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ORIGINAL RESEARCH ARTICLE

Comparative Bioavailability of Methylphenidate Powder for Prolonged-Release Oral Suspension and Methylphenidate Prolonged-Release Chewable Tablets versus Methylphenidate Immediate-Release Tablets: Phase 1, Single-Dose, Randomised, Crossover Studies in Healthy Adults

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Abstract

Background Various oral methylphenidate formulations are available to treat attention-deficit/hyperactivity disorder, but unmet needs still exist, particularly for individuals with swallowing difficulties or those requiring more flexible dosing options. Two phase 1 studies evaluated the comparative bioavailability and safety/tolerability of two prolonged-release (PR) methylphenidate formulations, an oral suspension and a chewable tablet, compared with an established immediate-release (IR) oral tablet formulation.

Methods Healthy volunteers were randomised to receive a single dose of methylphenidate PR oral suspension (total dose 60 mg; study 1) or chewable tablet (total dose 40 mg; study 2) and methylphenidate IR tablets (total dose 60 mg in study 1 and 40 mg in study 2) in a crossover manner, with a 7-day washout between treatment periods. Blood samples were collected over the 24-h post-administration period. Comparative bioavailability was defined as the 90% confidence interval (CI) of the relative mean plasma D-methylphenidate area under the plasma concentration–time curve from zero to last measurable concentration (AUC_{last}) of methylphenidate PR formulation to methylphenidate IR being between 80 and 125%. Adverse events (AEs) were documented.

Results In total, 24 individuals (mean age 39–42 years, approximately 50% male) were randomised in each study, of whom 23 received methylphenidate PR oral suspension in study 1 and 23 received methylphenidate PR chewable tablets in study 2; 24 received methylphenidate IR tablets in each study. The relative mean plasma D-methylphenidate AUC_{last} ratios for methylphenidate PR formulation to methylphenidate IR tablets had 90% CIs of 82.30–87.18% in study 1 and 90.01–97.52% in study 2. Treatment-emergent AEs were reported in 26% and 22% of participants receiving the oral suspension and chewable tablets, respectively (versus 50% and 33% of those receiving the IR tablets in the respective studies). These AEs were typical of orally administered methylphenidate, mild in severity and, in general, resolved prior to study end.

Conclusions The methylphenidate PR oral suspension and chewable tablet formulations are bioequivalent in terms of the total extent of exposure (AUC_{last}) to methylphenidate IR tablets and are tolerable in healthy adults.

Plain Language Summary

Methylphenidate is a drug often used to treat attention-deficit/hyperactivity disorder (ADHD). Various products (formulations) containing methylphenidate are available for doctors to prescribe, but it would be useful for additional formulations to be available to allow treatment to be more precisely tailored for each patient. In particular, formulations that release methylphenidate slowly into the bloodstream ('prolonged-release' [PR] formulations) are more effective at controlling symptoms over the course of each day than those that release methylphenidate more quickly ('immediate-release' [IR] formulations). Two studies were conducted to assess how two PR formulations of methylphenidate—a powder mixed with water (oral suspension) and a chewable tablet—compared with a commonly prescribed IR oral tablet formulation of methylphenidate in terms of the concentration of the drug achieved in the blood (termed 'exposure' to methylphenidate) and safety. In total,

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24 healthy adults participated in each study. The studies were divided into two parts—initially, participants received either the PR formulation or the IR formulation; 7 days later, they received whichever formulation they had not received in the first part of the study. Over the 24 h, after each treatment was received, blood samples were taken to determine methylphenidate concentrations, and adverse effects were assessed. Exposure to methylphenidate was similar with each PR formulation versus the IR formulation. Further, the PR formulations were well-tolerated by participants, having adverse effects similar to those previously reported for methylphenidate. Therefore, the methylphenidate PR oral suspension and chewable tablet formulations can be considered important additions to the treatment options available for ADHD.

Key Points

Stimulants, such as methylphenidate, are first-line treatment options for attention-deficit/hyperactivity disorder (ADHD); various oral formulations are available, but additional options are required to allow personalized treatment.

Phase 1 studies evaluated the bioavailability and safety/tolerability of two methylphenidate prolonged-release (PR) formulations—an oral suspension and a chewable tablet—compared with an established immediate-release (IR) oral tablet formulation in 24 healthy adults.

The methylphenidate PR oral suspension and chewable tablets demonstrated comparative bioavailability in terms of the total extent of exposure (relative mean plasma D-methylphenidate area under the plasma concentration–time curve from zero to last measurable concentration [AUC_{last}]) to methylphenidate IR tablets in healthy adults; treatment-emergent adverse events (which were typical of orally administered methylphenidate) were reported in 26% of participants receiving the oral suspension (versus 50% receiving the IR tablets) and 22% of participants receiving the chewable tablets (versus 33% receiving the IR tablets).

1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder. A meta-analysis published in 2023 reported the international prevalence of ADHD to be 7.6% in children (< 12 years old) and 5.6% in adolescents (12–18 years) [1]. While ADHD typically begins during childhood, it often persists into adulthood, with large systematic reviews and meta-analyses reporting the prevalence of ADHD in adults to be approximately 3% [2, 3]. The prevalence of ADHD appears to be lower in many European countries (with the exception of Spain) than in North America and Australasia [4].

The most commonly used diagnostic systems indicate that the defining feature of ADHD is a persistent (≥ 6 months) pattern of inattention and/or hyperactivity–impulsivity that interferes with academic, social and/or occupational functioning or development, which began before the age of 12 years [5, 6]. ADHD has marked negative effects on patients' education and work achievement, social interactions, family life and general quality of life [7]; is associated with an increased risk of mortality [7, 8]; and has a large economic impact [9].

Stimulants, such as methylphenidate, are recommended by international guidelines as one of the first-line treatment options for ADHD (after behavioural interventions, particularly in younger children) [10–12]. The pharmacokinetics and clinical efficacy of methylphenidate are well-described [13, 14]. Long-acting/prolonged-release (PR) formulations of stimulants that allow once-daily administration have been produced, which have advantages over immediate-release (IR) formulations in terms of adherence [15] and risk of misuse [16]. However, the current PR formulations have some limitations, particularly regarding the ability to implement body weight-based dosing to allow the minimum efficacious dose with the best benefit–risk balance to be reached in individual patients; thus, additional PR formulations have been developed.

Two of the newer PR oral formulations of methylphenidate are a powder for oral suspension (from here on referred to as 'oral suspension') and chewable tablets. These formulations aim to address unmet needs of patients with ADHD, particularly those who have difficulties swallowing the previously available oral formulations, and to allow more flexibility in dosage adjustment than can be achieved with current methylphenidate formulations. Further, these new formulations provide physicians with more options to personalise treatment for individuals living with ADHD on the basis of patient and caregiver preferences.

Phase 1 studies were performed to evaluate the comparative bioavailability and safety/tolerability of the methylphenidate PR oral suspension and chewable tablets compared

with an established IR oral tablet formulation. The results of these studies are described in this article.

2 Methods

2.1 Study Designs and Objectives

These phase 1 comparative bioavailability studies had an open-label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover design (Fig. 1) and were conducted by Pharma Medica Research Inc. at a clinical facility in Toronto, Ontario, Canada.

The primary objective of the studies was to compare the bioavailability of methylphenidate hydrochloride (from here on referred to as 'methylphenidate') as a PR oral suspension (in study 1: LESVIMETHYL/21/BQ-10; Health Canada file no. HC6-24-c258053) or PR chewable tablets (in study 2: LESVIMETHYL/21/BQ-9; Health Canada file no. HC6-24-c258051) with that of an IR methylphenidate tablet formulation commonly used to manage ADHD (Ritalin®). The secondary objective of the studies was to evaluate the safety and tolerability of the PR methylphenidate formulations.

2.2 Study Participants

Healthy, non-smoking, male and female volunteers aged 18–55 years were eligible for inclusion in the studies. Full study inclusion and exclusion criteria are presented in Online Resource Table S1.

The protocol for each study was approved by the Institutional Review Board of Optimum Clinical Research on 6 January 2022. Written consent, in compliance with local legislation and regulations, was obtained from each individual before they entered the studies. The studies were conducted in accordance with the current European Medicines Agency guidance document, Directive 2001/20/European Community, Good Clinical Practice (as established by the International Council for Harmonisation), Division 5 of the Canadian Food and Drugs Regulation and the principles enunciated in the World Medical Association Declaration of Helsinki.

2.3 Treatments

Methylphenidate PR 25 mg/5 mL oral suspension (Tris Pharma, Inc., Monmouth Junction, NJ, USA; study 1) or methylphenidate PR 40 mg chewable tablets (Tris Pharma, Inc., Monmouth Junction, NJ, USA; study 2) and methylphenidate IR 10 mg tablets (Novartis Pharma GmbH, Nuremberg, Germany) were given in a crossover manner over two study periods (Fig. 1). In the first treatment period, study participants received either methylphenidate PR (oral suspension [study 1] or chewable tablet [study 2]) or methylphenidate IR tablets (study 1 and study 2), according to a predetermined computer-generated randomisation scheme (procedure PLAN in SAS®, version 9.4 [Cary, NC, USA]). In the second treatment period, participants were crossed over to the other study treatment. The two treatment periods were separated by a washout period of 7 days.

A population pharmacokinetics model with allometric scaling was developed on the basis of adult plasma concentration data to determine weight-based central methylphenidate pharmacokinetic parameters of total clearance (CL) and volume of distribution for the peripheral compartments (V2) in paediatric patients, to match adult exposure. The scaled population pharmacokinetics model was used to simulate paediatric exposures. To confirm the expected exposure, this was qualified with plasma concentration data generated in

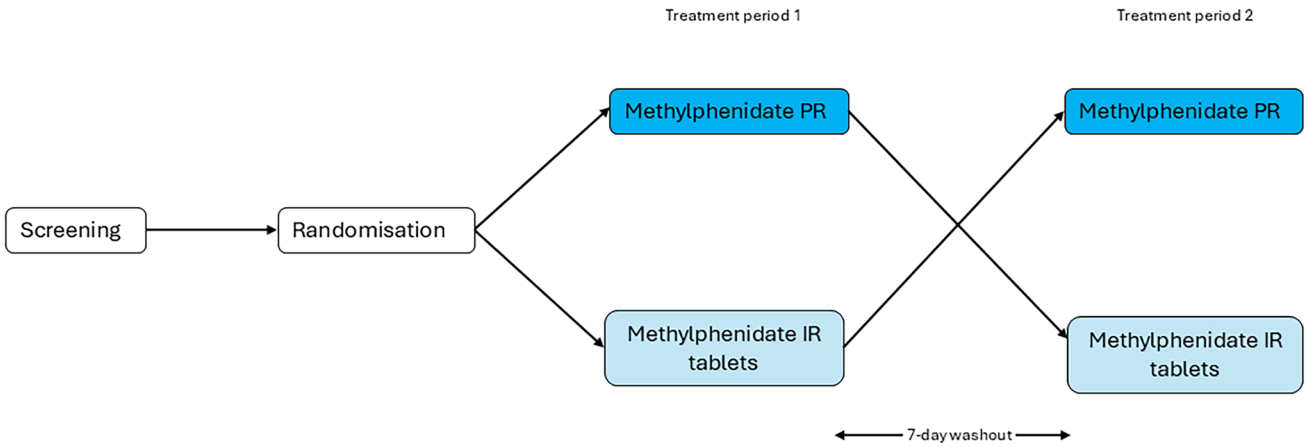

Fig. 1 Design of the phase 1 studies. The methylphenidate prolonged-release formulation was an oral suspension in study 1 and chewable tablets in study 2. *IR* immediate-release, *PR* prolonged-release

children and adolescents aged 6–17 years dosed with the oral suspension.

Dose recommendations were based on body weight but not set on a weight-based regimen, as per the European summary of product characteristics for the approved product (Tuzulby) [17], which advises tailoring the dose according to the treatment needs and responses of the patient. In children and adolescents, the recommended starting dose is 20 mg given orally once daily in the morning. The dose may subsequently be titrated once weekly upwards or downwards in increments of 10 mg, 15 mg or 20 mg. The PR product doses should be equal to the total daily dose of the IR methylphenidate-containing formulation but should not exceed 60 mg.

The treatment schedule is shown in Fig. 2. All treatments were administered 30 min after consumption of a high-fat, high-calorie breakfast (consistent with the European guideline that recommends a high-fat meal for modified-release products [18]), following an overnight fast of ≥ 10 h, and water was restricted from 1 h prior to drug administration. At baseline (0 h), methylphenidate PR oral suspension was given as a single 60-mg dose (12 mL of 25 mg/5 mL oral suspension; study 1) and methylphenidate PR chewable tablet was given as a single 40-mg tablet (study 2). At baseline (0 h) and 6 h, methylphenidate IR was given as 3 × 10 mg tablets (total dose of 60 mg) in study 1 or 2 × 10 mg tablets (total dose of 40 mg) in study 2. Full details of study drug administration are provided in the Supplementary Methods of the Online Resource. After drug administration, study participants were instructed to fast for ≥ 5.5 h (at baseline) and ≥ 4 h (at the 6-h administration point), and water was restricted until 1 h after both administrations. During each treatment period, participants remained at the clinical trial facility for ≥ 10.5 h prior to drug administration until ≥ 24 h after the baseline drug administration.

2.4 Sample Collection and Pharmacokinetic Analysis

Blood samples for pharmacokinetic analysis were collected by direct venipuncture or from an indwelling cannula placed in an arm vein. Samples were collected prior to baseline drug administration 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 h after administration (Fig. 2). Full details of sample collection and the methodology for sample processing and storage are provided in the Supplementary Methods of the Online Resource.

Enantioselective (D-threo-(2*R*,2′*R*)-methylphenidate and L-threo-(2*S*,2′*S*)-methylphenidate) analytical methods validated by Pharma Medica Research Inc. were used to analyse plasma samples from both studies. The methodology is based on liquid–liquid extraction (liquid chromatography–tandem mass spectrometry [LC–MS/MS]). Methylphenidate-*D*9 was used as the internal standard. The

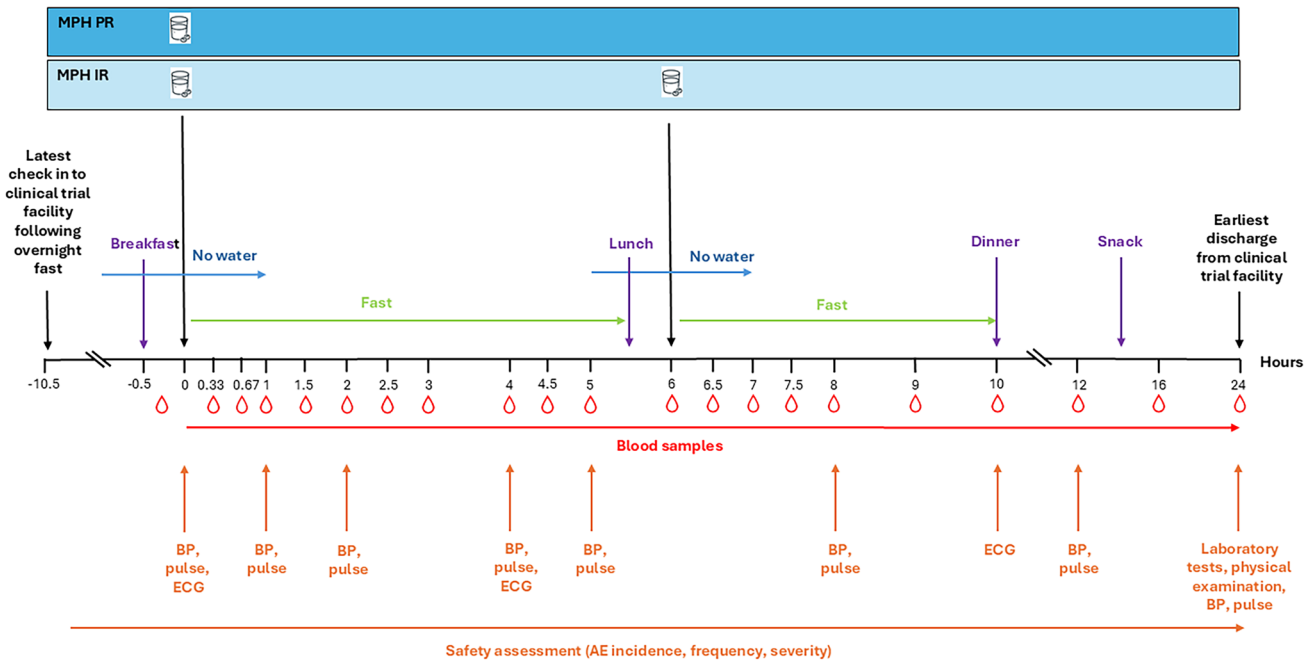

Fig. 2 Treatment administration, sample collection and safety assessment schedule for each treatment period. The two treatment periods were separated by a washout of 7 days. The methylphenidate prolonged-release formulation was an oral suspension in study 1 and chewable tablets in study 2; methylphenidate immediate-release tablets were administered in both studies. *AE* adverse event, *BP* blood pressure, *ECG* electrocardiogram, *IR* immediate-release, *MPH* methylphenidate, *PR* prolonged-release

lower limit of quantification (LLOQ) for both enantiomers was 0.2 mg/mL. The active enantiomer D-threo-(2*R*,2′*R*)-methylphenidate was used to assess relative bioavailability. On the basis of D-methylphenidate levels, area under the plasma concentration versus time curve (AUC) from time 0 to 2 h ($AUC_{0–2}$), AUC from time 0 to 6 h ($AUC_{0–6}$), AUC from time 0 to the time of the last measurable analyte concentration (AUC_{last}), AUC from time 0 to infinity (AUC_{inf}) and maximum plasma concentration (C_{max}) were estimated to characterise the extent and rate of study drug absorption using a noncompartmental approach in Phoenix™ WinNonlin®, version 8.3 (Certara, Princeton, NJ, USA). The isomers of methylphenidate (D and L) were measured separately; however, D-methylphenidate is more pharmacologically active and more prevalent than L-methylphenidate. Other pharmacokinetic parameters determined in the studies are presented in Online Resource, Supplementary Table S2.

2.5 Safety Assessments

The incidence, frequency and severity of adverse events (AEs) were documented from the time that participants signed the consent form. AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA), version 24.1, using system organ class and preferred terms.

Serious AEs (SAEs) were defined as adverse reactions that resulted in death; were life-threatening adverse experiences; required hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability or incapacity, a congenital anomaly or birth defect, or were medically significant events that, while not resulting in death, were life-threatening or required hospitalisation; may have jeopardized the participant and required medical intervention to prevent one of the outcomes listed previously; or involved suspected transmission of an infectious agent via a medicinal product. An AE that did not meet any of the criteria for seriousness was regarded as a non-serious AE.

AEs were classified as mild, moderate or severe and assessed for their relationship to study treatment (causality: reasonably possible or not reasonably possible). Non-treatment-emergent AEs (NTEAEs) were defined as AEs occurring before drug administration in the first treatment period, while treatment-emergent AEs (TEAEs) were defined as AEs that occurred after the start of drug administration.

Vital signs and electrocardiogram monitoring were also performed prior to drug administration and at various timepoints post-administration (Fig. 2); clinical laboratory tests and physical examination were conducted at the end of the studies.

2.6 Statistical Analysis

The sample size was calculated as follows. In-house data obtained from other studies performed by the sponsor with the same products indicated a coefficient of variation (CV) for D-methylphenidate C_{max} of approximately 20%. Assuming a 20% intra-individual variability and a difference between the treatment means of ≤ 5%, the necessary sample size for an 80% probability of the 90% confidence interval (CI) of the treatment means ratio being within a range of 80–125% was estimated to be 20 individuals. We planned to include four extra individuals in each study to account for potential dropouts; therefore, target recruitment was 24 individuals in each study.

The safety analysis set included all participants who received ≥ 1 administration of any study drug. The pharmacokinetic analysis set included participants for whom the estimation of D-methylphenidate C_{max} and/or AUC parameters was possible for both treatment periods and who complied with all protocol requirements sufficiently such that any protocol deviation did not impact the estimation of pharmacokinetic parameters. Participants who exhibited pre-dose concentrations > 5% of the corresponding D-methylphenidate C_{max} and who exhibited a lack of any measurable concentrations or only very low plasma concentrations for methylphenidate IR were excluded.

Descriptive statistics for the pharmacokinetic parameters of D-methylphenidate were calculated and included number of observations, arithmetic mean, standard deviation (SD), geometric mean (where applicable), CV, median and range (minimum, maximum). Statistical analysis was performed on quality-assured data from study participants in the statistical analysis set using the PROC GLM procedure from SAS®, version 9.4. Analysis of variance (ANOVA) was performed on log-transformed plasma D-methylphenidate $AUC_{0–2}$, $AUC_{0–6}$, AUC_{last}, AUC_{inf} and C_{max} parameters.

The significance (5% significance level) was tested for the sequence, period, treatment and participant (sequence) effects (all fixed). Using the same statistical model, the least-squares-means (LSM), differences between the treatments LSM, and corresponding standard errors of these differences were estimated for log-transformed D-methylphenidate $AUC_{0–2}$, $AUC_{0–6}$, AUC_{last}, AUC_{inf} and C_{max} parameters, and the ratios of the geometric means for different formulations (and the corresponding 90% CIs) were calculated. On the basis of the log-transformed pharmacokinetic parameters, comparative bioavailability between the methylphenidate PR formulations and methylphenidate IR tablets was determined by a statistical comparison of the D-methylphenidate AUC_{last} and was defined as the 90% CI of the relative mean plasma D-methylphenidate AUC_{last} of

methylphenidate PR formulations to methylphenidate IR being between 80 and 125%.

A descriptive analysis of the safety results was conducted.

3 Results

Treatments were administered on 6 February 2022 (first treatment period) and 13 February 2022 (second treatment period) in study 1 and on 8 February 2022 (first treatment period) and 15 February 2022 (second treatment period) in study 2.

3.1 Study Participants

The baseline characteristics of individuals enrolled in each study are presented in Table 1. In total, 24 individuals were randomised and enrolled in each study. The mean (SD) age was 42 (12) years in study 1 and 39 (10) years in study 2; more study participants were in the 41–64-year age category in study 1, whereas more were in the 18–40-year category in study 2. Approximately 50% of the participants in each study were male, and the mean body mass index of the participants was approximately 25 kg/m^2 in both studies.

One individual (4.2%) in each study discontinued prior to the second treatment period (owing to a positive urine drug test for tricyclic antidepressants in study 1 and personal reasons in study 2); both individuals received methylphenidate IR tablets only. In total, 23 individuals received a single dose of methylphenidate PR oral suspension in study 1, and 23 individuals received a single dose of methylphenidate PR chewable tablets in study 2; 24 individuals received a single dose of methylphenidate IR tablets in each study.

In both studies, the 23 participants for whom the estimation of D-methylphenidate C_{max} and/or AUC parameters was possible for both treatment periods comprised the pharmacokinetic set (none were excluded). All 24 participants in each study were included in the safety analysis set.

3.2 Pharmacokinetic Analysis

The concentrations of L-methylphenidate were below the detection limit for most study participants, and therefore pharmacokinetic parameters were not estimated for this analyte.

The mean plasma D-methylphenidate concentration versus time profiles observed in study 1 and study 2 are shown in Figs. 3 and 4, respectively. Table 2 presents a summary of the statistical analysis of plasma D-methylphenidate concentrations determined in each study.

In study 1, the relative mean plasma D-methylphenidate AUC_{last} ratio for methylphenidate PR oral suspension to methylphenidate IR tablets had a 90% CI of 82.30–87.18%. The relative mean plasma D-methylphenidate C_{max} ratio for

Table 1 Baseline characteristics of study participants

Characteristic	Study 1: methylphenidate PR oral suspension versus methylphenidate IR tablets		Study 2: methylphenidate PR chewable tablets versus methylphenidate IR tablets	
	PK analysis set, $N = 23$	Safety analysis set, $N = 24$	PK analysis set, $N = 23$	Safety analysis set, $N = 24$
Age, years				
Mean (SD)	42 (12)	42 (12)	39 (10)	39 (10)
Median (range)	47 (18–55)	47 (18–55)	36 (22–54)	37 (22–54)
Age group, n (%)				
18–40 years	10 (43.5)	10 (41.7)	14 (60.9)	14 (58.3)
41–64 years	13 (56.5)	14 (58.3)	9 (39.1)	10 (41.7)
Sex, male, *n* (%)	13 (56.5)	13 (54.2)	11 (47.8)	12 (50.0)
Race, n (%)				
Asian	4 (17.4)	4 (16.7)	1 (4.3)	2 (8.3)
Black/African American	3 (13.0)	3 (12.5)	6 (26.1)	6 (25.0)
White	16 (69.6)	17 (70.8)	16 (69.6)	16 (66.7)
Ethnicity, Hispanic/Latino, *n* (%)	9 (39.1)	10 (41.7)	7 (30.4)	7 (29.2)
BMI, kg/m^2				
Mean (SD)	25.8 (2.5)	25.7 (2.5)	25 (3)	25 (3)
Median (range)	26.1 (21.6–29.5)	25.7 (21.6–29.5)	24 (21–30)	24 (21–30)

BMI body mass index, *IR* immediate-release, *PK* pharmacokinetic, *PR* prolonged-release, *SD* standard deviation

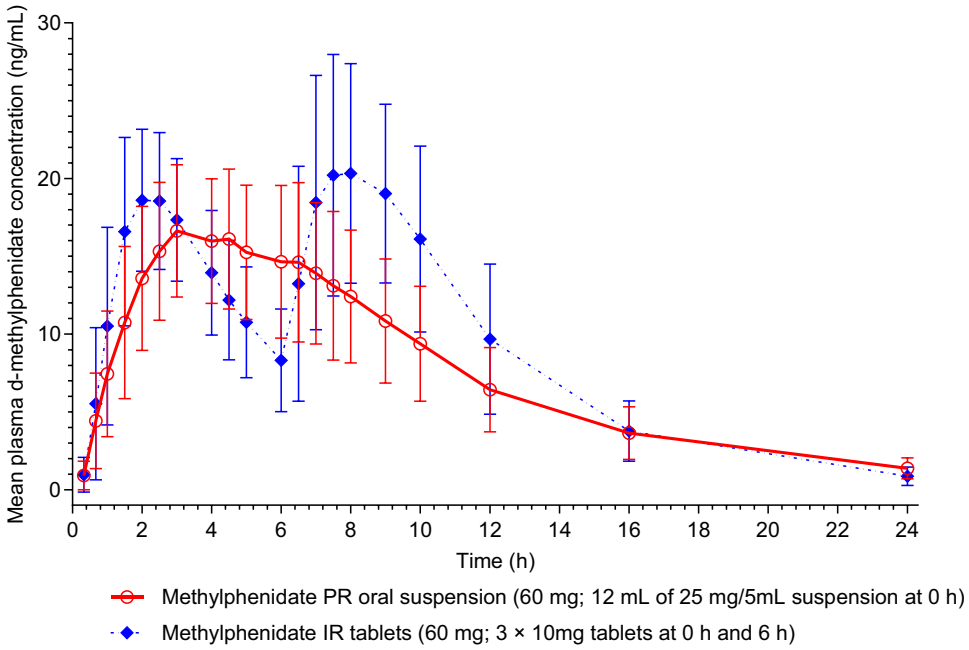

Fig. 3 Mean plasma D-methylphenidate concentration versus time profile in study 1 (methylphenidate PR oral suspension [$N = 23$] versus methylphenidate IR tablets [$N = 23$]). *h* hours, *IR* immediate-release, *PR* prolonged-release

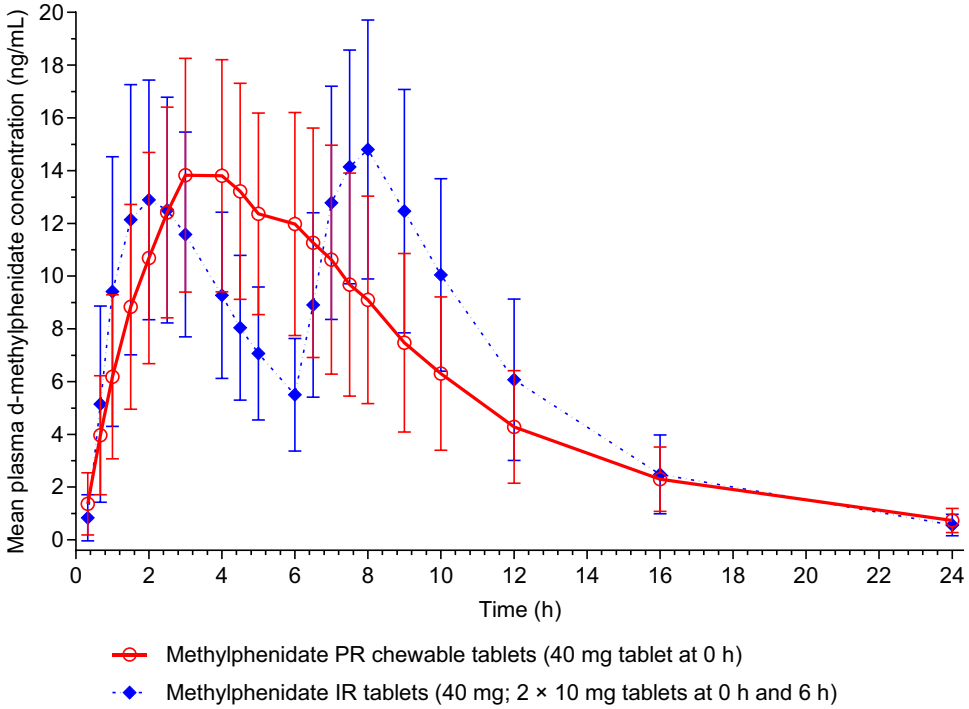

Fig. 4 Mean plasma methylphenidate concentration-time profile in study 2 (methylphenidate PR chewable tablets [$N = 23$] versus methylphenidate IR tablets [$N = 23$]). *h* hours, *IR* immediate-release, *PR* prolonged-release

methylphenidate PR oral suspension to methylphenidate IR fell outside the comparative bioavailability parameters, having a 90% CI of 67.6–79.8%. A significant treatment effect was detected by ANOVA for the D-methylphenidate AUC_{last}, ($p < 0.0001$), AUC_{inf} ($p < 0.0001$), AUC_{0-2} ($p = 0.0031$) and C_{max} ($p < 0.0001$). Despite the statistical significance, the approximate 15% difference in the D-methylphenidate AUC_{last} of the two formulations was believed to have no clinical importance since the 90% CI for the methylphenidate PR oral suspension to methylphenidate IR tablets ratio was entirely contained within the predefined range for comparative bioavailability.

In study 2, the relative mean plasma D-methylphenidate AUC_{last} ratio for methylphenidate PR chewable tablets to methylphenidate IR had a 90% CI of 90.01–97.52%. The relative mean plasma D-methylphenidate C_{max} ratio for methylphenidate PR chewable tablets to methylphenidate IR also fell within the comparative bioavailability

Table 2 Summary of plasma D-methylphenidate concentrations in study 1 (methylphenidate PR oral suspension versus methylphenidate IR) and study 2 (methylphenidate PR chewable tablets versus methylphenidate IR)[a]

D-Methylphenidate parameter	Arithmetic mean (CV%)		Geometric mean		Methylphenidate PR versus methylphenidate IR					
					Geometric mean ratio (%)		90% CI		Intra-subject CV (%)	
	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
AUC_{last} *(h × ng/mL)*										
Methylphenidate PR[b]	178.990 (33)	133.197 (34)	170.132	126.357	84.70	93.69	82.30–87.18	90.01–97.52	6	8
Methylphenidate IR	211.403 (32)	141.773 (33)	200.853	134.872						
AUC_{inf} *(h × ng/mL)*										
Methylphenidate PR[b]	189.606 (34)	138.240 (35)	179.909	130.824	87.86	94.86	85.37–90.42	91.32–98.54	6	8
Methylphenidate IR	215.896 (32)	145.081 (33)	204.774	137.908						
C_{max} *(ng/mL)*										
Methylphenidate PR[b]	18.180 (26)	14.935 (29)	17.510	14.359	73.44	89.28	67.57–79.82	83.57–95.39	17	13
Methylphenidate IR	24.709 (26)	16.591 (26)	23.843	16.083						
$AUC_{0–2}$ *(h × ng/mL)*										
Methylphenidate PR[b]	13.603 (46)	11.439 (43)	11.780	10.317	65.84	75.47	53.08–81.67	58.74–96.96	44	53
Methylphenidate IR	19.425 (41)	15.182 (43)	17.893	13.671						
$AUC_{0–6}$ *(h × ng/mL)*										
Methylphenidate PR[b]	75.900 (29)	62.885 (29)	72.655	60.519	100.31	120.93	94.72–106.22	111.02–131.73	11	17
Methylphenidate IR	75.043 (26)	52.269 (30)	72.433	50.044						

[a]The pharmacokinetic dataset comprised 23 participants in each study

$AUC_{0–2}$ area under the plasma concentration versus time curve, from time 0–2 h, $AUC_{0–6}$ area under the plasma concentration versus time curve, from time 0–6 h, AUC_{last} area under the plasma concentration versus time curve, from time 0 to the time of the last measurable concentration, AUC_{inf} area under the plasma concentration versus time curve, from time 0 to infinity, C_{max} maximum plasma concentration over the sampling period, *CI* confidence interval, *CV* coefficient of variation, *IR* immediate release, *PR* prolonged-release

[b]The methylphenidate PR formulation was oral suspension in study 1 and chewable tablets in study 2

parameters, having a 90% CI of 83.57–95.39%. A significant treatment effect was detected by ANOVA for D-methylphenidate AUC_{last}, ($p < 0.0107$), AUC_{inf} ($p \leq 0.0266$), AUC_{0-6} ($p \leq 0.0009$) and C_{max} ($p \leq 0.0076$). Similar to study 1, despite the statistical significance, the approximate 6% difference in the D-methylphenidate AUC_{last} of the two formulations was not considered to be clinically relevant since the 90% CI for the ratio of methylphenidate PR chewable tablets to methylphenidate IR tablets fell within the prespecified comparative bioavailability range.

Numerical differences were noted for some other D-methylphenidate pharmacokinetic parameters for the methylphenidate PR formulations versus methylphenidate IR tablets (i.e. shorter time to the maximum plasma concentration and longer apparent elimination half-life with methylphenidate PR formulations compared with methylphenidate IR tablets; Online Resource, Supplementary Tables S3 and S4). However, no significant differences were detected in any pharmacokinetic parameters for sequence or period effects in study 1 or study 2.

3.3 Safety Analysis

In study 1, 24 TEAEs were reported by 13 participants (54.2%), all of which were considered to be related to the study drug. A total of 6 participants (26.1%) experienced 6 TEAEs following administration of methylphenidate PR oral suspension, and 12 participants (50.0%) experienced 18 TEAEs after receiving methylphenidate IR tablets (Table 3). Headache and tachycardia were the most frequent AEs, occurring in six and five participants, respectively (seven headache events in six participants [25%], and six tachycardia events in five participants [20.8%]). Both of these AEs were more frequent during treatment with methylphenidate IR tablets (headache, 25%; tachycardia, 20.8%) than with methylphenidate PR oral suspension (headache, 4.3%; tachycardia, 4.3%). Dry mouth was the most frequent AE during treatment with methylphenidate PR oral suspension (8.7%). Palpitations were reported by one participant receiving methylphenidate IR tablets (4.2% versus 0% with methylphenidate PR oral suspension) and QC prolongation

Table 3 Incidence of treatment-emergent adverse events in study 1[a]

MedDRA SOC term MedDRA PT	Methylphenidate PR oral suspension $N = 23$	Methylphenidate IR tablets $N = 24$
Participants with no AEs	17 (73.9)	12 (50.0)
Participants with ≥ 1 TEAE, *n* (%)	6 (26.1)	12 (50.0)
Cardiac disorders, n (%)		
Palpitations	0	1 (4.2)
Tachycardia	1 (4.3)	5 (20.8)
Gastrointestinal disorders, n (%)		
Abdominal discomfort	0	1 (4.2)
Dry mouth	2 (8.7)	0
General disorders and administration site conditions, n (%)		
Pyrexia	0	1 (4.2)
Investigations, n (%)		
Blood bilirubin increased	1 (4.3)	0
Electrocardiogram QT prolonged	1 (4.3)	0
Nervous system disorders, n (%)		
Dizziness	0	1 (4.2)
Headache	1 (4.3)	6 (25.0)
Psychiatric disorders, n (%)		
Anxiety	0	1 (4.2)
Respiratory, thoracic and mediastinal disorders, n (%)		
Oropharyngeal discomfort	0	1 (4.2)
Skin and subcutaneous tissue disorders, n (%)		
Rash	0	1 (4.2)

[a]Although participants may have had ≥ 2 AEs, they were counted only once within a treatment. The same participant may appear in different treatments

AE adverse event, *IR* immediate-release, *MedDRA* Medical Dictionary for Regulatory Activities, *PR* prolonged-release, *PT* preferred term, *SOC* system organ class, *TEAE* treatment-emergent adverse event

was reported by one participant receiving methylphenidate PR oral suspension (4.3% versus 0% with methylphenidate IR tablets).

All TEAEs were mild in severity and resolved prior to the end of the study. With the exception of blood bilirubin that increased in one participant (mild in severity and resolved by the end of the study), all end-of-study laboratory results were either within the normal ranges or assessed by the investigator as not clinically significant; there were no significant findings detected by physical examinations.

In study 2, 19 TEAEs were reported by 11 participants (45.8%); 17 of the TEAEs (7 events in 5 participants receiving methylphenidate PR chewable tablets and 10 events in 7 participants receiving methylphenidate IR tablets) were considered drug-related. In addition, one participant (4.2%) reported a single NTEAE. A total of five participants (21.7%) experienced 8 TEAEs after methylphenidate PR chewable tablet administration, and eight participants (33.3%) experienced 11 TEAEs after receiving methylphenidate IR tablets (Table 4). Headache was the most frequent AE, occurring in five participants (20.8%; six headache events in total); for all events, the causality to the study drug was considered to be reasonably possible. Headache was more frequent during treatment with methylphenidate IR tablets (16.7%) than during treatment with methylphenidate PR chewable tablets (8.7%).

All TEAEs were mild in severity and all resolved prior to the end of the study except for mild anaemia in one study participant (see below); the NTEAE was also considered mild in severity, and it resolved.

Two participants (8.4%) experienced a clinically significant laboratory value at the end-of-study evaluation. One participant experienced mild anaemia, which was assessed as related to drug treatment; the individual was advised to follow-up with their family doctor. The other participant experienced a mild urinary tract infection, which was assessed as not related to drug treatment and resolved at the end of the study. All other end-of-study

Table 4 Incidence of treatment-emergent adverse events in study 2[a]

MedDRA SOC MedDRA PT	Methylphenidate PR chewable tablets $N = 23$	Methylphenidate IR tablets $N = 24$
Participants with no AEs	18 (78.3)	16 (66.7)
Participants with ≥ 1 TEAE, *n* (%)	5 (21.7)	8 (33.3)
Blood and lymphatic system disorders, n (%)		
Anaemia	1 (4.3)	0
Cardiac disorders, n (%)		
Palpitations	0	1 (4.2)
Tachycardia	0	1 (4.2)
Gastrointestinal disorders, n (%)		
Abdominal discomfort	0	1 (4.2)
Diarrhoea	0	1 (4.2)
General disorders and administration site conditions, n (%)		
Catheter site pain	0	1 (4.2)
Feeling hot	1 (4.3)	0
Infections and infestations, n (%)		
Urinary tract infection	1 (4.3)	0
Nervous system disorders, n (%)		
Dizziness	1 (4.3)	1 (4.2)
Headache	2 (8.7)	4 (16.7)
Psychiatric disorders, n (%)		
Anxiety	1 (4.3)	0
Bruxism	0	1 (4.2)
Skin appendage conditions and subcutaneous tissue disorders, n (%)		
Hyperhidrosis	1 (4.3)	0

[a]Although participants may have had ≥ 2 AEs, they were counted only once within a treatment. The same participant may appear in different treatments

AE adverse event, *IR* immediate-release, *MedDRA* Medical Dictionary for Regulatory Activities, *PR* prolonged-release, *PT* preferred term, *SOC* system organ class, *TEAE* treatment-emergent adverse event

laboratory results were either within the normal ranges or were assessed by the investigator as not clinically significant. There were no significant findings detected by physical examinations.

One participant (4.2%) reported a TEAE of tachycardia, and one (4.2%) reported a TEAE of palpitations, both after receiving methylphenidate IR tablets. Both events were assessed as drug-related and mild in severity and resolved prior to the end of the study.

No deaths, SAEs or other significant AEs occurred during either study.

4 Discussion

Data from the two phase 1 studies described in this article indicate that a single dose of the methylphenidate PR oral suspension or the chewable tablet formulation is bioequivalent to two doses of methylphenidate IR tablet (given 6 h apart) in terms of the total extent of exposure (C_{max} and AUC_{last}) when administered under fed conditions to healthy adult volunteers. Further, the PR formulations were tolerable by the study populations.

These findings are consistent with those of previously published pharmacokinetic analyses of methylphenidate PR oral suspension and chewable tablet formulations. A single-dose, randomised, open-label, crossover study of healthy adults ($n = 33$) reported that the bioavailability of a single dose of a methylphenidate extended-release (ER) chewable tablet formulation was comparable with that of methylphenidate IR chewable tablets (two doses, given 6 h apart) [19]. A study of similar design that also included healthy adults ($n = 30$) found that a single dose of methylphenidate ER oral suspension was bioequivalent to two doses of a methylphenidate IR oral solution formulation given 6 h apart [20]. In both these studies, the ER formulation met the criteria for comparative bioavailability when assessed via AUC, but not C_{max}, parameters. A further study in adults ($n = 12$) found that there was no difference in the rate or extent of absorption of methylphenidate when a methylphenidate ER chewable tablet was chewed versus swallowed whole [21]. While these studies were conducted in healthy adults, a study has reported on the pharmacokinetic profile of the methylphenidate ER oral suspension, given as a single dose of 20 mg or 60 mg, in children (aged 9–12 years, $n = 7$) and adolescents (13–15 years, $n = 7$) with ADHD [22]. The pharmacokinetic parameters were linear and proportional to dose, and there was no evidence of age-related differences in the parameters assessed.

Published data indicate that methylphenidate ER oral suspension and chewable tablet formulations are effective in reducing ADHD symptoms in children and adolescents aged 6–12 years when administered for up to 6 weeks as open-label treatment followed by a 1- or 2-week double-blind, crossover period [23, 24]. The effects of these formulations versus placebo on symptoms were assessed in a laboratory classroom setting. The ER oral solution effectively reduced symptoms ($n = 45$) compared with placebo, beginning at 45 min after administration and continuing for 12 h [24]. Similarly, the ER chewable tablet formulation significantly improved symptoms compared with placebo ($n = 85$), with effects observed from 2 h to at least 8 h post-dose [23].

The methylphenidate PR oral suspension and chewable tablet formulations appear to be well-tolerated, with the TEAEs observed in our phase 1 studies typical of those associated with orally administered methylphenidate, such as headache and tachycardia. All TEAEs were mild in severity and, in general, resolved prior to the end of the studies; no SAEs were observed. These results are consistent with those reported in the previous single-dose pharmacokinetic studies [19–22]. More marked psychiatric/nervous system disorder-related TEAEs (affect lability, aggression, irritability, mood swings and insomnia) and gastrointestinal effects (decreased appetite and upper abdominal pain) were reported in the efficacy studies of children and adolescents with ADHD [23, 24], but this may have been related to the longer treatment duration in these studies versus the pharmacokinetic studies. Nevertheless, in the efficacy studies [23, 24], no SAEs were reported, and the TEAEs were consistent with those commonly associated with methylphenidate.

The methylphenidate PR oral solution and chewable tablet formulations are likely to be particularly useful for the management of ADHD in paediatric patients who have difficulty swallowing and thus have poor adherence to treatment. Difficulty in swallowing medication has been reported to be a reason for discontinuation of stimulant medication in some patients with ADHD [25], and swallowing tablets may be particularly difficult for younger children and those with comorbidities associated with ADHD, such as autism spectrum disorder [26]. The prescribing information of some currently available oral capsule formulations of stimulants states that the capsules can be opened and the contents sprinkled onto food to aid administration [27–29], but this has the potential to lead to under- or over-dosing. Pill-swallowing techniques have been reported to be successful in some children [30, 31], but the development of easy-to-swallow formulations would negate the need for such initiatives. Improved adherence to medication in patients with ADHD can be expected to improve outcomes, including symptoms and quality of life. Effective treatment of ADHD may also reduce the social costs associated with the disorder. Indeed, a study in Sweden demonstrated a 32% and 41% reduction in criminality rate among men and women with ADHD, respectively, during periods of treatment with medication versus non-medication periods [32]. While further studies

are needed to determine whether the methylphenidate PR oral suspension and chewable tablet formulations lead to improved adherence, these formulations may have inherent advantages over other oral PR methylphenidate formulations given potential issues with inaccurate dosing if capsule contents are sprinkled on food.

The methylphenidate PR oral solution may also help physicians to individualise treatment for people with ADHD, as this formulation offers greater flexibility in terms of dose adjustment than currently available oral methylphenidate formulations. Doses of the oral solution can be adjusted in increments of 2.5 mg by varying the volume administered; the dosing syringe is marked every 0.5 mL to allow ease of dose adjustment [33]. More refined dose adjustments based on patient body weight (i.e. mg/kg/day) can be made, which is important for children and adolescents who are continuing to grow, allowing effective doses to be rapidly reached and then reliably maintained.

The availability of new and flexible methylphenidate formulations, such as the PR oral solution and chewable tablets, also provides physicians with more treatments options to offer patients. This increases the likelihood of identifying a formulation that is effective, well-tolerated and that accords with the preferences of patients and their caregivers, thus enhancing the shared decision-making process [34].

The limitations of the phase 1 studies must be considered when interpreting their results. These include the small sample sizes ($n = 23/24$) in each study, and that the population studied was healthy adults, not individuals with ADHD or children and adolescents who are the target patient population. However, studies in healthy volunteers allow for extensive plasma sampling required for PR characterisation that is not feasible in children. In this context, the use of healthy adult volunteers can be considered as representative of the target paediatric population (children with ADHD aged ≥ 6 years) given that absorption is the only phase among the four processes describing medication disposition (absorption, distribution, metabolism and excretion) that should, in principle, differ between formulations. Importantly, the processes of both passive and active transport affecting gastrointestinal absorption appear to be fully mature in infants by approximately 4 months of age [35]. Similarly, the physiological functions of the gastrointestinal tract (gastrointestinal motility and pH) are similar to the adult pattern within the first year of life [36–40], and consequently no changes in the rate and extent of absorption are expected above this age. This is consistent with the observation by Childress et al. that methylphenidate shows similar pharmacokinetics in children with ADHD and in healthy adults [20, 22]. It is known that the meal provided to induce a fed state may not be reflective of meals consumed during real-world use (in terms of calorific value and fat/protein content), and that this may be responsible for some variation between individuals in clinical practice. Finally, the objective of the phase 1 studies was not to assess efficacy, which was demonstrated in dedicated studies in school-aged children [23, 24]. Additional studies have been conducted that provide more data on the bioavailability and safety/tolerability of methylphenidate PR oral suspension and chewable tablet formulations to support the adequate use in patients with ADHD [17]. The findings from efficacy studies in children [23, 24] account for differences in central nervous sensitivity in patients with ADHD and underline the efficacy of both prolonged-release products.

5 Conclusions

The findings of these two phase 1 studies indicate that the methylphenidate PR oral suspension and chewable tablet formulations are bioequivalent to methylphenidate IR in terms of total extent of exposure (AUC) and are well-tolerated in healthy adults, with AEs typical of orally administered methylphenidate. Previously published studies in children with ADHD have demonstrated the efficacy of these methylphenidate PR formulations in improving ADHD symptoms. Therefore, the methylphenidate PR oral suspension and chewable tablet formulations represent an important addition to the treatment options for the management of ADHD. They may be particularly useful for those patients who have difficulties swallowing traditional tablet formulations, and they provide flexibility in dosing adjustments, allowing a more individualised approach to the treatment of ADHD.

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Declarations

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Conflict of interest J.A.R.Q. has been on the speakers' bureau and/or acted as a consultant for Biogen, Idorsia, Casen-Recordati, Janssen-Cilag, Novartis, Takeda, Bial, Sincrolab, Neuraxpharm, Novartis, BMS, Medice, Rubió, Uriach, Technofarma and Raffo in the last 3

years. He has also received travel support (air tickets and hotel) for taking part in psychiatric meetings from Idorsia, Janssen-Cilag, Rubió, Takeda, Bial and Medice. The Department of Psychiatry chaired by him has received unrestricted educational and research support from the following companies in the last 3 years: Exeltis, Idorsia, Janssen-Cilag, Neuraxpharm, Oryzon, Roche, Probitas and Rubió. M.F.F. and A.S.P. are full-time employees of Neuraxpharm. M.B. has no conflicts of interest to declare.

Availability of data and material The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval The protocol for each study was approved by the Institutional Review Board of Optimum Clinical Research on 6 January 2022. The studies were conducted in accordance with the current European Medicines Agency guidance document, Directive 2001/20/European Community, Good Clinical Practice (as established by the International Council for Harmonisation), Division 5 of the Canadian Food and Drugs Regulation and the principles enunciated in the World Medical Association Declaration of Helsinki.

Consent to participate Written consent, in compliance with local legislation and regulations, was obtained from each individual before they entered the studies.

Consent for publication Not applicable.

Code availability Not applicable.

Author contributions J.A.R.Q.: conceptualisation, methodology, investigation, formal analysis and writing—review and editing. M.F.F.: conceptualisation, methodology, investigation, formal analysis and writing—review and editing. A.S.P.: conceptualisation, methodology, investigation, formal analysis, funding acquisition, writing and original draft preparation and writing—review and editing. M.B.: conceptualisation, methodology, investigation, formal analysis and writing—review and editing. All the authors approved the final version for publication and agree to be accountable for the work presented.

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