12 December 2024
EMA/19754/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tuzulby

International non-proprietary name: methylphenidate hydrochloride

Procedure No. EMEA/H/C/005975/0000

Note

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

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List of abbreviations

AAS	Atomic Absorption Spectrometry
AE	Adverse Event
AP	Applicant's Part (or Open Part) of a ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CMS	Concerned Member State
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
CV	Coefficient of Variation
DP	Decentralised (Application) Procedure
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EP	European Pharmacopoeia
ERA	Environmental Risk Assessment
FT-IR	Fourier Transform infrared spectroscopy
GC	Gas Chromatography
GCP	Good Clinical Practise
HDPE	High Density Polyethylene
HPLC	High Performance Liquid Chromatography
ICP-OES	Inductively coupled Plasma – Optical Emission Spectroscopy
IMP	Investigational Medicinal Product
IPC	In-process Control
IR	Infrared
ISR	Incurred Sample Reanalysis
ITT	Intention To Treat
IU	International Units
LDPE	Low Density Polyethylene
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
LSM	Least-Squares-Means
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MEB	Medicines Evaluation Board
MEK	Methyl Ethyl Ketone
MO	Major Objection
MS	Mass Spectrometry
M&S	Modelling and Simulation
MTBE	Methyl *tert*-Butyl Ether
NCA	Noncompartmental
ND	Not Detected
NI	Noninferiority

NLT	Not Less Than
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
OC	Other Concern
OOS	Out of Specifications
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PNEC	Predicted No Effect Concentration
PP	Polypropylene
PVC	Poly Vinyl Chloride
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of a ASMF
RPM	Reference Medicinal Product
RRT	Relative Retention Time
RSD	Relative Standard Deviation
SAE	Serious Adverse Events
SKAMP	Swanson, Kotin, Agler, M-Flynn, and Pelham Rating Scale
SmPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
TEA	Triethylamine
TEAE	Treatment-Emerging Adverse Events
TTC	Threshold of Toxicological Concern
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Neuraxpharm Pharmaceuticals S.L. submitted on 24 November 2022 an application for a Paediatric Use marketing authorisation in accordance with Article 30 of Regulation (EC) No 1901/2006, to the European Medicines Agency (EMA) for Tuzulby, through the centralised procedure under Article 31 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 July 2021.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Tuzulby is indicated as part of a comprehensive treatment programme for Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6 years of age and over when remedial measures alone prove insufficient. Treatment must be under the supervision of a specialist in childhood behavioural disorders. Diagnosis should be made according to the current DSM criteria or ICD guidelines and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptoms.

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and specialised psychological, educational, and social resources.

A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising children with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal electroencephalogram (EEG). Learning may or may not be impaired.

Tuzulby treatment is not indicated in all children with ADHD and the decision to use the medicinal product must be based on a very thorough assessment of the severity and the chronicity of the child's symptoms in relation to the child's age.

Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a stimulant must be based on rigorous assessment of the severity of the child's symptoms. Methylphenidate should always be used in the way according to the licensed indication and according to prescribing/diagnostic guidelines.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, a bioequivalence study with the reference medicinal product Ritalin and appropriate non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Ritalin 10 mg Tabletten, tablet
- Marketing authorisation holder: INFECTOPHARM Arzneimittel und Consilium GmbH
- Date of authorisation: 15-01-1997
- Marketing authorisation granted by:
  - Member State (EEA): Germany
    - National procedure
- Marketing authorisation number: 6094573.00.00

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Ritalin 10 mg Tabletten, tablet
- Marketing authorisation holder: INFECTOPHARM Arzneimittel und Consilium GmbH
- Date of authorisation: 15-01-1997
- Marketing authorisation granted by:
  - Member State (EEA): Germany
    - National procedure
- Marketing authorisation number: 6094573.00.00

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Ritalin 10 mg Tabletten, tablet
- Marketing authorisation holder: SIA Novartis Baltics Date of authorisation
- Date of authorisation: 15-01-1997
- Marketing authorisation granted by:
  - Member State (EEA): Latvia
    - National procedure
  - Marketing authorisation number(s): LV 00-0118
- Bioavailability study number(s): 2021-5129

1.3. Information on paediatric requirements

Pursuant to Article 30 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0057/2023 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver from birth to less than 6 years of age.

At the time of submission of the application, the PIP EMEA-003189-PIP01-22-M01 was completed.

The PDCO issued an opinion on compliance for the PIP EMEA-003189-PIP01-22-M01.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 March 2021	EMA/SA/0000052001	Mario Miguel Rosa, Flora Musamba

The scientific advice pertained to the following clinical aspects:

The applicant received scientific advice on the development of methylphenidate hydrochloride for treatment of attention-deficit hyperactivity disorder (ADHD) from the CHMP on 25 March 2021 (EMA/SA/0000052001). The scientific advice pertained to the following clinical aspects:

• the pharmacokinetic bridge to Ritalin tablets or alternatively the clinical development programme to support a marketing authorisation application.

1.6. Steps taken for the assessment of the product

The Rapporteur and appointed by the CHMP were:

Rapporteur: Ewa Balkowiec Iskra Co-Rapporteur: N/A

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	24 November 2022
The procedure started on	23 February 2023
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	9 May 2023
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	30 May &02 June 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 June 2023
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	8 June 2023
The applicant submitted the responses to the CHMP consolidated list of questions on	16 August 2024

The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs joint assessment report on the applicant's responses to the list of questions to all CHMP members on	18 September 2024
The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on	03 October 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	17 October 2024
The applicant submitted the responses to the CHMP consolidated list of outstanding issues on	12 November 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	21 November 2024 & 27 November 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tuzulby on	12 December 2024

2. Scientific discussion

2.1. Introduction

Problem statement

ADHD is the most common neurobehavioural disorder of childhood and can profoundly affect academic achievement, well-being and social interactions of children *(Posner et al., 2020)*. MPH is the drug most often prescribed to treat children and adolescents with ADHD. It is a central nervous system (CNS) stimulant belonging to a class of piperidine-derived compounds. It is a racemic mixture comprised of the d- and l-threo enantiomers, the d-threo- being more pharmacologically active than the l-threo enantiomer. Its main mechanism of action is considered to be the blockade of dopamine (DAT) and norepinephrine transporters (NET), thus blocking the reuptake of dopamine (DA) and norepinephrine (NE) into the presynaptic neuron and increasing the release of these monoamines into the extraneuronal space *(Volkow et al., 2002; Jaeschke et al., 2021)*. MPH has received the ATC DDD code N06BA04, for being a psychostimulant agent use for ADHD, centrally acting sympathomimetic *(WHOCC ATC DDD Index Methylphenidate)*.

About the product

MPH or methyl 2-phenyl-2-piperidin-1-ium-2-ylacetate chloride (IUPAC) has the molecular formula of C14H20ClNO2 and a molecular weight of 269.77 g/mol. In its pure form, it appears as a white, odourless, fine crystalline powder that is freely soluble in water, 0.1 N hydrochloric acid, and methanol, soluble in ethanol (95%), and slightly soluble in chloroform and acetone. MPH contains two chiral centres, it is the racemate of the threo-form and is not optically active. It does not exhibit polymorphism. MPH is currently marketed in Europe as immediate release (IR) formulations for oral administration; the designated EU reference product is Ritalin® 10 mg tablets (Novartis Pharma). Also, modified (prolonged) release formulations exist, e.g. Ritalin® XL modified-release capsules (Novartis Pharma) and Concerta® prolonged-release tablets (Janssen-Cilag). The newly developed product formulations are designed as PR forms to be compared to the designated IR innovator formulation, Ritalin® (MPH) 10 mg film-coated tablets. The scope of these developments is to provide age-

appropriate paediatric formulations for once-daily dosing, addressing the unmet medical need of children with difficulty to swallow solid dosage forms. In this way, the risk of medication errors associated to the mixing of Ritalin® crushed tablets with food is minimised. The two formulations have already been approved by US Food and Drug Administration (FDA).

The development programme/compliance with CHMP guidance/scientific advice

Relevant for the assessment are the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev.1), Guideline on the pharmacokinetic and clinical evaluation of modified-release dosage forms (EMA/CHMP/EWP/280/96 Rev.1).

The applicant received CHMP Scientific Advice EMA/SA/0000052001 pertinent to the clinical investigation. This advice concerned the following topics:

- the pharmacokinetic bridge to Ritalin tablets or alternatively the clinical development programme to support a marketing authorisation application.

The CHMP considered that a direct comparison between the two proposed formulations and the IR reference European formulation should be presented. This was fulfilled by the applicant.

Steady state studies were considered not necessary provided a justification for the waiver of these studies according to the criteria outlined in section 6.1 of the guideline. This was submitted by the applicant. The CHMP also recommended to adequately address dose proportionality and evaluate factors that may affect the performance of the formulations, including food. Moreover, the need for further therapeutic studies was discussed at the time of the SA. The CHMP considered that the applicant's approach to waive additional therapeutic studies based on the already available efficacy data obtained on own clinical trials and a PK/PD study as well as the presented PopPK/PD model should be considered acceptable to explain the PK profile of the IR and ER formulations, the inter-subject variability and the observed efficacy. It was stressed that the PopPK should be further optimised with the PK data obtained in the new studies and the European IR formulation PK should be used for the efficacy simulations for comparison. This was performed by the applicant.

Quality aspects

2.1.1. Introduction

The finished product is presented as prolonged-release chewable tablet containing 20 mg, 30 mg or 40 mg of methylphenidate hydrochloride as active substance (equivalent to 17.30 mg, 25.95 mg and 34.59 mg of methylphenidate, respectively).

Other ingredients are: sodium polystyrene sulfonate, povidone (E 1201), triacetin (E 1518), polyvinyl acetate, sodium lauryl sulfate, mannitol (E 421), xanthan gum (E 415), crospovidone (E 1202), microcrystalline cellulose (E 460), guar gum (E 412), aspartame (E 951), citric acid, cherry flavour, talc (E 553b), silica colloidal hydrated, magnesium stearate, polyvinyl alcohol, macrogol, polysorbate 80 (E 433).

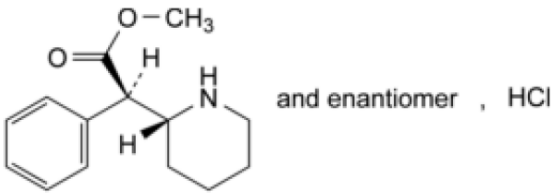
The product is available in a HDPE bottle including a 2 g desiccant canister with a child-resistant cap (PP).

2.1.2. Active substance

General information

The chemical name of the active substance methylphenidate hydrochloride (Ph. Eur.) is methyl (2RS)-phenyl[(2RS)-piperidin-2-yl]acetate hydrochloride, corresponding to the molecular formula: $C_{14}H_{19}NO_2$ ••HCl. It has a relative molecular mass of 269.8 g/mol and the following structure given in Figure 1:

Figure 1: structure of the active substance



Methylphenidate hydrochloride is white or almost white, fine, crystalline powder, freely soluble in water, soluble in ethanol (96 per cent), slightly soluble in methylene chloride. Its melting point is 224-226ºC, pKa: 8.77. Polymorphism has not been observed. The active substance is a racemate.

As there is a monograph of methylphenidate hydrochloride in the European Pharmacopoeia, the manufacturer of the active substance has been granted a certificate of suitability of the European Pharmacopoeia (CEP) for methylphenidate hydrochloride which has been provided within the current marketing authorisation application. A copy of the certificate of suitability has been provided in Module 1 and Module 3.2.R of the dossier. This certificate of suitability is considered valid according to EDQM database. However, according to the applicant's information this CEP is currently under revision. The new version should be submitted when available.

The following additional information is stated on the CEP:

- Test for residual solvents by gas chromatography and loss on drying
- A risk management summary for elemental impurities has been provided
- Test for elemental impurity by IPC-MS
- Test for particle size by sieve method
- The re-test period of the substance if stored either in double polyethylene bags placed in a polyethylene container, or in an amber glass bottle with a phenolic resin cap
- The holder of the certificate has declared the absence of use of material of human or animal origin in the manufacture of the substance.

Manufacture, characterisation and process controls

The active substance is manufactured at the sites listed on the CEP.

The relevant information has been assessed by the EDQM before issuing the certificate of suitability.

Specification

The active substance specification includes tests for appearance, identity (IR, identification of chloride), loss on drying (Ph. Eur.), assay (HPLC), related substances (HPLC), residual solvents (GC), palladium (ICP-MS), sulphated ash (Ph. Eur.), and particle size (Ph. Eur.).

Appropriate specifications have been set in line with the Ph. Eur. monograph and the CEP.

The analytical methods used have been adequately described and non-compendial/in house methods for residual solvents and palladium have been appropriately validated. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented and it is considered adequate.

Batch analysis data (3 batches) of the active substance are provided. The control tests were carried out to comply with the specifications and additional tests on CEP. The results are within the specifications and consistent from batch to batch.

Stability

The stability results assessed during the CEP procedure indicate that the active substance is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.1.3. Finished medicinal product

Description of the product and pharmaceutical development

The appearance of the prolonged-release chewable tablets is given below:

Tuzulby 20 mg chewable tablets are speckled, off white, 6.8 x 14.7 mm capsule shaped coated tablet, debossed with “N2” “N2” on one side and bisect on the other side.

Tuzulby 30 mg prolonged-release chewable tablets are speckled, off white, 7.7 x 16.8 mm capsule shaped coated tablet, debossed with “N3” “N3” on one side and bisect on the other side.

Tuzulby 40 mg prolonged-release chewable tablets are speckled, off white, 8.5 x 18.5 mm capsule shaped coated tablet, debossed with “NP14” on one side and plain on the other side.

The proposed differentiation among the three strengths is now considered acceptable as the appearance of the tablet has been modified to address a major objection (MO1) raised by the CHMP relating to the tablet appearance, in view of the fact that different strengths (sometimes halved) are used by the same patient for titration purposes and dose adjustment; hence, differentiation can have an impact on the accurate dosing of the finished product.

The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards where applicable, except for the mixture of microcrystalline cellulose and guar gum, cherry flavour, and Opadry II clear for which in-house quality standards are proposed. There are no novel excipients used in the finished product formulation. Sodium polystyrene sulfonate is present as an excipient whereas current marketed medicinal products include it as active substance. The choice of excipients is based on the applicant’s experience with similar products for the USA market. To address MO, requesting a detailed justification of the choice of the excipients, a compatibility study was conducted demonstrating the compatibility of the formulation.

Acceptance limits for relevant functionally related characteristics are laid down for several excipients. Several tests for functionality related characteristics are included in the specifications of the excipients of the tablets. In response to the MO, related to the composition of the finished product, the relevance of and a justification for the functional related characteristics (FRCs) tested and their limits were provided. The absence of control of other FRC parameters, mentioned in Ph. Eur. monographs has been adequately justified. Certificates of analysis have been provided for excipients from exemplary suppliers and from finished product manufacturer.

The non-pharmacopoeial excipients (mixture of microcrystalline cellulose and guar gum, cherry flavour and Opadry II clear) are controlled according to in-house specifications. An identification test using IR method is employed in those specifications. Analytical procedures in conformance with current Ph. Eur. and in-house methods are used to control non-compendial excipients. In-house methods are sufficiently described and validated. Certificates of analysis have been provided for all excipients from their suppliers and from drug product manufacturer. Information on non-compendial excipients used in the manufacturing of the applied products is acceptable. Moreover, a declaration confirming compliance with regulation EC no. 1334/2008 for cherry flavour has been presented.

The mixture of microcrystalline cellulose and guar gum is a co-processed excipient, its components comply with the respective Ph. Eur. monographs. Its supplier has been qualified and compliance with GMP for excipients has been verified. During the procedure, in response to MO, requesting to improve the differentiation among the tablet, lithol rubine BK (E 180), an azo colorant which is also an allergen, was removed from the 40 mg strength for safety reasons, also taking into consideration the paediatric target population and the length of treatment. Through a risk assessment and the provision of batch data (including comparison of the average dissolution results), it has been demonstrated that the change does not impact the CQAs and hence the efficacy of the product. No excipients of human or animal origin and no novel excipients are used for the manufacture of the finished product.

The pharmaceutical development includes elements of Quality by Design (QbD).

The goal of the pharmaceutical development was to develop a prolonged-release chewable tablet formulation designed to provide a fast onset of action and a sustained release for up to 12 hours suitable for the selected paediatric target population (6 years and above).

The quality target product profile (QTPP) is summarised in table 1.

Table 1: QTPP of Tuzulby prolonged-release chewable tablets

QTPP Elements	**Target**
Dosage form	Chewable Tablet
Route of administration	Oral
Dosage strength	20 mg, 30 mg and 40 mg
Pharmacokinetics	• Comparable *in vivo* profile (established via relative bioavailability assessment) of a single ER dose compared to the equivalent dose of the reference product (Immediate Release (IR) Chewable Tablet) • 90% confidence interval of the pharmacokinetic (PK) parameters, AUC_{0-t} and $AUC_{0-\infty}$, within 80-125% limit to the reference product
Stability	At least 24-month shelf-life at room temperature
Drug Product Quality Attributes	Identification, Assay, Degradation Products, Drug Release and Residual Solvents: Must meet compendial and/or other applicable (quality) standards (identity, assay, purity and quality).
Container Closure System	Container closure system qualified as suitable for this drug product: HDPE white container with CRC cap
Administration/ Labeling	• Pediatric (6 years and above), start at 20 mg once daily in the morning. Dose can be titrated weekly in increments of 10-20 mg. Doses greater than 60 mg are not recommended • Not recommended for patients under 6 years of age
Alternative methods of administration	None

The formulation has been evaluated through the use of risk assessment to identify the critical product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations as well as on the experience from formulation development.

The critical quality attributes identified are summarised below: appearance, odour, identification, assay, degradation products, drug release and residual solvents.

To better reflect the release of the active substance, the pharmaceutical dosage form was changed to "prolonged-release chewable tablet".

The release of the active is also reflected in the SmPC with the following text: "*Tuzulby prolonged-release chewable tablets consists of an immediate release component (30% of the dose, which ensures rapid onset of action) and a prolonged-release component (70% of the dose, which is designed to maintain therapeutic plasma levels over an extended period), it is designed to deliver therapeutic plasma levels for a period of approximately 8 hours following administration*".

A major objection (MO) which was raised in relation to the impact of chewing versus swallowing the tablet on the release of the active substance is resolved by comparison of *in vivo* results for tablets chewed vs tablet swallowed (study C11-0082). Additionally, the results for F2 statistic comparison confirm similarity of *in vitro* dissolution profiles. Even though the *in vivo* study had demonstrated that there are no safety or efficacy concerns associated with swallowing the whole tablet, the pharmaceutical form includes the term 'chewable' because the product is intended to be marketed to improve acceptability for children who are not able or are unwilling to swallow. The product fulfils the unmet medical need of an age-appropriate formulation to overcome swallowing difficulties in children and reduce the risk of choking.

MO regarding acceptability of the chewable tablets (palatability, dimension and compatibility with food) for the intended paediatric target population, with particular focus on the youngest patients (6 years old) has been adequately addressed by analysing the available clinical data which demonstrate that the pharmaceutical form is well accepted by the intended patient population. The applicant has also justified the absence of a 10 mg formulation based on the target patient population.

The reference medicinal product of Tuzulby prolonged-release chewable tablets (20, 30 and 40 mg) is Ritalin 10 mg. Tuzulby however is presented with a different pharmaceutical form and strengths (i.e. quantitative change to the active substance). The EU pivotal bioequivalence study confirms equivalence with the reference product. The test product used in the clinical study with significant clinical data had only a small difference in composition compared to the formulation proposed for marketing (lithol rubine BK (E 180) was removed from the 40 mg strength). A biowaiver for the strengths 20 mg, 30 mg, has been granted as the 20, 30 and 40 mg doses have been demonstrated to be dose proportional and meeting the general requirements according to Guideline on Investigation on Bioequivalence (CHMP/EWP/QWP/1401/98 Rev 01). A MO was raised in relation to some discrepancies in the naming of the clinical batches described in the pharmaceutical development section and those included in the batch analysis data. The MO has been resolved by providing a tabular description of the batches used for the EU and USA market (supportive of the EU application).

The choice of the QC dissolution method has been adequately justified based on the active substance solubility, in order to ensure sink conditions without impacting the release profile of the active substance. In response to MO, during the procedure, the dissolution limits and time points have been amended to fully cover the release profile of the formulation.

The discriminatory power of the dissolution method has been demonstrated.

The manufacturing process of the product does not influence the physicochemical properties of the active substance. The choice of process has been justified. Critical process parameters, relevant for

subsequent process validation are identified. Process parameter ranges are satisfactorily investigated/supported by pharmaceutical development. The process compensates for the variability in the material attributes. The identification of the critical process parameters was performed on an empirical basis and through systematic evaluation using risk assessment methodologies. The manufacturing process was based mainly on previous knowledge on similar products.

The finished product is packed in wide-mouth, round, white HDPE bottles of 60 mL nominal capacity, safely closed with 33 mm child resistant closure cap induction liner including a 2 g silica gel desiccant HDPE canister. The HDPE bottles are subsequently packed into cardboard boxes.

Appropriate specifications and quality control information for the proposed container closure system have been provided. Compliance for primary packaging material with the current EU regulations on plastic materials and articles intended to come into contact with food has been presented.

To minimise the risk for accidental intake of the medicinal product by children, the product is packaged in a child-resistant container/closure. Compliance with ISO 8317:2015 has been declared for the child resistant screw cap. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured at one manufacturer. The manufacturing process consists of eight main steps.

The level of details of a description of the manufacturing process is adequate. Critical steps are clearly defined and manufacturing process parameters ensuring appropriate control are specified. Information is provided on process parameters considered as critical or non-critical.

Control tests during all steps of the manufacturing process of the finished product have been described. Analytical methods used are described and validated sufficiently. In-process controls for packaging step are described adequately.

The manufacturing process is a non-standard process and satisfactory process validation data for three consecutive production scale batches have been provided in the registration dossier. For all intermediates, specific holding times and specifications were defined.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form: description, identification (UPLC, UV-PDA), uniformity of dosage units (in house, Ph. Eur.), microbial limits (Ph. Eur.), assay (UPLC), dissolution (HPLC), impurities (UPLC), hardness (Ph. Eur), moisture content (loss on drying, Ph. Eur.), nitrosamine impurities (LC-MS in-house).

Finished product specification covers adequate parameters for the proposed pharmaceutical form. The determination of appearance has been updated in line with the changes implemented to distinguish the three strengths.

The dissolution specification limits have been updated to reflect the resolution of the MO.

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

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed, as requested by the CHMP (MO), considering all suspected and actual root causes in line with the “Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products” (EMA/409815/2020) and the “Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products” (EMA/369136/2020). Based on the information provided, two specified nitrosamine impurities and total nitrosamines are controlled at the level of the finished product.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Forced degradation studies (acid, base, oxidation, UV and dry heat) showed that the analytical methods for assay and for the determination of related substances are stability indicating. The major degradant observed was Impurity-1 in acid, base and dry heat conditions.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

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

Stability of the product

Stability data from two pilot scale batches and two laboratory scale batches of finished product of strengths 20 mg and 40 mg under long term conditions and, under intermediate conditions, and for under accelerated conditions according to the ICH guidelines were provided. The pilot batches were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, related substances and dissolution. The analytical procedures used are stability indicating. No significant changes have been observed for tested parameters. However, noting the results of accelerated stability studies and the presence of desiccant in the container, the storage conditions have been updated to read ‘Keep the bottle tightly closed to protect from moisture’. The statement “This product does not require any special storage conditions” was revised to read “This medicinal product does not require any special temperature storage conditions”.

Tuzulby 30 mg prolonged-release chewable tablets were not included in the stability studies as a bracketing approach has been applied and justified in line with the Note for Guidance on Bracketing and Matrixing designs for Stability Testing of Drug Substances and Drug Products (CPMP/ICH/4104/00) a reduced design (bracketing design); this is acceptable.

The photostability studies have been performed on samples of each strength and show that the product is not light sensitive.

In-use stability studies and stress testing have been performed on one batch of the 20 mg and 40 mg strengths. In the in-use stability studies all the results comply with the proposed specifications.

The proposed shelf-life of 3 years and storage condition (This medicinal product does not require any special temperature storage conditions. Keep the bottle tightly closed in order to protect from moisture), as stated in SmPC (sections 6.3 and 6.4) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.1.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product is now presented in a satisfactory manner.

Several major objections were raised during the procedure, pertaining to: appearance of the tablet (MO), justification of the choice of the excipients (MO), impact of chewing versus swallowing the tablet on the release of the active substance (MO), acceptability of the chewable tablets for the intended paediatric target population (MO), discrepancies in the nomenclature of the declared clinical batches (MO), dissolution limits and time points (MO) and nitrosamine risk-assessment (MO). These MOs have been resolved adequately by provision of additional data by the applicant and updating of the relevant MA dossier sections.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.1.6. Recommendations for future quality development

Not applicable.

2.2. Non-clinical aspects

2.2.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Pharmacodynamic, pharmacokinetic and toxicological properties of methylphenidate are well known. As methylphenidate is a widely used, well-known active substance, the applicant has not provided additional studies, and further studies are not required. The overview based on literature review is, thus, appropriate. The non-clinical aspects of the Summary of Product Characteristics (SmPC) are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable. Therefore, the CHMP agreed that no further non-clinical studies are required.

2.2.2. Ecotoxicity/environmental risk assessment

The applicant submitted an environmental risk assessment (ERA). According to the calculation, the PEC value was 0.3 mcg/l and was above the action limit. Therefore, the applicant performed a refinement of Fpen based on consumption data. The applicant presented a detailed consumption data (as kg of methylphenidate hydrochloride sold during the last years) in the countries where the product is intended to be commercialised. The PEC values were calculated, and they were far below the action limit. The concentration was below the recommended value according to the EMA guideline (0.01 µg/L)

for Bulgaria, Croatia, Czech Republic, Greece, Hungary, Italy, Latvia, Lithuania, Poland, Romania, Serbia and Slovakia. Therefore, a Phase II environmental fate and effect analysis as described in the Guideline on the environmental risk assessment of medicinal products for human use" Doc. Ref. EMEA/CHMP/SWP/4447/00 corr* 2. (2006) should not be performed for these countries. Although the concentration was above the action limit for Austria, Belgium, Denmark, Estonia, Finland, France, Germany, Ireland, Luxembourg, Netherlands, Norway, Portugal, Slovenia, Spain and Sweden, it could be agreed that, based on the published available information, methylphenidate hydrochloride is not expected to pose a risk to the environment. Moreover, it is acknowledged that no ecotoxicological date are available to provide a predicted no effect concentration (PNEC) which precluded calculation of PNEC. Moreover, it could be agreed that, since the product is intended to be marketed in European countries where the reference product was marketed since many years, no increase of the exposure to methylphenidate hydrochloride to the environment is expected after Methylphenidate 20 mg, 30 mg and 40 mg prolonged-release chewable tablets marketing. Furthermore, the potential for bioaccumulation in the environment seems to be low and methylphenidate is not expected to accumulate significantly in organisms or sediments. However, the applicant is reminded of their responsibility to complement ERA in accordance with the recently revised Guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr).

2.2.3. Discussion on non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of methylphenidate are well known. As methylphenidate is a widely used, well-known active substance, the applicant has not provided additional studies, and further studies are not required. Overview based on literature review is, thus, appropriate.

2.2.4. Conclusion on the non-clinical aspects

Tuzulby is approvable from a non-clinical perspective.

2.3. Clinical aspects

2.3.1. Introduction

This is a hybrid application for Tuzulby containing methylphenidate hydrochloride. The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of methylphenidate based on published literature. The SmPC is in line with the SmPC of the reference product.

CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) and Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1) in their current version, are of particular relevance.

To support the marketing authorisation application the applicant performed dissolution studies for MPR chewable tablets in three different pH (0.1 M HCl, pH 4.5 and pH 6.8) and rotation conditions (50, 75 or 100 rpm). An f2 calculation for the different strengths was >50, which supports the strength waiver. Dissolution study with the reference product Ritalin showed a very rapid *in vitro* dissolution in all

dissolution media tested (>85% within 15 minutes).

Dissolution studies in alcohol containing media showed similar profiles of MPH PR oral suspension in up to and including 10% alcohol, elevation in drug release was observed at 20% alcohol.

As per the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1), *for multiple unit formulations of a medicinal product with several strengths, it is sufficient to conduct the studies listed in section 6.1.1 only at the highest/most sensitive strength if the compositions of the strengths are proportional, the formulations contain identical beads or pellets (and these are produced by the same manufacturing process) and the dissolution profiles are similar.* Therefore, BE studies for other strengths are not required.

GCP aspect

The clinical trials were performed in accordance with good clinical practice (GCP) as claimed by the applicant.

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

Table 2 Dissolution studies

Protocol number	Title	Country
2021-5128	Single-Dose, Dose Proportionality Study of Methylphenidate HCl Extended-Release Chewable Tablets under Fed Conditions	Canada
2021-5129	A Single-Dose, Comparative Bioavailability Study of Methylphenidate HCl 40 mg Extended-Release Chewable Tablets and Ritalin® 10 mg Tablets under Fed Conditions	Canada
2021-5130	A Single-Dose, Comparative Bioavailability Study of Methylphenidate HCl 5 mg/mL	Canada

These clinical studies were carried out in compliance with the GCP as are detailed in the Guidelines (ICH E6), the local regulatory requirements and statements included in the Helsinki Declaration.

Exemption

The applicant performed dissolution studies for MPR chewable tablets in three different pH (0.1 M HCl, pH 4.5 and pH 6.8) and rotation conditions (50, 75 or 100 rpm). An f2 calculation for the different strengths was >50, which supports the strength waiver. Dissolution study with the reference product Ritalin showed a very rapid *in vitro* dissolution in all dissolution media tested (>85% within 15 minutes).
Dissolution studies in alcohol containing media showed similar profiles of MPH PR oral suspension in up to and including 10% alcohol, elevation in drug release was observed at 20% alcohol.

As per Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1), *for multiple unit formulations of a medicinal product with several strengths, it is sufficient to conduct the studies listed in section 6.1.1 only at the highest/most sensitive strength if the compositions of the strengths are proportional, the formulations contain identical beads or pellets (and these are produced by the same manufacturing process) and the dissolution profiles are similar.* Therefore, BE studies for other strengths are not required.

Tabular overview of clinical studies

To support the application, the applicant has submitted pivotal bioequivalence study with the EU reference medicinal product (2021-5129), 1 dose proportionality study (2021-5128), 2 supportive US bioavailability studies (509-0238 and 2012-2950), additional BE study (2021-5130), 1 supportive single dose PK study in the target population (NWP06-PPK-101), 1 study evaluating tablet and oral suspension formulation BA (C11-0082), 2 Phase 3 efficacy and safety studies (significant clinical study NWP09-ADHD-300 and study NWP06-ADD-100) and MS study evaluating PD properties of methylphenidate hydrochloride in an oral suspension and a chewable tablet formulation versus the reference medicinal product.

However, since an oral formulation suspension was withdrawn during the procedure, only studies conducted with chewable tablets formulation were considered relevant for the MAA.

Table 3. Tabular overview of clinical studies

EU studies:

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Drug Products; Dosage Regimen and Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	2021-5129	5.3.1.2	Primary objective: To to evaluate *the comparative* bioavailability between Methylphenidate Hydrochloride HCl 40 mg extended-release chewable tablets manufactured by Tris Pharma, Inc., USA administered as a single dose at 0-hour and Ritalin® 10 mg tablets manufactured by Novartis Pharma GmbH, Germany administered as a single-dose at 0 and 6 hours in healthy subjects under fed conditions. Secondary objective: To evaluate the safety and tolerability of the study treatments.	Open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, comparative bioequivalence study	Methylphenidate HCl 40 mg ER chewable tablets single, oral dose at 0 and 6 hours (PO)	24 (23 completed)	Healthy Subjects	A single, oral dose twice in each of the two periods, separated by a 7-day washout between drug administrations	Complete; Full Report
BE	2021-5130	5.3.1.2	The primary objective of this study was to evaluate the comparative bioavailability between Methylphenidate Hydrochloride (HCl) 25 mg/5 mL extended-release (ER) oral suspension from Tris Pharma, Inc., USA administered as a single dose at 0 hour and Ritalin® 10 mg tablets from Novartis Pharma GmbH, Germany administered as a single-dose at 0- and 6-hours in healthy subjects under fed conditions. The secondary objective of this study was to evaluate the safety and tolerability of the study treatments.	This was an Open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, comparative bioequivalence study	Methylphenidate HCl 5 mg/mL oral suspension single oral dose (oral suspension) Ritalin® 10 mg tablets, 30 mg (3 × 10 mg tablets) single oral dose at 0 and 6 hours (Total dose = 60 mg)	24 (23 completed)	Healthy Subjects	A single, oral dose in each of the two periods separated by a 7-day washout between drug administrations	Complete; Full Report
BE	2021-5128	5.3.1.2	Primary Objective: to evaluate the dose proportionality between 20 mg, 30 mg, and 40 mg doses of Methylphenidate HCl ER chewable tablets manufactured by Tris Pharma Inc., USA after a single-dose in healthy subjects under fed conditions Secondary Objective: to evaluate the safety and tolerability of the study treatments	Open-label, single-dose, randomized, three-period, three-treatment, three-sequence, crossover, dose proportionality study	Methylphenidate HC1 ER chewable tablets single, oral dose (20 mg, 30 mg, and 40 mg)	24 (23 completed)	Healthy Subjects	A single, oral dose in each of the three periods separated by a 7-day washout between drug administrations	Complete; Full Report

Supportive US studies:

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Drug Products; Dosage Regimen and Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I PK BA	S09-0238	5.3.1.2	To compare the bioavailability of a 60 mg dose of NWP06 under fasting and fed conditions with two 30 mg doses of Methylin® Oral Solution under fasting conditions.	Single-dose, randomized, open-label, 3-way crossover, 1 comparator	A: 60 mg oral dose of NWP06 (fed) B: 60 mg oral dose of NWP06 (fasted) C: Methylin Oral Sol. 60 mg (2 30 mg) oral dose (fasted)	30 enrolled, 28 completed	Healthy adults 19 to 68 years 25 males, 5 females	Single-dose	Complete; Full Report
Phase I PK BA	2012-2950	5.3.1.2	To evaluate the relative BA of the intended commercial formulation of methylphenidate HCl ERCT (fasted) versus Methylin® Chewable Tablets (IR; fasted) and to assess the effect of food on the methylphenidate HCl ERCT formulation when administered with food.	A single-dose, 3-way crossover relative BA study conducted in 33 healthy adult subjects	Test Product A Methylphenidate HCl extended release 40 mg chewable tablets and Methylin™ 10 mg chewable tablets (immediate release) - Fasting Test Product B Methylphenidat HCl extended release 40 mg chewable tablets- Fasting and Fed Reference Product Two equal doses of 20 mg (2 x 10 mg/tablet), 6 hours apart (total dose 40 mg), first dose administered under fasting conditions	33 Enrolled; 31 Completed	Non smoking, male and female volunteers from18 to 55 years of age, with a BMI from 18.0 to 30.0 kg/m2 and weight ≥ 50 kg, who were judged to be healthy based on a medical history, ECG, laboratory evaluation, physical examinatio n, and vital signs measureme nts	Single Dose	Complete; Full Report
Phase I PK	NWP06-PPK-101	5.3.3.2	To evaluate the single dose PK of orally administered NWP06 in children and adolescents with ADHD.	Single-dose, open-label	20 or 60 mg oral dose of NWP06	14 enrolled, 14 completed	Children and adolescent s with ADHD 6 to 17 years 11 males, 3 females	Single-dose	Complete; Full Report
Phase III	NWP09-ADHD-300	5.3.5.1	To evaluate the efficacy of methylphenidate HCl ERCT in pediatric patients with attention deficit hyperactivity disorder (ADHD) in a laboratory classroom. This study enrolled 90 subjects (ages 6 to12 years) with ADHD into an open-label dose optimization period, followed by a randomized parallel group, double-blind treatment period. Efficacy was measured using the Swanson, Kotkin, Agler, M-Flynn, and Pelham rating scale (SKAMP) and permanent product measures of performance (PERMP) at pre-dose and 0.75, 2, 4, 8, 10, 12 and 13 hours post dose.	A multicenter, dose optimized, double-blind, randomized, placebo-controlled Phase 3 study	Six-week Openlabel Dose Optimization Period NWP09 20-60 mg/day taken orally once daily in the morning before 10:00 am One-week Doubleblind Treatment Period Optimal dose of NWP09 from the Open-label Dose Optimization Period (20-60 mg/day) taken orally once daily in the morning before 10:00 am	ITT= 85 43 Placebo/ 42 Active	Males or females, ages 6 through 12 years, with a diagnosis of ADHD and need for pharmacol ogic treatment for their condition	7 weeks	Complete; Full Report

Phase I PK BA	C11-0082	5.3.1.1	To evaluate methylphenidate HCl ERCT tablet formulation (Prototype 1) (administered chewed and swallowed whole) versus methylphenidate HCl 25 mg/ 5 mL ER oral suspension under fasted conditions.	A pilot, single-dose, 3-way cross-over relative BA study conducted in 12 healthy adult subjects	Test product A 1 x 40 mg ER chewable tablet given as a single dose chewed for 20 seconds) followed by 240 mL (8 fluid ounces) of room temperature water after an overnight fast of at least 10 hours Test product B 1 x 40 mg ER chewable tablet given as a single dose (swallowed whole) with approximately 240 mL (8 fluid ounces) of room temperature water after an overnight fast of at least 10 hours Reference product 1 x 8 mL ER suspension given as a single dose followed by 240 mL (8 fluid ounces) of room temperature water after an overnight fast of at least 10 hours	12 Enrolled; 9 Completed	Healthy male and female volunteers. All subjects were to have an acceptable medical history, laboratory evaluation, ECG and physical examinatio n prior to study entry	Single dose	Complete; Full Report
					(Methylphenidate 25 mg/5 mL ER powder for oral suspension				
Phase III	NWP06-ADD-100	5.3.5.1	To evaluate the effect of NWP06 vs placebo on the signs and symptoms of ADHD in children.	Randomized, double-blind, placebo controlled, crossover	20 to 60 mg daily oral doses of NWP06	45 enrolled, 39 completed	Children with ADHD 6 to 12 years 32 males, 12 females	Multipledose 5 to 7 weeks	Complete; Full Report

NWP06 = the intended commercial formulation of Methylphenidate HCl Extended-Release Powder for Oral Suspension (25 mg/5 mL)
MPH = methylphenidate; ER = extended-release; IR = immediate-release; ADHD = attention deficit hyperactivity disorder;
PK = pharmacokinetics; BA = bioavailability

Modelling & Simulation:

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Drug Products; Dosage Regimen and Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Modelling & Simulation	NA	5.3.3.5	Model & simulation evaluation of the pharmacokinetic and pharmacodynamic (SKAMP) properties of methylphenidate hydrochloride in an oral suspension (ER) and a chewable tablet (ER) formulation versus Ritalin® tablets (IR) in pediatrics	Model & simulation evaluation	Methylphenidate HCl oral suspension Methylphenidate HCl chewable tablets Ritalin tablets	NA	Healthy subjects and patients	NA	Complete; Full Report

2.3.2. Clinical pharmacology

The applicant withdrew the 5 mg/ml powder for prolonged release oral suspension presentation; however, clinical pharmacology studies regarding this formulation are presented for completeness of supportive data.

2.3.2.1. Pharmacokinetics

Study 2021-5129 (LESVIMETHYL/21/BQ-9): A Single-Dose, Comparative Bioavailability Study of Methylphenidate HCl 40 mg Extended-Release Chewable Tablets and Ritalin® 10 mg Tablets under Fed Conditions

Methods

- Study design

Study 2021-5129 was an open-label, single-dose, randomised, two-period, two-treatment, two sequence, crossover, comparative bioequivalence study designed to evaluate the bioavailability of methylphenidate, between the test and reference product in healthy male and female subjects under fed conditions.

Each subject was administered an oral dose of either treatment A or treatment B according to the randomisation scheme 30 minutes after the start of a high-fat, high calorie breakfast. Treatment A consisted of a single 40 mg dose (1 ER chewable tablet) of the Drug Product 1 and treatment B consisted of a 20 mg dose (2 × 10 mg tablets) of the Drug Product 2 administered at 0 and 6 hours (Total dose = 40 mg). Concentrations of *d*-methylphenidate and *l*-methylphenidate were measured in plasma from plasma samples collected over a 24-hour interval after dosing. Pharmacokinetic blood samples were collected prior to dosing (0-hour) and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 4.5, 5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 16, and 24 hours after drug administration, totalling 21 samples in each period. The pre-dose samples were collected within 120 minutes of dosing. The PK parameters, AUC0-2, AUC0-6, AUCt, AUCinf, Cmax, Tmax, Kel, and Thalf were estimated for *d*-methylphenidate using a noncompartmental approach.

Administration of a single, oral dose of either the test or reference product in each period was separated by a washout of 7 days between drug administrations.

- Test and reference products

Test product:

Methylphenidate HCl 40 mg ER chewable tablets
Lot No: 38643
Manufacturer: Tris Pharma, Inc., USA
Dose: 40 mg tablets

Reference product:

Ritalin® 10 mg tablets
Batch No: BVV23
Manufacturer: Novartis Pharma GmbH, Germany
Country of Purchase: Latvia
Marketing Authorisation Holder: SIA Novartis Baltics, Latvia
Dose: 20 mg (2 × 10 mg tablets) at 0 and 6 hours.

- Population(s) studied

The study population included non-smoking, male and female volunteers from 18 to 55 years of age, with a body mass index ≥18.5 and ≤30 kg/m2 and weight >50 kg. Volunteers were assessed as healthy based on a screening evaluation, medical history, 12-lead electrocardiogram, laboratory evaluation (haematology, biochemistry, serology, and urinalysis), physical examination, and vital signs measurements (blood pressure, pulse rate, respiration rate, and temperature). At screening, eligible

subjects did not test positive for urine cotinine or urine drugs of abuse and female subjects had negative test results for serum human chorionic gonadotropin.

Twenty-four subjects were randomised and enrolled into the study. One subject (4.2% of subjects dosed) discontinued from the study prior to check-in of period 2 due to personal reason. Accordingly, 23 subjects received a single dose of the drug product 1 (as administered in treatment A) and 24 subjects received a single dose of the drug product 2 (as administered in treatment B).

- Analytical methods

A validation was performed to approve reliable detection of analytes during clinical studies –2021-5129, 2021-5130 and 2021-5128 - Validation of a liquid chromatographic tandem mass spectrometric method for the determination of d-threo-(2R,2'R)-methylphenidate and l-threo-(2S,2'S)-methylphenidate in human plasma - PMRI-1904-21.

The method was found to be reliable for both enantiomers in the range of 0.200 to 30.0 ng/mL. During validation following parameters were addressed and met the acceptance criteria for d-threo-(2R,2'R)-methylphenidate and l-threo-(2S,2'S)-methylphenidate: intra-day precision and accuracy, inter-day precision and accuracy, stability in biological matrix (after 3 freeze-thaw at -25 ± 10 °C, after 4.5 hours at room temperature (RT), after 18.75 hours refrigerated at 5 ± 3 °C, after 2 hours in RT in whole blood and after 2 hours in ice-water bath in whole blood), stability of processed samples (for 46.50 hours and 98.25 hours in autosampler in 5 °C, for 2.00 hours at RT), stability in solutions (for 6.25 hours in short term stock solution at RT and for 6.25 hours in working solution at RT). The accuracy and precision for 2x and 5x dilution for both enantiomers were approved. No carryover and matrix effects were seen. No interference in the presence of haemoglobin and lipemic particles were notable. No interference was found for both enantiomers detection during concomitant medication and contraceptives administration. Long term stability of d-threo-(2R,2'R)-methylphenidate (R(-)-methylphenidate) and l-threo-(2S,2'S)-methylphenidate (S(+)-methylphenidate) in human plasma at -25 ± 10 °C was approved for 46 days. Long term stock solution stability at 5 ± 3 °C was demonstrated for 10 days for both enantiomers.

All parameters recommended for analytical method validation using chromatographic tandem mass spectrometric method were addressed (EMEA/CHMP/EWP/192217/2009) and met the acceptance criteria.

Bioanalytical report – Determination of d-methylphenidate and l-methylphenidate in human plasma - BSAP-2021-5129.

Human plasma samples (n=1974) with K2EDTA as anticoagulant were collected during 2021-5129 clinical study, received in a good condition and stored within long term stability conditions. 987 of them were analysed for d-methylphenidate and l-methylphenidate in human plasma. The precision and accuracy were acceptable for all batches. All samples were tested within the stability window. Incurred sample reanalysis (ISR) was performed for 10.5 % of the samples. The ISR is considered acceptable as 99.0% of the repeated results for d-methylphenidate and 100.0% of the repeated results for l-methylphenidate were within the acceptance criteria of 20%. Most of the samples were within the calibration range of the curve. The bioanalysis is acceptable.

- Pharmacokinetic variables

AUC0-2: The area under the analyte concentration versus time curve, from time zero (0) to 2 hours, as calculated by the linear up/log down variant of the trapezoidal method.

AUC0-6: The area under the analyte concentration versus time curve, from time zero (0) to 6 hours, as calculated by the linear up/log down variant of the trapezoidal method.

AUCt: The area under the analyte concentration versus time curve, from time zero (0) to the time of the last measurable analyte concentration (t), as calculated by the linear up/log down variant of the trapezoidal method.

AUCinf: The area under the analyte concentration versus time curve from time zero to infinity. AUCinf = AUCt + Ct/Kel, where Ct is the last measurable analyte concentration.

Cmax: Maximum measured analyte concentration over the sampling period.

Tmax: Time of the maximum measured analyte concentration over the sampling period.

Kel: The apparent first-order elimination rate constant.

Thalf: The apparent elimination half-life.

- Statistical methods

Descriptive statistics for the PK parameters of d-methylphenidate were calculated and included number of observations, arithmetic mean, standard deviation (SD), geometric mean (where applicable), coefficient of variation (CV), median, minimum, and maximum.

Statistical analysis was performed on quality assured data from subjects in the statistical dataset.

The PROC GLM procedure from SAS® (version 9.4) was used.

Analysis of variance (ANOVA) was performed on log-transformed plasma d-methylphenidate AUC0-2, AUC0-6, AUCt, AUCinf, and Cmax parameters. The significance (5% significance level) of the sequence, period, treatment, and subject(sequence) effects (all fixed) were tested.

Using the same statistical model, the least-squares-means (LSM), the differences between the treatments LSM, and the corresponding standard errors of these differences were estimated for log-transformed AUC0-2, AUC0-6, AUCt, AUCinf, and Cmax parameters. Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals (CIs) were calculated.

In-house data indicated a coefficient of variation (CV) for methylphenidate Cmax of approximately 20%. Assuming a 20% intra-subject variability and a difference between the treatment means of 5% or less, the necessary sample size for an 80% probability of the 90% CI of the treatment means ratio to be within the 80.00 to 125.00% range is estimated to be 20 subjects. Four extra subjects were included into the study to account for potential dropouts. Therefore, 24 subjects were enrolled into this study.

Results

Table 4. Summary of Study Results Based on Plasma d-Methylphenidate Levels

Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_t	**A**	23	133.197 (34)	126.357	**A vs B**	93.69	90.01 - 97.52	8
*(hr*ng/mL)*	**B**	23	141.773 (33)	134.872				
AUC_{inf}	**A**	23	138.240 (35)	130.824	**A vs B**	94.86	91.32 - 98.54	8
*(hr*ng/mL)*	**B**	23	145.081 (33)	137.908				
C_{max}	**A**	23	14.935 (29)	14.359	**A vs B**	89.28	83.57 - 95.39	13
(ng/mL)	**B**	23	16.591 (26)	16.083				
AUC_{0-2}	**A**	23	11.439 (43)	10.317	**A vs B**	75.47	58.74 - 96.96	53
*(hr*ng/mL)*	**B**	23	15.182 (43)	13.671				
AUC_{0-6}	**A**	23	62.885 (29)	60.519	**A vs B**	120.93	111.02 - 131.73	17
*(hr*ng/mL)*	**B**	23	52.269 (30)	50.044				

Treatment A - Methylphenidate HCl 40 mg extended-release chewable tablets, Lot No.: 38643 (Tris Pharma Inc.)
Treatment B - Ritalin® (Methylphenidate hydrochloride) 10 mg tablets, Batch No.: BVV23 (Novartis Pharma GmbH)

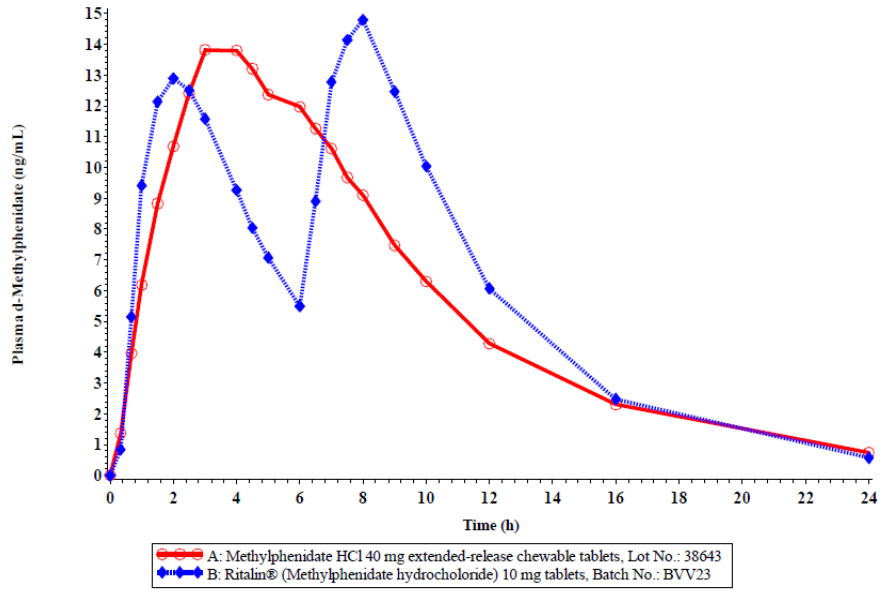


Figure 2. Mean Plasma d-Methylphenidate Concentration-Time Profile Linear Scale (A: n=23 / B: n=23)

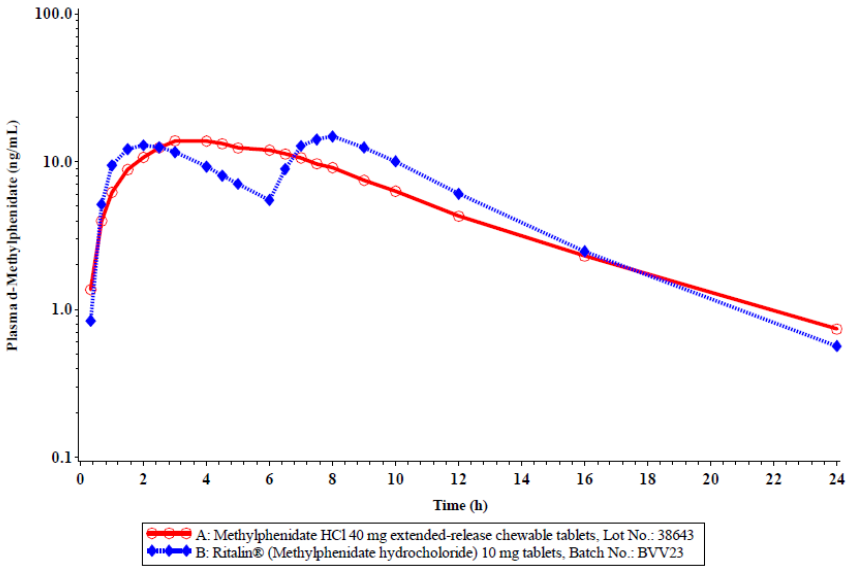


Figure 3. Mean Plasma d-Methylphenidate Concentration-Time Profile Semi-Log Scale (A: n = 23 / B: n = 23)

The 90% CI of the relative mean plasma d-methylphenidate AUCt and AUC inf and Cmax of test to reference products were between 80.00 and 125.00%. However, the 90% CI of the relative mean plasma d-methylphenidate AUC 0-2 and AUC 0-6 of test to reference products were not between 80.00 and 125.00%.

A significant treatment effect was detected by ANOVA for AUCt, (p<0.0107), AUCinf (p=<0.0266), AUC0-6 (p=<0.0009), and Cmax (p=<0.0076) parameters.

Despite the statistical significance, the approximate 6% difference in the AUCt of the two formulations was believed to have no clinical importance, since the 90% CIs of the test to reference ratio was entirely contained within the 80.00-125.00% bioequivalence range. ANOVA did not detect a significant difference in any other PK parameters for sequence or period effects.

- Safety data

Twenty-four subjects were enrolled into this study, receiving a 40 mg dose of methylphenidate (40 mg or 20 mg dose of 2x10 mg tablet at 0 and 6 hrs) in each of two periods. One subject (4.2% of subjects dosed) discontinued from the study prior to period 2 check in dosing and was, thus, administered a single 40 mg dose in period 1.

Table 5. Summary of Treatment-Emergent Adverse Events

	Severity			Relation to the IMP		Intervention	
TRT	Mild	Moderate	Severe	Reasonably possible	Not reasonably possible	DT	NDT
A	8	0	0	7	1	1	1
B	11	0	0	10	1	0	3
Total	19	0	0	17	2	1	4

IMP, investigational medicinal product; Trt, treatment; NDT, non-drug therapy: DT drug therapy

Treatment A (Drug Product 1)	Methylphenidate HCl 40 mg extended-release chewable tablets, Lot No.: 38643 (Tris Pharma, Inc.)
Treatment B (Drug Product 2)	Ritalin® (Methylphenidate hydrochloride) 10 mg tablets, Batch No.: BVV23 (Novartis Pharma GmbH,)

A total of 11 subjects (45.8% of subjects dosed) experienced 19 TEAEs during the conduct of this study. Five subject (21.7%) receiving treatment A experienced 8 TEAE and 8 subjects (33.3%) receiving treatment B experienced 11 TEAEs.

Of the 19 TEAEs reported in this study, 7 events affecting 5 subjects (21.7%) were assessed as drug-related (reasonably possible in relation to the investigational medicinal product - IMP) occurred after administration of the treatment A, and 10 events affecting 7 subjects (29.2%) were assessed as drug-related (reasonably possible in relation to the IMP) occurred after administration of the treatment B.

Headache was the most frequent AE occurring in 5 subjects (6 headache events in 5 subjects [20.8%], all events were mild in severity, assessed as reasonably possible in relation to the IMP and resolved prior to the end of the study.

One (1) subject (4.2% of subjects dosed) reported 1 TEAE of tachycardia, and one (1) subject (4.2% of subjects dosed) reported 1 TEAE of palpitations. Both events were assessed as reasonably possible in relationship to the IMP, mild in severity, and resolved prior to the end of the study.

All of the TEAEs were mild in severity and resolved prior to the end of the study, except for one subject, advised to follow up with a family doctor. One (1) subject (4.2% of subjects dosed) experienced 1 clinically significant (CS) laboratory value at end-of-study. The TEAEs (anaemia) was mild in severity and assessed as reasonably possible in relationship to the IMP; the subject was advised to follow with family doctor. One (1) subject (4.2% of subjects dosed) experienced 1 CS laboratory value at end-of-study (Urinary tract infection), mild in severity and assessed as not reasonably possible in relationship to the IMP; it resolved at the end of the study.

Study 2021-5128: A Single-Dose, Dose Proportionality Study of Methylphenidate HCl Extended-Release Chewable Tablets under Fed Conditions

Methods

- Study design

This was an open-label, single-dose, randomised, three-period, three-treatment, three sequence, crossover, dose proportionality study designed to evaluate the dose proportionality of methylphenidate, between drug product 1, drug product 2, and drug product 3, in healthy male and female subjects under fed conditions.

Each subject was administered an oral dose of either treatment A, treatment B, or treatment C according to the randomisation scheme 30 minutes after the start of a high-fat, high-calorie breakfast.

Treatment A consisted of a single 20 mg dose (1 ER chewable tablet) of drug product 1, treatment B consisted of a 30 mg dose (1 ER chewable tablet) of drug product 2, and treatment C consisted of a 40 mg dose (1 ER chewable tablet) of drug product 3.

Concentrations of d-methylphenidate and l-methylphenidate were measured in plasma from plasma samples collected over a 24-hour interval after dosing.

The PK parameters, AUCt, AUCinf, Cmax, Tmax, Kel, Thalf, and dose-normalised AUCt, AUCinf, and Cmax (AUCt/D, AUCinf/D, and Cmax/D) were estimated for d-methylphenidate and l-methylphenidate using a noncompartmental approach.

- Test products

Treatment A (Drug Product 1): Methylphenidate HCl 20 mg extended-release chewable tablets

Lot No.: 28310
Manufacturer: Tris Pharma, Inc., USA
Dose: 20 mg (1 ER chewable tablet)

Treatment B (Drug Product 2): Methylphenidate HCl 30 mg extended-release chewable tablets
Lot No.: 28312
Manufacturer: Tris Pharma, Inc., USA
Dose: 30 mg (1 ER chewable tablet)
Mode of Administration: Oral under fed conditions

Treatment C (Drug Product 3):
Methylphenidate HCl 40 mg extended-release chewable tablets
Lot No.: 38643
Manufacturer: Tris Pharma, Inc., USA
Dose: 40 mg (1 ER chewable tablet)
Mode of Administration: Oral under fed conditions

- Population(s) studied

The study population included non-smoking male and female volunteers from 18 to 55 years of age, with a body mass index ⩾18.5 and ≤30 kg/m2 and weight >50 kg. Volunteers were assessed as healthy based on a screening evaluation, medical history, 12-lead electrocardiogram, laboratory evaluation (haematology, biochemistry, serology, and urinalysis), physical examination, and vital signs measurements (blood pressure, pulse rate, respiration rate, and temperature). At screening, eligible subjects did not test positive for urine cotinine or urine drugs of abuse and female subjects had negative test results for serum human chorionic gonadotropin.

Analytical methods

The determination of d- methylphenidate and l- methylphenidate in human plasma was performed according to the Validation Method PMRI-1904-21.

Bioanalytical report – Determination of d- methylphenidate and l- methylphenidate in human plasma - BSAP-2021-5128:

Human plasma samples (n=3220) with K2EDTA as anticoagulant were collected during 2021-5128 clinical study, received in a good condition and stored within long term stability conditions. 1610 of them were analysed for d- methylphenidate and l- methylphenidate in human plasma. The precision and accuracy were acceptable for 11 form 12 batches. All samples were tested within the stability window. ISR was performed for 8.5 % of the samples. The ISR is considered acceptable as 98.5% of the repeated results for d-methylphenidate and 100.0% of the repeated results for l-methylphenidate were within the acceptance criteria of 20%. The samples were within the calibration range of the curve. The bioanalysis is acceptable.

- Pharmacokinetic variables

The following PK parameters and observations were estimated for d-methylphenidate and l-methylphenidate:

AUCt: The area under the analyte concentration versus time curve, from time zero (0) to the time of the last measurable analyte concentration (t), as calculated by the linear up/log down variant of the trapezoidal method.

AUCt/D: Dose normalised area under the analyte concentration versus time curve, from time zero to

the time of the last measurable analyte concentration. AUCt/D = AUCt/Dose.

AUCinf: The area under the analyte concentration versus time curve from time zero to infinity.

AUCinf = AUCt + Ct/Kel, where Ct is the last measurable analyte concentration.

AUCinf/D: Dose normalised area under the analyte concentration versus time curve from time zero to infinity.AUCinf/D = AUCinf/Dose

Cmax: Maximum measured analyte concentration over the sampling period.

Cmax/D: Dose normalised maximum measured analyte concentration over the sampling period.

Cmax/D = Cmax/Dose.

Tmax: Time of the maximum measured analyte concentration over the sampling period.

Kel: The apparent first-order elimination rate constant.

Thalf: The apparent elimination half-life.

AUCt/AUCinf: The ratio of AUCt to AUCinf.

TLIN: Start time for linear regression.

LQCT: Last quantifiable concentration time.

R2: Coefficient of determination obtained from regression analysis.

- Statistical methods

Dose Proportionality Assessment:

The dose-proportionality analyses of the drug products in this study were exploratory. It was not the intent of this study to evaluate the results according to the equivalence criterion. The relationship between the logarithmically transformed PK response (AUCt, AUCinf, and Cmax) and the logarithm of dose was assessed by power model $\ln(PK)=\alpha + \beta \ln(D)$. The estimate of slope (β) of the regression line and corresponding 90% confidence intervals (CIs) were calculated.

Bioavailability Assessment:

Analysis of variance (ANOVA) (PROC GLM) was performed on dose-normalised log-transformed plasma d-methylphenidate and l-methylphenidate AUCt/D, AUCinf/D, and Cmax/D. Based on dose-normalised log-transformed data, ratios of the geometric means for treatments and the corresponding 90% CIs were calculated for AUCt/D, AUCinf/D, and Cmax/D parameters for the following comparisons:

• Treatment A versus Treatment C;

• Treatment B versus Treatment C; and

• Treatment A versus Treatment B.

These contrasts were estimated separately using only the data from the treatments involved in the comparison.

Based on the log-transformed parameters, the following criteria were used to evaluate the dose

proportionality between the drug products:

The 90% CI of the slope for plasma d-methylphenidate AUCt, AUCinf, and Cmax of the drug products should be between 1+ln(0.8)/ln(r) and 1+ln(1.25)/ln(r), where r is the ratio of the highest dose and the lowest dose.

Data from d-methylphenidate was the main criteria for dose proportionality evaluation. Data from l-methylphenidate was reported and presented as supportive data.

Results

Study population

24 subjects were planned for inclusion, randomised, and enrolled into the study. 23 subjects completed the study.

One subject discontinued from the study prior period 2 dosing due to treatment-emergent adverse events (TEAEs, decreased appetite, fatigue, depressed mood, and back pain).

24 subjects were included in the safety, PK and statistical analyses.

The subject who discontinued from the study accrued sufficient data to allow for the estimation of Cmax and AUC parameters from one period. Therefore, the subject's data was included in the PK and statistical analyses for d-methylphenidate and l-methylphenidate.

The measured concentrations of plasma l-methylphenidate were below the lower limit of quantitation or insufficient for the estimation of Cmax and AUC parameters in 13 subjects for period 1, 12 subjects for period 2, and 11 subjects for period 3. Accordingly, the affected data from these subjects was excluded from the PK and statistical analyses of l-methylphenidate.

Dose Proportionality Assessment:

The assessment of dose-proportionality for d-methylphenidate across treatments A, B, and C is presented in Table 5.

Table 6. Assessment of Dose Proportionality across *d*-Methylphenidate Doses of 20 mg, 30 mg, and 40 mg

Parameter	*Slope Estimate (90% CI)*	*Criteria*[a]	*Conclusion*[b]
AUC_t (hr*ng/mL)	0.9996(0.9610-1.0382)	(0.6781-1.3219)	Proportional
AUC_{inf} (hr*ng/mL)	0.9732(0.9318-1.0146)	(0.6781-1.3219)	Proportional
C_{max} (ng/mL)	1.0661(1.0139-1.1183)	(0.6781-1.3219)	Proportional

Power Model: $\ln(PK) = \ln(ß_0) + ß_1 * \ln(Dose) + e$, where PK is the pharmacokinetic parameter tested, $\ln(ß_0)$ is the y intercept, $ß_1$ is the slope, and e is the error term.

a: Criteria is 1+ln(0.8)/ln(r) and 1+ln(1.25)/ln(r), where r is the ratio of the highest dose and the lowest dose.
b: Dose proportionality will be concluded if the 90% CI for Slope is contained within criteria limits.

Bioavailability Assessment:

The summary results of the statistical analysis for the PK parameters of d-methylphenidate following treatments A, B, and C are presented in Tables 6 to 8.

Table 7. Summary of Study Results Based on Plasma *d*-Methylphenidate Levels – Treatment A vs. C

AUC_t/D	**A**	23	4.350 (49)	4.055	**A vs C**	99.91	96.90 - 103.01	6
*(hr*ng/mL/mg)*	**C**	23	4.388 (52)	4.058				
AUC_{inf}/D	**A**	23	5.058 (82)	4.410	**A vs C**	101.61	98.65 - 104.67	6
*(hr*ng/mL/mg)*	**C**	23	4.924 (76)	4.340				
C_{max}/D	**A**	23	0.426 (30)	0.411	**A vs C**	95.05	91.24 - 99.01	8
(ng/mL/mg)	**C**	23	0.451 (34)	0.433				

Treatment A (Drug Product 1): Methylphenidate HCl 20 mg extended-release chewable tablets, Lot No.: 28310 (Tris Pharma, Inc.

Treatment C (Drug Product 3): Methylphenidate HCl 40 mg extended-release chewable tablets, Lot No.: 38643 (Tris Pharma, Inc.

Table 8. Summary of Study Results Based on Plasma *d*-Methylphenidate Levels – Treatment B vs. C

Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_t/D	**B**	24	4.306 (45)	4.036	**B vs C**	98.75	95.94 - 101.64	6
*(hr*ng/mL/mg)*	**C**	23	4.388 (52)	4.087				
AUC_{inf}/D	**B**	24	4.779 (65)	4.314	**B vs C**	98.83	95.80 - 101.95	6
*(hr*ng/mL/mg)*	**C**	23	4.924 (76)	4.365				
C_{max}/D	**B**	24	0.423 (31)	0.407	**B vs C**	93.07	90.46 - 95.75	6
(ng/mL/mg)	**C**	23	0.451 (34)	0.437				

Treatment B (Drug Product 2): Methylphenidate HCl 30 mg extended-release chewable tablets, Lot No.: 28312 (Tris Pharma, Inc.

Treatment C (Drug Product 3): Methylphenidate HCl 40 mg extended-release chewable tablets, Lot No.: 38643 (Tris Pharma, Inc.

Table 9. Summary of Study Results Based on Plasma *d*-Methylphenidate Levels – Treatment A vs. B

Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_t/D	**A**	23	4.350 (49)	4.083	**A vs B**	101.17	98.75 - 103.66	5
*(hr*ng/mL/mg)*	**B**	24	4.306 (45)	4.036				
AUC_{inf}/D	**A**	23	5.058 (82)	4.435	**A vs B**	102.82	99.91 - 105.82	6
*(hr*ng/mL/mg)*	**B**	24	4.779 (65)	4.314				
C_{max}/D	**A**	23	0.426 (30)	0.415	**A vs B**	102.12	98.70 - 105.66	7
(ng/mL/mg)	**B**	24	0.423 (31)	0.407				

Treatment A (Drug Product 1): Methylphenidate HCl 20 mg extended-release chewable tablets, Lot No.: 28310 (Tris Pharma, Inc.)

Treatment B (Drug Product 2): Methylphenidate HCl 30 mg extended-release chewable tablets, Lot No.: 28312 (Tris Pharma, Inc.)

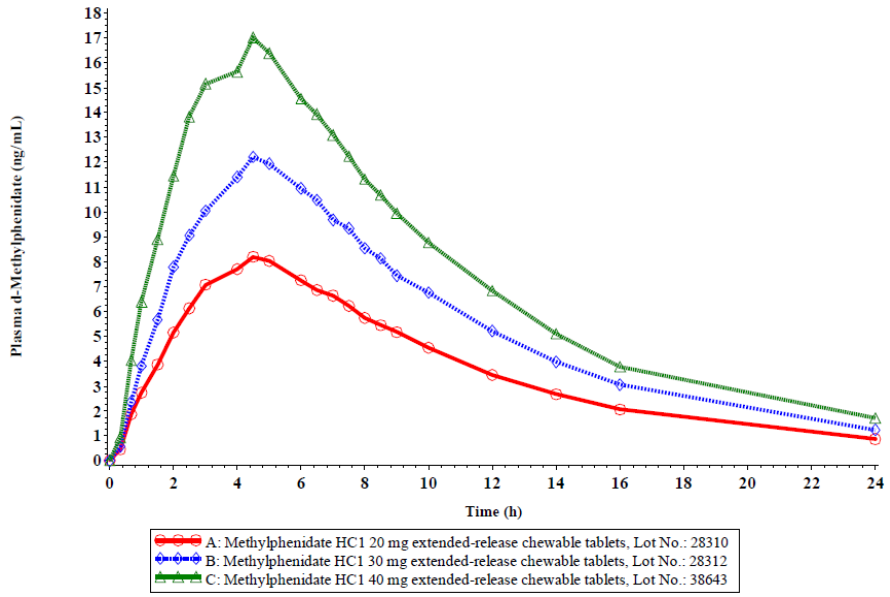


Figure 4. Mean Plasma *d*-Methylphenidate Concentration-Time Profile Linear Scale (A: n = 23 / B: n = 24 / C: n = 23)

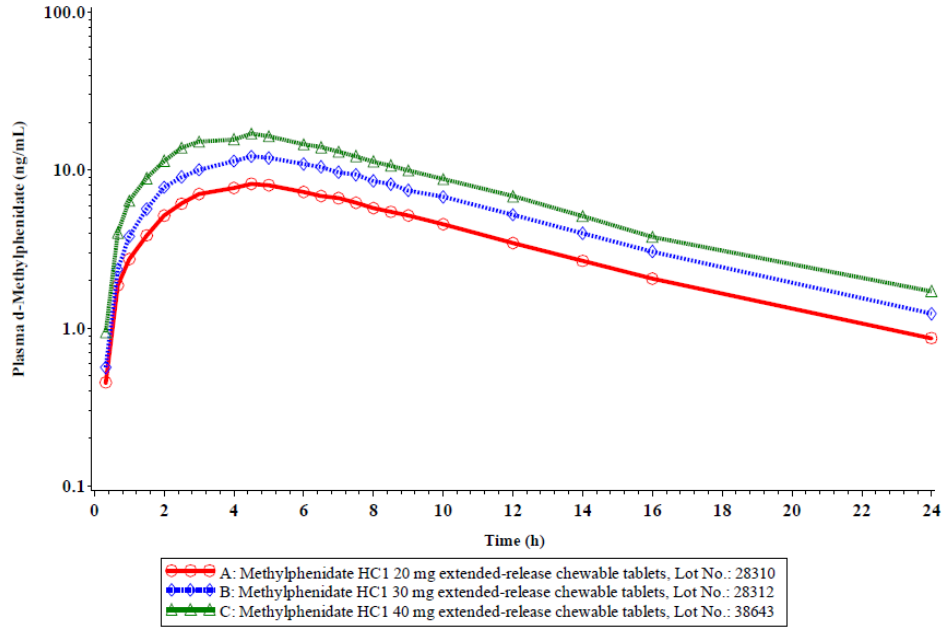


Figure 5. Mean Plasma *d*-Methylphenidate Concentration-Time Profile Semi-Log Scale (A: n = 23 / B: n = 24 / C: n = 23)

Dose Proportionality Assessment

Dose proportionality was assessed following administration of three different doses of Methylphenidate HCl extended-release chewable tablets from Tris Pharma, Inc. (20 mg, 30 mg, and 40 mg). The 90% CI of the slope for plasma d-methylphenidate AUCt, AUCinf, and Cmax of the drug products were between 1+ln(0.8)/ln(r) and 1+ln(1.25)/ln(r); as such, the drug products exhibited dose proportionality between the dose range of 20 mg, 30 mg and 40 mg after a single dose in healthy subjects under fed conditions.

Bioavailability Assessment

Treatment A vs. Treatment C

The peak exposure of d-methylphenidate, as measured by dose-normalised Cmax (Cmax/D), and the total extent of exposure, as measured by dose-normalised AUCt and AUCinf (AUCt/D and AUCinf/D), were similar for drug product 1 compared to drug product 3 (Cmax/D ratio = 95.05%; AUCt/D ratio = 99.91%; AUCinf/D ratio = 101.61%).

Treatment B vs. Treatment C

The peak exposure of d-methylphenidate, as measured by Cmax/D, and the total extent of exposure, as measured by AUCt/D and AUCinf/D, were similar for drug product 2 compared to drug product 3 (Cmax/D ratio = 93.07%; AUCt/D ratio = 98.75%; AUCinf/D ratio = 98.83%).

Treatment A vs. Treatment B

The peak exposure of d-methylphenidate, as measured by Cmax/D, and the total extent of exposure, as measured by AUCt/D and AUCinf/D, were similar for drug product 1 compared to drug product 2 (Cmax/D ratio = 102.12%; AUCt/D ratio = 101.17%; AUCinf/D ratio = 102.82%).

- *Safety data*

The administration of the study drugs was well tolerated by the healthy subjects participating in this study.

Overall, 20 TEAEs were reported by 11 subjects (45.8% of subjects dosed) during the conduct of this study. Of the 20 TEAEs, 12 TEAEs affecting 5 subjects (20.8%) were assessed as drug-related (reasonably possible).

Four (4) subject (17.4%) experienced 4 TEAEs after administration of treatment A (drug product 1). Six (6) subjects (25.0%) experienced 13 TEAEs after administration of treatment B (drug product 2). Three (3) subjects (13.0%) experienced 3 TEAEs after administration of treatment C (drug product 3).

One TEAE was moderate in severity and the others were mild. Resolution details for one TEAE are not available because the subject was lost to follow up. All other TEAEs resolved prior to end-of-study.

No serious adverse events (SAEs were) reported during the conduct of this study and none of the TEAEs compromised subject safety or had a significant impact on the integrity of the study results.

Supportive US studies

Study Number: 2012-2950

Title of Study:
A Three-Way Crossover Relative Bioavailability Study Comparing Methylphenidate HCl Extended-Release Chewable Tablets and Methylin Chewable Tablets under Fasting Conditions and Determining the Effect of Food on 40 mg Methylphenidate ER Chewable Tablets

Objective:
To evaluate the relative bioavailability after a single dose in healthy subjects between:

• methylphenidate HCl extended release 40 mg chewable tablets from Tris Pharma, Inc., USA and Methylin™ 10 mg chewable tablets (immediate release) from Mallinckrodt, Inc., USA administered

under fasting conditions

and

• methylphenidate HCl extended release 40 mg chewable tablets from Tris Pharma, Inc., USA administered under fasting and fed conditions.

Methodology:
This is an open-label, single- and multi-dose, randomised, 3-period, 3-sequence, 3-treatment, crossover study, designed to evaluate the relative bioavailability of methylphenidate HCl extended-release chewable tablets, administered to healthy male and female subjects under fasting conditions as compared to Methylin™ 10 mg chewable tablets (immediate release). This study also assessed the impact of food on the bioavailability of Methylphenidate HCl extended release 40 mg chewable tablets by comparing the pharmacokinetic parameters under fasted and fed conditions. The following treatments were administered to subject in accordance with the randomisation scheme:

• Treatment A: test product (1 tablet, 40 mg) administered under fasting conditions

• Treatment B: test product (1 tablet, 40 mg) administered under fed conditions

• Treatment C: reference product 2 equal doses of 20 mg (2 x 10 mg/tablet), 6 hours apart (total dose 40 mg), first dose administered under fasting conditions

The study population included non-smoking, male and female volunteers from 18 to 55 years of age, with a BMI from 18.0 to 30.0 kg/m2 and weight $\geqslant$ 50 kg, who were judged to be healthy based on a medical history, ECG, laboratory evaluation, physical examination, and vital signs measurements. Thirty-three (33) subjects were dosed in Period 1 and thirty-one (31) subjects are included in the pharmacokinetic analysis and the statistical analyses.

All the dosed subjects were included in the safety dataset. An assessment of safety was based primarily on the frequency and severity of AEs. There was no formal evaluation of safety or tolerability. There were no deaths, serious adverse events (SAEs), or other significant adverse events during the conduct of this study. None of the reported AEs had a significant impact on the safety of the subjects or on the integrity of the study results.

Concentrations of total (racemic mixture) methylphenidate were measured from samples collected over a 24-hour interval after dosing in each period used a validated LC-MS/MS method.

The following pharmacokinetic parameters were estimated using a non-compartmental approach: Cmax, AUCt, AUCinf, AUC0–0.5, AUC0–2, AUC0–3, AUC0–4, Tmax, Kel, and Thalf.

Descriptive statistics are estimated for the pharmacokinetic parameters in each treatment.

Analysis of variance (ANOVA) was performed on log-transformed Cmax, AUCt, AUCinf, AUC0–0.5, AUC0–2, AUC0–3, AUC0–4 and on untransformed Tmax, Kel and Thalf parameters. The significance of the sequence, period, treatment and subject-within-sequence effects was tested.

Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals were calculated for the following contrasts:

• Treatment A versus Treatment C (relative bioavailability under fasting conditions)

• Treatment B versus Treatment A (food effect for the test formulation)

These statistics were used to evaluate the performance of the test formulation in relation to the reference product and the test product as fed versus fasting.

All treatments under either fasted or fed conditions were well tolerated by all subjects in the study. Based on the results of the study, the test product has similar mean maximum concentration (Cmax) and exposure (AUC) characteristics when administered under fasting and fed conditions, suggesting no significant food effect on the test product. Methylphenidate HCl 40 mg ER chewable tablets administered under fasted conditions have comparable Cmax and AUC as the Methylin™ (immediate release) given 2 equal doses of 20 mg (2 x 10 mg/tablet), 6 hours apart (total dose 40 mg).

Pharmacokinetic and Statistical Conclusions

Methylphenidate

Table 10. Methylphenidate Results, PK Parameters

Based on Measured Plasma Methylphenidate Concentrations								
Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
C_{max} *(ng/mL)*	**A**	31	12.513 (29)	12.081	**B vs A**	104.05	99.38 - 108.94	11
	B	31	12.998 (29)	12.571	**A vs C**	80.00	76.30 - 83.87	11
	C	29	15.572 (27)	15.102				
AUC_t *(ng.h/mL)*	**A**	31	111.782 (31)	107.493	**B vs A**	120.61	117.02 - 124.31	7
	B	31	133.437 (27)	129.651	**A vs C**	87.64	84.96 - 90.41	7
	C	29	127.646 (31)	122.653				
AUC_{inf} *(ng.h/mL)*	**A**	31	118.122 (30)	113.642	**B vs A**	121.40	118.04 - 124.86	7
	B	31	142.590 (29)	137.963	**A vs C**	89.11	86.57 - 91.73	7
	C	29	132.388 (30)	127.525				
T_{max} *(h)*	**A**	31	4.16 (28)					
	B	31	4.27 (27)					
	C	29	6.43 (40)					
k_{el} *(1/h)*	**A**	31	0.1366 (18)					
	B	31	0.1349 (13)					
	C	29	0.2141 (21)					
T_{half} *(h)*	**A**	31	5.21 (15)					
	B	31	5.24 (15)					
	C	29	3.38 (21)					
			Median	*Range*				
T_{max} *(h)*	**A**	31	5.00	2.00- 5.92				
	B	31	5.00	2.50- 6.50				
	C	29	7.50	0.75- 8.57				

Table 11. Methylphenidate Results, Partial AUCs

Based on Measured Plasma Methylphenidate Concentrations								
Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
$AUC_{0-0.5}$ *(ng.h/mL)*	**A**	31	0.227 (104)	0.163	**B vs A**	150.28	110.60 - 204.21	76
	B	31	0.337 (100)	0.245	**A vs C**	30.70	22.53 - 41.83	76
	C	29	0.753 (96)	0.532				
AUC_{0-2} *(ng.h/mL)*	**A**	31	9.786 (51)	8.797	**B vs A**	88.81	77.81 - 101.38	32
	B	31	8.692 (49)	7.813	**A vs C**	57.93	50.55 - 66.38	32
	C	29	16.054 (36)	15.186				
AUC_{0-3} *(ng.h/mL)*	**A**	31	19.741 (43)	18.339	**B vs A**	96.22	87.36 - 105.99	23
	B	31	19.013 (43)	17.646	**A vs C**	74.66	67.58 - 82.47	23
	C	29	25.712 (32)	24.565				
AUC_{0-4} *(ng.h/mL)*	**A**	31	30.307 (38)	28.566	**B vs A**	100.86	93.13 - 109.24	19
	B	31	30.521 (38)	28.812	**A vs C**	89.00	81.98 - 96.61	19
	C	29	33.465 (30)	32.098				

A significant treatment effect was detected by ANOVA for the AUC0-0.5(p=<.0001), AUC0 2(p=<.0001), AUC0-3 (p=<.0001), AUC0-4 (0.0388), Tmax (p = <.0001), kel (<.0001), and Thalf (<.0001) parameters.

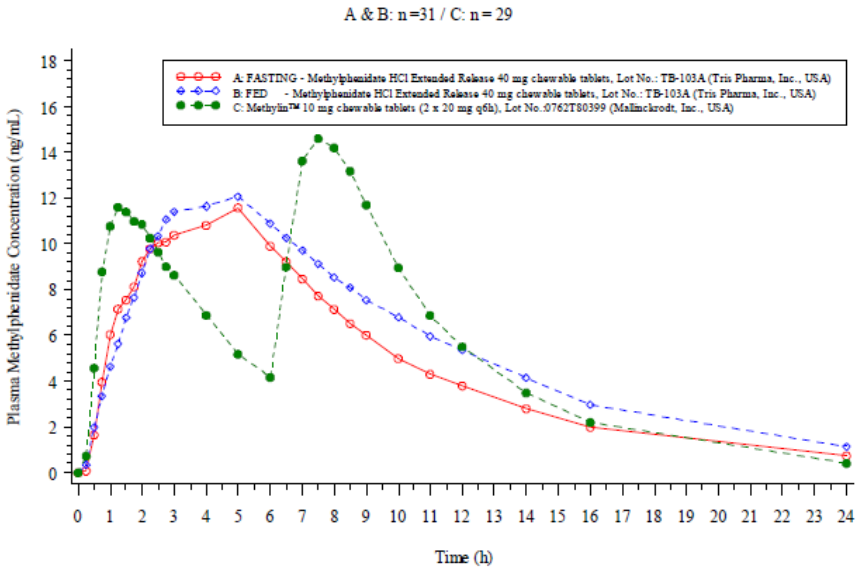


Figure 6. Mean Plasma Methylphenidate Concentration vs. Time Profiles

Treatment B vs Treatment A (food effect for the test formulation)

Treatment A: Methylphenidate HCl Extended Release 40 mg chewable tablets – Fasting

Treatment B: Methylphenidate HCl Extended Release 40 mg chewable tablets – Fed

The pharmacokinetic parameters obtained under fasting and fed conditions are similar.

The ratios and the 90% confidence intervals obtained for Cmax, AUCt and AUCinf indicate that the products have equivalent mean peak concentrations (Cmax) and exposure (AUC) under fasting and fed conditions, based on standard bioequivalence criteria, demonstrating no significant food effect.

Initially (AUC0-0.5) the extent of absorption is higher under fed conditions. However, after only 2 hours (AUC0-2) the extent becomes more similar with only an 11% difference in extent of absorption, with fasting conditions being higher. By the 3rd hour, the extent of absorption is similar between fasting and fed conditions.

Treatment A vs Treatment C (relative bioavailability under fasting conditions)

Treatment A: Methylphenidate HCl Extended Release 40 mg chewable tablets - Fasting

Treatment C: Methylin™ 10 mg chewable tablets (immediate release) - Fasting

The extent of absorption was similar between the two products under fasting conditions as the reference product had only a 12% and 11% higher extent of absorption as estimated by AUCt and AUCinf.

In this study, the ratios for the extent of exposure, as indicated by AUC0-t and AUC0-inf, were within the standard 80.00-125.00% bioequivalence acceptance criteria.

The mean peak concentration, of the reference product is 20% higher than the peak concentrations of the test product. This generally occurs due to the second larger peak of the reference product as the reference was an immediate release product.

The results from the partial AUCs (AUC0-0.5 to AUC0-4) analysis indicate that the reference product has a higher absorption initially than the test product. The test product absorption gradually increases to match the reference product.

In summary, this study showed similar maximum concentration (Cmax) and exposure (AUC) characteristics when the Methylphenidate HCl Extended Release 40 mg chewable tablets were administered under fasting and fed conditions, suggesting no significant food effect. AUC0-t and AUC0-inf (indicative of the extent of absorption) of Methylphenidate HCl 40 mg ER chewable tablets and Methylin™ (immediate release) tablets, administered under fasted conditions, meet the standard 80.00-125.00% bioequivalence acceptance criteria.

Modelling and Simulation Study

Title: Model & simulation evaluation of the pharmacokinetic and pharmacodynamic (SKAMP) properties of methylphenidate hydrochloride in an oral suspension (ER) and a chewable tablet (ER) formulation versus Ritalin® tablets (IR) in paediatrics.

Objectives:

The analysis had 5 major objectives:

1. Develop population PK (popPK) models for MPH with observations from the Oral Suspension ER (NWP06), the Chewable Tablet ER (NWP09) and the reference product IR Ritalin® in adults.

2. Develop a combined popPK model for adult and paediatric ER Oral Suspension with PK

observations in both.

3. Develop population PK/PD models in two ADHD paediatric groups (treated with NWP06 and NWP09, respectively) based on SKAMP observations from one of each of the ER formulations with the corresponding PK appropriately scaled to paediatrics.

4. Predict the NWP09 SKAMP in paediatrics using also Oral Suspension PD parameters.

5. Predict the SKAMP of Ritalin IR® and compare statistically via non-inferiority versus observed from the ER formulations.

Studies included in the MS study

Study S09-0238 data

This was a study in healthy adults to determine the relative bioavailability of a single dose of 60 mg Methylphenidate Polistirex ER Powder for Oral Suspension (ER Oral Suspension) vs Methylin® IR Oral Solution (10 mg / 5 mL Methylphenidate HCl), and to determine the effect of a high fat meal on the PK of 60 mg MPH ER Oral Suspension. The MPH fed occasion was kept for further analysis.

Study LESVIMETHYL/21/BQ-9 (BQ-9) (Study 2021-5129) data

This was a healthy adult single dose, comparative bioavailability study of MPH 40 mg ER Chewable Tablets and Ritalin® 10 mg Tablets under fed conditions. Ritalin IR was administered as 20 mg (2 × 10 mg tablets) at 0 and 6 hours (Total dose = 40 mg).

Study LESVIMETHYL/21/BQ-10 (BQ-10) (Study 2021-5130) data

This was a healthy adult single dose, comparative bioavailability study of MPH 5 mg/mL ER Oral Suspension and Ritalin® 10 mg Tablets under fed conditions. MPH was administered as 60 mg (12 mL of 5 mg/mL oral suspension) and Ritalin IR was administered as 30 mg (3 × 10 mg tablets) at 0- and 6- hours (Total dose = 60 mg).

Study NWP06-PPK-101 data

This was a study to evaluate the single dose PK of ER Oral Suspension (NWP06) in children and adolescents with ADHD. Patients were to receive a single oral dose of either 20 mg (4 mL) or 60 mg (12 mL) of NWP06.

Study NWP06-ADD-100 data

This was a randomised, double-blind, placebo-controlled, crossover design, optimised-dose, Phase 3 trial to evaluate the safety and efficacy of ER Oral Suspension (NWP06, 25 mg/5 mL) in the treatment of ADHD in paediatric patients. The duration of treatment was 6 weeks. The initial dose was 20 mg/kg, similar to that of other once-daily approved MPH products. During the first 4 weeks subjects were titrated at open label to achieve optimal dose for efficacy and tolerability (Max. daily dose 60 mg) followed by 2 weeks of stable dosing of double blind NWP06 or placebo and SKAMP evaluation.

Study NWP09-ADHD-300 data

This was a randomised, double-blind, placebo-controlled Phase 3 laboratory classroom study to assess the efficacy and safety of MPH ER chewable tablets (NWP09) compared with placebo in children with ADHD. The duration of treatment was 7 weeks. During the first 6 weeks subjects were titrated at open label to achieve optimal dose for efficacy and tolerability (Max. daily dose 60 mg) followed by 1 week of stable dosing of double blind NWP09 or placebo with SKAMP evaluation.

Three adult pop PK models were built one for each formulation.

- For Oral Suspension, the 60 mg arms from studies S09-0238 and BQ-10 were used.
- For Chewable Tablet, the 40 mg arm from study BQ-9 was study.
- For Ritalin IR the 40 and 60 mg daily total dose arms from BQ-9 and BQ-10, respectively, were used.

A paediatric pop PK model with Oral Suspension from study NWP06-PPK-101 at 20 and 60 mg was intermediate to the combined dataset in adults and children.

Two population PKPD models were developed for Oral Suspension and Chewable Tablet using the respective NWP06 and NWP09-ADHD studies.

Exploratory Data Analysis

Exploratory data analysis (EDA) is pivotal in assuring correct data extraction, evaluating potential outliers and judging the type of model structure most likely to be representative. EDA was performed of the observations from the four PK and two PKPD studies with the primary objective to guide modelling in terms of the log-linearity of the PK profiles (number of compartments) and the shapes of absorption profiles across formulations, as well as to observe differences in relative bioavailability. Similarly, the SKAMP score evolution in time for placebo and active treatment was observed to compare with earlier analyses and provide guidance for PKPD modelling. The noncompartmental (NCA) variables AUC[0-last] and Cmax were calculated for each treatment arm of the PK datasets and correlations made with body weight, age and sex.

Population PK & PKPD analysis

Nonlinear mixed effects modelling was performed using the computer program NONEM® (ICON Plc, Dublin, Ireland; version 7.3 or higher) [2], installed on a computer running under the Windows 10 Professional (64 bit) operating system. NONMEM executable files were compiled using the Intel Visual FORTRAN Compiler Professional (version 11.1 or higher). Data presentation and construction of plots were done using S+ (S-Plus – Spotfire®, Tibco Software, Palo Alto, CA, USA; version 6 or higher).

Procedure for PK & PKPD modelling and efficacy comparison

All available data were included in population models, the objective being comparison of efficacy (combined SKAMP outcome) after dosing with different MPH formulations. The PK in adults for the different formulations, as well as in paediatrics for Oral Suspension ER, was used to provide (via allometric scaling) the MPH concentrations for PKPD modelling in paediatrics using the observations for SKAMP data from the Oral Suspension and Chewable Tablet ER efficacy trials.

For comparison and testing of differences between ER formulations and Ritalin® IR, as the reference had no reported SKAMP, a three-step procedure of prediction / validation was followed.

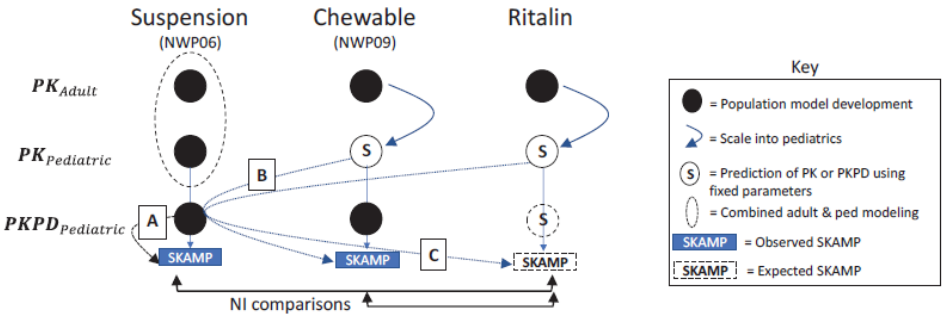
In each step, all mixed effects parameters, for both PK and PD, were fixed to their final model estimates, and the models ran on the respective formulation posology in the NWP06 or NWP09 efficacy trials and NWP06 posology for Ritalin split in a dose at 0 and another at 6 hours.

First, an internal validation on oral suspension SKAMP was performed, corollary to the actual PKPD modelling with the formulation that was complete with adult and paediatric PK and efficacy, in order to set the stage for further comparisons.

Second, an external-like validation and test of the predictive capacity using a different formulation, but the Oral Suspension PD, was performed by predicting the Chewable Tablet observed SKAMP.

Finally, and once similarity across ER treatments at the PD level was shown, the paediatric scaled Ritalin® IR MPH kinetics and the PD parameters from oral suspension were used to predict the (Combined) SKAMP after dosing with Ritalin® IR in the 0 and 6 hr split daily regime. This SKAMP prediction was used to assess the NI comparison of both ER formulations against Ritalin® IR.

The scheme in Figure 6 depicts the validation and predictions performed.



Note to Figure 1:

A. **PKPD model confirmation**: PK parameters of MPH from Oral Suspension in adults and paediatrics and PD parameters from Oral Suspension PKPD used to predict the observed SKAMP after Oral Suspension ER treatment.

B. **External-like validation**: PK parameters of MPH scaled to paediatrics for Chewable Tablet used to "drive" the PKPD using PD parameters of Oral Suspension & direct comparison of predicted profiles with the observed SKAMP after Chewable Tablet ER.

C. **Prediction & NI comparison**: PK parameters of MPH scaled to paediatrics for IR Ritalin® used to "drive" the PKPD using PD parameters of Oral Suspension & Non-Inferiority comparison of Ritalin® IR predicted SKAMP with NWP06 as well as NWP09 observed SKAMP.

Figure 7. Overview of the Modelling and Prediction Analyses Performed.

Allometrically scaled population PK from adults (combined with paediatric PK for Oral Suspension) was used to provide MPH concentrations for PKPD modelling and comparison among formulations: A = model confirmation; B = External -like prediction / validation; C = Prediction & NI comparison.

PK & PKPD structural model building

In both PK and PKPD population models and as a first step, the structures tested carried minimum complexity but represented adequately the observations. On these models, random effects were tested. Inter individual variability (IIV) was tested on all structural parameters but prioritizing the estimation of IIV on CL and V2 for the PK. The number of random IIV effects were occasionally reduced to ensure that the model minimises successfully, and all parameters were adequately estimated. Expansion as far as a full block variance covariance matrix (Ω) for all parameters with modelled IIV was also assessed.

For population model discrimination and decisions both NONMEM OFV, minimisation success and goodness of fit (GoF) evaluations were performed. The difference in the OFV between models is asymptomatically χ^2 distributed with d.f. equal to the difference in number of estimated parameters between two hierarchical models. A OFV with a χ^2 probability less than or equal to 0.01 (6.64 points of OFV, d.f. = 1) favours the model with the lower OFV.

The GoF for both PK and PKPD models was assessed by a variety of plots and computed metrics. The GoF plots included data points for observed and predicted data, reference lines (identity, zero line, etc.), and smooth lines through the data.

For the systemic PK of MPH mono-compartmental structures to include random effects were tested. For the absorption phase, primarily of the Oral Suspension data, various structures were also tested including a 1st plus a 0th order absorption phases model and a Weibull absorption rate model. A time delay was also included.

Covariate model building

The objective of the analysis was to produce population predictions of SKAMP outcomes after two different MPH extended-release formulations and compare also with the expected SKAMP after Ritalin® IR. Therefore, covariate exploration was primarily with body weight (WT), the variable used to scale the PK from adults to children. Secondarily sex and age were judged vs. individual subject central parameter (CL and V2) estimates in correlations external to mixed effects and if confounding with weight was not indicated ($r < 0.5$) then they were tested within NONMEM.

For paediatric subjects, weight and age are correlated hence confounded in regression, while for adult subjects there is little or no correlation. So, in paediatric alone and in combined adult and paediatric dataset modelling, WT was the only covariate tested.

In PKPD modelling, age and dose were tested as covariates, the former when feasible (i.e. random effects were estimable) and then indicated by correlation plotting and the latter was tested “ad hoc” on key parameters Emax, EC50 and AA.

Continuous covariates (COV) age or dose, when appropriate, were modelled either on the PK or the PD parameters with an intercept relation and slope centred at its typical value (TVCOV).

Results

PK databases

Summary statistics of six treatment arms within four PK studies in adults and paediatrics (two parallel increasing dose arms) are listed in Table 12.

Table 12. Subject characteristics in MPH pharmacokinetic studies

STUDY							
S09-0238 – 60 mg Oral Suspension							
Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
	Subjects						
Age (years)	28	36.5	13.6	33.5	19	68	AGE
Weight (kg)	28	76.5	12.8	74.2	56	104	WT
Sex (M/F)	23/5	-	-	-	-	-	NSEX
Race (WHITE/OTHER)	18/10	-	-	-	-	-	NRACE
BQ-9 – 40 mg Chewable Tablet & BQ-9 – Ritalin IR 40 mg							
Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
	Subjects						
Age (years)	24	39.2	10.3	37	22	54	AGE
Weight (kg)	24	73.9	14.4	73.6	51	97	WT
Sex (M/F)	12/12	-	-	-	-	-	NSEX
Race (WHITE/OTHER)	16/8	-	-	-	-	-	NRACE
BQ-10 – 60 mg Oral Suspension & BQ-10 – Ritalin IR 60 mg							
Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
	Subjects						
Age (years)	24	42.2	11.6	47	18	55	AGE
Weight (kg)	24	74.3	11.5	73.8	51	95	WT
Sex (M/F)	13/11	-	-	-	-	-	NSEX
Race (WHITE/OTHER)	17/7	-	-	-	-	-	NRACE
NWP06-PPK-101 – 20 mg Oral Suspension in paediatrics							
Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
	Subjects						
Age (years)	7	12.3	1.8	12	10	14	AGE
Weight (kg)	7	38.2	6.0	38.2	26	44.5	WT
Sex (M/F)	6/1	-	-	-	-	-	NSEX
Race (WHITE/OTHER)	4/3	-	-	-	-	-	NRACE
NWP06-PPK-101 – 60 mg Oral Suspension in paediatrics							
Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
	Subjects						
Age (years)	7	13	2.1	13	9	15	AGE
Weight (kg)	7	54	27	51	18	106	WT
Sex (M/F)	5/2	-	-	-	-	-	NSEX
Race (WHITE/OTHER)	6/1	-	-	-	-	-	NRACE

The SKAMP assessment datasets in paediatric ADHD patients for the two MPH ER formulations are listed in Table 13.

Table 13. Subject characteristics from two SKAMP paediatric studies with MPH treatment of ADHD

STUDY							
NWP06-ADD-100 (titrated with cross over design for SKAMP; Statistics for the Combined score).							
Oral Suspension ER or Placebo – Week 5 or 6							
20 mg: Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
Age (years)	1	8	-	-	-	-	AGE
Weight (kg)	1	58	-	-	-	-	WT
30 mg: Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
Age (years)	10	8.9	1.6	9	7	11	AGE
Weight (kg)	10	77	24	74	45	124	WT
40 mg: Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
Age (years)	8	8.1	1.5	8	6	11	AGE
Weight (kg)	8	59.5	16.7	52	47	92	WT
50 mg: Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
Age (years)	4	8	0.8	8	7	9	AGE
Weight (kg)	4	61	13	57	50	79	WT
60 mg: Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
Age (years)	4	9	1.1	9	8	10	AGE
Weight (kg)	4	58	21	54	38	86	WT
Overall Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
Age (years)	27	8.5	1.4	8	6	11	AGE
Weight (kg)	27	66	20.6	62	38	124	WT
Sex (M/F)	18/9	-	-	-	-	-	NSEX
Race (WHITE/OTHER)	21/6	-	-	-	-	-	NRACE
STUDY							
NWP09-ADHD-300 (titrated with parallel design for SKAMP; Combined score)							
Oral Suspension ER or Placebo – Week 7							
20 mg: Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
NWP09							
Age (years)	4	8.7	2	8.5	7	11	AGE
Weight (kg)	4	31	5.2	31.2	26	37	WT
PLACEBO							
Age (years)	7	8.2	2.22	9	6	12	AGE
Weight (kg)	7	27	7.5	26	18	39	WT
30 mg: Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
NWP09							
Age (years)	4	11.2	0.95	11.5	10	12	AGE
Weight (kg)	4	34	5.8	37	25	37	WT
PLACEBO							
Age (years)	8	8.5	1.7	9	6	10	AGE
Weight (kg)	8	33	11.0	32	18	46	WT
40 mg: Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
NWP09							
Age (years)	15	9.8	1.7	10	7	12	AGE
Weight (kg)	15	32.5	9.1	31	20	52	WT
PLACEBO							
Age (years)	9	10	1.3	10	8	12	AGE
Weight (kg)	9	33	7.2	35.5	22	42	WT
50 mg: Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
NWP09							
Age (years)	9	10	1.6	10	7	12	AGE
Weight (kg)	9	39	15.2	33	23	68	WT
PLACEBO							
Age (years)	10	9.3	1.2	9	7	11	AGE
Weight (kg)	10	28.6	6.2	29	17	41	WT
60 mg: Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
NWP09							
Age (years)	10	9.7	1.8	10.5	7	12	AGE
Weight (kg)	10	32	12.9	29.3	15	51	WT
PLACEBO							
Age (years)	9	9.9	1.4	10	7	12	AGE
Weight (kg)	9	19	8.6	33.5	19	47	WT
Overall Demographics	**n**	**Mean**	**(SD)**	**Median**	**min**	**max**	**Symbol**
Age (years)	85	9.6	1.7	10	6	12	AGE
Weight (kg)	85	33	9.7	30.1	15	69	WT
Sex (M/F)	53/32	-	-	-	-	-	NSEX
Race (WHITE/OTHER)	49/36	-	-	-	-	-	NRACE

Exploratory data analysis

An overlay of dose-normalised PK as observed in 7 treatment arms from 4 PK trials is shown in Figure 7.

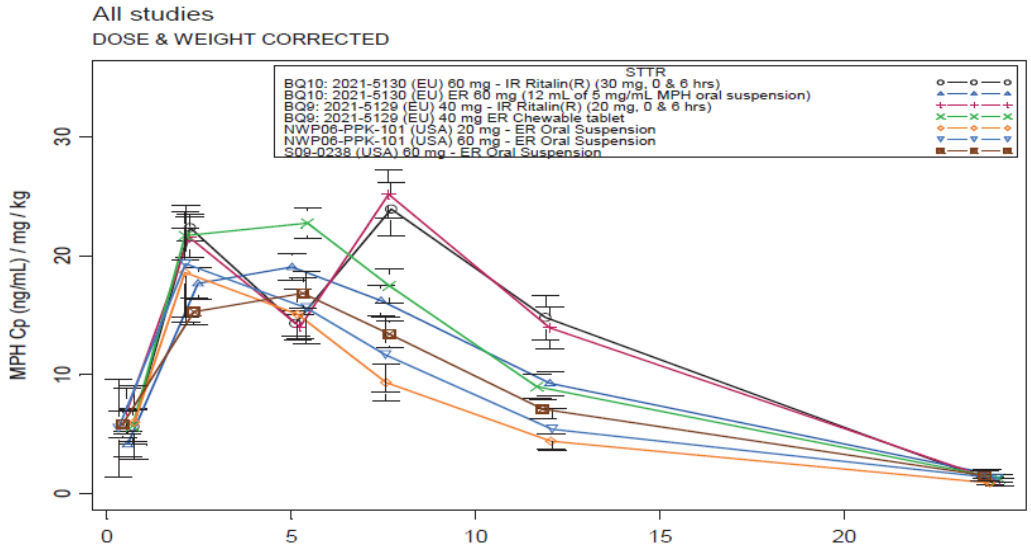


Figure 8. Overlay of Dose and Weight Normalised Observed MPH PK from 7 Treatment Arms in 3 Adult and 1 Paediatric Trial and 3 Different Formulations. The plot shows means at binned times and the corresponding 90% CI.

The difference in regime between the ER single daily dose and the twice daily IR Ritalin is apparent. Still, Ritalin appears with different daily profile shape compared to the ER formulations, a difference whose significance regarding efficacy remains to be observed when modelling its PKPD given the complexity of its overall kinetics (significant loss of MPH levels of Ritalin IR around 6 hours). The relation between the adult and paediatric kinetics is highly dependent on body weight. The crude adjustment by weight here leads to largely coincident profiles. Some differences in the later stage remain, that could be related to study effects, still each case carried its own popPK model in the end.

The progression in time of SKAMP observed with the ER Oral Suspension treatment in weeks 5 and 6 of paediatric ADHD subjects is seen in Figure 8. The display corresponds to what was actually modelled (un-transformed raw value data).

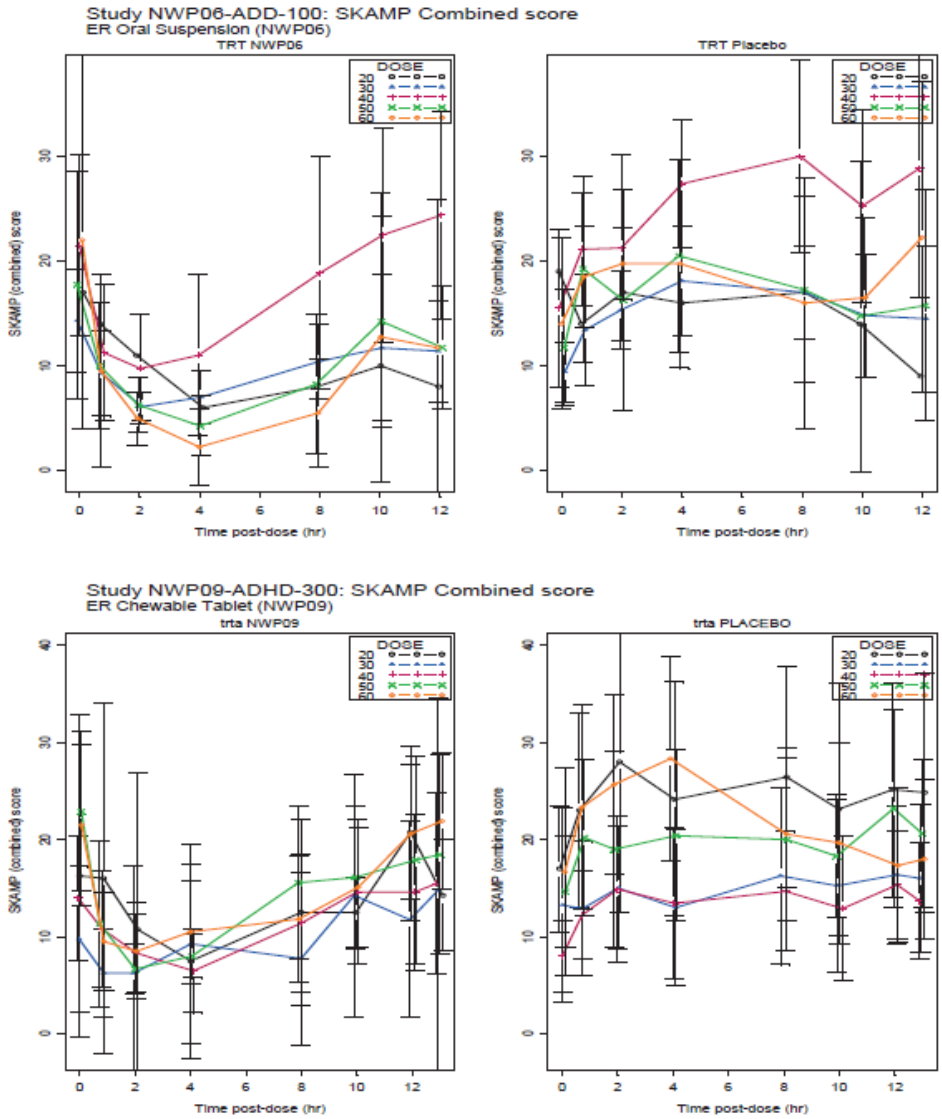


Figure 9. Observed SKAMP (Combined score) across time after MPH treatment in paediatric ADHD subjects from study NWP06-ADD-100 (upper panel) and NWP09-ADHD-300 (lower panel) (observed mean and 90% CI shown).

MPH shows efficacy (SKAMP reduction) versus placebo at all dose levels and for both ER formulations without significant differentiation by dose. There is variability and apparent differences in the evolution by dose group and formulation. Although some individual profiles with Chewable Tablet have apparently faster onset on average, the behaviour of NWP06 and NWP09 treatments with SKAMP is quite similar (mean profiles).

Similarity is also observed when extracting NCA variables AUCE[0-12h] and Emax from the observations of the NWP06 and NWP09 treatment arms and relating graphically vs body weight (WT), age, dose, race and sex. The only apparently important relation is of WT with the peak effect variable Emax. This serves as indication for testing the effect on those PD model parameters most related to the observed peak SKAMP under treatment.

Population PK modelling for MPH in adults and paediatrics

Five population PK models were developed from the evaluable MPH data in four PK trials. Three models were in adults, one for children with paediatric PK data and a final model with adult and paediatric PK combined for Oral Suspension as shown in Table 14. All data corresponded to the fed state.

Table 14.: Population PK models with study name, sample size and dose levels.

In adults:
For ER Oral Suspension (NWP06) (N=50):
• S09-0238 (N=28 @ 60 mg; ID 317 was removed so N=27 was modelled) • BQ10 Test arms (N=23 @ 60 mg)
For ER Chewable tablet (NWP09) (N=23):
• BQ9 Test arms (N=23 @ 40 mg)
For IR Ritalin® (N=48):

• BQ9 and BQ10 Reference arms (N= 24 + 24)
  ○ BQ9 had 2 x 10 mg at 0 and 6 hours = 20 mg x 2 = 40 mg daily
  ○ BQ10 had 3 x 10 mg at 0 and 6 hours = 30 mg x 2 = 60 mg daily

In children:
For ER Oral Suspension (NWP06) (N=14; ID 003 – 60 mg - was excluded as outlying on observations so N=13 were modelled):
• NWP06-PPK-101 (N=13 @ 20 and 60 mg)
Adults and children combined (NWP06 – Oral Suspension):
For ER Oral Suspension (NWP06) (N=40):
• S09-0238 (N=28 @ 60 mg; ID 317 was removed so N=27 was modelled) • NWP06-PPK-101 (N=13 @ 20 and 60 mg)

A representative correlation matrix plot for the Oral Suspension combined (adult + paediatric) final model with WT as predictor for CL and V2 variability is shown in Figure 9.

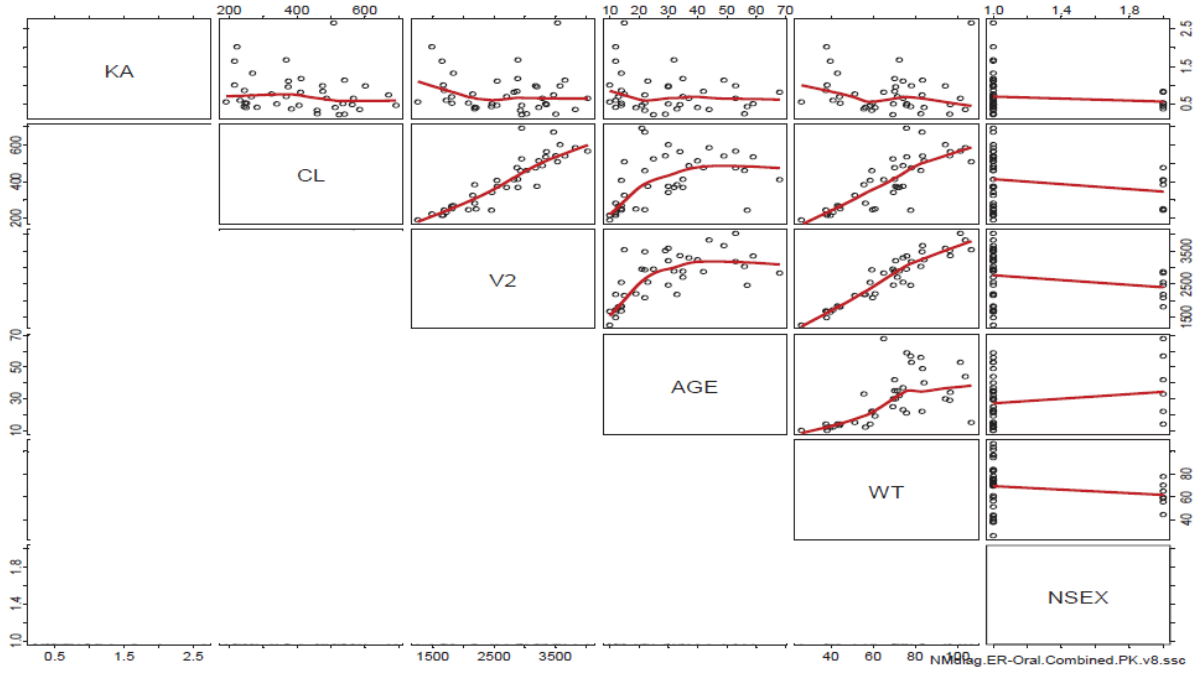


Figure 10. Correlation matrix plot of individual PK parameters from the combined adult + paediatric NWP06 datasets (NSEX: 1 = Male; 2 = Female)

Female subjects tend to have reduced weight. No correlations are observed with the 1st order absorption rate.

For the combined Oral Suspension model, the relationship of CL and V2 vs body weight is separately depicted in Appendix 6.2 with the standard allometric and NONMEM CL/F, V2/F ~ WT models overlaid. It is seen that the regression derived with the actual combined dataset has improved accuracy.

The final covariate-inclusive combined Oral Suspension pop PK parameters (NWP06) are listed in Table 15.

Table 15.: Population PK parameters from the combined adult and paediatric dataset for ER Oral Suspension MPH (NWP06) (two study-arms).

OBJ	1138.91	
N = 40	FOCE	
Parameter	**Estimate**	**CV% (SEE%)**
KA (1/hr)	0.663	12.4
CL/F.s (L/hr)	408	4.1
V2/F.s (L)	2780	3.3
ALAG1 (hr)	0.297	10
CL.WTpwr	0.937	10
V2.WTpwr	0.847	11.3
ω_{KA} (%)	63%	28.5
ω_{CL} (%)	20%	37.3
ω_{V2} (%)	12%	55.4
σ_prop (%)	35%	9

Note: Shrinkage of the random effect variances for KA, CL/F and V2/F was 6.5%, 5% and 31%, respectively.

PKPD-SKAMP model for MPH in ADHD paediatrics

The popPK models for MPH from the two ER formulations were linked to the SKAMP dynamics via an indirect effect relation for the Placebo with time-decay of its onset and modulated by an Emax relationship for the added treatment effect. SKAMP observations were in two paediatric ADHD treatment efficacy studies one each for the ER formulations of MPH, NWP06 and NWP09.

A limited series of pre-dose trough MPH concentrations were assessed in some of the patients from the NWP06-ADD-100 trial. Their median (1.23 ng/mL) was less than 10% of the Cmax of the post-dose MPH PK from the NWP06-PPK-101 trial (13.4 ng/mL – average across 20 to 60 mg).

Also, these troughs resulted from the history of titration dosing prior to the test day (that was not modelled) hence there was no direct PK correspondence between the test day pre-dose troughs and the actual final dose PK. Due to the missingness, unknown actual history and reduced magnitudes these troughs observations were not used when predicting the paediatric MPH PK in PKPD modelling.

Scaling of PK to paediatrics was based solely on body weight (WT). For NWP06 and Ritalin® IR, the adult popPK parameters were scaled to the corresponding paediatric PK using the combined adult and paediatric popPK model derived CL/F, V2/F ~ WT exponents. For NWP09, the adult popPK parameters were scaled to paediatric PK again using the adult derived exponents of the CL/F ~ WT relationship only.

The basis of mechanistic PKPD modelling is that the PD parameters derived are closely related to the inherent pharmacology and the PD is solely dependent on drug concentration at the site of action, thus

being independent of drug delivery method or formulation. With Ritalin® IR and no SKAMP assessments made during its development, the PD parameters of the ER oral suspension formulation were first validated for universality versus the chewable tablet SKAMP PD and then used to predict the SKAMP evolution in time after Ritalin® IR.

In PKPD modelling of the observed SKAMP datasets, the PK parameters were set to be sampled by NONMEM from their fixed and scaled typical population estimates and IIV variances for KA, CL/F and V2/F for each corresponding of the ER formulations. Raw, rather than e.g. change from baseline SKAMP data were modelled. Baseline SKAMP was the initial condition for the K_{in}/K_{out} ratio. Table 16. lists the parameters from the NWP06 and NWP09 SKAMP PKPD modelling.

Table 16.: PKPD-SKAMP model parameters after single dose of MPH as ER Oral Suspension.

NWP06 paediatric popPKPD - SKAMP		
OBJ	1492.914	
N = 53	FOCE	
PK Parameters (fixed)	**Estimate**	**CV% (SEE%)**
KA (1/hr)	0.663	NA
CL/F.s (L/hr)	408	NA
V2/F.s (L)	2780	NA
ALAG1 (hr)	0.297	NA
CL.WTpwr	0.937	NA
V2.WTpwr	0.847	NA
PD parameters		
Emax	1.2	12.8
EC50 (ng/mL)	17.3	20.9
Hill	1.19	21.2
AA	430	57.9
P1 (1/hr)	0.545	46.2
Kin (1/hr)	0.0124	59.1
Kout (1/hr)	0.524	52.1
ω_{KA} (%)*	63%	NA
ω_{CL} (%)	20%	NA
ω_{V2} (%)	12%	NA
ω_{EC50} (%)	23%	47%
ω_{AA} (%)	63%	46%
σ_prop (%)	11%	23%
σ_add (SKAMP)	3.69	13%

*PK variances are fixed as are systemic PK parameters
Note: Shrinkage of the random effect variances for EC50 and AA was 59% and 16%, respectively.

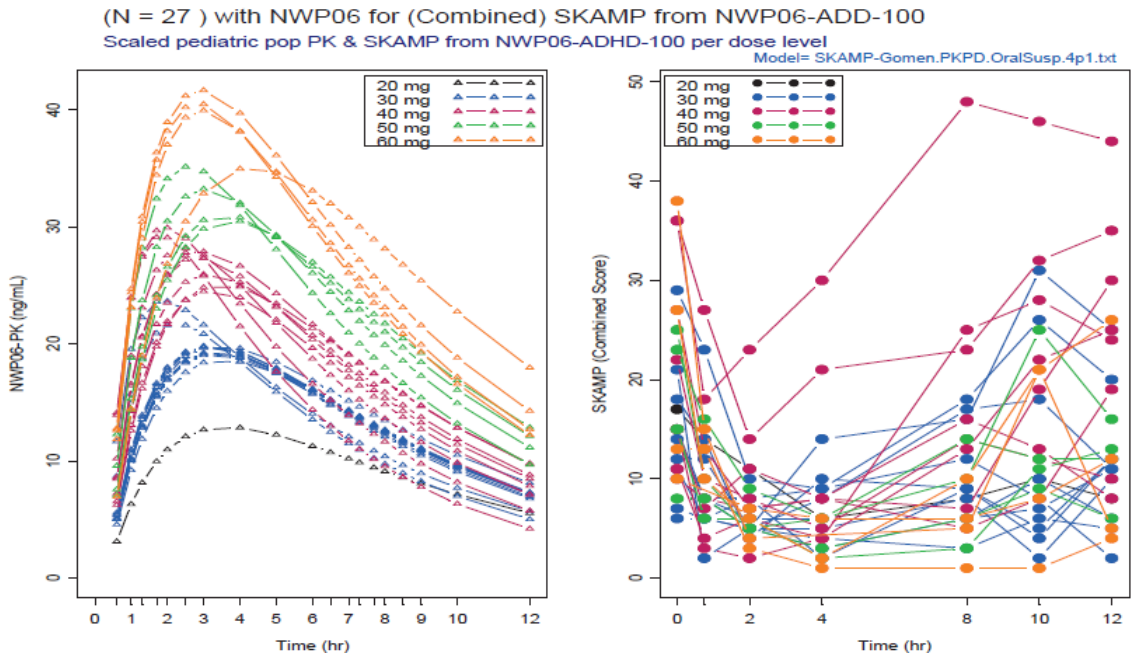
Table 17.: PKPD-SKAMP model parameters after single dose of MPH as ER Chewable Tablet.

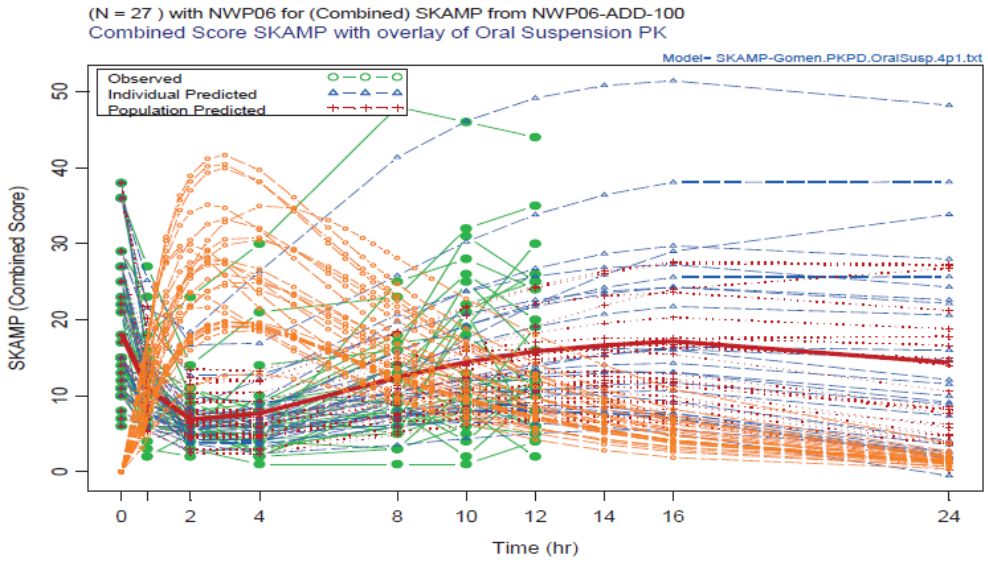
NWP09 paediatric popPKPD - SKAMP		
OBJ	4181.708	
N = 85	FOCE	
PK Parameters (fixed)	**Estimate**	**CV% (SEE%)**
KA (1/hr)	0.506	NA
CL/F.s (L/hr)	314	NA
V2/F.s (L)	1890	NA
ALAG1 (hr)	0.192	NA
CL.WTpwr	0.818	NA
PD parameters		
Emax	1.16	37.1
EC50 (ng/mL)	25.3	63.6
Hill	1.12	55
AA	338	218.3
P1 (1/hr)	0.489	89
Kout (1/hr)	0.414	190.6
Kin (1/hr)	0.0138	90.1
ω_{KA} (%)*	51%	NA
ω_{CL} (%)	30%	NA
ω_{V2} (%)	28%	NA
ω_{AA} (%)	77%	40%
σ_prop (%)	11%	193%
σ_add (SKAMP)	8.43	11%

*PK variances are fixed as are systemic PK parameters
Note: Shrinkage of the random effect variance for AA was 19%.

The mechanistic PKPD model applied was complex but was needed in order to fit a framework of true PKPD i.e. where the sole driver of the PD is MPH concentration. Minimisation was successful overall in spite of the model complexity but limited sample size for the large number of parameters.

As a counterpart, however, some of the parameters had elevated coefficients of variation. Random effects were not estimable on PD parameters more than for EC50 and the SKAMP amplitude AA for NWP06, Oral Suspension, and solely for AA with the chewable tablet, NWP09, dataset. Figure 10 for ER oral suspension and chewable tablet SKAMP, respectively, depict the PKPD model fit as overlay of observed vs predicted SKAMP. The extracted MPH PK, corresponding to the efficacy study posologies, is also displayed. An extrapolation to a full day for the expected SKAMP after the single dose was performed and also shown in order to evaluate the potential rebound effect.


(N = 27) with NWP06 for (Combined) SKAMP from NWP06-ADD-100
Scaled pediatric pop PK & SKAMP from NWP06-ADHD-100 per dose level
Model= SKAMP-Gomen.PKPD.OralSusp.4p1.txt
20 mg
30 mg
40 mg
50 mg
60 mg
NWP06-PK (ng/mL)
SKAMP (Combined Score)
Time (hr)


(N = 27) with NWP06 for (Combined) SKAMP from NWP06-ADD-100
Combined Score SKAMP with overlay of Oral Suspension PK
Model= SKAMP-Gomen.PKPD.OralSusp.4p1.txt
Observed
Individual Predicted
Population Predicted
SKAMP (Combined Score)
Time (hr)

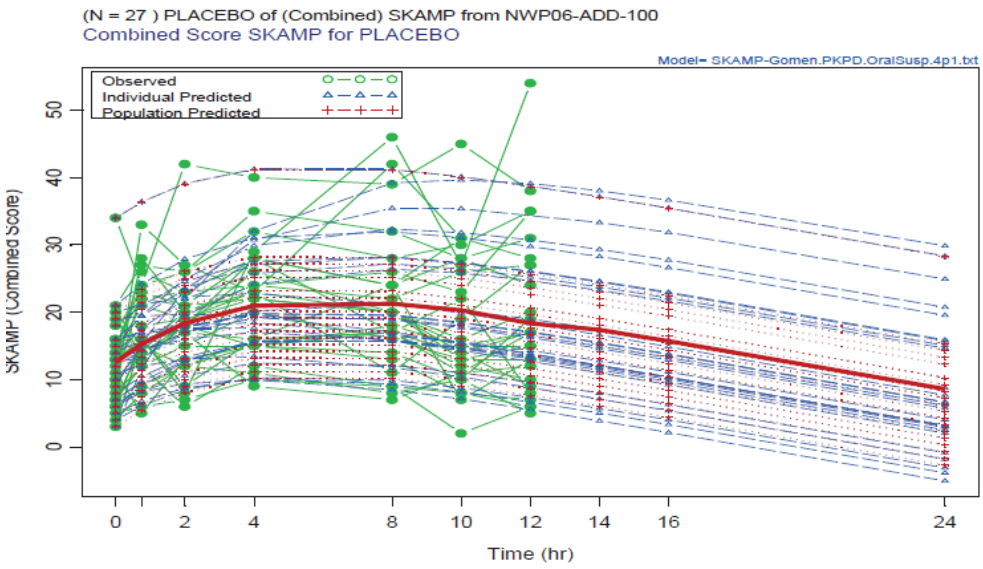


Figure 11. Observed vs population PKPD-SKAMP model predicted across time for SKAMP after ER Oral Suspension MPH from paediatric ADHD patient study NWP06-ADD-100.
The PK of MPH was extracted from the popPK model for ER oral suspension scaled to children and predicted at the dosing regime in the SKAMP study (upper left panel). The corresponding observed SKAMP in NW06-ADD-100 is shown in the right panel. The lower two panels are the NWP06 treatment (central panel) and placebo (lower panel) SKAMP response observed (green circles) and predicted (population and individual – dashed lines) and extrapolated to 24 hrs. The solid red line is the average of individual predictions.

The SKAMP response is decoupled from dose levels with both formulations. This is seen in the observations and reflected in the model where Dose was not a significant covariate for the PD parameters.

However, the dose range from 40 mg and above seems to be at the efficacy plateau. Although with no significant difference, the dose-response is depicted in Figure 11. as a dose response constructed with the change from placebo (reversed to positive numbers) from NWP06 treatment.

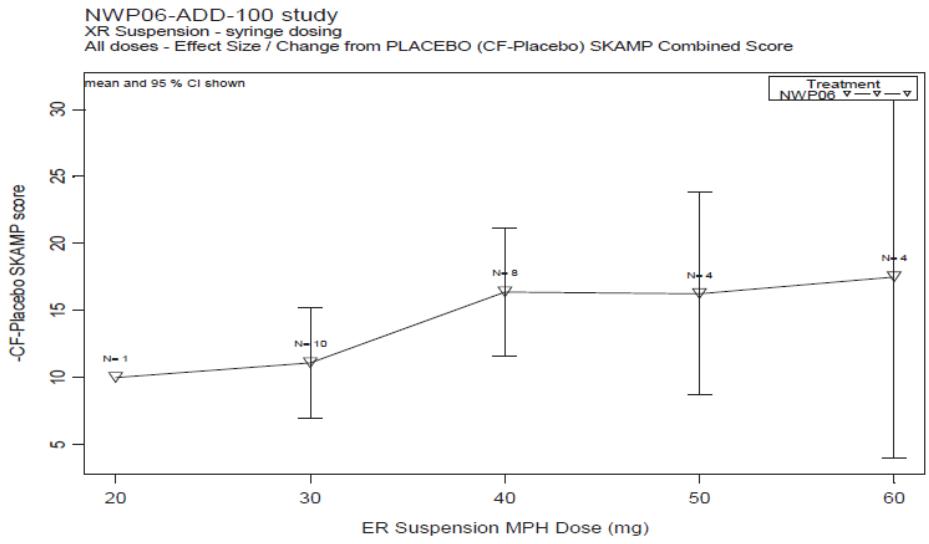


Figure 121. Dose-response for SKAMP with change from Placebo (CFPlacebo) after MPH in the Oral Suspension (NWP06-ADD-100) paediatric study. CFPlacebo has been reversed in sign for visualisation purposes.

All patients in the titration phase were started at 20 mg daily. However, on weeks 5 and 6 of SKAMP assessment only 1 patient remained at that level. The majority of subjects were either at 30 or 40 mg corroborating clinically the efficacy plateau range.

Validation & comparison

A visual evaluation of the oral suspension PKPD Model on a baseline normalised scale is done in Scenario A. Efficacy study posology-based predicted MPH concentrations from Oral Suspension PK were used to predict the SKAMP observations after NWP06 using own PKPD model PD parameters (Figure 12).

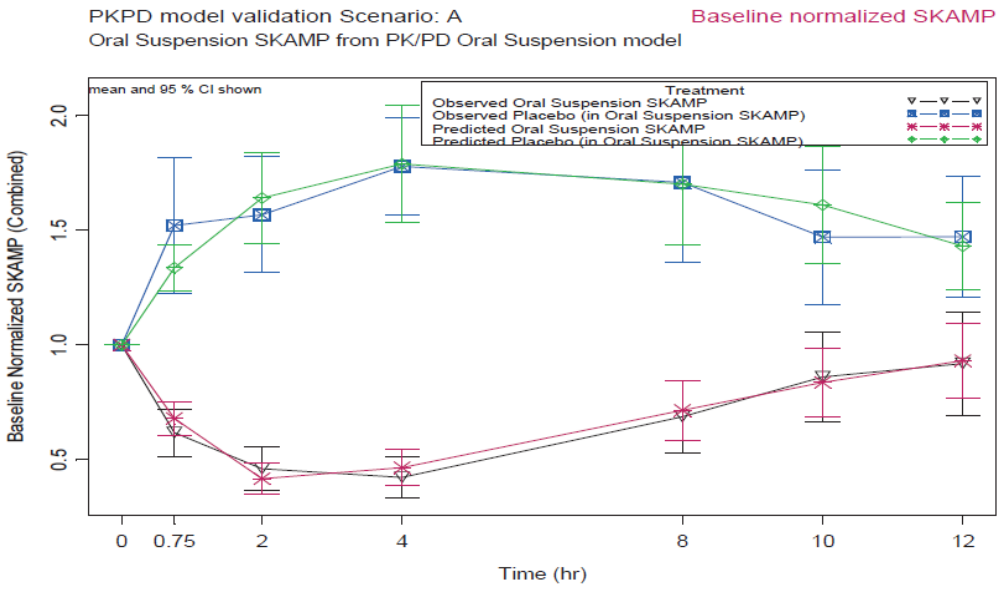


Figure 13. Scenario A = PKPD model confirmation: Prediction of Oral Suspension SKAMP after Oral Suspension MPH and using the Oral Suspension PKPD model parameters (Baseline normalised scale).

No significant difference is observed between observed and predicted Oral Suspension SKAMP confirming the PKPD model and qualifying the PD parameter set for further use in prediction.

External-like validation of the estimated SKAMP, testing the method to be applied in the following step with Ritalin® IR, was done in Scenario B. Efficacy study posology-based predicted MPH concentrations from Chewable Tablet PK were used to predict the SKAMP observations after NWP09 but using the PD parameters of Oral Suspension.

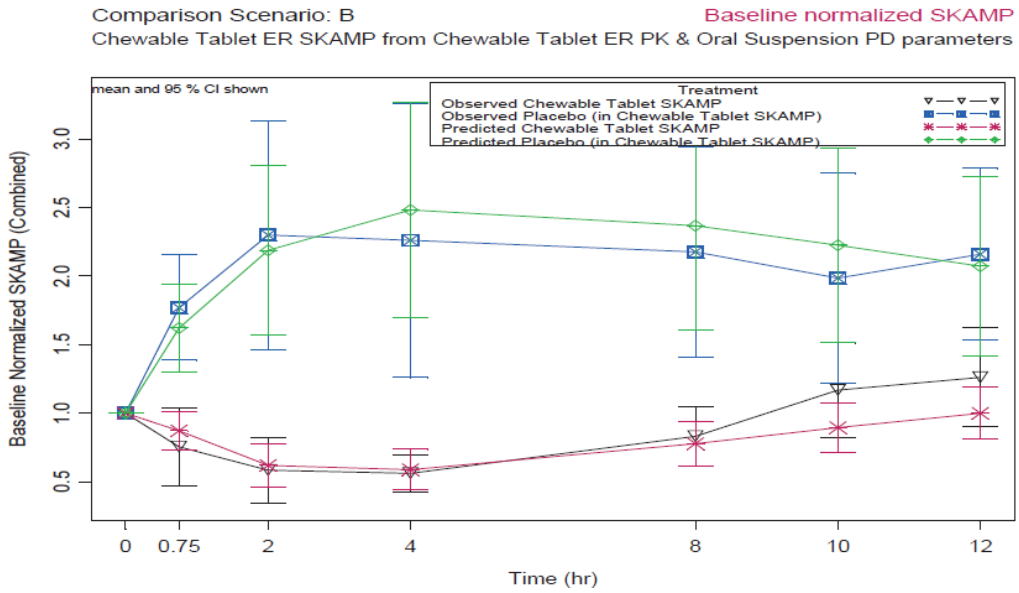
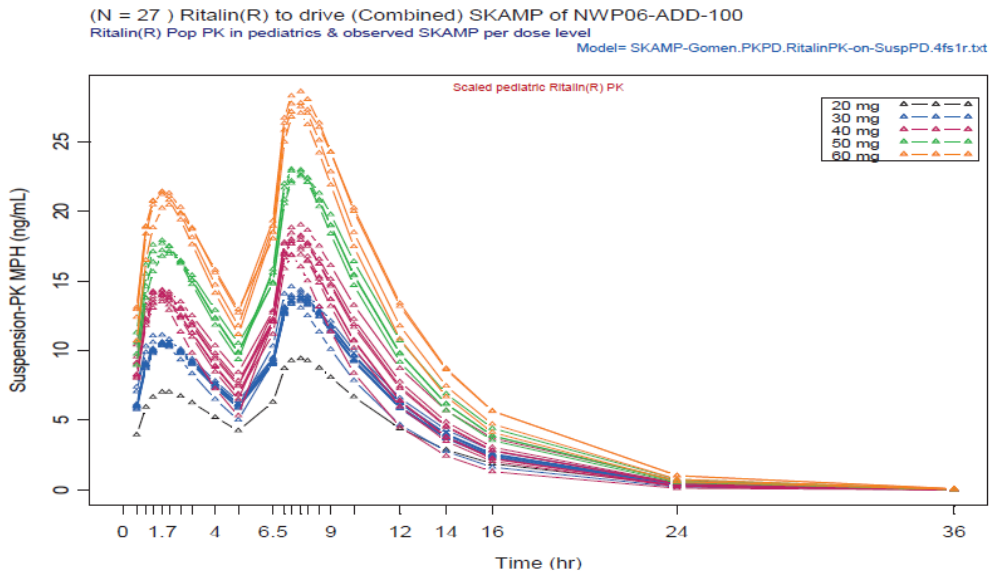


Figure 14. Scenario B = External-like validation: Prediction of Chewable Tablet ER SKAMP after Chewable Tablet ER MPH and using the Oral Suspension PKPD model parameters (Baseline normalised scale).

