Clinical trial results:
Efficacy of propiverine hydrochloride extended release (ER) 45 mg in patients with neurogenic detrusor overactivity – an active-controlled single center crossover trial

Summary

EudraCT number	2012-003159-12
Trial protocol	DE
Global end of trial date	16 December 2013

Results information

Result version number	v1 (current)
This version publication date	09 September 2023
First version publication date	09 September 2023

Trial information

Trial identification

Sponsor protocol code	8405011

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	APOGEPHA Arzneimittel GmbH
Sponsor organisation address	Kyffhäuserstr. 27, Dresden, Germany, 01309
Public contact	Clinical Development Department, APOGEPHA Arzneimittel GmbH, +49 35133633, Studien@apogepha.de
Scientific contact	Clinical Development Department, APOGEPHA Arzneimittel GmbH, +49 35133633, Studien@apogepha.de

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	16 December 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 December 2013
Global end of trial reached?	Yes
Global end of trial date	16 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare the efficacy of propiverine hydrochloride ER 45 mg s.i.d. versus propiverine hydrochloride IR 15 mg t.i.d. in patients with NDO in terms of percent change of bladder volume at first detrusor contraction in relation to the baseline value measured after the run-in phase.

Protection of trial subjects:

Safety was evaluated by collecting reported adverse events (AEs) at regular intervals throughout the study and by the assessment of physical examination findings, vital signs, clinical laboratory parameters, and ECGs.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 November 2012
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	Germany: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	17
From 65 to 84 years	3

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patients were recruited from the ambulatory study center patient pool or from patients who had been treated acutely in the clinic (BDH Klinik Greifswald, Neurologisches Rehabilitationszentrum und Querschnittgelähmtenzentrum, Germany) after the neurologic status had been stabilized.

Pre-assignment

Screening details:

- Female and male patients aged 18 years or older with NDO due to spinal cord injuries.
- Primarily proven NDO with evidence of reflex detrusor contractions in previous pressure-flow-studies.
- Ability to practice clean intermittent catheterization (by the patient himself or a nurse/relative) at least 4 to 6 times daily.

Period 1

Period 1 title	Treatment A
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Arm title	Treatment A

Arm description:

Treatment A:
Mictonorm Uno® 45 mg, 1 capsule (45 mg propiverine hydrochloride ER) s.i.d. and one tablet of placebo matching Mictonorm ®.

Arm type	Experimental
Investigational medicinal product name	Mictonorm Uno 45 mg
Investigational medicinal product code	84546.00.00
Other name	Propiverine ER
Pharmaceutical forms	Modified-release capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Each patient had to take 1 capsule of Mictonorm Uno® 45 mg and 1 tablet of placebo matching Mictonorm® in the morning, 1 tablet at noon and 1 tablet in the evening at approximately 8 h intervals.

Number of subjects in period 1	Treatment A
Started	20
Completed	20

Period 2

Period 2 title	Treatment B
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Arm title	Treatment B

Arm description:

Treatment B:
Mictonorm® coated tablets (15 mg propiverine hydrochloride IR) t.i.d. and one capsule of placebo matching Mictonorm Uno® 45 mg

Arm type	Active comparator
Investigational medicinal product name	Mictonorm®
Investigational medicinal product code	3000574.00.00
Other name	Mictonorm 15 mg, Propiverine IR
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Each patient had to take 1 capsule of placebo matching Mictonorm Uno® 45 mg and 1 tablet of Mictonorm® in the morning, 1 tablet at noon and 1 tablet in the evening at approximately 8 h intervals.

Number of subjects in period 2	Treatment B
Started	20
Completed	20

Baseline characteristics

Reporting groups	
Reporting group title	Treatment A

Reporting group description: -

Reporting group values	Treatment A	Total	
Number of subjects	20	20	
Age categorical Units: Subjects			
Patients aged 18 years or older	20	20	
Age continuous Units: years median standard deviation	 45.5 ± 14.7	 -	
Gender categorical			
18 patients were males and 2 females.			
Units: Subjects			
Female	2	2	
Male	18	18	

End points

End points reporting groups

Reporting group title	Treatment A

Reporting group description:

Treatment A:
Mictonorm Uno® 45 mg, 1 capsule (45 mg propiverine hydrochloride ER) s.i.d. and one tablet of placebo matching Mictonorm ®.

Reporting group title	Treatment B

Reporting group description:

Treatment B:
Mictonorm® coated tablets (15 mg propiverine hydrochloride IR) t.i.d. and one capsule of placebo matching Mictonorm Uno® 45 mg

Subject analysis set title	IIT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All 20 subjects received double-blind medication according to protocol. Per-protocol and ITT population consisted of these 20 patients and were identical.

