions can be drawn from the study.

It is agreed that the genotype strata were prespecified consisting of these three groupings: SCA1 & 2; SCA3; and SCA 6, 7, 8, & 10). Initially the applicant proposed an indication for the SCA3 genotype stratum. However this was done based on post-hoc analyses and after unblinding and examination of the results of the phase 3 double blind placebo controlled study 206.

It was not clear why the effect of troriluzole treatment should be different in patients with SCA3 genotype than in patients with ALL SCA genotypes. Of note, the secondary efficacy endpoints in SCA3 population analyses were not supportive. Overall, the study results did not demonstrate benefit with troriluzole treatment.

The natural history of disease progression has been estimated at approximately 0.7 points annual decline using the f-SARA scale and was also observed in the case of EUROSCA and CRC-SCA (within 0.4-0.8). Apart from knowing the natural disease decline, it would have been useful to define which values constitute a clinically meaningful effect in f-SARA compared to the baseline value and which represent the minimally clinically important difference.

The unmet medical need in SCAs is clearly acknowledged. However, it is also acknowledged that the pre-specified primary analysis using the f-SARA scale in the All SCA population failed such that no confirmatory conclusions can be drawn from the study and all post-hoc analyses are considered exploratory and data-driven.

The primary analysis in study 206 was based on the mITT analysis set, which excluded all patients without post-baseline data. However, all treated patients should have been included in the primary analysis to avoid any selection bias.

The SCACOMS development with subjects from the CRC-SCA US natural history cohort and the European EUROSCA were performed with a selection/enrichment of patients and a selection/enrichment of endpoints. There were a number of limitations, also admitted by the applicant, with respect to endpoints/scales used for the "creation" of SCACOMS. A number of assumptions were required for the development of SCACOMS (enrichment of patients, limitations with the scales/endpoints part of the SCACOMS and differences in SCACOMS between the two natural history registries), which the render the SCACOMs results when used for the study BHV4157-206 findings very difficult to interpret.

For the long term 3-year comparison of All SCA and SCA3 Data in study 206 with natural history cohort using MAIC a number of issues have been identified. The f-SARA was the endpoint used for the comparison. However, since there were no f-SARA results in the natural history datasets a transformation of the available SARA scores was necessary. A Matching Adjusted Indirect Comparison (MAIC) was performed to match natural history subjects from the registries to subjects in study 206 to account for potential baseline confounding. It is not understood why MAIC was used, as it is a technique when no individual patient data (IPD) but only aggregate data are available from the external data source that is intended to be used for the comparison, which is not the case here as IPD are available from the registries. Finally, the timing of the results had to be adjusted within time windows for the EUROSCA patients.

In the case of the Video Analysis of Gait in study 206, the sensitivity of Pose Dispersion Index to change with troriluzole treatment over 48 weeks for the tandem walk for All SCA subjects was nominally statistically significant ($p = 0.010$) compared to placebo treatment. However, the results for the normal walk-derived Pose Dispersion Index (N=56) were less compelling and did not reach statistical significance ($p=0.30$). Inconsistent results were obtained with an analysis attempting to correlate Baseline Pose Dispersion Index distributions with the risk of subsequent falls. In this analysis the reverse situation from the one above was observed. The results for the normal walk were more positive and had a nominal statistical p value of 0.041, whilst the results for the tandem walk had a value of 0.231.

Some examples of stick figure videos (from which the Pose Dispersion Index is calculated) in MP3 format were received from the applicant in an effort to examine whether simple visual observations of these videos can be helpful or whether achieved milestones, which have not been seen before in SCAs,

can be detected. However, by simple visual observation no striking differences between baseline and follow-up at 48 weeks could be detected. The applicant was requested to discuss the reliability of the Video Assessment method when the results for the risk of falls from the tandem walk were not consistent with the ones for the normal walk-derived Pose Dispersion Index. The Video analysis of gait method is under development. As stated by the applicant, it is an emerging technology which could serve as a tool to assess a patient's ambulation and an important supplement to traditional clinical assessment of gait using structured ratings scales. Several video analyses are being currently developed (https://pmc.ncbi.nlm.nih.gov/articles/PMC8736327/) as useful addition to clinical trial assessments. None of these video assessments has been validated and established as evidence or tools for demonstration of efficacy. These preliminary post-hoc findings could be used supportively for the design of another confirmatory study.

In the open label extension of study 206, at the extension week 156, the mean change in f-SARA from extension baseline is 1.6 for the troriluzole-troriluzole (N=5) and 2.6 for the placebo-troriluzole group (N=5). The mean change of 1.6 points corresponds to approximately 30% of the mean extension baseline value. One could argue that a 30% deterioration in the condition of the participants after 3 years as measured by f-SARA is an expected decline in the patients' condition and can be attributed to the natural history of the disease. It is noted that after the results of the study 206-RWE were known, the applicant changed the proposed indication and the currently intended to treat population is patients with all genotypes of SCA.

With respect to the external comparisons with natural history cohorts it is pointed out that while such a comparison may contribute to the totality of evidence, it cannot be the only basis for approval here, particularly as results are inconsistent to the results from the randomised controlled study. This is due to the general limitations of comparisons to external controls with several potential sources for bias. A major concern is the observation that in the randomised controlled study 206 statistically significant results were not achieved in 1 year. The difference for f-SARA total score change from baseline at 1 year (48 weeks) was -0.06 (0.20) [95% CI: -0.47, 0.34] in favour of troriluzole treatment with a p=0.7581 However, in the external comparison between troriluzole treatment group from study 206 and the US natural history cohort CRC-SCA, at 1 year, the difference for f-SARA total score change from baseline was -0.45 (0.22) and marginally statistically significant [95% CI: -0.88, -0.01] p= 0.0464. This discrepant observation makes the results of the external comparisons to natural history cohorts less credible. The separation between troriluzole-treated patients and matched NH controls in Year 1 strongly suggests that the set of matching variables may have not included all prognostic factors.

Furthermore, differences in the results from the comparisons were observed between CRC-SCA and EUROSCA cohorts. These differences cannot be justified by the composition of the matched groups or the rates of progression for certain SCA genotypes. Lastly, it is interesting that the applicant did not explore ataxin or any other relevant biomarker in any of the studies. Ataxin is believed to be closely associated with the disease and an analysis on its levels could have provided useful information on any potential target engagement and pharmacodynamic effect of troriluzole.

4.4. Unfavourable effects

At present, the following ARDs of troriluzole are identified by the applicant based on a higher comparative incidence of TEAEs considered treatment related by the investigator in troriluzole vs. placebo treated patients in pivotal study 206, applying the following criteria: reported in ≥ 2 patients in the troriluzole group and reported with a numerically higher incidence in the troriluzole vs. placebo group. (Proposed frequency in SmPC: common each).

- Abnormal liver function tests (including PTs ALT increased, AST increased, GGT increased, LFT increased) most frequently concerned ALT increased (reported as TEAE in 3 of 108 [2.8%] troriluzole vs. 1 of 109 [0.9%] placebo patients in study 206). ALT elevation > x 3 ULN (> 5 x ULN) was reported in 1.9% (0.9%) troriluzole vs. no placebo patients in pivotal study 206 and in 3.2% of the Pooled All troriluzole exposure subject population - across indications. A TEAE of LFT increased (PT) led to discontinuation of troriluzole in one patient (0.9%) in pivotal study 206. ALT increase usually started within the first 3 months of treatment. Derived from patients in whom data are available, ALT increase > 3 x ULN was usually transient.

Across indications, hepatotoxicity related SAEs were considered related to troriluzole in 3/1,778 patients (including PTs liver function test increased/abnormal and hepatic lesion). No cases of severe DILI or Hy's law were reported in the Clinical development programme (as of the cut-off dates applied to the SCS, dated between March and July 2023).

- Gastrointestinal events (including, nausea [reported as ADR in 4.6% troriluzole vs. 0.9% placebo patients in study 206], and abdominal discomfort [reported as ADR in 1.9% troriluzole vs. 0.9% placebo patients in study 206]). Nausea was the most frequent of the gastrointestinal TEAEs of troriluzole (reported in 6.5% troriluzole vs. 0.9% placebo patients) in study 206, and led to discontinuation of one troriluzole patient in this study.
- Fatigue (reported as ADR in 9.3% troriluzole vs. 0.9% placebo patients), and
- Insomnia (reported as ADR in 1.9% troriluzole vs. 0% placebo patients and as TEAE in 4.6% troriluzole vs. 1.8% placebo patients in study 206)

Apart from insomnia, these would be expected for troriluzole based on the established safety profile of riluzole (Rilutek).

Abdominal pain and vomiting are both established ADRs of riluzole and had been identified by the applicant based on an imbalance regarding TEAEs in study 206 and. These should be reintroduced in section 4.8 of the SmPC as common events as originally proposed by the applicant (**OC**).

4.5. Uncertainties and limitations about unfavourable effects

As troriluzole exerts is pharmacodynamic effects nearly exclusively via its active metabolite riluzole and as riluzole exposure with the intended troriluzole dose exceeds the riluzole exposure following the approved dose of Rilutek, it is not immediately obvious, why ADRs established for Rilutek would not occur with Dazluma. This is also true for potentially life-threatening events of severe neutropenia or interstitial lung disease (ILD), which have been evaluated among the Adverse Events of Special Interest, but have not been reported during the CDP of troriluzole as of the cut-off dates for the current MAA submission. It is possible, that these events have not been reported so far because of their rarity, which is particularly true for severe neutropenia, which was reported in 3 among approx. 5,000 patients treated with riluzole. Information regarding the risk of severe neutropenia as well as ILD disease associated with riluzole should therefore also be included in the SmPC of troriluzole (**OC**). Dizziness and somnolence are established ADR of riluzole. An imbalance with regard to TEAEs and ADRs each of dizziness and somnolence was found in study 201 but not in pivotal study 206. From these data, it cannot not be clearly derived, that troriluzole may also cause these events. The applicant proposes to monitor cases of dizziness as part of routine pharmacovigilance. This may be agreed; however, it is noted, that evaluation of one SAE of vertigo that was considered related to troriluzole by the investigator is still requested. In addition, because of the potential relevance for the patients, somnolence should also be further followed post marketing. As of the updated (Jun/Jul 2024) safety cut-off date, TEAEs of tachycardia were infrequently reported in the Pooled All troriluzole exposure population (5/1,778; 0.3%), all of which were considered unlikely or not related to troriluzole. No TEAE

of tachycardia was reported during randomised part of study 206. It can therefore be accepted that tachycardia, although an established for riluzole, is currently not included in the SmPC, however, the potential ADR of tachycardia and should be further followed post marketing.

Taking the established safety profile of riluzole into consideration, an evaluation and discussion of any labelling consequences which may result from the following SAEs (PT) reported once each in the all troriluzole exposure population across indications and considered related to troriluzole by the investigator still needs to be provided: Anaemia, vertigo, pancreatitis acute, asthenia and respiratory failure (OC).

In the All Troriluzole Exposure Population across indications, SAEs in the immune system disorders SOC (irrespective of causality) were reported in 3 of 1,778 subjects, and included the PTs anaphylactic shock, drug hypersensitivity and hypersensitivity, respectively. One case was considered treatment-related by the investigator; however, the time course of the event was not typical for a type I hypersensitivity reaction, the two other cases were attributed to other medicinal products and considered not related to troriluzole each. These data do not clearly indicate, that troriluzole is associated with hypersensitivity. However, because of the severity of respective ADRs established for riluzole (anaphylactoid reaction, angioedema) the potential risk of hypersensitivity should be further followed post marketing.

The applicant claims a reduced risk of hepatotoxicity with troriluzole compared to riluzole. A reduced riluzole burden on the liver via bypass of the first-pass metabolism could provide a possible explanation for this. In the clinical studies with troriluzole, ALT increase > ULN, > 3 x ULN and > 5 x ULN was reported in 38.0%, 3.2% and 0.9% of patients in the Pooled all troriluzole exposure population across indications (as of the updated Jun/Jul 2024 data-cut offs) and was reported in approx. 50%, 8% and 2% of patients in clinical studies with riluzole. However, there are uncertainties regarding the claim of reduced hepatotoxicity, as the differences in ALT increase are not large and are derived from an indirect comparison of current troriluzole studies with studies that have been performed with riluzole in a different population decades ago.

In order to better characterise the hepatotoxicity risk of troriluzole, detailed information regarding reversibility including time to reversibility in patients with ALT increase > 5 x ULN should be provided in a comprehensible way (OC). In the pooled all troriluzole exposure subject population across indications (as of the updated cut-off dates applied with the response), any hepatotoxicity-related TEAE considered related to treatment by the investigator occurred in 4.7% (84/1,778) subjects. According to Appendix 2.1.2.3 – R2 of the Day 120 response (provided in module 5.3.5.3 among "Select updated MAA ISS output"), the respective events also concerned the following PTs, which are not proposed to be labelled so far: blood bilirubin increased (in 5 [3%] patients), international normalised ratio and prothrombin time prolonged (in one [0.1%] patient each), hepatic failure (in 2 [0.1%] patients), and hepatic lesion, hyperbilirubinaemia and ocular icterus (in one [0.1%] patients each). The applicant is requested to thoroughly evaluate these cases and discuss whether any of these PTs needs to be added to SmPC section 4.8 (OC). Additional information should further be provided regarding to hepatotoxicity related SAEs, considered related to troriluzole by the investigator (with PTs liver function test abnormal and hepatic lesion in one case each) and respective labelling consequences should be discussed as appropriate (OC).

Rilutek is contraindicated in patients with hepatic disease or with baseline transaminases > 3 x ULN; and patients with active liver disease or a history of hepatic intolerance to medications, that in the investigator's judgment was medically significant, were excluded from pivotal study 206. As requested, the applicant has introduced a contraindication regarding hepatic disease to the SmPC, however, the wording needs to be further amended taking into consideration the exclusion criteria of the pivotal

study and the finding, that troriluzole like riluzole is associated with hepatotoxicity (OC, see attached documents).

In pivotal study 206, a somewhat higher incidence of TEAEs of hypertension was reported in the troriluzole (4 [3.7%]) vs. the placebo group (1 [0.9%]), however, none of the events was considered related to IMP. Across all randomised troriluzole studies, neither a consistent trend towards increased blood pressure values nor consistent imbalances regarding hypertension AEs was found. Hypertension is also not listed as ADR of in the EMA label of Rilutek. It can therefore be agreed at present, that the overall trial data hypertension do not warrant inclusion of hypertension as an ADR. Nevertheless, the FDA label informs about a 5% incidence of hypertension among 313 patients treated with 50 mg riluzole twice daily compared to 4% among 320 placebo treated patients (in two pooled placebo-controlled studies) and mild systolic hypertension was also found in pre-clinical studies (see Non-clinical Report of this AR). Therefore, the potential ADR of hypertension should be further followed post marketing.

Renal impairment is not expected to have a relevant effect on PK of troriluzole. However, no phase I clinical study in patients with renal impairment has been performed with troriluzole and patients with severe renal impairment were excluded from the pivotal troriluzole study. In patients with severe renal impairment, in line with riluzole, troriluzole should not be administered, as no data are available. No safety signals arose from few patients with moderate renal impairment that were included in the pivotal study. Because of the limited data available, caution should be advised in patients with moderate renal impairment. This needs to be adequately implemented in the SmPC.

It cannot be excluded, that the safety profile of troriluzole might be somewhat less favourable in Patients > 65 compared to ≤ 65 years. In the pivotal study, a higher placebo-subtracted and also overall rate of TESAEs and TEAEs leading to discontinuation in the troriluzole treatment group was found in patients ≥ 65 compared to patients < 65 years. However, the low number of patients ≥ 65 years in this study (i.e., 13 in the troriluzole and 8 in the placebo treatment group) precludes any firm conclusions. In AD study 203 the incidence of TEAES, SAEs and AEs leading to withdrawal was higher each in older compared to younger troriluzole subgroups, also when taking the rates in the respective placebo subgroups into consideration, indicating a worse safety profile by age. Reassuringly, there were no respective imbalances with regard to fatal events in this study. It is not clear though, in how far these results derived from a daily dose of 280 mg troriluzole in the AD indication would translate into a worse safety profile by age in the SCA indication. As of the SCS cut-off dates, a total of 53 SCA patients and 287 subjects across the CDP were ≥ 65 years and received least one dose of troriluzole. No clear safety signals are derived from the subgroup analyses of the pooled All troriluzole exposure subjects across indications by age; nevertheless, due to the open-label nature of these data as well as combination of different underlying diseases, the informational value of these analyses is limited. These limitations should be further evaluated post-marketing. From the provided TEAE tables by age there appears to be a striking trend towards higher incidences of anticholinergic syndrome TEAEs (based on the narrow and broad SMQ) in the troriluzole vs. placebo groups, irrespective of age and across indications. Riluzole is not an anticholinergic substance, however, it is associated e.g. with tachycardia (common), which is also a symptom of anticholinergic syndrome. In contrast, tachycardia is not proposed to be labelled for troriluzole so far. The applicant is requested to evaluate the rather consistent imbalance with regard to anticholinergic syndrome TEAEs across the placebo controlled studies with troriluzole, to explain, which TEAEs (by PT) exactly cause these imbalances and to discuss whether labelling of further ADRs is warranted (OC).

It further cannot be excluded, that the safety profile of troriluzole might be somewhat less favourable in the SCA3 subpopulation compared to the sought overall SCA population, which appeared to be mainly driven by a higher rate of related TEAEs of dizziness and nausea.

4.6. Effects Table

Table 40: Effects Table for Dazluma (Efficacy data cut-off: 21 July 2023; Safety data cut-off: July 2023 [OLE of pivotal study]; March 2023 [other ongoing safety studies]

Effect	Short Description	Unit	Troriluzole	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
All SCAs group (primary analysis)						
f-SARA change from baseline LS mean (SE) at week 48	Functional Scale for the Assessment and Rating of Ataxia	Score	N=106 0.20 (0.19)	N=107 0.27 (0.18)	**Unc:** Difference from placebo: **-0.063** (0.20), **p=0.7581** (MMRM) **Secondary endpoints**: PIFAS total score change from baseline, FARS-ADL total score change from baseline, FARS-FUNC total score change from baseline – **Not significant**	(1)
SCA3 genotype subgroup (post-hoc model)						
f-SARA change from baseline LS mean (SE) at week 48	Functional Scale for the Assessment and Rating of Ataxia	Score	N=44 -0.03 (0.20)	N=45 0.53 (0.19)	**Unc:** Difference from placebo: **-0.56** (0.28), **nominal p=0.045** (MMRM) Post-hoc after unblinding analysis with knowledge of the data; marginally significant with nominal p-value **Secondary endpoints**: PIFAS total score change from baseline, FARS-ADL total score change from baseline, FARS-FUNC total score change from baseline – **Not significant**	(1)
Unfavourable Effects						

Effect	Short Description	Unit	Troriluzole	Placebo	Uncertainties/ Strength of evidence	References
Hepato-toxicity	Incidence of ALT increase > 3 x ULN > 5 x ULN AST increase > 3 x ULN > 5 x ULN	%	 1.9 0.9 0.9 Study 206: 0 Study 202 (OCD): 1.8 Study 207 (GAD): 1.1	 0 0 0 0 0 0	Established ADR of riluzole; also higher incidence vs. placebo in ALT increase, AST increase, GGT increase, LFT increase reported as TEAEs and ADR (common each); further evaluation of ADRs related to hepatotoxicity across indications still requested; three hepatotoxicity-related SAEs related to IMP (2) Hy's law cases not reported as of SCS cut-off date; confirmation with regard to updated safety cut-off date requested	(1), (2), (4), (5)
Nausea	Incidence of TEAE ADR	%	6.5 4.6	0.9 0.9	Higher incidence vs. placebo; established ADR of riluzole	(1)
Vomiting	Incidence of TEAE	%	2.8	0.9	Higher incidence vs. placebo; established ADR of riluzole; should be reintroduced to SmPC section 4.8	(1)
Fatigue	Incidence of ADR	%	9.3	4.6	Higher incidence vs. placebo; asthenia established for riluzole	(1)

Effect	Short Description	Unit	Troriluzole	Placebo	Uncertainties/ Strength of evidence	References
Established ADRs of riluzole	Severe neutropenia (reported in ~3/5,000 riluzole treated patients)		So far not reported with troriluzole		Would also be expected with troriluzole which exerts PD effect almost exclusively via riluzole;	(2),
	Interstitial lung disease (uncommon frequency with riluzole)		So far not reported with troriluzole		updated troriluzole safety data base (1,778 patients;) not large enough to exclude rare events;	(2),
	Anaphylactoid reaction/angio-edema (uncommon frequency with riluzole)		Related SAE of hypersensitivity (PT) in 1/1,778 patients n (2);		no typical onset of related SAE of hypersensitivity with regard to start of troriluzole	(2)
	Pancreatitis (uncommon frequency with riluzole)		related SAE of pancreatitis acute (PT) in 1/1,778 patients		further evaluation requested	
	Others (including					
			TEAE:	TEAE:	imbalance of dizziness and somnolence in supportive study 201 (dizziness: any TEAE/related TEAE: 11.3% vs. 1.4%; somnolence any TEAE: 2.8% v.s 0%) but not in pivotal study 206	(1), (6)
	dizziness,	%	9.3	10.1		
	somnolence	%	1.9	1.8		

Abbreviations:

Notes: (1) Study 206, placebo-controlled part; (2) All Troriluzole Exposure Population across indications (comprising 1,778 patients across phase 2/3 studies as of updated Jun/Jul 2024 data cut-off; (4) Study 202 placebo-controlled part; (5) Study 207 placebo-controlled part; (6) Study 201, placebo-controlled part

#The results from the study BHV4157-206-RWE are not considered acceptable to be included in the effects Table.

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

Efficacy:

The unmet medical need in spinocerebellar ataxias is definitely acknowledged. It is also probably true that the 2 randomised clinical studies in SCA (06 and 201), in which 340 subjects received at least one dose of troriluzole in either the double-blind or OLE phase, represent the largest, multicentre, placebo-controlled dataset for SCA (N = 358). However, the pre-specified primary analysis in the ALL SCA group using the f-SARA scale failed to show an effect of troriluzole such that no confirmatory conclusions can be drawn from the study and all further analyses need to be considered exploratory and hypothesis generating.

SCA presents with high heterogeneity and is comprised of different genotypes resulting in similar clinical pictures. The proposed synaptic glutamate modulating activity of troriluzole is hypothesised to address the widely documented glutamatergic dysregulation that underlies neurodegeneration and Purkinje cell dysfunction in patients with SCA. The postulated mechanism of action of troriluzole, which is rapidly transformed to riluzole in the body, is unspecific as a glutamate modulating agent.

Both double blind, placebo controlled studies 206 and 201 conducted by the applicant formally failed. The post-hoc analysis for the SCA3 group after unblinding showed at week 48 a very small difference of -0.56 between troriluzole and placebo in the f-SARA change from baseline, with a marginally nominally statistical significance (p=0.0450). Notably, for the model corresponding to the one used for primary analysis in the overall population, the difference was slightly smaller (-0.53; p=0.065). Use of alternative methods of analysing the data provided even smaller differences between troriluzole and placebo. The secondary endpoints did not provide results in favour of the troriluzole treatment. Attempts to develop another more sensitive composite scale, SCACOMS, from the CRC-SCA and EUROSCA registries and use it for the randomised controlled study 206 findings, were characterised by the enrichment of patients, the limitations with the scales/endpoints part of the SCACOMS (even differences in SCACOMS between the two natural history registries) and the number of assumptions needed. As such the interpretation of SCACOMS results becomes very difficult. REDACTED The Automated Video analysis study produced inconsistent results. In a small sample (36 placebo- and 31 troriluzole-treated subjects), the results for the tandem walk reached statistical significance (p = 0.010), while the results for the normal walk-derived Pose Dispersion Index (N=56) were less compelling and did not reach statistical significance (p=0.30). Attempting to correlate Baseline Pose Dispersion Index distributions with the risk of subsequent falls, the results for the normal walk were more positive and had a nominal statistical p value of 0.041, whilst the results for the tandem walk had a value of 0.231.

REDACTED

It is further unclear, why ataxin or another relevant biomarker, which is believed to be closely associated with the disease, was not investigated in any of the studies.

It should be also pointed out that statistically significant results in OCD, Alzheimer's disease and GAD were not obtained with troriluzole. This creates a negative impression for the potential treatment capabilities of troriluzole, with an unspecific mechanism of action, in various diseases/conditions.

Therefore, the CHMP is of the opinion that available efficacy data are considered insufficient to support a favourable benefit risk balance in the currently intended to treat population (all genotypes of SCA). At this stage it is not expected that extensive or additional analyses will significantly influence the B/R discussion. A positive benefit/risk ratio is a pre-requisite of any MAA including MAUEC.

Safety:

The most relevant safety concern identified for troriluzole so far relates to hepatotoxicity, which mainly manifested in ALT increase. ALT increase > 3 x ULN usually occurred within the first three months and appeared to be transient. In patients with ALT increase > 5 ULN troriluzole was usually discontinued with missing experience with re-challenge of troriluzole. No severe cases of DILI and Hy's law were

reported with troriluzole as of the SCS cut-off date; however, confirmation is requested that this still holds true as of the updated safety data cut-off (Jun/Jul 2024;**OC**). SAEs related to hepatotoxicity occurred rather infrequently during the clinical development programme with troriluzole (in 7/1,778 [0.4%] patients across indications, three of which were considered related to troriluzole). However, further evaluation of AEs and SAEs related to hepatotoxicity is still requested (**OC**). As the applicant has now implemented a contraindication to troriluzole in patients with hepatic disease in the SmPC, there is no further MO with regard to safety. Nevertheless, the wording of the contraindication needs to be amended taking into consideration the inclusion criteria of the pivotal study and the finding, that troriluzole is associated with hepatotoxicity (**OC**). Other ADRs identified for troriluzole relate to gastrointestinal events, including the PTs vomiting and abdominal pain (both of which need to be reintroduced to SmPC section 4.8; **OC**), fatigue and insomnia (all with common frequency).

As troriluzole exerts is pharmacodynamic effects nearly exclusively via its active metabolite riluzole, and as riluzole exposure in plasma with the posology proposed for Dazluma is expected to exceed that resulting from the approved Rilutek posology, it is not immediately obvious, why ADRs established for Rilutek would not occur with Dazluma. This is also true for severe neutropenia or interstitial lung disease (ILD). These have not been reported during the clinical development programme of troriluzole so far, potentially due to the rarity of these events. Nevertheless, because of their potentially life-threatening nature information regarding the risk of severe neutropenia as well as ILD associated with riluzole should be included in the SmPC of troriluzole (**OC**). The data available for troriluzole do not conclusively suggest, that troriluzole leads to dizziness, somnolence, hypersensitivity, tachycardia, and hypertension. However, apart from hypertension, which was also found in pre-clinical studies, these are among the established ADRs of Rilutek. These potential ADRs should therefore be further followed post marketing.

Compared to the established safety profile of riluzole, no unexpected serious safety concerns have arisen from the clinical development programme of troriluzole. The identified safety issues are considered to be manageable with appropriate labelling in the product information, which however is still issue of discussion. Apart from the above points, there are still further **OCs** regarding safety, which need to be adequately addressed, mainly relating to reversibility of ALT increase > 5x ULN, as well as an evaluation of some related SAEs reported across indications.

Current limitations of the safety database mainly pertain to the limited interpretability of safety data of troriluzole in patients ≥ 65 years compared to younger patients, although no clear safety signal can be derived from the data available so far. These limitations should be further evaluated post-marketing.

4.7.2. Balance of benefits and risks

A chain of evidence for a treatment effect and benefit for SCA patients (all genotypes) has not been demonstrated with troriluzole:

- A target engagement with troriluzole has not been shown.
- The mechanism of action of troriluzole-riluzole is very unspecific (glutamate modulating agent).
- A pharmacodynamic effect on a biomarker (e.g. reduction of ataxin protein levels) has not been demonstrated.
- A randomised controlled clinical trial Study 206 failed to meet its primary objective in the pre-specified "all SCA" population and did not show statistically significant and clinically meaningful effects for the All SCA patient population. No confirmatory conclusions can be drawn from the study.

- All post-hoc analyses were performed with knowledge of the study results and are considered hypothesis generating.
- Real World Evidence in the form of external comparisons with natural history cohorts (CRC-SCA, EUROSCA, Global) generated some results. However, inconsistencies between RWE and placebo controlled data, differences between the groups selected with propensity score matching, the composition in SCA genotypes and inexplicable differences in the comparisons between regions challenges that conditional exchangeability has been attained. That makes extremely difficult to interpret and raise concerns as to the sensitivity of the methods and the consistency of all the results.
- The analyses of the RWE were conducted post-hoc, with prior knowledge of the findings of the pivotal study BHV4157-206. Results of a RWE study are not considered adequate to replace results of a properly designed and conducted placebo-controlled study. The method of analysis (MMRM) used in this exercise is not considered appropriate.

The safety profile of troriluzole is only considered acceptable in case there is adequate proof of a clinically relevant efficacy. However, there are still safety issues (**OCs**) that need to be adequately addressed.

A favourable benefit risk for troriluzole treatment in patients with all genotypes of SCA cannot be concluded.

4.7.3. Additional considerations on the benefit-risk balance

EMA has invited a healthcare professionals organisation to share their perspectives.

The healthcare association described the main symptoms of SCA3 and its devastating effects. It is of interest that ataxia experts avoid prescribing the drugs that are supported by only weak to conflicting evidence (i.e. riluzole, valproic acid).

The urgent unmet medical need to have access to proven symptomatic and disease-modifying strategies for SCA3 is certainly acknowledged.

SARA is considered by the experts the mostly used and best validated rating scale and combined with ataxia-specific ADL scales are perhaps the best outcome parameters.

The applicant is requested to discuss the criticism that there is lack of prior validation and lack of any longitudinal data on the natural history progression of the f-SARA scale.

EMA has also invited **a patient's organisation** to share their perspectives.

The patients' association have described aspects of the impact that SCA has on the daily life of patients, their expectations from treatment and flagged additional points for the evaluation of efficacy.

From the patients' perspective it is important for the treatment to demonstrate the ability to slow down the disease progression. In that way, patients could live longer in normal conditions to benefit from possible future treatments.

With respect to the issue of women of childbearing potential, it is noted the applicant has already included a contraindication and a warning in the SmPC for the use in pregnant or lactating patients, as there is a lack of clinical experience in these populations.

Marketing authorisation under exceptional circumstances

As comprehensive data on the product are not available, a marketing authorisation under exceptional circumstances was requested by the applicant in the initial submission.

The pivotal study failed to demonstrate a positive B/R of the product in the primary analysis population. Consequently, no confirmatory conclusions can be drawn from the study. The SCA3 subgroup, which is currently proposed for the indication, was identified as a population positively responding to troriluzole treatment only in the post-hoc analysis. Therefore, the results of the analysis in the SCA3 population cannot be considered reliable, appear to be a chance finding, and cannot serve as proof of efficacy of troriluzole. It is also not clear why, based on the mechanism of action, troriluzole would only be effective in SCA3 patients. The applicant's request for an MA under exceptional circumstances cannot be accepted since a positive benefit/risk ratio in the target population was not established.

4.8. Conclusions

The overall benefit /risk balance of Dazluma is negative.

5. Recommended conditions for marketing authorisation and product information in case of a positive opinion

In view of the major objections, it is premature to recommend any conditions for marketing authorisation and to propose changes in the product information (SmPC, Annex II, labelling, PL).

5.1. Conditions for the marketing authorisation

In view of the major objections, it is premature to recommend any conditions for a marketing authorisation under exceptional circumstances.

5.2. Proposed list of post-authorisation measures

In view of the major objections it is premature to recommend any post-authorisation measures or specific obligations (SOBs) for a marketing authorisation under exceptional circumstances.

User consultation

Conclusion from the checklist for the review of user consultation

The PL has been initially tested in a total of 23 participants. It was found to be clear and easy to understand, with an acceptable design, layout and font size. With respect to content, the information was clear, understandable and easy to find in the leaflet. At least 90% of the participants were able to find each point of information. It also showed that at least 90% of those participants were able to understand the information. The leaflet therefore fulfils the EU requirements for User Testing and no further testing is considered necessary.