No significant difference is observed between observed and predicted Chewable Tablet SKAMP confirming the potential universality of the PD parameters (from Oral Suspension) and adequacy to predict SKAMP independent of formulation and posology.

The PK of Ritalin® IR was scaled to paediatrics and used to predict Ritalin IR MPH and drive SKAMP placebo and treatment response using the PD parameters from the NWP06 study. Figure 14 (upper panel) shows the predicted Ritalin® IR MPH following administration of Ritalin® IR, on the NWP06 efficacy study posology. Then, following is an overlay of the Ritalin® IR expected average response SKAMP compared to the average observed SKAMP from NWP06 and NWP09, both baseline normalised (Figure 14, lower panel).



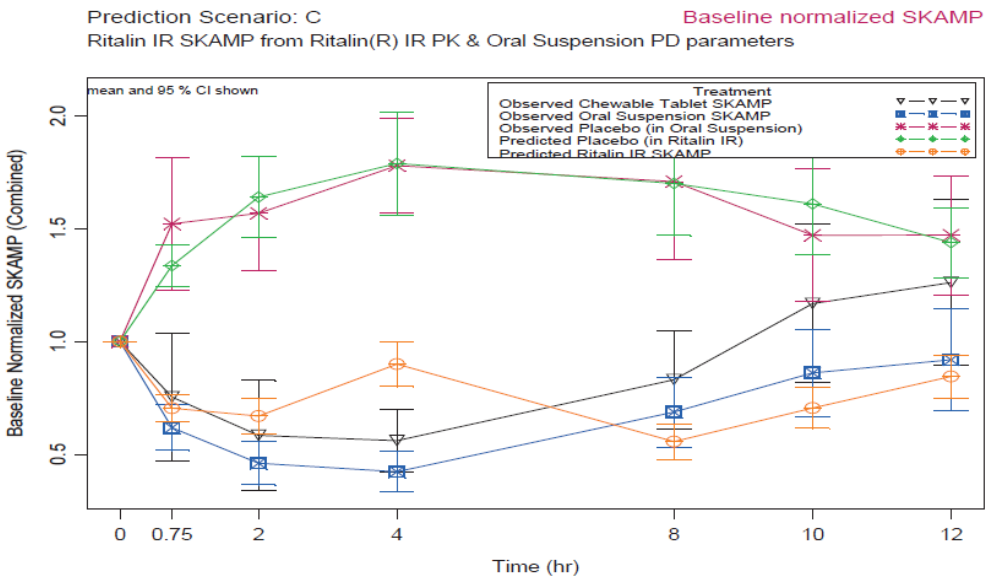


Figure 15. Upper panel: Paediatric scaled Ritalin IR MPH with the NWP06-ADD-100 posology from the Ritalin® IR popPK model. Lower panel: Overlay of Ritalin IR expected SKAMP response using the NWP06 PD parameters on observed ER Oral Suspension ER SKAMP (NWP06) and observed ER Chewable Tablet SKAMP (NWP09) (Baseline Normalised scale).

The Ritalin® IR SKAMP response predictions show the effect of twice daily dosing with the IR formulation and consequent partial loss of efficacy at intermediate times, but the delayed dose achieves improved outcomes at later times.

Non-inferiority comparison

The NWP06-ADD-100 and NWP09-ADHD-300 observed SKAMP were compared for noninferiority (NI) versus the predicted Ritalin® IR SKAMP. The NI margin was -0.25. An absolute difference of less than 0.25 is considered not clinically relevant.

Table 18.: Non-Inferiority (NI) comparison of expected Ritalin® IR SKAMP vs observed Oral Suspension ER ("Suspension", NWP06) and Chewable Tablet ER ("Chewable", NWP09) SKAMP Combined score across the 0.75h – 12h time interval (NI margin = -0.25).

TIME START	TIME END	SKAMP TYPE.NI.COMPARE	mean DIFFERENCE	CI95 lower	CI95 upper	p-value mu025
0.75	12	Ritalin® - Suspension	0.111	0.052	0.17	0
0.75	12	Ritalin® - Chewable	-0.052	-0.168	0.065	0

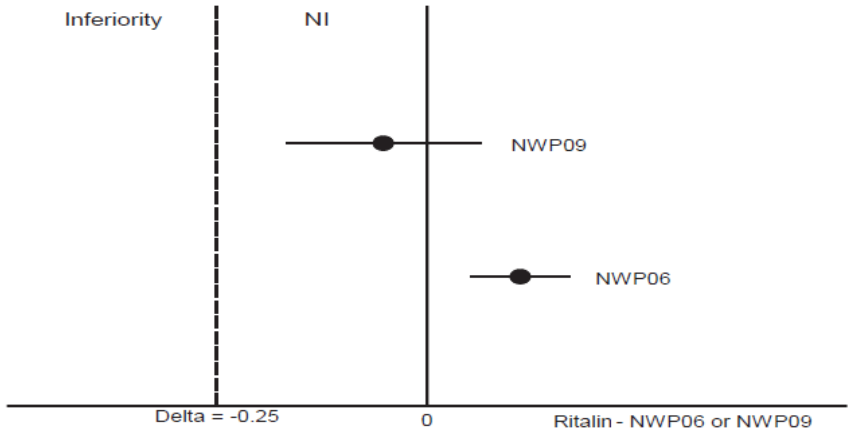


Figure 16. Results of non-inferiority (NI) between Combined SKAMP response in paediatric patients after oral suspension ER (NWP06) or chewable tablet ER (NWP09) formulations versus Ritalin® IR ("Ritalin"). Mean difference (solid circle) and 95% CI shown.

Neither the mean difference in the SKAMP Combined score between oral suspension ER or chewable tablet ER and Ritalin® IR, nor the respective confidence intervals were less than the NI margin of -0.25.

The applicant provided modelling and simulation (M&S) exercise to assess the impact of differences in PK profile shape between ER and IR release formulations on efficacy, represented as SKAMP score in the target population of children with ADHD. The applicant based on the PK/PD published by Gomenin et al., (2020), which was developed for a delayed-release/extended-release methylphenidate formulation to describe the time course of effect in response to range of doses and administration times.

Three adult single-dose, fed, Phase 1 bioavailability studies (including 2 PK BE studies with the EU reference medicinal product used), 1 dedicated PK study in paediatrics and 2 efficacy trials in paediatric population were included in the model. As an outcome in the analysis, the SKAMP score was used. No SKAMP score were available for the reference product Ritalin. SKAMP score results were available from 2 placebo-controlled efficacy studies tested ER formulations, NWP06 and NWP09 (oral suspension ER and chewable tablet ER, respectively) in ADHD paediatric patients aged 6 to 12 years. However, in these 2 studies no PK assessment was performed.

Population PK models were developed for MPH one for each ER and the IR formulations, with random effects estimated on the absorption rate, clearance and volume. Body weight was a pivotal covariate.

Since similarity across ER treatment with respect to the PD outcome was shown, the oral suspension PD parameters were used to predict Ritalin IR expected SKAMP. This was followed by non-inferiority comparison (NI margin 0.25) was conducted among SKAMP observations for ER forms vs IR predictions.

The results of the analysis supported the claimed clinical NI in the 12 hours post dose time frame for the proposed extended-release formulations compared to the IR formulation.

The applicant performed analysis per age groups. It is acknowledged that an average for all post-dose SKAMP-Combined scores the 8 – 10- and 11–12-year-old groups was lower but not statistically significant, probably due to the small sample size.

However, the PKPD model describing the relationship between MPH plasma concentrations and SKAMP scores has limitations. The main limitation should be considered that the dose was titrated based on response in the dataset used to develop the PKPD model.

2.3.2.2. Pharmacokinetic Conclusion

The applicant conducted in total 7 PK/comparative bioavailability studies to support the MAA. Two bioequivalence studies were performed with the EU reference product, and one is considered pivotal for bridging to the EU reference medicinal product and thus allowing the extrapolation of the non-clinical and clinical data of the reference medicinal product in support of this hybrid application. Oral solution formulation has been withdrawn during the procedure.

According to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1), to waive a comparative efficacy and safety study, it is necessary to justify that the different shape of the plasma-concentration time curve has no relevance for efficacy, safety or tolerance development. It is agreed that there are no foreseen safety issues, given the equivalent or lower C_{max} for the MR product, compared to the reference product. However, from the efficacy perspective it is considered that achieving plasma levels above 6 ng/ml and indirect comparisons to approved products is not sufficient to waive a comparative efficacy and safety study with the reference product. Nevertheless, based on the totality of the data provided by the applicant (including placebo-controlled efficacy and safety study with prolonged-release chewable tablet) the CHMP considered the proposed data package sufficient to support a positive opinion for this MAA.

2.3.2.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application since no new pharmacodynamic effects are expected compared to the reference medicinal product.

2.3.3. Discussion on clinical pharmacology

The applicant conducted, in total, 7 PK/comparative bioavailability studies to support the MAA. However, 3 studies were conducted with oral suspension formulation and therefore were not considered essential to support this MAA. Therefore, below only studies conducted with chewable tablets formulation are discussed.

One pivotal bioequivalence study LESVIMETHYL/21/BO-9 (Study 2021-5129) was performed with the EU reference product. Study 2021-5129 was an open label, single dose, randomised, two-period, two-treatment, crossover, comparative bioequivalence study designed to evaluate comparative bioavailability of Methylphenidate HCl 40 mg extended-release chewable tablets (Test product) and Ritalin 10 mg tablets (EU Reference product) in adult healthy volunteers under fed conditions. The overall design of the study is considered adequate.

The 90% CI of the relative mean plasma *d*-methylphenidate $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ of test to reference products were between 80.00 and 125.00%. However, the 90% CI of the relative mean plasma *d*-methylphenidate $AUC_{0\text{-}2}$ of test to reference products were not between 80.00 and 125.00%.

Moreover, the 90% CI of the relative mean plasma *d*-methylphenidate $AUC_{0\text{-}6}$ was not between 80.00 and 125.00%. The shape of the plasma-concentration time curve differs when comparing the MR formulation to the IR formulation.

Dose proportionality was demonstrated for ER chewable tablets of 20 mg, 30 mg and 40 mg in the study 2021-5128.

To conclude, the submitted PK data is sufficient to characterise the PK profile of the applied MR formulation. The applied MR formulation (chewable tablets) shows a similar total bioavailability of methylphenidate as the reference product (IR tablets), but as the concentration-effect curve has a different shape, normally PK data alone would not be sufficient to bridge to the efficacy data of the reference product.

The applicant performed a modelling and simulation exercise, which was intended to support the claimed clinical NI in the 12 hours post dose time frame for the proposed extended-release formulations compared to the IR formulation. However, the PKPD model describing the relationship between MPH plasma concentrations and SKAMP scores has limitations. The main limitation is that the dose was titrated based on the response in the dataset used to develop the PKPD model. The applicant clarified that that a PK/PD model was built to integrate the available data and not to replace a clinical study.

According to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1) it is necessary to justify that the different shape of the plasma-concentration time curve has no relevance for efficacy, safety or tolerance development to waive a comparative efficacy and safety study. There were no new or concerning safety findings reported in the clinical studies provided in the dossier. It is agreed that there are no foreseen safety issues given the equivalent or lower C_{max} for the MR product, compared to the reference product.

However, from the efficacy perspective it is considered that achieving plasma levels above 6 ng/ml and indirect comparisons to approved products is not sufficient to waive a comparative efficacy and safety study. Nevertheless, the totality of the data submitted by the applicant, which included a placebo-controlled efficacy and safety study of prolonged-release chewable tablets were considered sufficient to justify a waiver of the comparative efficacy/safety study.

2.3.4. Clinical efficacy

2.3.4.1. Main study(ies)

Study NWP09-ADHD-300: A Multicenter, Dose-optimized, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of NWP09 in Pediatric Patients with Attention Deficit Hyperactivity Disorder (ADHD) in a Laboratory Classroom

Methods

This was a dose-optimised, randomised, double-blind, placebo-controlled, laboratory classroom study in 90 paediatric patients with ADHD. After Screening and Baseline evaluations were completed, eligible enrolled subjects took open-label NWP09 orally once daily for 6 weeks, beginning with a dose of 20 mg/day. During the 6-week Open-label Dose Optimisation Period, the investigator was allowed to titrate the dose of NWP09 up or down to achieve the optimal dose for efficacy and tolerability.

After completing the Open-label Dose Optimisation Period, subjects were evaluated for ADHD symptoms and signs using the Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) and Permanent Product Measure of Performance (PERMP) assessment in a laboratory classroom setting at multiple time points (abbreviated laboratory classroom day or Visit 8). Subjects who achieved a stable dose of NWP09 and successfully completed the pre-dose and 0.75- and 2-hour post-dose laboratory classroom sessions during Visit 8 were randomised to take double-blind study drug (NWP09

or placebo) orally once daily for 1 week. However, any subjects who did not complete the 4-hour post-dose laboratory session during Visit 8 were to have been withdrawn and not allowed to receive any double-blind study drug.

At the end of the 1-week Double-blind Treatment Period, subjects were evaluated for ADHD symptoms and signs using the SKAMP and PERMP assessment in a laboratory classroom setting at multiple time points throughout the day (complete laboratory classroom day or Visit 9). Seven to 14 days after the complete laboratory classroom day, subjects were contacted by phone or in person to assess any adverse events (AEs) and concomitant medications.

- Study Participants

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or females, aged 6 through 12 years, with a diagnosis of ADHD and need for pharmacologic treatment for their condition. The diagnosis of ADHD had to be made by a qualified practitioner at Screening using the Schedule for Affective Disorders and Schizophrenia (K-SADS), Clinical Global Impression of Severity (CGI-S; score ≥3), and Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS; ≥90th percentile in hyperactive-impulsive subscale, inattentive subscale, or total score).

Randomisation criteria
Study subjects who enrolled into the Open-label Dose Optimisation Period were evaluated for randomisation eligibility at Visit 8. To be randomised to the Double-blind Treatment Period, subjects were required to meet all the following criteria:
• Stable dose of open-label NWP09 (defined as no change in dose between Visits 7 and 8).
• Optimal dose of NWP09 at Visit 8 in the judgment of the investigator.
• No change in medical condition that precluded administration of blinded study drug.
• Completion of the pre-dose and 0.75- and 2-hour post-dose laboratory classroom sessions during Visit 8; however, subjects who did not complete the 4-hour classroom session at Visit 8 were withdrawn from the study and not allowed to receive double-blind study drug.

- Treatments

Study drug (NWP09 or placebo) was administered orally once daily before 10 AM with or without food. Subjects were instructed to chew the tablet(s) thoroughly and swallow. On the morning of Day 2, subjects took their first dose of open-label NWP09 once daily starting at 20 mg/day. The investigator could titrate the dose up (to maximum of 60 mg/day) or down in 10-20 mg/day increments at scheduled study Visits 3, 4, 5, 6, and/or 7 until a stable dose was achieved that was optimal for efficacy and tolerability based on physician clinical judgment.

Investigators were able dose titrate in 10-20 mg/day increments at weekly intervals until an optimal dose or the maximum dose of 60 mg/day is reached. Dose adjustments could be made at the following weekly Study Visits:
- Day 8±2d (Study Visit 3)
- Day 15±2d (Study Visit 4)
- Day 22±2d (Study Visit 5)
- Day 29±2d (Study Visit 6)
- Day 36±2d (Study Visit 7)

The investigator could down-titrate at any time during the Open-label Dose Optimisation Period to ensure subject safety.

- Objectives

Primary objective: to assess the efficacy of NWP09 in paediatric patients with ADHD
Secondary objective: to assess the safety and tolerability of NWP09 in paediatric patients with AD

- Outcomes/endpoints

The primary efficacy variable was the model-adjusted average of all post-dose SKAMP-Combined scores measured on the classroom study day (Visit 9).

Key secondary efficacy variables were the onset and duration of efficacy (clinical effect) of NWP09 versus placebo using the SKAMP-Combined scores at 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose on the classroom study day (Visit 9).

Other secondary efficacy variables included:
• SKAMP-Attention and SKAMP-Deportment subscale scores at Visit 9
• PERMP scores at Visit 9
• CGI-S, Clinical Global Impression of Improvement (CGI-I), ADHD-RS, and Conners' Parent Rating Scale (CPRS) (Visits 1 and 2)

During the laboratory classroom day at Visit 8, the SKAMP scale and PERMP were assessed before administration of open-label NWP09 and 0.75, 2, and 4 hours post-dose. During the laboratory classroom day at Visit 9, the SKAMP scale and PERMP were assessed before administration of double-blind study drug and 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose.

- Sample size

The primary efficacy outcome was the model-adjusted average of all post-dose SKAMP-Combined scores measured during the classroom day (Visit 9). Assuming an effect size of 0.85 between NWP09 and placebo, with approximately 30 subjects in each treatment group completing the double-blind treatment, this study had 90% power at the level of 0.05 (2-sided) using a 2-sample t-test. To allow for potential dropouts, the study planned to enrol approximately 80 subjects to ensure that at least 70 were randomised.

The assumed effect size was a conservative estimate based on differences measured between active and placebo in a previous laboratory classroom study conducted with a similar drug formulation.

- Randomisation and Blinding (masking)

Randomisation to double-blind study drug (NWP09 or placebo) was performed during Visit 8. To participate in randomisation, a subject must have successfully completed the pre-dose and 0.75- and 2-hour post-dose laboratory classroom sessions and met all other randomisation criteria. Subjects also had to complete the 4-hour classroom session at Visit 8 in order to receive blinded study treatment. Subjects were randomised to 1 of the 2 treatment arms in a 1:1 ratio. Subjects in Arm 1 received NWP09, and subjects in Arm 2 received placebo.

During the last week of study drug treatment, the study staff, subjects, and parents/guardians were blinded to treatment assignment (NWP09 or placebo).

- Statistical methods

Analysis populations
Enrolled population – all subjects who gave informed consent (parent/guardian) and assent (child), were initially eligible at Screening, continued to be eligible at Baseline, and were enrolled in the study. Intent-to-treat population – all randomised subjects who received at least 1 dose of double-blind study drug and had at least 1 post-Baseline assessment of the primary efficacy variable. The ITT population formed the basis for the primary and secondary efficacy analyses.

Clinically evaluable population – all Intention-To-Treat (ITT) subjects who received the full prescribed dose of double-blind study drug at the test laboratory classroom day (Visit 9), completed all laboratory classroom tests, did not miss more than 2 days of therapy during the Double-blind Treatment Period, and did not use prohibited medication during the Double-blind Treatment Period.

Enrolled safety population – all enrolled subjects who received at least 1 dose of open-label study drug and had at least 1 post-Baseline safety assessment.

Randomised safety population – all randomised subjects who received at least 1 dose of double-blind study drug and had at least 1 post-Baseline safety assessment.

Efficacy analysis

The primary efficacy variable was the model-adjusted average of all post-dose SKAMP-Combined scores measured on the test classroom day (Visit 9). The primary analysis used the ITT population and a mixed-model, repeated-measures analysis with subject's intercept as a random effect and the following variables as fixed effects:

- Treatment (class effect: NWP09 and placebo)
- Study centre (class effect)
- Time point (class effect: 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose)
- Time point-by-treatment interaction

The average treatment difference over all post-dose time points was estimated using least–squares (LS) means from the mixed-effects, repeated-measures model. The treatment comparison was conducted as a 2-sided test at the 5% level of significance. The standard error and 95% confidence interval (CI) for the treatment difference was provided.

Analyses of the key secondary efficacy variables (onset and duration of efficacy by SKAMP-Combined scores) were performed on the ITT population and repeated on the clinically evaluable population. If the primary efficacy endpoint was statistically significant ($p < 0.05$), the key secondary outcomes of onset and duration of efficacy (clinical effect) of NWP09 versus placebo using the SKAMP-Combined scores would be tested using a fixed-sequence testing procedure. These analyses used the same mixed-model, repeated-measures method as for the primary efficacy variable.

Secondary efficacy analyses included a repeat of the primary analysis on the clinically evaluable population and mixed-model, repeated-measures analyses of SKAMP-Attention, SKAMP-Deportment, and PERMP scores for the ITT and clinically evaluable populations. The latter analyses used the same mixed-model, repeated-measures method as for the primary analysis. The LS means and associated standard error bars were plotted over time by treatment group.

Other efficacy analyses included summaries of CGI-S, CGI-I, ADHD-RS, and CPRS rating scales by time point using descriptive statistics that included the change in CGI-S (i.e., CGI-I), ADHD-RS, and CPRS rating scores from Baseline. The proportion of responders (subjects with a change from baseline in the ADHD-RS of 50% or greater) was also presented.

Results

- Recruitment

Of the 90 subjects enrolled in the open-label dose optimisation period, 86 were randomised, 42 to treatment with NWP09 and 44 to treatment with placebo. Eighty-five subjects (94.4% of the enrolled population) completed the study.

Table 19. Subject Disposition (Enrolled Population)

Disposition	Not Randomized N = 4 n (%)	Placebo N = 44 n (%)	NWP09 N = 42 n (%)	Total N = 90 n (%)
Enrolled	4 (100)	44 (100)	42 (100)	90 (100)
Randomized	--	44 (100)	42 (100)	86 (95.6)
Completed study	--	43 (97.7)	42 (100)	85 (94.4)
Discontinued study	4 (100)[1]	1 (2.3)	0	5 (5.6)
Reason for discontinuation[2]				
Adverse event(s)	1 (25.0)	0	0	1 (20.0)
Protocol deviation	0	0	0	0
Noncompliance	0	0	0	0
Withdrawal of consent	3 (75.0)	0	0	3 (60.0)
Lost to follow-up	0	1 (100)	0	1 (20.0)
Unable to achieve stable dose	0	0	0	0
Other	0	0	0	0

- Conduct of the study

A total of 52 (57.8%) subjects had 144 protocol deviations during the study, 11 of whom had 11 deviations during the double-blind treatment period, i.e., between Visits 8 and 9 or at Visit 9.
The most common category of protocol deviation, overall, was dosing error, which included missed dose, late dose, dosing at home on the practice classroom day (Visit 8), incorrect dose, and lost pill. A total of 97 dosing errors were reported in 46 subjects, or 51.1% of the enrolled population. An incorrect dose was given to 6 subjects during the open-label dose optimisation period. Two of these subjects received an incorrect dose that exceeded the prescribed dose; these dosing errors qualified as major deviations, which are discussed at end of this section.
The second and third most common categories of protocol deviations were other protocol deviation (not otherwise defined) (19 subjects, 21.1%) and informed consent form/consent process deviation (6 subjects, 6.7%), respectively. The predominant subtype of deviation under “other” was an out-of-window time during classroom session of SKAMP or PERMP evaluation(s) for Visit 8.

A total of 9 major deviations were identified in 9 subjects (4 in the NWP09 group and 5 in the placebo group). The major deviations included missed dose of study drug during the double-blind treatment period (5 subjects), taking more than the prescribed dose of study drug (2 subjects), use of exclusionary medication (1 subject), and randomisation error (1 subject).

The impact of these deviations was minimised by the following criteria for inclusion in the ITT population. The ITT population consisted of 85 randomised subjects who received at least 1 dose of double-blind study drug and had at least 1 post-Baseline assessment of the primary efficacy variable. 82 subjects in the ITT population met the 4 criteria to be included in the clinically evaluable population:
1. Received the full prescribed dose of double-blinded study drug at the test laboratory classroom day,
2. Completed all laboratory classroom tests,
3. Did not miss more than 2 days of therapy during the double-blind Treatment Period, and
4. Did not use prohibited medication during the double-blind Treatment Period.

The randomisation error occurred in one subject, who received his assigned bottle of blinded study drug (bottle 431-062, placebo) at randomisation Visit 8, but was inadvertently administered a dose of study drug from bottle 431-061 (active drug) at Visit 9.
The 5 subjects who missed a dose of study drug during the double-blind treatment period missed 1 dose.
Of the 2 subjects who took more than the prescribed dose of study drug, one subject took 2/3 of a pill in the AM and another pill in the PM of a day during the open-label dose optimisation period; one

subject took 2 extra doses between Visits 3 and 4. The prohibited medication taken by one subject was promethazine, which was taken for a viral infection during the open-label dose optimisation period.

- Baseline data

In the ITT population, the overall mean age of subjects was 9.6 years, and a majority of subjects (52.9%) were 8 to 10 years old, male (62.4%), white (57.6%), non-Hispanic/Latino (84.7%), and had combined type ADHD (72.9%). Demographic characteristics were similar between the NWP09 and placebo groups with several exceptions. Compared with the placebo group, the NWP09 group had a smaller proportion of 8–10-year-olds (40.5% versus 65.1%) and a larger proportion of 11–12-year-olds (47.6% versus 16.3%). The NWP09 group also had a larger proportion of males (71.4% versus 53.5%) and whites (64.3% versus 51.2%) and a smaller proportion of black/African Americans (28.6% versus 41.9%). Most subjects (82.2%) did not have any other comorbid psychiatric diagnoses, but of those that did, the most common was oppositional defiant disorder (7.8% of the enrolled safety population).

- Numbers analysed

The enrolled population was composed of 90 subjects who gave informed consent/assent and were eligible up until baseline. Of these subjects, all 90 received at least 1 dose of open-label study drug and had at least 1 post-baseline safety assessment to comprise the enrolled safety population. Eighty-six subjects in the enrolled safety population were included in the randomised safety population, i.e., these subjects received at least 1 dose of double-blind study drug.

The ITT population consisted of 85 randomised subjects who received at least 1 dose of double-blind study drug and had at least 1 post-baseline assessment of the primary efficacy variable. Eighty-two subjects in the ITT population met the 4 criteria to be included in the clinically evaluable population (received the full prescribed dose of double-blind study drug at the test laboratory classroom day, completed all laboratory classroom tests, did not miss more than 2 days of therapy during the double-blind treatment period, and did not use prohibited medication during the double-blind treatment period).

Table 20. Analysis Populations (Enrolled Population)

Population	Not Randomized N = 4 n (%)	Placebo N = 44 n (%)	NWP09 N = 42 n (%)	Total N = 90 n (%)
Enrolled safety	4 (100)	44 (100)	42 (100)	90 (100)
Randomized safety	--	44 (100)	42 (100)	86 (95.6)
Intent-to-treat	--	43 (97.7)	42 (100)	85 (94.4)
Clinically evaluable	--	41 (93.2)	41 (97.6)	82 (91.1)

- Outcomes and estimation

The primary efficacy variable was the model-adjusted average of all post-dose SKAMP-Combined scores measured on the test classroom day (Visit 9).

The model-adjusted average of all SKAMP-Combined scores was statistically significantly lower (i.e., improved) for those receiving NWP09 treatment compared with placebo. The LS mean SKAMP-Combined score was 12.1 in subjects receiving NWP09 compared with 19.1 in subjects receiving placebo (LS mean treatment difference = -7.0; $p < 0.001$).