Primary: Reflex volume

End point title	Reflex volume

End point description:

The reflex volume, defined as volume at "starting of first hyperactive detrusor contraction", has been chosen as primary efficacy outcome since it reflects the main treatment aims in patients with NDO: reduction of intravesical pressure in order to minimize or even eliminate complications of the upper urinary tract and increase of maximum bladder capacity with reduction of incontinence episodes or achievement of continence.
If no RV occurred during the cystometric measurement, RV was equated to the maximum bladder capacity, in this case to the predefined filling volume of 450 mL.

End point type	Primary

End point timeframe:

Cystometric measurements were performed three times: after the run-in period, but before randomization into the two treatment periods, and after each treatment period of at least 21 days duration. Each patient received cross-over treatment.

End point values	Treatment B	Treatment A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: millilitre(s)				
median (standard deviation)	320 (± 149)	340 (± 135)		

Statistical analyses

Statistical analysis title	GEE proportional odds model

Statistical analysis description:

Generalized estimating Equations (GEE), an extension of generalized linear models, using logit or cumulative logits as link function. Anticipated statistical method if more than 25% of the urodynamic parameters were censored. Effects considered were treatment, seqeunce and study period.
It must be considered that the so-called baseline was determined under active treatment with propiverine IR (Mictonorm ® 15 mg t.i.d.), which was identical to the reference treatment (propiverine

IR). T

Comparison groups	Treatment B v Treatment A
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.1575
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.4594
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1563
upper limit	1.3509

Notes:

[1] - The primary variable RV with values >450 ml was censored in 35% of cases after all treatments. Thus, the preconditions for evaluation according to a mixed effect model were not given. For such a case, the statistical analysis plan foresaw an evaluation by means of a three level score using a GEE proportional odds dole. The levels were: <200 ml, inadequate effect; 200 - 400 ml, acceptable effect, >400 ml, good effect.

Secondary: Maximum cystometric capacity

End point title	Maximum cystometric capacity

End point description:

End point type	Secondary

End point timeframe:

Cystometric measurements were performed three times: after the run-in period, but before randomization into the two treatment periods, and after each treatment period of at least 21 days duration. Each patient received cross-over treatment.

End point values	Treatment B	Treatment A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: ml				
median (standard deviation)	450 (± 98.9)	450 (± 88.8)		

Statistical analyses

Statistical analysis title	GEE proportional odds model MCC
Comparison groups	Treatment B v Treatment A
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3335
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.7849

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4805
upper limit	1.2823

Secondary: Detrusor pressure

End point title	Detrusor pressure

End point description:

End point type	Secondary

End point timeframe:

Cystometric measurements were performed three times: after the run-in period, but before randomization into the two treatment periods, and after each treatment period of at least 21 days duration. Each patient received cross-over treatment.

End point values	Treatment B	Treatment A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: cm H20				
median (standard deviation)	6 (± 23)	6.5 (± 18.8)		

Statistical analyses

Statistical analysis title	GEE proportional odds model Pdet
Comparison groups	Treatment B v Treatment A
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6774
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.2273
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4677
upper limit	3.2203

Secondary: Maximum detrusor pressure

End point title	Maximum detrusor pressure

End point description:

End point type	Secondary

End point timeframe:

Cystometric measurements were performed three times: after the run-in period, but before randomization into the two treatment periods, and after each treatment period of at least 21 days duration. Each patient received cross-over treatment.

End point values	Treatment B	Treatment A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: cm H20				
median (standard deviation)	12 (± 28.7)	11.5 (± 27.5)		

Statistical analyses

Statistical analysis title	GEE proportional odds model Pdet max
Comparison groups	Treatment B v Treatment A
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9898
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.0042
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5249
upper limit	1.9215

Adverse events

Adverse events information	
Timeframe for reporting adverse events: at visit 2 for run-in phase, at visit 3 for treatment periode 1 and at visit 4 for treatment periode 2.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1
Reporting groups	
Reporting group title	Treamtent A - Propiverine ER
Reporting group description: All randomised patient treated with Treatment A	
Reporting group title	Treatment B - Propiverine IR
Reporting group description: All randomised patient treated with Treatment B	

Serious adverse events	Treamtent A - Propiverine ER	Treatment B - Propiverine IR	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treamtent A - Propiverine ER	Treatment B - Propiverine IR	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 20 (30.00%)	4 / 20 (20.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			

Acne			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 20 (10.00%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Nasopharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Gingivitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Bacteriuria			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 January 2013	Adaption of inclusion criteria, agreed by investigator
09 July 2013	Brief description of change: The term "laboratory" was deleted in section 4.4. In the routine way of clinical work, the laboratory samples will be sent for evaluation to the laboratory. The samples are no pseudonymised because the results will be used for further treatment of the patients. The results will be stored in the ambulatory medical patient file and will not be passed on to the Sponsor or any other third parties.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported