Clinical trial results:
EMPHAS

Evaluation of Methylphenidate (MPH) in adults with ADHD and SUD - clinical pharmacology study

A Cross-sectional, Open-label, Non-randomized Single-Center Study on Adults with ADHD and Substance Use Disorder (SUD) Treated with Methylphenidate in Routine Clinical Practice.

Summary

EudraCT number	2013-002720-16
Trial protocol	SE
Global end of trial date	21 January 2020

Results information

Result version number	v1 (current)
This version publication date	25 June 2022
First version publication date	25 June 2022

Trial information

Trial identification

Sponsor protocol code	CPPM2013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Stockholms Läns Sjukvårdsområde (SLSO)
Sponsor organisation address	Box 179 14, Stockholm, Sweden, 11895
Public contact	Clinical Trials Information, Stockholms Läns Landsting, Beroendecentrum Stockholm, 46 08123 400 00, infoberoendecentrum@sll.se
Scientific contact	Clinical Trials Information, Stockholms Läns Landsting, Beroendecentrum Stockholm, 46 08123 400 00, infoberoendecentrum@sll.se

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 January 2020
Global end of trial reached?	Yes
Global end of trial date	21 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the inter- and intraindividual variability of plasma concentrations of MPH, its enantiomers and metabolites in adults with ADHD and comorbid SUD.

Protection of trial subjects:

The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies, the Declaration of Helsinki, and the International Conference on Harmonization guidelines for Good Clinical Practice. Informed consent was obtained from all study subjects before inclusion. Safety were evaluated throughout the study by monitoring of adverse events (AEs), by rating symptom scale, performing laboratory tests, measurement of vital signs.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 28
Worldwide total number of subjects	28
EEA total number of subjects	28

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	28

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient in: 27-MAY-2015; last patient out: 8-SEP-2017 recruitment at out-patient clinics at the Stockholm Centre for Dependency Disorders, Sweden.

Pre-assignment

Screening details:

Outpatients with clinically defined ADHD according to the DSM-IV or DSM-5 were recruited. Based primarily on logistic reasons such as the number of patients per unit, four out-patient units were chosen as study sites. The recruitment of patients was consecutive and independent of the dose of MPH prescribed.

Period 1

Period 1 title	Methylphenidate (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cross-sectional study Methylphenidate Men

Arm description:

The recruitment of patients was consecutive and independent of the dose of MPH prescribed. Subjects were eligible if they were between 18 and 64 years of age, diagnosed with ADHD according to DSM-IV or DSM-5, had at least one non-nicotine substance use disorder according to the DSM-IV or DSM-5, and treated with MPH with a minimum duration of 14 days. Twenty-eight patients with ADHD and SUD were included between 2015 and 2017. The patients could participate in the study either on a single day (assessment of inter-individual variability) or up to four separate days with 1 – 2 weeks intervals (assessment of intra-individual variability). The patients continued treatment as usual during and after study visits.

Arm type	Experimental
Investigational medicinal product name	Methylphenidate
Investigational medicinal product code	
Other name	Concerta, Ritalin, Medikinet
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

Eleven subjects were prescribed daily doses higher than 180 mg, with a median dose of 324 mg (range 198¬¬600 mg). Sixteen patients were prescribed extended-release MPH (Ritalin® or Medikinet®), eight patients osmotic-release oral system (OROS)-MPH (Concerta®), two patients an immediate-release formulation of MPH (Medikinet®), and two patients a combination of Ritalin® and Concerta®. Thirteen subjects were prescribed three or more MPH doses per day and only two patients received MPH once a day in the morning. There were no changes in the dosing or formulations of MPH during the participation in the study.

Arm title	Cross-sectional study Methylphenidate Women

Arm description:

The recruitment of patients was consecutive and independent of the dose of MPH prescribed. Subjects were eligible if they were between 18 and 64 years of age, diagnosed with ADHD according to DSM-IV or DSM-5, had at least one non-nicotine substance use disorder according to the DSM-IV or DSM-5, and treated with MPH with a minimum duration of 14 days. Twenty-eight patients with ADHD and SUD were included between 2015 and 2017. The patients could participate in the study either on a single day (assessment of inter-individual variability) or up to four separate days with 1 – 2 weeks intervals (assessment of intra-individual variability). The patients continued treatment as usual during and after study visits.

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Number of subjects in period 1	Cross-sectional study Methylphenidate Men	Cross-sectional study Methylphenidate Women
Started	24	4
Completed	24	4

Baseline characteristics

Reporting groups	
Reporting group title	Methylphenidate

Reporting group description:

The subjects were instructed not to take their MPH morning dose on the study visits. Instead, they received their prescribed MPH morning dose under supervision at the study unit. Venous blood samples were drawn before MPH intake and approximately five hours post-dose for drug concentration analysis. The exact times of drug intake and blood sampling were recorded. The subjects were free to leave the unit between the two sampling times. Venous blood was collected into 3 mL tubes containing an FC mixture. The samples were centrifuged within 30 minutes, after which plasma was transferred into polypropylene tubes and frozen within 15 minutes at -20°C. The frozen samples were then transported to the laboratory and analyzed with a validated enantioselective LC-MS/MS at the Department of Clinical Pharmacology, Karolinska University Hospital.

Reporting group values	Methylphenidate	Total	
Number of subjects	28	28	
Age categorical Units: Subjects			
Age continuous Units: years median full range (min-max)	 44.5 27 to 60	 -	
Gender categorical Units: Subjects			
Female Male	4 24	4 24	
Weight Units: kg median full range (min-max)	 81 62 to 193	 -	
Diastolic Blood Pressure Units: mm Hg median full range (min-max)	 85 65 to 113	 -	
Systolic Blood Pressure Units: mm Hg median full range (min-max)	 131 106 to 166	 -	
Pulse rate Units: bpm median full range (min-max)	 80 64 to 114	 -	
ASRS Units: points median full range (min-max)	 46 19 to 64	 -	

Subject analysis sets

Subject analysis set title	MPH plasma concentrations
Subject analysis set type	Full analysis

Subject analysis set description:

The subjects were instructed not to take their MPH morning dose on the study visits. Instead, they received their prescribed MPH morning dose under supervision at the study unit. Venous blood samples were drawn before MPH intake and approximately five hours post-dose for drug concentration analysis. The exact times of drug intake and blood sampling were recorded. The subjects were free to leave the unit between the two sampling times. Venous blood was collected into 3 mL tubes containing an FC mixture. The samples were centrifuged within 30 minutes, after which plasma was transferred into polypropylene tubes and frozen within 15 minutes at -20°C. The frozen samples were then transported to the laboratory and analyzed with a validated enantioselective LC-MS/MS at the Department of Clinical Pharmacology, Karolinska University Hospital.

Subject analysis set title	RA plasma concentrations
Subject analysis set type	Full analysis

Subject analysis set description:

The subjects were instructed not to take their MPH morning dose on the study visits. Instead, they received their prescribed MPH morning dose under supervision at the study unit. Venous blood samples were drawn before MPH intake and approximately five hours post-dose for drug concentration analysis. The exact times of drug intake and blood sampling were recorded. The subjects were free to leave the unit between the two sampling times. Venous blood was collected into 3 mL tubes containing an FC mixture. The samples were centrifuged within 30 minutes, after which plasma was transferred into polypropylene tubes and frozen within 15 minutes at -20°C. The frozen samples were then transported to the laboratory and analyzed with a validated enantioselective LC-MS/MS at the Department of Clinical Pharmacology, Karolinska University Hospital.

Reporting group values	MPH plasma concentrations	RA plasma concentrations	
Number of subjects	21	21	
Age categorical Units: Subjects			
Age continuous Units: years median full range (min-max)	 44 34 to 60	 44 34 to 60	
Gender categorical Units: Subjects			
Female	3	3	
Male	18	18	
Weight Units: kg median full range (min-max)	 80 60 to 193	 80 60 to 193	
Diastolic Blood Pressure Units: mm Hg median full range (min-max)	 85 65 to 113	 85 65 to 113	
Systolic Blood Pressure Units: mm Hg median full range (min-max)	 134 106 to 166	 134 106 to 166	
Pulse rate Units: bpm median full range (min-max)	 84 66 to 114	 84 66 to 114	

ASRS			
Units: points			
median	44	44	
full range (min-max)	19 to 64	19 to 64	

End points

End points reporting groups

Reporting group title	Cross-sectional study Methylphenidate Men

Reporting group description:

The recruitment of patients was consecutive and independent of the dose of MPH prescribed. Subjects were eligible if they were between 18 and 64 years of age, diagnosed with ADHD according to DSM-IV or DSM-5, had at least one non-nicotine substance use disorder according to the DSM-IV or DSM-5, and treated with MPH with a minimum duration of 14 days. Twenty-eight patients with ADHD and SUD were included between 2015 and 2017. The patients could participate in the study either on a single day (assessment of inter-individual variability) or up to four separate days with 1 – 2 weeks intervals (assessment of intra-individual variability). The patients continued treatment as usual during and after study visits.

Reporting group title	Cross-sectional study Methylphenidate Women

Reporting group description:

The recruitment of patients was consecutive and independent of the dose of MPH prescribed. Subjects were eligible if they were between 18 and 64 years of age, diagnosed with ADHD according to DSM-IV or DSM-5, had at least one non-nicotine substance use disorder according to the DSM-IV or DSM-5, and treated with MPH with a minimum duration of 14 days. Twenty-eight patients with ADHD and SUD were included between 2015 and 2017. The patients could participate in the study either on a single day (assessment of inter-individual variability) or up to four separate days with 1 – 2 weeks intervals (assessment of intra-individual variability). The patients continued treatment as usual during and after study visits.

Subject analysis set title	MPH plasma concentrations
Subject analysis set type	Full analysis

Subject analysis set description:

The subjects were instructed not to take their MPH morning dose on the study visits. Instead, they received their prescribed MPH morning dose under supervision at the study unit. Venous blood samples were drawn before MPH intake and approximately five hours post-dose for drug concentration analysis. The exact times of drug intake and blood sampling were recorded. The subjects were free to leave the unit between the two sampling times. Venous blood was collected into 3 mL tubes containing an FC mixture. The samples were centrifuged within 30 minutes, after which plasma was transferred into polypropylene tubes and frozen within 15 minutes at -20°C. The frozen samples were then transported to the laboratory and analyzed with a validated enantioselective LC-MS/MS at the Department of Clinical Pharmacology, Karolinska University Hospital.

Subject analysis set title	RA plasma concentrations
Subject analysis set type	Full analysis

Subject analysis set description:

The subjects were instructed not to take their MPH morning dose on the study visits. Instead, they received their prescribed MPH morning dose under supervision at the study unit. Venous blood samples were drawn before MPH intake and approximately five hours post-dose for drug concentration analysis. The exact times of drug intake and blood sampling were recorded. The subjects were free to leave the unit between the two sampling times. Venous blood was collected into 3 mL tubes containing an FC mixture. The samples were centrifuged within 30 minutes, after which plasma was transferred into polypropylene tubes and frozen within 15 minutes at -20°C. The frozen samples were then transported to the laboratory and analyzed with a validated enantioselective LC-MS/MS at the Department of Clinical Pharmacology, Karolinska University Hospital.

Primary: Pharmacokinetic parameter MPH and RA plasma concentration

End point title	Pharmacokinetic parameter MPH and RA plasma concentration

End point description:

Methylphenidate (MPH) and ritalinic acid (RA) plasma concentrations were analyzed with an enantioselective LC-MS/MS method.

End point type	Primary

End point timeframe:

Venous blood samples were drawn before MPH intake and approximately five hours post-dose for drug concentration analysis.

End point values	Cross-sectional study Methylphenidate Men	Cross-sectional study Methylphenidate Women	MPH plasma concentrations	RA plasma concentrations
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	24	4	18	3
Units: ng/mL				
number (not applicable)	24	4	18	3

Statistical analyses

Statistical analysis title	Plasma concentrations of MPH and RA

Statistical analysis description:

The subjects were instructed not to take their MPH morning dose on the study visits. Instead, they received their prescribed MPH morning dose under supervision at the study unit. Venous blood samples were drawn before MPH intake and approximately five hours post-dose for drug concentration analysis. The exact times of drug intake and blood sampling were recorded. The subjects were free to leave the unit between the two sampling times. Venous blood was collected into 3 mL tubes containing an FC m

Comparison groups	Cross-sectional study Methylphenidate Men v Cross-sectional study Methylphenidate Women
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Pharmacokinetic parameters - plasma conc
Point estimate	79
Confidence interval	
level	95 %
sides	1-sided
upper limit	79
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start time of the first administration of the IMP until the final visit.

Assessment type	Systematic

Dictionary used

Dictionary name	SNOMED CT
Dictionary version	2014

Reporting groups

Reporting group title	Methylphenidate

Reporting group description:

About 200 patients treated with MPH from all out-patient units were listed and, based primarily on logistic reasons such as the number of patients per unit, four out-patient units were chosen as study sites. The recruitment of patients was consecutive and independent of the dose of MPH prescribed. Subjects were eligible if they were between 18 and 64 years of age, diagnosed with ADHD according to DSM-IV or DSM-5, had at least one non-nicotine substance use disorder, and treated with MPH with a minimum duration of 14 days. Patients who declined to participate continued with their usual care at the clinic. The patients could participate in the study either on a single day (assessment of inter-individual variability) or up to four separate days with 1 – 2 weeks intervals (assessment of intra-individual variability). The patients continued treatment as usual during and after study visits.

Serious adverse events	Methylphenidate		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Methylphenidate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 28 (17.86%)		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Psychiatric disorders			

Mild anxiety subjects affected / exposed occurrences (all) Feeling irritable subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1 1 / 28 (3.57%) 1		
Infections and infestations Common cold subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study sample was small. Different pharmaceutical formulations of MPH were used, in some cases concomitantly. The study was performed in out-patients, and variable adherence to the prescribed dosing regimen may have influenced the results.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35040257