Table 21. Summary and Analysis of Post-dose SKAMP-Combined Scores at Visit 9 (ITT Population)

Visit 9 Post-dose Time Point Statistic	Placebo N = 43	NWP09 N = 42	Treatment Difference (NWP09 - placebo)
Average over all post-dose time points			
n	43	42	
Mean (SD)	19.0 (10.59)	12.6 (8.90)	
Median (Q1, Q3)	18.1 (11, 22)	9.9 (6, 15)	
Range (min, max)	(3, 46)	(4, 42)	
LS mean (SE)	19.1 (1.39)	12.1 (1.41)	-7.0 (1.99)
95% CI	(16.4, 21.8)	(9.3, 14.9)	(-10.9, -3.1)
p-value			<0.001

CI = confidence interval; ITT = intent-to-treat; LS = least squares; max = maximum; min = minimum; Q = quartile; SD = standard deviation; SE = standard error; SKAMP = Swanson, Kotin, Agler, M-Flynn, and Pelham Rating Scale.

The primary endpoint of the study was met.

Analysis was conducted per age group. The primary endpoint, average for all post-dose SKAMP-Combined scores was statistically significantly lower (i.e. improved) compared to placebo for the 6 – 7-year-old group, and lower but not statistically significant in the 8 – 10- and 11–12-year-old groups. This may be attributed to the small sample size.

ADHD-RS scores for each group show a steady decline week after week (Figures 16, 17 and 18 below)

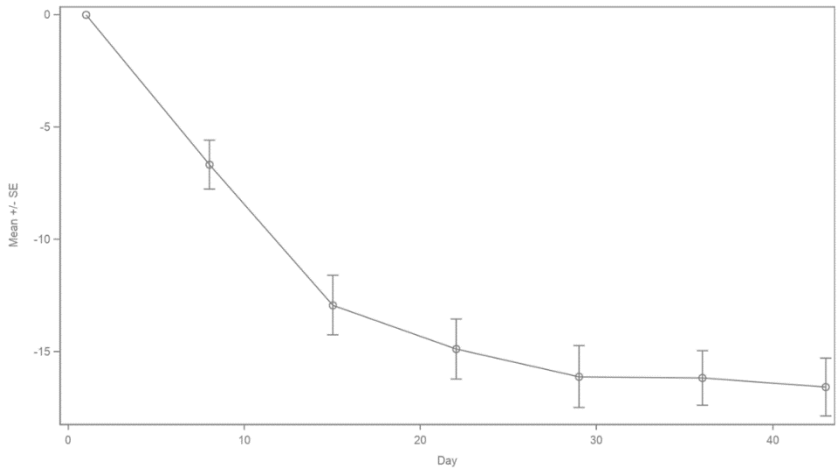


Figure 17. Change in ADHD-RS (6 - 7 Years Old)

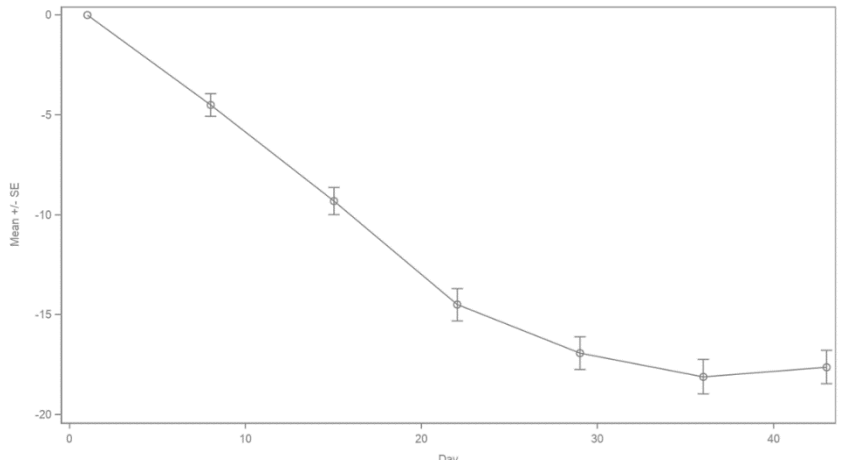


Figure 18. Change in ADHD-RS (8 - 10 Years Old)

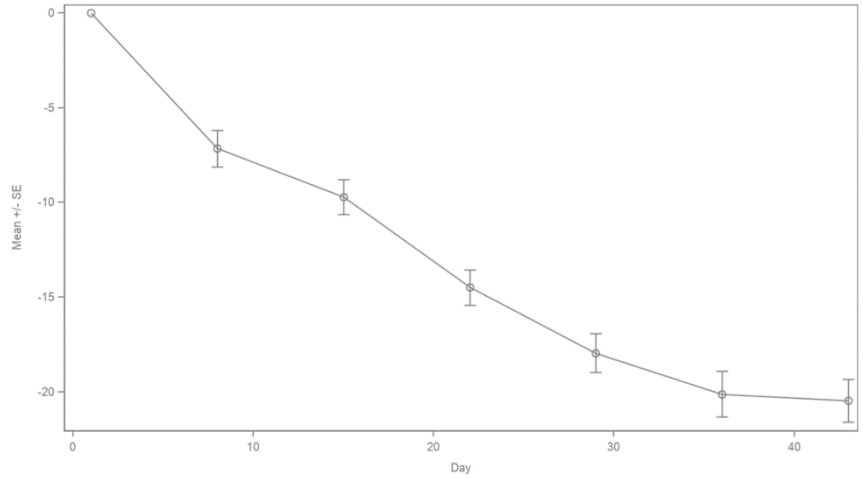


Figure 19. Change in ADHD-RS (11 - 12 Years Old)

Secondary Efficacy Results

The model-adjusted average of all SKAMP-Combined scores was statistically significantly lower for those receiving NWP09 treatment (LS mean = 12.3) than for those receiving placebo treatment (LS mean = 18.1; LS mean treatment difference = -5.8; p = 0.003) in the clinically evaluable population.

Table 22. Summary and Analysis of Post-dose SKAMP-Combined Scores at Visit 9 (Clinically Evaluable Population)

Visit 9 Post-dose Time Point Statistic	Placebo N = 41	NWP09 N = 41	Treatment Difference (NWP09 - placebo)
Average over all post-dose time points			
n	41	41	
Mean (SD)	18.1 (9.99)	12.8 (8.95)	
Median (Q1, Q3)	17.6 (11, 22)	10.0 (6, 15)	
Range (min, max)	(3, 46)	(4, 42)	
LS mean (SE)	18.1 (1.36)	12.3 (1.36)	-5.8 (1.92)
95% CI	(15.4, 20.8)	(9.6, 15.0)	(-9.6, -2.0)
p-value			0.003

CI = confidence interval; ITT = intent-to-treat; LS = least squares; max = maximum; min = minimum; Q = quartile; SD = standard deviation; SE = standard error; SKAMP = Swanson, Kotin, Agler, M-Flynn, and Pelham Rating Scale.

In the sensitivity analysis, SKAMP-Combined scores were statistically significantly lower for those receiving NWP09 compared with placebo at 0.75, 2, 4, and 8 hours post-dose.

Table 23. Sensitivity Analysis of Primary Efficacy and Key Secondary Efficacy Results (SKAMP-Combined Scores at Visit 9) via an Unstructured Covariance Matrix (ITT Population)

Visit 9 Post-dose Time Point	Treatment Difference (NWP09 - placebo) LS Mean (SE)	Nominal P-value	Adjusted P-value
Average over all post-dose time points	-7.0 (1.99)	<0.001	
0.75 hours post-dose	-8.2 (2.32)	<0.001	0.122
2 hours post-dose	-12.8 (2.20)	<0.001	<0.001
4 hours post-dose	-12.3 (2.18)	<0.001	<0.001
8 hours post-dose	-7.8 (2.18)	<0.001	<0.001
10 hours post-dose	-3.5 (2.21)	0.122	0.122
12 hours post-dose	-2.9 (2.55)	0.257	0.122
13 hours post-dose	-1.6 (2.33)	0.500	0.122

ITT = intent-to-treat; LS = least squares; SE = standard error; SKAMP = Swanson, Kotin, Agler, M-Flynn, and Pelham Rating Scale.

NOTE: Nominal p-values were generated using a repeated measures analysis, with treatment (NWP09/Placebo), study center, time point, and time point by treatment interaction as main effects using an unstructured within-subject covariance matrix, with SKAMP-Combined score as the dependent variable. Adjusted p-values were generated using a fixed sequence testing procedure from p-values generated from the model.

Key Secondary Efficacy Variables

The key secondary efficacy variables were the onset and duration of efficacy (clinical effect) of NWP09 versus placebo using the SKAMP-Combined scores at 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose on the classroom study day (Visit 9). The analyses of the key secondary efficacy variables were performed on the ITT population and repeated on the clinically evaluable population.

In the ITT population, SKAMP-Combined scores were statistically significantly lower for those receiving NWP09 compared with placebo at 0.75, 2, 4, and 8 hours post-dose. When the p-values were adjusted

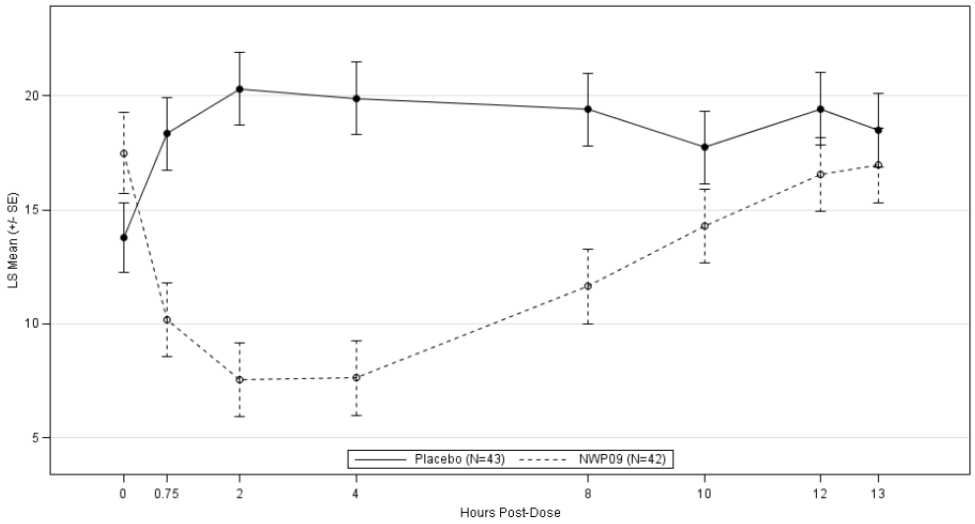
using a fixed sequence testing procedure, the treatment difference was no longer statistically significant at 0.75 hour post-dose (p = 0.133).

Therefore, based on the statistical analysis methodology used in this study, the onset of efficacy was determined to be 2 hours post-dose, and efficacy was maintained through the 8-hour time point. The LS mean of the statistically significant treatment difference between NWP09 and placebo ranged from -7.8 at 8 hours post-dose (p <0.001) to -12.8 at 2 hours post-dose (p <0.001). No statistically significant differences were observed after 8 hours post-dose.

Table 24. Analysis of Post-dose SKAMP-Combined Scores at Visit 9 (ITT Population)

Visit 9 Post-dose Time Point	Treatment Difference (NWP09 – Placebo) LS Mean (SE)	Nominal p-value	Adjusted p-value
Average over all post-dose time-points	-7.0 (1.99)	<0.001	
0.75 hour post-dose	-8.2 (2.28)	<0.001	0.133
2 hours post-dose	-12.8 (2.28)	<0.001	<0.001
4 hours post-dose	-12.3 (2.28)	<0.001	<0.001
8 hours post-dose	-7.8 (2.28)	<0.001	<0.001
10 hours post-dose	-3.4 (2.28)	0.133	0.133
12 hours post-dose	-2.9 (2.28)	0.206	0.133
13 hours post-dose	-1.6 (2.28)	0.496	0.133

ITT = intent-to-treat; LS = least squares; SE = standard error; SKAMP = Swanson, Kotin, Agler, M-Flynn, and Pelham Rating Scale.



ITT = intent-to-treat; LS = least squares; SE = standard error; SKAMP = Swanson, Kotin, Agler, M-Flynn, and Pelham Rating Scale.

Figure 19. SKAMP-Combined Scores Over Time (LS Mean ± SE) by Treatment Group (ITT Population)

The onset of efficacy was shown to be 2 hours post-dose. No statistically significant effect was observed after 8 h post-dose.

Secondary Efficacy Variables

SKAMP-Attention and SKAMP-Deportment Scores

In general, SKAMP subscale scores in the ITT population paralleled the SKAMP-Combined score. For the Attention and Deportment subscales, scores were statistically significantly lower for those receiving NWP09 than for those receiving placebo at 0.75, 2, 4, and 8 hours after dosing during Visit 9.

Results for the SKAMP-Attention and SKAMP-Deportment subscale scores at each post-dose time point in the clinically evaluable population were similar to those in the ITT population, except that significant differences were not observed at any time points subsequent to 4 hours post-dose for the SKAMP-Deportment subscale.

PERMP Scores

At the 0.75, 2, 4, and 8 hour post-dose time points evaluated during the laboratory classroom day, the number of problems attempted, and the number of problems correct on the PERMP were statistically significantly higher for those receiving treatment with NWP09 compared with placebo in the ITT population.

For the number of problems attempted, the LS mean of the treatment difference between NWP09 and placebo ranged from 25.3 at 0.75 hours post-dose (p = 0.024) to 36.1 at 2 hours post-dose (p = 0.001). For the number of problems correct, the LS mean of the treatment difference between NWP09, and placebo ranged from 22.6 at 0.75 hour post-dose (p = 0.049) to 34.4 at 2 hours post-dose (p = 0.003).

PERMP score results in the clinically evaluable population were similar to those in the ITT population, except that significant differences were not observed until 2 hours post-dose for the PERMP score for number of problems correct.

Table 25. Summary and Analysis of Post-dose PERMP Scores at Visit 9 (ITT Population)

Visit 9 Post-dose Time Point Statistic	Placebo N = 43	NWP09 N = 42	Treatment Difference (NWP09-placebo)
Number of problems attempted			
Average over all post-dose time points			
n	43	42	
Mean (SD)	102.9 (48.99)	125.6 (54.70)	
Median (Q1, Q3)	99.4 (65, 133)	117.7 (80, 162)	
(min, max)	(21, 224)	(45, 312)	
LS mean (SE)	103.5 (7.20)	128.0 (7.30)	24.5 (10.25)
95% CI	(89.4, 117.6)	(113.7, 142.4)	(4.4, 44.7)
p-value			0.017

CI = confidence interval; ITT = intent-to-treat; LS = least squares; max = maximum; min = minimum; Q = quartile; SD = standard deviation; SE = standard error; PERMP = Permanent Product Measure of Performance.

Examination of Subgroups

The primary, key secondary, and secondary efficacy analyses were repeated for the following subgroups:

- Final dose (20 mg, 30/40 mg, and 50/60 mg)
- Age (6-7 years, 8-10 years, and 11-12 years)
- Gender (male and female)
- Type of ADHD (inattentive, hyperactive/impulsive, combined, and not otherwise specified)
- Clinical site (SKAMP-Combined scores only)
- Race (SKAMP-Combined scores and SKAMP-subscale scores only)

NOTE: The number of subjects in each subgroup is typically small, and the study was not powered to detect differences between the subgroups.

SKAMP-Combined Scores

Improvement in SKAMP-Combined scores with NWP09 treatment compared with placebo treatment varied by final dose. For those subjects with a final dose of 20 mg (placebo n = 7, NWP09 n =4), there was not a significant treatment difference on average or at any individual postdose time point during Visit 9. For subjects receiving 30 mg or 40 mg (placebo n = 17, NWP09 n = 19) of NWP09 treatment, there was a significant treatment difference (LS mean = -7.0, p = 0.034) observed at 2 hours post-dose compared with placebo treatment.

No other significant differences were observed at this dose. For those subjects with a final dose of 50 mg or 60 mg (placebo n = 19, NWP09 n = 19), the LS mean of the treatment difference between NWP09 and placebo was significant at 0.75, 2, 4, and 8 hours post-dose and averaged over all post-dose time points (p = 0.003).

Statistically significantly improvements in SKAMP-Combined scores at Visit 9 with NWP09 treatment compared with placebo treatment were observed for all age groups. The largest treatment difference was observed in 6–7-year-old subjects (placebo n = 8, NWP09 n = 5) at 2 hours post-dose when the LS mean of the treatment difference was -25.9 (p <0.001). There were significant treatment effects observed in the 6–7-year-old age group beginning at 0.75 hour post-dose (-15.6, p = 0.033) and lasting through 4 hours post-dose (-19.9, p = 0.007). Significant treatment differences were observed in 8–10-year-olds (placebo n = 28, NWP09 n = 17) at the 2-hour (-8.5, p = 0.008) and 4-hour time points (-10.8, p <0.001). In the 11–12-year age group (placebo n = 7, NWP09 n = 20), a significant treatment difference was only observed at the 2-hour time-point dose, when the LS mean of the treatment difference was -9.6 (p = 0.027).

Statistically significantly improvements in SKAMP-Combined scores at Visit 9 with NWP09 treatment compared with placebo treatment were observed for both males (placebo n = 23, NWP09 n = 30) and females (placebo n = 20, NWP09 n = 12). For male subjects, the LS mean of the treatment difference averaged over all time points was -12.2 (p <0.001) with significant treatment differences observed at 0.75 hours post-dose (-12.9, p <0.001) lasting through 12 hours post-dose (-7.5, p = 0.012). The largest treatment difference in males was observed at 2 hours post-dose when the LS mean of the treatment difference was -19.7 (p <0.001). For female subjects, the LS mean of the treatment difference averaged over all time points was not significant (-3.3, p = 0.189); however, significant treatment differences were observed at 2 hours post-dose (-6.3, p = 0.040) lasting through 4 hours post-dose (-6.7, p = 0.028).
SKAMP-Combined scores were statistically significantly lower with NWP09 treatment than with placebo treatment for subjects with both combined (placebo n = 32, NWP09 n = 30) and inattentive (placebo n = 11, NWP09 n = 12) type ADHD.

Both types showed significant treatment differences at 0.75 hours post-dose, with effects lasting through 10 hours for inattentive type (-9.0, p = 0.029) and 8 hours for combined type ADHD (-8.0, p = 0.003). There were no subjects in the study with hyperactive/impulsive type ADHD.

Statistically significant treatment differences between NWP09 and placebo were observed at all sites except Sites 01 and 02. The analysis of SKAMP-Combined Scores by site revealed no significant treatment differences between subjects receiving NWP09 treatment compared with placebo treatment at Site 01 (placebo n= 8, NWP09 n = 9) and Site 02 (placebo n = 6, NWP09 n = 7). Significant treatment differences were observed for the average over all post-dose time points, with significant treatment differences observed at 0.75 hours post-dose lasting through 4, 8, and 10 hours post-dose at Site 03 (placebo n = 7, NWP09 n = 7), Site 06 (placebo n = 7, NWP09 n = 7), and Site 07 (placebo n = 7, NWP09 n = 6), respectively. A statistically significant treatment difference between NWP09 and placebo was observed at Site 04 (placebo n = 8, NWP09 n = 6) but only at 4 hours post-dose (-6.1, p = 0.017).

SKAMP-Subscale Scores

Results for the SKAMP subscale scores by final dose, ADHD type, and race are similar to those for the combined scores. Those receiving 50 mg or 60 mg as the final dose had statistically significant treatment differences at multiple time points for both SKAMP subscale scores. Significant treatment differences were also observed at multiple time points for 11–12-year-olds, subjects with both types of ADHD (inattentive and combined) and for white and black/African American subjects.

For the age subgroup analysis with SKAMP-Attention scores, the only time point when significant treatment differences were observed was at 2 hours post-dose among 6–7-year-olds, and at 4 hours post-dose among 8–10-year-olds; however, for 11-12 year-olds significant treatment differences were observed beginning at 0.75 hour post-dose and lasting through 4 hours post-dose. Results for the SKAMP-Deportment subscale scores were similar to those for the combined scores for 8–10-year-olds, but not for the other age groups. Significant treatment differences were observed among subjects in the 6–7-year age group at 0.75, 2 and 4 hours post-dose, and no significant treatment differences were observed among 11–12-year-olds at any post-dose time point for the SKAMP-Deportment subscale scores.

Results for the SKAMP subscale scores are similar to those for the combined scores for males, but not for females. There were no significant treatment differences observed among females for SKAMP-Attention scores, and the only time points where significant treatment differences were observed for the SKAMP-Deportment subscale were at 0.75 and 4 hours post-dose.

Safety evaluation

All 90 subjects in the enrolled safety population were exposed to the 20-mg daily dose of NWP09. The number of subjects exposed to higher daily doses of NWP09 tended to decrease with increasing dose, ending with 21 subjects exposed to the 60-mg dose of NWP09.

Forty-three subjects received placebo during the study. The mean (SD) durations of exposure to any daily dose of NWP09 during the Double-blind Treatment Period, Open-label Dose Optimisation Period, and entire study were 6.9 (0.26) days, 41.2 (4.80) days, and 44.5 (6.37) days, respectively. During the Double-blind Treatment Period, the mean length of exposure to all daily doses of NWP09 and placebo was approximately 7 days, the same as the duration of the study period. During the Open-label Dose Optimisation Period, the mean (SD) duration of exposure was longest for the highest daily dose of NWP09: 18.7 (8.55) days for NWP09 60 mg versus a mean duration of 11.6 (10.39) to 14.8 (9.31) days for NWP09 20 mg and NWP09 40 mg, respectively. This pattern was also observed for the entire study: 22.0 (9.73) days for NWP09 60 mg versus a mean duration of 11.9 (11.08) to 16.4 (11.43) days for NWP09 20 mg and NWP09 40 mg, respectively. The majority (61.1%) of subjects in the enrolled safety population were exposed to NWP09 for over 43 days. The mean (SD) daily dose of NWP09 during the entire study was 33.0 (9.01) mg.

Exposure to Final Daily Dose of NWP09 as Assigned for the Double-blind Treatment Period
The number of subjects receiving a given final (assigned) daily dose of NWP09 ranged from 11 subjects for NWP09 20 mg to 25 subjects for NWP09 40 mg.

During the Double-blind Treatment Period, the mean duration of exposure to each final (assigned) daily dose of treatment was approximately 7 days. During the Open-label Dose Optimisation Period, the mean (SD) duration of exposure was longest for the lowest final dose of NWP09: 37.0 (7.78) days for NWP09 20 mg versus a duration of 18.8 (6.63) to 27.6 (10.08) days for NWP09 50 mg and NWP09 30 mg, respectively.

Adverse Events
No deaths, SAEs, severe AEs, or life-threatening AEs were reported during any study Period.

A total of 24 subjects (approximately 28% of the randomised safety population) reported at least 1 TEAE during the 1-week Double-blind Treatment Period. The proportions of subjects with TEAEs were

generally similar between the NWP09 and placebo groups (26.2% and 29.5%, respectively). Three subjects (1 placebo, 2 NWP09) had TEAEs considered related to study drug during the Double-blind Treatment Period. Sixty-five subjects (72.2% of the enrolled safety population) reported at least 1 TEAE during the 6-week Open-label Dose Optimisation Period. Fifty-two subjects (57.8%) had TEAEs considered related to study drug during this period. Two subjects experienced TEAEs that led to premature discontinuation of study drug. A similar overall pattern of TEAEs was observed for the randomised safety population, except that no subject had a TEAE leading to premature discontinuation of study drug.

During the entire study, the frequency of TEAEs was slightly greater in the NWP09 group than the placebo group (78.6% versus 70.5%). Fourteen subjects reported AEs during the pretreatment period, and 5 subjects (4 in the NWP09 group and 1 in the placebo group) reported AEs during the follow-up period.

Table 26. Overview of Treatment-emergent Adverse Events During the Entire Study (Enrolled Safety Population)

Category of Event	Not Randomized N = 4 n (%)	Placebo N = 44 n (%)	NWP09 N = 42 n (%)	Total N = 90 n (%)
TEAEs	7	122	114	243
Subjects with any TEAEs	3 (75.0)	31 (70.5)	33 (78.6)	67 (74.4)
Treatment-related TEAEs	5	74	65	144
Subjects with any treatment-related TEAEs[1]	3 (75.0)	25 (56.8)	25 (59.5)	53 (58.9)
Severe TEAEs	0	0	0	0
Subjects with any severe TEAEs	0	0	0	0
Serious TEAEs	0	0	0	0
Subjects with any serious TEAEs	0	0	0	0
Subjects who died	0	0	0	0
Subjects with TEAEs leading to premature discontinuation of study drug[2]	2 (50.0)	0	0	2 (2.2)

Displays of Adverse Events Double-blind Treatment Period

A total of 24 (approximately 28%) subjects experienced TEAEs during this period, with the frequency being generally similar between the NWP09 and placebo groups (26.2% and 29.5%, respectively). During the DB period the most common system organ classes of TEAEs in both treatment groups were infections and infestations (7.1% and 9.1% for NWP09 and placebo, respectively); injury, poisoning, and procedural complications (4.8% and 11.4%); and psychiatric disorders (2.4% and 6.8%).

Table 27. Treatment-emergent Adverse Events During the Double-blind Treatment Period (Randomised Safety Population)

System Organ Class Preferred Term	Placebo N = 44 n (%)	NWP09 N = 42 n (%)
All TEAEs	13 (29.5)	11 (26.2)
Infections and infestations	4 (9.1)	3 (7.1)
Upper respiratory tract infection	3 (6.8)	3 (7.1)
Pharyngitis	1 (2.3)	0
Injury, poisoning and procedural complications	5 (11.4)	2 (4.8)
Snake bite	0	1 (2.4)
Subcutaneous hematoma	0	1 (2.4)
Contusion	2 (4.5)	0
Nail injury	1 (2.3)	0
Wound	2 (4.5)	0
Respiratory, thoracic, and mediastinal disorders	0	2 (4.8)
Cough	0	1 (2.4)
Oropharyngeal pain	0	1 (2.4)
Gastrointestinal disorders	1 (2.3)	1 (2.4)
Nausea	0	1 (2.4)
Vomiting	1 (2.3)	0
Investigations	0	1 (2.4)
Weight decreased	0	1 (2.4)
Metabolism and nutrition disorders	1 (2.3)	1 (2.4)
Decreased appetite	0	1 (2.4)
Increased appetite	1 (2.3)	0
Nervous system disorders	1 (2.3)	1 (2.4)
Headache	0	1 (2.4)
Tremor	1 (2.3)	0
Psychiatric disorders	3 (6.8)	1 (2.4)
Aggression	0	1 (2.4)
Emotional poverty	0	1 (2.4)
Anxiety	1 (2.3)	0
Initial insomnia	2 (4.5)	0
General disorders and administration site conditions	1 (2.3)	0
Feeling jittery	1 (2.3)	0
Renal and urinary disorders	1 (2.3)	0
Enuresis	1 (2.3)	0

Open-label Dose Optimisation Period

A total of 65 (72.2%) subjects reported TEAEs during the 6-week Open-label Dose Optimisation Period. The most frequently reported (≥20%) system organ classes of TEAEs were metabolism and nutrition disorders (36.7%), psychiatric disorders (31.1%), gastrointestinal disorders (26.7%), infections and infestations (22.2%), and nervous system disorders (22.2%). The most common (≥5%) preferred terms of TEAEs during this period were decreased appetite (36.7%), upper abdominal pain (14.4%), mood swings (13.3%), irritability (13.3%), insomnia (11.1%), upper respiratory tract infection (11.1%), dysgeusia (8.9%), and headache (8.9%). The randomised safety population had a generally similar pattern of TEAEs during the Open-label Dose Optimisation Period.

Table 28. Most Common **(≥2%)** Preferred Terms of Treatment-emergent Adverse Events During the Open-label Dose Optimisation Period (Enrolled Safety Population)

Preferred Term	NWP09 N = 90 n (%)
All TEAEs	65 (72.2)
Decreased appetite	33 (36.7)
Upper abdominal pain	13 (14.4)
Mood swings	12 (13.3)
Irritability	12 (13.3)
Insomnia	10 (11.1)
Upper respiratory tract infection	10 (11.1)
Dysgeusia	8 (8.9)
Headache	8 (8.9)
Initial insomnia	4 (4.4)
Vomiting	4 (4.4)
Viral infection	4 (4.4)
Tic	3 (3.3)
Dry mouth	3 (3.3)
Nausea	3 (3.3)
Gastroenteritis	3 (3.3)
Excoriation	3 (3.3)
Middle insomnia	2 (2.2)
Abdominal pain	2 (2.2)
Diarrhea	2 (2.2)
Dizziness	2 (2.2)
Lethargy	2 (2.2)
Fatigue	2 (2.2)
Feeling jittery	2 (2.2)
Contusion	2 (2.2)
Laceration	2 (2.2)
Nasal congestion	2 (2.2)
Oropharyngeal pain	2 (2.2)
Rhinorrhea	2 (2.2)
Tachycardia	2 (2.2)
Tinnitus	2 (2.2)

Adverse Event Severity

For 19.0% of NWP09 subjects and 27.3% of placebo subjects, the greatest severity of TEAE during this period was mild. Four subjects (3 in the NWP09 group and 1 in the placebo group) had at least 1 moderate TEAE during the Double-blind Treatment Period. The moderate TEAEs in the NWP09 group were upper respiratory tract infection, aggression (1 of 2 moderate events in the same subject), emotional poverty (second moderate event in the same subject), and decreased appetite. The moderate TEAE in the placebo group was enuresis. No severe, life-threatening, or fatal TEAEs were reported during the Double-blind Treatment Period.

Table 29. Severity of Treatment-emergent Adverse Events During the Double-blind Treatment Period (Randomised Safety Population)

Severity Preferred Term (for moderate or greater severity)	Placebo N = 44 n (%)	NWP09 N = 42 n (%)
Mild	12 (27.3)	8 (19.0)
Moderate	1 (2.3)	3 (7.1)
Upper respiratory tract infection (Subject 03-045)		1 (2.4)
Aggression (Subject 02-100)		1 (2.4)
Emotional poverty (Subject 02-100)		1 (2.4)
Decreased appetite (Subject 01-006)		1 (2.4)
Enuresis (Subject 02-089)	1 (2.3)	
Severe	0	0
Life-threatening	0	0
Fatal	0	0

Open-label Dose Optimisation Period

During this period, 19 (21.1%) subjects reported a greatest TEAE severity of mild, and 46 (51.1%) reported a greatest severity of moderate. No higher grade of TEAE severity was reported during the Open-label dose optimisation period. Four subjects (3 in the NWP09 group and 1 in the placebo group) had at least 1 moderate TEAE during the double-blind treatment period. The moderate TEAEs in the NWP09 group were upper respiratory tract infection, aggression (1 of 2 moderate events in the same subject), emotional poverty (second moderate event in the same subject), and decreased appetite. The pattern of TEAE severity in the randomised safety population during the Open-label dose optimisation period was generally similar to the enrolled safety population.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Potentially clinically significant vital sign values

A total of 13 (15.1%) subjects had increases in DBP from Baseline of ≥10 mmHg during the double-blind treatment period, which was the most frequent PCS vital sign abnormality during this period. The proportions of subjects with this abnormality were similar between the NWP09 and placebo groups (14.3% and 15.9%, respectively). The number of subjects with PCS vital sign values in all other category was 3 or less.

Table 30. Potentially Clinically Significant Vital Sign Values During the Double-blind Treatment Period (Randomised Safety Population)

Vital Sign Variable PCS Category	Placebo N = 44 n (%)	NWP09 N = 42 n (%)	Total N = 86 n (%)
Systolic blood pressure			
Post-Baseline value >95th percentile	1 (2.3)	2 (4.8)	3 (3.5)
Increase from Baseline of ≥20 mmHg	1 (2.3)	0	1 (1.2)
Diastolic blood pressure			
Post-Baseline value >95th percentile	0	0	0
Increase from Baseline of ≥10 mmHg	7 (15.9)	6 (14.3)	13 (15.1)
Pulse			
Post-Baseline value >110 bpm	0	1 (2.4)	1 (1.2)
Increase from Baseline of ≥25 bpm	0	2 (4.8)	2 (2.3)

The most frequent PCS vital sign value for the entire study was an increase in DBP from Baseline of ≥10 mmHg (41.1%), followed by a post-Baseline SBP >95th percentile (18.9%) and an increase in pulse rate from Baseline of ≥25 bpm (18.9%). No subject in the nonrandomised group (N = 4) had a PCS vital sign value. The placebo group had a larger proportion of subjects with an increase in DBP

from Baseline of ≥10 mmHg (50.0% versus 35.7% for NWP09), and the NWP09 group had a larger proportion of subjects with a pulse of ≥25 bpm (23.8% versus 15.9% for placebo). The placebo group also had larger proportions of subjects with an increase in SPB from Baseline of ≥20 mmHg (11.4% versus 4.8%) and a post-Baseline DBP >95th percentile (11.4% versus 7.1%).

Table 31. Potentially Clinically Significant Vital Sign Values During the Entire Study (Enrolled Safety Population)

Vital Sign Variable PCS Category	Not Randomized N = 4 n (%)	Placebo N = 44 n (%)	NWP09 N = 42 n (%)	Total N = 90 n (%)
Systolic blood pressure				
Post-Baseline value >95th percentile	0	9 (20.5)	8 (19.0)	17 (18.9)
Increase from Baseline of ≥20 mmHg	0	5 (11.4)	2 (4.8)	7 (7.8)
Diastolic blood pressure				
Post-Baseline value >95th percentile	0	5 (11.4)	3 (7.1)	8 (8.9)
Increase from Baseline of ≥10 mmHg	0	22 (50.0)	15 (35.7)	37 (41.1)
Pulse				
Post-Baseline value >110 bpm	0	4 (9.1)	4 (9.5)	8 (8.9)
Increase from Baseline of ≥25 bpm	0	7 (15.9)	10 (23.8)	17 (18.9)

- Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 32. Summary of efficacy for trial NWP09-ADHD-300

Title: A Multicenter, Dose-optimized, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of NWP09 in Pediatric Patients with Attention Deficit Hyperactivity Disorder (ADHD) in a Laboratory Classroom		
Study identifier	NWP09-ADHD-300	
Design	This was a multicentre, dose-optimised, double-blind, randomised, placebo-controlled laboratory classroom study in 90 paediatric patients with ADHD.	
	Duration of main phase:	Approximately 4 months
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Superiority Primary objective: to assess the efficacy of NWP09 in paediatric patients with ADHD Secondary objective: to assess the safety and tolerability of NWP09 in paediatric patients with ADHD	

Treatments groups	Test product: NWP09		Six-week open-label dose optimisation period NWP09 20-60 mg/day taken orally once daily in the morning before 10:00 am. The starting dose of 20 mg/day could be titrated up or down by the investigator at weekly intervals in 10-20 mg/day increments to achieve a stable dose of 20-60 mg/day. NWP09 batch numbers: TB-104A (20 mg), TB-105A (30 mg), and TB-103A (40 mg) One-week double-blind treatment period Optimal dose of NWP09 from the open-label dose optimisation period (20-60 mg/day) taken orally once daily in the morning before 10:00 am. NWP09 batch numbers: TB-104A (20 mg), TB-105A (30 mg), and TB-103A (40 mg)
	Reference therapy: Placebo		One-week double-blind treatment period Placebo matching optimal dose of NPW09 taken orally once daily in the morning before 10:00 am. Placebo batch numbers: TB-104A (20 mg), TB-105A (30 mg), and TB-103A (40 mg)
Endpoints and definitions	Primary efficacy variable	Efficacy	The primary efficacy variable was the model-adjusted average of all post-dose SKAMP-Combined scores measured on the classroom study day (Visit 9).
	Key secondary efficacy variable	Efficacy	Key secondary efficacy variables were the onset and duration of efficacy (clinical effect) of NWP09 versus placebo using the SKAMP-Combined scores at 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose on the classroom study day (Visit 9).
	Other secondary efficacy variables	Efficacy	• SKAMP-Attention and SKAMP-Deportment subscale scores at Visit 9 • PERMP scores at Visit 9 • CGI-S, Clinical Global Impression of Improvement (CGI-I), ADHD-RS, and Conners' Parent Rating Scale (CPRS) (Visits 1 and 2)
	Safety assessments	Safety	AE recording, blood and urine clinical laboratory tests (haematology, serum chemistry, serum and urine pregnancy, screening for drugs of abuse), vital sign measurements, physical examination, 12-lead electrocardiogram (ECG), and the Columbia Suicide Severity Rating Scale (C-SSRS).
Database lock	03 December 2012		
Results and Analysis			
Analysis description	Primary Analysis		

Analysis population and time point description	The primary efficacy analysis was performed on the ITT population. The primary efficacy variable was the model-adjusted average of all post-dose SKAMP-Combined scores measured on the test classroom day (Visit 9). The primary analysis used mixed-model, repeated-measures analysis with subject's intercept as a random effect and the following variables as fixed effects: • Treatment (class effect: NWP09 and placebo) • Study centre (class effect) • Time point (class effect: 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose) • Time point-by-treatment interaction The null hypothesis was that the model-adjusted average of SKAMP-Combined scores over all post-dose time points on the test classroom day was the same for NWP09 and placebo. The null hypothesis was tested against the 2-sided alternative hypothesis that the model-adjusted average of SKAMP-Combined scores over all post-dose time points on the test classroom day was not the same for NWP09 and placebo. The average treatment difference over all post-dose time points was estimated using least–squares (LS) means from the mixed-effects, repeated-measures model. The treatment comparison was conducted as a 2-sided test at the 5% level of significance. The standard error and 95% CI for the treatment difference was provided.			
Descriptive statistics and estimate variability Primary Efficacy Results *Summary and Analysis of Post-dose SKAMP-Combined Scores at Visit 9 (ITT Population)*	Treatment group	Reference therapy: Placebo	Test product: NWP09	Treatment Difference (NWP09 - placebo)
	Number of subjects	43	42	
	Mean (SD)	19.0 (10.59)	12.6 (8.90)	
	Median (Q1, Q3)	18.1 (11, 22)	9.9 (6, 15)	
	Range (min, max)	(3, 46)	(4, 42)	
	LS mean (SE)	19.1 (1.39)	12.1 (1.41)	-7.0 (1.99)
	95% CI	(16.4, 21.8)	(9.3, 14.9)	(-10.9, -3.1)
	p-value			<0.001
Supportive Analysis of the Primary Efficacy Variable *Summary and Analysis of Post-dose SKAMP-Combined Scores at Visit 9 (Clinically Evaluable Population)*	Treatment group	Reference therapy: Placebo	Test product: NWP09	Treatment Difference (NWP09 - placebo)
	Number of subjects	41	41	
	Mean (SD)	18.1 (9.99)	12.8 (8.95)	
	Median (Q1, Q3)	17.6 (11, 22)	10.0 (6, 15)	
	Range (min, max)	(3, 46)	(4, 42)	
	LS mean (SE)	18.1 (1.36)	12.3 (1.36)	-5.8 (1.92)
	95% CI	(15.4, 20.8)	(9.6, 15.0)	(-9.6, -2.0)
	p-value			0.003

Key Secondary Efficacy Variables *Analysis of Post-dose SKAMP-Combined Scores at Visit 9 (ITT Population)*	Visit 9 Post-dose Time Point	Treatment Difference (NWP09 – Placebo) LS Mean (SE)	Nominal p-value	Adjusted p-value
	Average over all post-dose time-points	-7.0 (1.99)	<0.001	
	0.75 hour post-dose	-8.2 (2.28)	<0.001	0.133
	2 hours post-dose	-12.8 (2.28)	<0.001	<0.001
	4 hours post-dose	-12.3 (2.28)	<0.001	<0.001
	8 hours post-dose	-7.8 (2.28)	<0.001	<0.001
	10 hours post-dose	-3.4 (2.28)	0.133	0.133
	12 hours post-dose	-2.9 (2.28)	0.206	0.133
	13 hours post-dose	-1.6 (2.28)	0.496	0.133

2.3.5. Discussion on clinical efficacy

Efficacy and safety study with chewable tablets was conducted by the applicant in the target population of patients and met it's prespecified primary endpoint.

Study NWP09-ADHD-300 was a dose-optimised, randomised, double-blind, placebo-controlled, laboratory classroom study in 90 paediatric patients with ADHD. After Screening and Baseline evaluations were completed, eligible enrolled subjects took open-label NWP09 orally once daily for 6 weeks, beginning with a dose of 20 mg/day. During the 6-week Open-label Dose Optimisation Period, the investigator was allowed to titrate the dose of NWP09 up or down to achieve the optimal dose for efficacy and tolerability. Titration was performed at weekly intervals in increments of 10-20 mg/day until the optimal dose or a maximum dose of 60 mg/day was reached. Subjects unable to tolerate a minimum dose of 20 mg/day or unable to achieve a stable dose (no change between Visits 7 and 8) during the open-label dose optimisation period were discontinued from the study. After completing the Open-label Dose Optimisation Period, subjects were evaluated for ADHD symptoms and signs using the Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) and Permanent Product Measure of Performance (PERMP) assessment in a laboratory classroom setting at multiple time points (abbreviated laboratory classroom day, or Visit 8). Subjects who achieved a stable dose of NWP09 and successfully completed the pre-dose and 0.75- and 2-hour post-dose laboratory classroom sessions during Visit 8 were randomised to take double-blind study drug (NWP09 or placebo) orally once daily for 1 week. However, any subjects who did not complete the 4-hour post-dose laboratory session during Visit 8 were to have been withdrawn and not allowed to receive any double-blind study drug.

At the end of the 1-week double-blind treatment period, subjects were evaluated for ADHD symptoms and signs using the SKAMP and PERMP assessment in a laboratory classroom setting at multiple time points throughout the day (complete laboratory classroom day, or Visit 9). Seven to 14 days after the complete laboratory classroom day, subjects were contacted by phone or in person to assess any adverse events (AEs) and concomitant medications.

The primary efficacy variable was the model-adjusted average of all post-dose SKAMP-Combined scores measured on the test classroom day (Visit 9).

The model-adjusted average of all SKAMP-Combined scores was statistically significantly lower (i.e., improved) for those receiving NWP09 treatment compared with placebo. The LS mean SKAMP-Combined score was 12.1 in subjects receiving NWP09 compared with 19.1 in subjects receiving placebo (LS mean treatment difference = -7.0; p <0.001).

Tuzulby is considered approvable from an efficacy perspective.

2.3.6. Clinical safety

Please see details for individual studies in section 2.3.4.

2.3.6.1. Post marketing experience

The applicant provided a concise summary of post-marketing safety data for both QUILLIVANT XR® (methylphenidate hydrochloride), and QuilliChew ER® (methylphenidate hydrochloride) extended-release chewable tablets, focused on adverse events (AEs), and presence of any emerging safety signals. The data from the FDA adverse Event Reporting System (FAERS), literature search, and Periodic Adverse Drug Experience Report (PADERs) were summarised.

The most common reported adverse reactions for Quillivant XR in the period from 2013 to September 2024 were “General disorders and administration site conditions (956 cases)”.

It is agreed that both Quillivant XR and QuilliChew ER maintain favourable safety profiles with no clinically significant safety signals identified in post-marketing surveillance.

2.3.7. Conclusions on clinical aspects

Based on the totality of the submitted data Tuzulby can be considered bioequivalent with the reference product Ritalin, since overall the data support that the differences in the shape of the plasma-concentration time curve have no relevance for efficacy, safety or tolerance development. Based on the totality of data is it agreed that waiving a comparative efficacy and safety study against an active comparator is acceptable. Further details are provided below.

To support the application, the applicant has submitted pivotal comparative bioavailability study with the EU reference medicinal product (2021-5129), 1 dose proportionality study (2021-5128), 2 supportive US bioavailability studies (509-0238 and 2012-2950), 1 supportive single dose PK study in the target population (NWP06-PPK-101), 1 study evaluating tablet and oral suspension formulation BA (C11-0082) under fasted conditions, additional BE study (2021-5130), 2 Phase 3 efficacy and safety studies (significant clinical data NWP09-ADHD-300 and study NWP06-ADD-100) and M&S study evaluating PD properties of methylphenidate hydrochloride in an oral suspension and a chewable tablet formulation versus the reference medicinal product.

The design of pivotal comparative bioavailability study (open-label, single-dose, randomised, two-period, two-treatment, two sequence, crossover, in healthy subjects under fed conditions, EU comparator) is considered adequate. The results of study 2021-5129 with 40 mg formulation can be extrapolated to other strengths of 20 mg and 30 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

Dose proportionality was demonstrated for ER chewable tablets of 20 mg, 30 mg and 40 mg in the study 2021-5128.

The applicant performed modelling and simulation exercise, which was intended to support the claimed clinical NI in the 12 hours post dose time frame for the proposed extended-release formulations compared to the IR formulation. However, the PKPD model describing the relationship between MPH plasma concentrations and SKAMP scores has limitations. The main limitation is that the dose was titrated based on response in the dataset used to develop the PKPD model. The applicant clarified that a PK/PD model was built to integrate the available data and not to replace a clinical study.

According to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1) it is necessary to justify that the different shape of the plasma-concentration time curve has no relevance for efficacy, safety or tolerance development to waive a comparative efficacy and safety study. It is agreed that there are no foreseen safety issues given the equivalent or lower Cmax for the MR product, compared to the reference product.

However, from the efficacy perspective it is considered that achieving plasma levels above 6 ng/ml and indirect comparisons to approved products is not sufficient to waive a comparative efficacy and safety study.

In response to the concern that the main limitation of the PD data used to develop the model is related to the fact that the individual dose was titrated based on efficacy, which can give considerable bias in the estimated exposure-response relationship, the applicant clarified that there is a fluctuation in SKAMP scores throughout the day that is linked to fluctuations in plasma concentrations. The applicant noted that an increase in dose of approximately 33%, from 30 mg to 40 mg, resulted in an approximate absolute difference of about 47%. Nevertheless, it should be noted that it is not possible to adequately characterise the exposure-response relationship in case the individual doses are titrated based on response.

With respect to concerns regarding adequacy of the proposed threshold of 6 ng/mL as the minimum dose to achieve efficacy with MPH, the applicant clarified that it was based on PET study results (estimation of dopamine transporter occupancies after different doses of oral MPH in healthy subjects) and clinical data demonstrating that plasma concentrations below 6 ng/mL for d-MPH enantiomer should not be expected to affect sleep. Moreover, the minimum effective concentration in adults and children for d-MPH, according to the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) guideline, are 6 ng/ml and 3 ng/ml, respectively.

While the rationale behind the 6 ng/mL threshold is acknowledged, even if plasma levels above this threshold support an overall clinical effect of the formulation, the shape of the plasma concentration-time curve may influence the efficacy profile over the day, onset, offset, effect magnitude etc. Thus, showing that a formulation results in plasma levels above 6 ng/ml is itself not sufficient to demonstrate that the differences in the shape of the plasma-concentration time curve have no relevance for efficacy, and that comparative efficacy and safety studies can be waived.

The applicant provided a summary of a systematic review of head-to-head studies of marketed long-acting MPH formulations in the treatment of ADHD, which showed comparable efficacy results between all the products assessed (Coghill et al., 2013). It was noted that, although differences in PK profiles, all formulations should be expected to be efficacious since all included products are marketed.

The applicant also referred to Lopez et al. study, which showed comparable efficacy up to 8 to 12 h post-dose between Concerta and Ritalin LA despite different PK shape profiles. Similarly, despite the differences of profile shape between Ritalin LA and Medikinet Retard, the combined SKAMP scores were considered similar in the first 4.5 hrs period. However, even if it can be considered as supportive information that other ER products have been approved, it is not agreed that such indirect comparisons to marketed products can be considered as sufficient information to waive a comparative study.

However, the main efficacy and safety study was conducted by the applicant in the target population of patients with ADHD. The study included a double-blind, placebo-controlled period. The PEP was met (the model adjusted average of all post-dose SKAMP-Combined scores in main study NWP09-ADHD-300 and SKAMP-Combined score at 4 hours post dose, in NWP06-ADD-100 study included in the M&S).

It is acknowledged that the main efficacy and safety study was conducted against a placebo comparator and not against an immediate release formulation. However, it can be agreed that the totality of the data provided by the applicant, consisting of a bioequivalence study 2021-5129 (LESVIMETHYL/21/BQ-9), which is pivotal for bridging to the non-clinical and clinical studies of the reference medicinal product, significant clinical data in efficacy/safety study (NWP09-ADHD-300) and additional data (1 BE study (2021-5130), 1 dose proportionality study (2021-5128), 2 supportive US bioavailability studies (509-0238 and 2012-2950), 1 supportive single dose PK study in the target population (NWP06-PPK-101), 1 study evaluating tablet and oral suspension formulation BA (C11-0082) under fasted conditions, Phase 3 efficacy and safety studies NWP06-ADD-100) and M&S study evaluating PD properties of methylphenidate hydrochloride in an oral suspension and a chewable tablet formulation versus the reference medicinal product) allowing to waive comparative efficacy and safety clinical studies in accordance with the Guideline, is considered adequate to justify a positive B/R of Tuzulby in the proposed indication.

A summary of the literature with regard to clinical data of methylphenidate was provided and is accepted by the CHMP.

2.4. Risk Management Plan

2.4.1. Safety concerns

Summary of safety concerns	
Important identified risks	Serious cardiovascular events Psychosis/Mania Verbal or motoric tics Depression Aggression Drug abuse/Drug dependence Withdrawal syndrome Reduced weight gain* Decreased rate of growth* Seizures Cerebrovascular disorders Neonatal toxicity**
Important potential risks	Suicidality Sexual Maturation delayed*
Missing information	Long-term effects

* Only relevant for products with paediatric indications.

** Only relevant for products with adult indications.

2.4.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.4.3. Risk minimisation measures

None.

2.4.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.5. Pharmacovigilance

2.5.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.5.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Product information

2.6.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed. The applicant presented a bridging report making reference to the full user consultation with target patient groups performed with another pharmaceutical form of the medicinal product (withdrawn during assessment), which was found acceptable. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This PUMA application concerns a hybrid version of methylphenidate prolonged-release chewable tablets (application for prolonged-release oral suspension was withdrawn during assessment). The reference product Ritalin 10 mg tablets is indicated as part of a comprehensive treatment programme for attention-deficit / hyperactivity disorder (ADHD) in children aged 6 years of age and over. No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient by the CHMP.

From a clinical perspective, this application contains new data on the pharmacokinetics. Pivotal study LESVIMETHYL/21/BO-9 (Study 2021-5129) was an open label, single dose, randomised, two-period, two-treatment, crossover, comparative bioequivalence study designed to evaluate comparative bioavailability of Methylphenidate HCl 40 mg extended-release chewable tablets (Test product) and Ritalin 10 mg tablets (EU Reference product) in adult healthy volunteers under fed conditions.

The overall design of the study is considered adequate to characterise the PK profile of the modified release formulation as well as to provide comparative bioavailability data between this formulation and

the reference product and was in line with the respective EMA Guidelines. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The relative bioavailability study LESVIMETHYL/21/BO-9 (study 2021-5129) confirmed a similar bioavailability of the test product Methylphenidate HCl 40 mg extended-release chewable tablets and the reference IR formulation, but with a different shape of the concentration-time curve.

The 90% CI of the relative mean plasma d-methylphenidate AUC0-inf and AUC0-t of test to reference products were between 80.00 and 125.00%. However, the 90% CI of the relative mean plasma d-methylphenidate AUC0-2 of test to reference products were not between 80.00 and 125.00%. Moreover, the 90% CI of the relative mean plasma d-methylphenidate AUC0-6 was not between 80.00 and 125.00%.

Furthermore, the applicant has provided a comparison of the PK profiles of the applied formulation and other extended-release formulations of methylphenidate on the market.

The applicant performed a modelling and simulation exercise, which was intended to support the claimed clinical NI in the 12 hours post dose time frame for the proposed extended-release formulations compared to the IR formulation. However, the PKPD model describing the relationship between MPH plasma concentrations and SKAMP scores has limitations. The main limitation is that the dose was titrated based on response in the dataset used to develop the PKPD model. The model could thus not be used to support that PK-curves of different shapes would have the same efficacy profile over the day.

According to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1), it is necessary to justify that the different shape of the plasma-concentration time curve has no relevance for efficacy, safety or tolerance development to waive a comparative efficacy and safety study. It is agreed that there are no foreseen safety issues given the equivalent or lower Cmax for the MR product, compared to the reference product.

However, from the efficacy perspective it was considered that achieving plasma levels above 6 ng/ml and indirect comparisons to approved products is not sufficient to waive a comparative efficacy and safety study.

Nevertheless, an efficacy and safety double-blind placebo-controlled Phase 3 study was conducted by the applicant with the chewable tablets in the target population of patients. The PEP (the model adjusted average of all post-dose SKAMP-Combined scores in study NWP09-ADHD-300) was met.

It is acknowledged that the efficacy and safety study was conducted against a placebo comparator and not against an immediate release formulation.

However, it can be agreed that the totality of the data provided by the applicant, consisting of a bioequivalence study 2021-5129 (LESVIMETHYL/21/BQ-9) which is pivotal for bridging to the non-clinical and clinical studies of the reference medicinal product, significant clinical data in efficacy/safety study (NWP09-ADHD-300) and additional data (1 BE study (2021-5130), 1 dose proportionality study (2021-5128), 2 supportive US bioavailability studies (509-0238 and 2012-2950), 1 supportive single dose PK study in the target population (NWP06-PPK-101), 1 study evaluating tablet and oral suspension formulation BA (C11-0082) under fasted conditions, Phase 3 efficacy and safety studies (NWP06-ADD-100) and M&S study evaluating PD properties of methylphenidate hydrochloride in an oral suspension and a chewable tablet formulation versus the reference medicinal product) allowing to waive comparative efficacy and safety clinical studies in accordance with the Guideline, is considered sufficient to demonstrate that the B/R for Tuzulby, in the proposed indication, is positive.

There were no new or concerning safety findings reported in the clinical studies provided in the dossier.

A benefit/risk ratio comparable to that of the reference product can therefore be concluded.

Having considered the data submitted in the application and available on the chosen reference medicinal product, no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tuzulby is favourable in the following indication:

Tuzulby is indicated as part of a comprehensive treatment programme for attention-deficit / hyperactivity disorder (ADHD) in children and adolescents 6-17 years old when remedial measures alone prove insufficient. Treatment must be under the supervision of a specialist in childhood behavioural disorders. Diagnosis should be made according to Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria or the guidelines in International Classification of Diseases, Tenth Revision (ICD-10) and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptoms.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- *Periodic Safety Update Reports*

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0057/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.