



## Clinical trial results:

### A Phase 4, Randomized-withdrawal, Double-blind, Placebo controlled, Parallel-group Study to Investigate the Clinical Benefit of Midodrine Hydrochloride in Male and Female Subjects with Symptomatic Orthostatic Hypotension

#### Summary

EudraCT number	2012-005760-99
Trial protocol	SK CZ PL
Global end of trial date	11 November 2013

#### Results information

Result version number	v2 (current)
This version publication date	25 November 2018
First version publication date	25 January 2015
Version creation reason	<ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Update day of actual start date of recruitment and non-serious adverse event.

#### Trial information

##### Trial identification

Sponsor protocol code	SPD426-405
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01515865
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Shire Development LLC
Sponsor organisation address	725 Chesterbrook Boulevard, Wayne, United States, 19087
Public contact	Medical Communications, Shire Pharmaceuticals Limited, 44 8000556614, medinfo@shire.com
Scientific contact	Medical Communications, Shire Pharmaceuticals Limited, 44 8000556614, medinfo@shire.com

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	11 November 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 November 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To assess the clinical benefit of midodrine hydrochloride (HCl) in subjects with symptomatic orthostatic hypotension (SOH) as determined by the proportion of subjects who fail to maintain an adequate response to treatment following randomized withdrawal of treatment (placebo) as compared to subjects remaining on active treatment (midodrine HCl).

Protection of trial subjects:

This study was conducted in accordance with ICH Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements. A data monitoring committee monitored safety data generated by the study at regular intervals for the duration of the study. Their role was to protect the interests of subjects in the study and of those still to be entered, by review of accumulating safety and tolerability data generated in this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United States: 90
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Poland: 5
Worldwide total number of subjects	98
EEA total number of subjects	8

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)	84
From 65 to 84 years	14
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This was a double-blind, placebo-controlled, randomized-withdrawal, parallel-group multicenter study conducted at 12 sites in the United States and 2 sites in the European Union (1 site in Poland and 1 site in Slovakia) to investigate the clinical benefit of midodrine HCl in male and female subjects with SOH.

### Pre-assignment

Screening details:

Screening procedures were completed within 28 days prior to Day -1, while subjects were on their current midodrine HCl dose schedule. All screening assessments and procedures were performed by the principal investigator or a qualified designee.

### Period 1

Period 1 title	Withdrawal
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	Midodrine HCL - Open-label Withdrawal
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Arm description:

On the morning of Day -1, subjects took their usual morning dose of midodrine HCl, using their own midodrine HCl supplies at approximately the same time before rising that they would normally take their morning dose. On the morning of Day 1, subjects had their usual morning dose of midodrine HCl withheld.

Arm type	Experimental
Investigational medicinal product name	Midodrine Hydrochloride (HCL)
Investigational medicinal product code	
Other name	ProAmatine
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2.5 and 10 mg tablets (United States) or 2.5 mg tablets (European Union), at the subject's current dose level.

Number of subjects in period 1	Midodrine HCL - Open-label Withdrawal
Started	98
Completed	95
Not completed	3
Not Specified	3

**Period 2**

Period 2 title	Dose-stabilization
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

**Arms**

<b>Arm title</b>	Midodrine HCL - Open-label
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## Arm description:

On Day 2, all eligible subjects continued on their midodrine HCL dose regimen over at least 14 days, using study-supplied investigational product.

Arm type	Experimental
Investigational medicinal product name	Midodrine Hydrochloride (HCL)
Investigational medicinal product code	
Other name	ProAmatine
Pharmaceutical forms	Capsule
Routes of administration	Oral use

## Dosage and administration details:

2.5 and 10 mg tablets (United States) or 2.5 mg tablets (European Union), at the subject's current dose level.

<b>Number of subjects in period 2<sup>[1]</sup></b>	Midodrine HCL - Open-label
Started	71
Completed	69
Not completed	2
Not Specified	1
Withdrawal by Subject	1

## Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Twenty-four subjects from the Open-label Withdrawal phase did not meet the criteria required to be enrolled into the Dose-stabilization phase.

**Period 3**

Period 3 title	Double-blind, Randomized-withdrawal
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

## Blinding implementation details:

The investigator designated a blinded qualified individual to administer the dose to the subject.

**Arms**

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Midodrine HCl - Randomized
Arm description: On Day 16 subjects received overencapsulated midodrine HCl tablets (equivalent to their previously prescribed dose).	
Arm type	Experimental
Investigational medicinal product name	Midodrine Hydrochloride (HCL)
Investigational medicinal product code	
Other name	ProAmatine
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 2.5 and 10 mg overencapsulated tablets (United States) or 2.5 mg overencapsulated tablets (European Union), at the subject's current dose level.	
<b>Arm title</b>	Placebo - Randomized
Arm description: On Day 16 subjects received matching placebo.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Subjects received a single dose of matching placebo.	

<b>Number of subjects in period 3<sup>[2]</sup></b>	Midodrine HCl - Randomized	Placebo - Randomized
Started	33	34
Completed	33	34

**Notes:**

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Two subjects from the Dose-stabilization phase did not meet the criteria required to be enrolled into the Double-blind, Randomized-withdrawal phase.

## Baseline characteristics

### Reporting groups

Reporting group title	Withdrawal
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Reporting group description: -

Reporting group values	Withdrawal	Total	
Number of subjects	98	98	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	45.5		
standard deviation	± 17.45	-	
Gender categorical			
Units: Subjects			
Female	76	76	
Male	22	22	
Region of enrollment			
Units: Subjects			
United States	90	90	
Slovakia	3	3	
Poland	5	5	

## End points

### End points reporting groups

Reporting group title	Midodrine HCL - Open-label Withdrawal
Reporting group description: On the morning of Day -1, subjects took their usual morning dose of midodrine HCL, using their own midodrine HCL supplies at approximately the same time before rising that they would normally take their morning dose. On the morning of Day 1, subjects had their usual morning dose of midodrine HCL withheld.	
Reporting group title	Midodrine HCL - Open-label
Reporting group description: On Day 2, all eligible subjects continued on their midodrine HCL dose regimen over at least 14 days, using study-supplied investigational product.	
Reporting group title	Midodrine HCL - Randomized
Reporting group description: On Day 16 subjects received overencapsulated midodrine HCL tablets (equivalent to their previously prescribed dose).	
Reporting group title	Placebo - Randomized
Reporting group description: On Day 16 subjects received matching placebo.	

### Primary: Percent of Subjects Who Failed to Maintain a Response

End point title	Percent of Subjects Who Failed to Maintain a Response
End point description: Failure to maintain a response was defined as any randomized subject that met both criterion 1 and criterion 2 below on Day 16: 1. The Orthostatic Hypotension Symptom Assessment (OHSA) Item 1 score increased by $\geq 4$ points compared to baseline. OHSA Item 1 is a dizziness scale that is scored on a range from 0 (no dizziness) to 10 (severe dizziness). A lower score indicates less severe symptoms. 2. There was an increase in the number of syncopal/near syncopal events or severity of events within 15 minutes of standing compared to those observed at baseline. Syncope was defined as a loss of consciousness, and near syncope was defined as a feeling (e.g., dizziness, lightheadedness, feeling faint, feeling as though one would black out) that, without intervention, would lead to a loss of consciousness. This end point used the Full Analysis Set, defined as all randomized subjects who received at least 1 dose of double-blind investigational product and had data available.	
End point type	Primary
End point timeframe: 30 minutes post-dose on Day 16	

End point values	Midodrine HCL - Randomized	Placebo - Randomized		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	34		
Units: percentage of subjects				
number (not applicable)	30.3	44.1		



## Statistical analyses

<b>Statistical analysis title</b>	Failure to maintain a response
Comparison groups	Placebo - Randomized v Midodrine HCl - Randomized
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3145
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	-13.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.6
upper limit	9.8

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

24 Days

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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### Reporting groups

Reporting group title	Midodrine HCl - Open-label (Part B)
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Reporting group description: -

Reporting group title	Placebo - Randomized Safety Analysis Set (Part C)
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Reporting group description: -

Reporting group title	Midodrine HCl - Randomized Safety Analysis Set (Part C)
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Reporting group description: -

Reporting group title	Midodrine HCl - Open-label Withdrawal (Part A)
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Reporting group description: -

Serious adverse events	Midodrine HCl - Open-label (Part B)	Placebo - Randomized Safety Analysis Set (Part C)	Midodrine HCl - Randomized Safety Analysis Set (Part C)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 71 (0.00%)	0 / 34 (0.00%)	0 / 33 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Midodrine HCl - Open-label Withdrawal (Part A)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 98 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

<b>Non-serious adverse events</b>	Midodrine HCl - Open-label (Part B)	Placebo - Randomized Safety Analysis Set (Part C)	Midodrine HCl - Randomized Safety Analysis Set (Part C)
Total subjects affected by non-serious adverse events subjects affected / exposed	2 / 71 (2.82%)	0 / 34 (0.00%)	0 / 33 (0.00%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 71 (2.82%)  2	0 / 34 (0.00%)  0	0 / 33 (0.00%)  0

<b>Non-serious adverse events</b>	Midodrine HCl - Open-label Withdrawal (Part A)		
Total subjects affected by non-serious adverse events subjects affected / exposed	5 / 98 (5.10%)		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	5 / 98 (5.10%)  5		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 September 2012	<p>This amendment included the following changes.</p> <p>1-Dates of the planned study period were updated to match agreement with the Food and Drug Administration (FDA):</p> <p>a-The definition of Part A (Withdrawal phase) was changed from 1 day (Day 1) to 2 days duration (Day -1 to Day 1);</p> <p>b-Discharge was on Day 17; and</p> <p>c-Follow-up was 5-7 days after discharge rather than 5-7 days after last dose of study drug.</p> <p>2-In order to better reflect the general patient population, qualification criteria for advancing from Part B to C (Dose-stabilization and Double-blind Randomized-withdrawal phases, respectively) were modified to indicate that the changes in orthostatic blood pressure should have been comparable at baseline and Part B, and that some subjects may not have exhibited a change.</p> <p>3-Methodology sections were amended to clarify that procedures for qualification of subjects into the study, including Parts A and B, may have been repeated once if necessary.</p> <p>4-Physical examination was removed as a safety assessment and secondary endpoint, since findings were to be included in the adverse events section.</p> <p>5-Exclusion criteria were modified.</p> <p>6-Sections detailing administration of investigational product were updated to address concerns expressed by the FDA.</p> <p>7-The timing of screening procedures was changed to within 28 days prior to Day -1, rather than 28 days prior to receiving the first dose of investigational product.</p> <p>8-Additional guidelines were added to address FDA recommendations concerning blood pressure measurements.</p> <p>9-Definitions of syncopal and near syncopal events were added.</p>
15 January 2013	<p>This amendment included the following changes.</p> <p>1-Text was added to include that in the European Union only the 2.5 mg dose strength was used.</p> <p>2-Text was added to clarify that a subject was eligible to enter Part B of the study if he was unable to stand for the assessments to be conducted, which meant either to start the assessments or to complete the entire assessment period.</p> <p>3-Text was added to clarify that the subject number and randomization number used in the SPD426-406 study could not be used in Study SPD426-405.</p> <p>4-Text was added to clarify that the capsules were to be swallowed whole and not opened, crushed, chewed, or cut.</p> <p>5-Text was updated to clarify that the physical examination was performed in Europe by a qualified registered physician.</p>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported