Clinical trial results:
A randomized, double-blind, placebo-controlled, study of oral treatment of piromelatine in patients with ocular hypertension (OHT) or primary open angle glaucoma (POAG).

Summary

EudraCT number	2016-002281-31
Trial protocol	ES
Global end of trial date	26 October 2017

Results information

Result version number	v1 (current)
This version publication date	22 July 2021
First version publication date	22 July 2021

Trial information

Trial identification

Sponsor protocol code	Piromelatine-IOP1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Neurim Pharmaceuticals (1991) Ltd.
Sponsor organisation address	27 HaBarzel St., Tel Aviv, Israel, 69710
Public contact	Clinical Trials Information, QPS Austria GmbH, 0043 31625811, Ricarda.Cerroni@qps.com
Scientific contact	Clinical Trials Information, QPS Austria GmbH, 0043 31625811, Ricarda.Cerroni@qps.com
Sponsor organisation name	Neurim Pharmaceuticals (1991)
Sponsor organisation address	HaBarzel 27, Tel Aviv, Israel,
Public contact	Tali Nir, Neurim Pahrmaceuticals, talin@neurim.com
Scientific contact	Tali Nir, Neurim Pahrmaceuticals, talin@neurim.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	01 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 October 2017
Global end of trial reached?	Yes
Global end of trial date	26 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of 30 days piromelatine treatment vs placebo in ocular hypertension (OHT) or primary open angle glaucoma (POAG) patients.

Protection of trial subjects:

This clinical trial was conducted in compliance with the current revision of the Declaration of Helsinki, ICH guideline for Good Clinical Practice (GCP) and current regulatory regulations (WMO).

The principles of informed consent were implemented according to the 2013 version of the Declaration of Helsinki, the ICH Guideline for Good Clinical Practice (GCP) and regulatory requirements (WMO).

Background therapy:

N.A.

Evidence for comparator:

A placebo group was required in order to differentiate any investigational drug effect from any improvement that could occur solely due to the close care and medical oversight given to the patients under trial conditions. The matching placebo tablets for piromelatine contained only the excipients and were indistinguishable from the piromelatine tablets.

Actual start date of recruitment	19 January 2017
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	Spain: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	21
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients had to be clinically diagnosed with either POAG or OHT in both eyes and hat to fulfill the following main criteria:
Aged between 40 and 80 years, of either sex.
Morning IOP: 22-30 mmHg (incl.)
not pregnant

Pre-assignment

Screening details:

Patients had to be clinically diagnosed with either POAG or OHT in both eyes and had to fulfill the following main criteria:
Aged between 40 and 80 years, of either sex.
Morning IOP: 22-30 mmHg (incl.)
No other glaucoma type, advanced visual field loss, ocular trauma, infection, pathology, progressive retinal disease
not pregnant, good health

Pre-assignment period milestones

Number of subjects started	40
Number of subjects completed	40

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Piromelatine 20mg/40mg

Arm description:

During dosing period each patient received an oral daily dose of piromelatine 20 mg or matching placebo and after 2 weeks non responders (Patients with no improvement in their IOP measurement, defined as decrease of <15% of baseline or worsening within the inclusion criteria range) received 40 mg (2 tablets of 20 mg) or matching placebo (2 tablets).

Arm type	Experimental
Investigational medicinal product name	Piromelatine
Investigational medicinal product code	Neu-P11
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Buccal use

Dosage and administration details:

20 mg oral administration

Arm title	placebo

Arm description:

Placebo - tablets similar in appearance to active

Arm type	Placebo

Investigational medicinal product name	Piromelatine
Investigational medicinal product code	Neu-P11
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Buccal use

Dosage and administration details:

20 mg oral administration

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Buccal use

Dosage and administration details:

2 tablets, oral administration

Arm title	Piromelatine 20 mg

Arm description:

During dosing period each patient received an oral daily dose of piromelatine 20 mg or matching placebo and after 2 weeks non responders (Patients with no improvement in their IOP measurement, defined as decrease of <15% of baseline or worsening within the inclusion criteria range) received 40 mg (2 tablets of 20 mg) or matching placebo (2 tablets).

Arm type	Experimental
Investigational medicinal product name	Piromelatine
Investigational medicinal product code	Neu-P11
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Buccal use

Dosage and administration details:

20 mg oral administration

Number of subjects in period 1	Piromelatine 20mg/40mg	placebo	Piromelatine 20 mg
Started	16	21	3
Completed	16	21	3

Baseline characteristics

Reporting groups	
Reporting group title	Piromelatine 20mg/40mg
Reporting group description:	
During dosing period each patient received an oral daily dose of piromelatine 20 mg or matching placebo and after 2 weeks non responders (Patients with no improvement in their IOP measurement, defined as decrease of <15% of baseline or worsening within the inclusion criteria range) received 40 mg (2 tablets of 20 mg) or matching placebo (2 tablets).	
Reporting group title	placebo
Reporting group description:	
Placebo - tablets similar in appearance to active	
Reporting group title	Piromelatine 20 mg
Reporting group description:	
During dosing period each patient received an oral daily dose of piromelatine 20 mg or matching placebo and after 2 weeks non responders (Patients with no improvement in their IOP measurement, defined as decrease of <15% of baseline or worsening within the inclusion criteria range) received 40 mg (2 tablets of 20 mg) or matching placebo (2 tablets).	

Reporting group values	Piromelatine 20mg/40mg	placebo	Piromelatine 20 mg
Number of subjects	16	21	3
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	12	2
From 65-84 years	9	9	1
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	9	12	1
Male	7	9	2

Reporting group values	Total		
Number of subjects	40		
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	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)	21		
From 65-84 years	19		

85 years and over	0		

Gender categorical Units: Subjects			
Female	22		
Male	18		

Subject analysis sets

Subject analysis set title	ASR Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

AST: All Subjects Randomized Set - all randomized patients

Subject analysis set title	AST Set
Subject analysis set type	Full analysis

Subject analysis set description:

AST: All Subjects Treated Set - all randomised patients who took at least one dose of IMP during the study period.

Reporting group values	ASR Set	AST Set	
Number of subjects	38	40	
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	21	21	
From 65-84 years	17	19	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	20	22	
Male	18	18	

End points

End points reporting groups

Reporting group title	Piromelatine 20mg/40mg

Reporting group description:

During dosing period each patient received an oral daily dose of piromelatine 20 mg or matching placebo and after 2 weeks non responders (Patients with no improvement in their IOP measurement, defined as decrease of <15% of baseline or worsening within the inclusion criteria range) received 40 mg (2 tablets of 20 mg) or matching placebo (2 tablets).

Reporting group title	placebo

Reporting group description:

Placebo - tablets similar in appearance to active

Reporting group title	Piromelatine 20 mg

Reporting group description:

During dosing period each patient received an oral daily dose of piromelatine 20 mg or matching placebo and after 2 weeks non responders (Patients with no improvement in their IOP measurement, defined as decrease of <15% of baseline or worsening within the inclusion criteria range) received 40 mg (2 tablets of 20 mg) or matching placebo (2 tablets).

Subject analysis set title	ASR Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

AST: All Subjects Randomized Set - all randomized patients

Subject analysis set title	AST Set
Subject analysis set type	Full analysis

Subject analysis set description:

AST: All Subjects Treated Set - all randomised patients who took at least one dose of IMP during the study period.

Primary: Primary endpoint: The safety parameters were summarized using descriptive statistics: n, mean, median, standard deviation (SD), standard error of the mean (SEM), minimum, maximum, number of out-of-range values if applicable.

End point title	Primary endpoint: The safety parameters were summarized using descriptive statistics: n, mean, median, standard deviation (SD), standard error of the mean (SEM), minimum, maximum, number of out-of-range values if applicable.[1]

End point description:

ANCOVA for Diastolic Blood Pressure - Comparison of Placebo with Piromelatine 20mg and Placebo with Piromelatine 20mg/40mg
ANCOVA for Systolic Blood Pressure - Comparison of Placebo with Piromelatine 20mg and Placebo with Piromelatine 20mg/40mg
ANCOVA for Heart Rate - Comparison of Placebo with Piromelatine 20mg and Placebo with Piromelatine 20mg/40mg

End point type	Primary

End point timeframe:

Assessment of this endpoints were conducted at following visits:
Visit 2 (Day 0), Visit 3 (Day 15 +/-2), Visit 3 (Day 30 +/-2)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: ANCOVA was performed for comparison of Placebo with Piromelatine 20mg and Placebo with Piromelatine 20mg/40mg. No data were evaluated for the Placebo treatement arm.

End point values	Piromelatine 20mg/40mg	Piromelatine 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	3		
Units: mmHg				
arithmetic mean (confidence interval 95%)				
Diastolic Blood Pressure	-4.4298 (-12.7446 to 3.8850)	6.1815 (-8.4513 to 20.8144)		
Systolic Blood Pressure	-4.5511 (-16.4099 to 7.3076)	26.3778 (5.7670 to 46.9886)		
Heart Rate	-5.3662 (-12.8798 to 2.1474)	-5.9334 (-20.4112 to 8.5444)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Piromelatine 20mg/40mg v Piromelatine 20 mg
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: IOP – Intraocular pressure at supine and sitting position at night time and during the day

End point title	IOP – Intraocular pressure at supine and sitting position at night time and during the day

End point description:

The efficacy analysis for the secondary and exploratory endpoints were carried out using an analysis of covariance (ANCOVA) model with treatment as the main effect and baseline score and study site as covariates.
For IOP, the statistical analysis was done for the data obtained from the eye with the higher baseline IOP. If baseline IOP was the same in the two eyes (±2 mm Hg) the right eye IOP was used.

End point type	Secondary

End point timeframe:

Assssments of this endpoint were conductd at the following visits:
Visit 2 (Day 0), Visit 3 (Day 15 +/-2), Visit 4 (Day 30 +/-2)

End point values	ASR Set	AST Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	40		
Units: mmHg				
median (confidence interval 95%)				

Daytime sitting IOP (Piromelatine vs Placebo)	-0.4562 (-1.7040 to 0.7916)	-0.4394 (-1.6201 to 0.7414)		
Daytime supine IOP (Piromelatine vs Placebo)	0.1638 (-1.0491 to 1.3766)	0.1092 (-1.0461 to 1.2645)		
Nighttime supine IOP (Piromelatine vs Placebo)	-0.3446 (-1.6800 to 0.9908)	-0.1670 (-1.4500 to 1.1160)		
Overall IOP (Piromelatine vs Placebo)	-0.2588 (-1.3975 to 0.8799)	-0.2383 (-1.3156 to 0.8390)		
Overall supine IOP (Piromelatine vs Placebo	-0.02481 (-1.1326 to 1.0830)	0.02946 (-1.0200 to 1.0789)		

Statistical analyses

No statistical analyses for this end point

Secondary: PF - The difference of IOP in the supine and sitting position at each time point

End point title	PF - The difference of IOP in the supine and sitting position at each time point

End point description:

End point type	Secondary

End point timeframe:

Assessment of this endpoint was calulated at following visits:
Visit 2 (Day 0), Visit 3 (Day 15 +/-2), Day 4 (Day 30 +/-2)

End point values	ASR Set	AST Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	40		
Units: mmHg				
median (confidence interval 95%)				
IOP Postural fluctuation (1-1.5 h)	-0.4466 (-1.7351 to 0.8419)	-0.4287 (-1.6556 to 0.7982)		
IOP Postural fluctuation (4-4.5h)	1.6944 (0.2955 to 3.0933)	1.3723 (-0.02757 to 2.7722)		
IOP Postural fluctuation (5-5.5h)	-0.00420 (-0.9819 to 0.9735)	0.02792 (-0.8944 to 0.9503)		
IOP Postural fluctuation (6-6.5h)	0.1578 (-0.7789 to 1.0945)	0.2100 (-0.6729 to 1.0929)		

Statistical analyses

No statistical analyses for this end point

Secondary: DV – The difference between maximum and minimum IOP during the 24 h period DV for sitting and supine postures

End point title	DV – The difference between maximum and minimum IOP during the 24 h period DV for sitting and supine postures

End point description:

End point type	Secondary

End point timeframe:

Assessment of this endpoints were conducted at following visits:
Visit 2 (Day 0), Visit 3 (Day 15 +/-2), Visit 4 (Day 30 +/-2)

End point values	ASR Set	AST Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	40		
Units: mmHg				
median (confidence interval 95%)				
IOP Diural Variations sitting	-0.2950 (-1.6354 to 1.0454)	-0.3694 (-1.6380 to 0.8992)		
IOP Diural Variations supine	0.3383 (-0.8530 to 1.5296)	0.2379 (-0.8964 to 1.3723)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Sleep questionnaire items - how long till fall asleep

End point title	Sleep questionnaire items - how long till fall asleep

End point description:

Change from Baseline

End point type	Other pre-specified

End point timeframe:

Assessment of this endpoints were conducted at following visits:
Visit 2 (Day 0), Visit 4 (Day 30 +/+2)

End point values	Piromelatine 20mg/40mg	placebo	Piromelatine 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	20	3	
Units: minutes				
arithmetic mean (standard deviation)				
ASR set	-10.3 (± 44.8)	-0.8 (± 27.0)	11.7 (± 48.6)	
AST set	-9.7 (± 43.3)	-0.8 (± 26.3)	11.7 (± 48.6)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Sleep questionnaire items - Feeling in the morning

End point title	Sleep questionnaire items - Feeling in the morning
End point description: Change from Baseline	
End point type	Other pre-specified
End point timeframe: Assessment of this endpoints were conducted at following visits: Visit 2 (Day 0), Visit 4 (Day 30 +/+2)	

End point values	Piromelatine 20mg/40mg	placebo	Piromelatine 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	20	3	
Units: N.A.				
arithmetic mean (standard deviation)				
ASR set	-0.3 (± 1.2)	-0.5 (± 0.8)	-0.7 (± 0.6)	
AST set	-0.7 (± 0.6)	-0.3 (± 1.2)	-0.4 (± 0.8)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Sleep questionnaire items - actual sleep

End point title	Sleep questionnaire items - actual sleep
End point description: Change from Baseline	
End point type	Other pre-specified
End point timeframe: Assessment of this endpoints were conducted at following visits: Visit 2 (Day 0), Visit 4 (Day 30 +/-2)	

End point values	Piromelatine 20mg/40mg	placebo	Piromelatine 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	20	3	
Units: hours				
arithmetic mean (standard deviation)				
ASR set	10.2 (± 15.5)	4.9 (± 21.0)	-7.7 (± 15.1)	
AST set	9.6 (± 15.2)	4.7 (± 20.5)	-7.7 (± 15.1)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Sleep questionnaire items - sleep quality overall

End point title	Sleep questionnaire items - sleep quality overall

End point description:

Change from Baseline

End point type	Other pre-specified

End point timeframe:

Assessment of this endpoints were conducted at following visits:
Visit 2 (Day 0), Visit 4 (Day 30 +/-2)

End point values	Piromelatine 20mg/40mg	placebo	Piromelatine 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	20	3	
Units: N.A.				
arithmetic mean (standard deviation)				
ASR set	-0.1 (± 0.9)	-0.5 (± 0.9)	0.0 (± 0.0)	
AST set	-0.1 (± 0.9)	-0.4 (± 0.9)	0.0 (± 0.0)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Ambulatory blood pressure monitoring (ABPM)

End point title	Ambulatory blood pressure monitoring (ABPM)

End point description:

Change from Baseline

End point type	Other pre-specified

End point timeframe:

The ABPM was measured at Visit 2 (baseline) and Visit 4. The ABPM was programmed to record blood pressure every 60 minutes during day time (8:00-1:00) and every 120 minutes at IOP measureme.

End point values	Piromelatine 20mg/40mg	placebo	Piromelatine 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	16	3	
Units: mmHg				
arithmetic mean (standard deviation)				
Diastolic blood pressure	-1.3 (± 9.4)	4.1 (± 12.5)	8.3 (± 14.2)	
Systolic blood pressure	-6.3 (± 9.9)	1.1 (± 18.8)	21.0 (± 22.3)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE collection started with administration of the IMP and continued until the follow-up assessment. At the follow-up Visit, information on new AEs or SAEs and stop dates for AEs recorded and ongoing during the dosig period were recorded.

Adverse event reporting additional description:

AEs which occurred after the subject had signed the Informed Consent Form but before the first administration of IMP (pre-treatment adverse events) were collected in the same manner as AEs which occured after the first administration of IMP.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

All subjects randomized to receive placebo.

Reporting group title	Piromelatine 20mg

Reporting group description:

All subjects randomized to receive Piromelatine 20 mg Tablets.

Reporting group title	Piromelatine 20mg/40mg

Reporting group description:

During dosing period each patient received an oral daily dose of piromelatine 20 mg or matching placebo and after 2 weeks non responders (Patients with no improvement in their IOP measurement, defined as decrease of <15% of baseline or worsening within the inclusion criteria range) received 40 mg (2 tablets of 20 mg) or matching placebo (2 tablets).

Serious adverse events	Placebo	Piromelatine 20mg	Piromelatine 20mg/40mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)	0 / 3 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Gastrointestinal infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 3 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	Piromelatine 20mg	Piromelatine 20mg/40mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 21 (28.57%)	1 / 3 (33.33%)	4 / 16 (25.00%)
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Vascular disorders			
Labile blood pressure			
subjects affected / exposed	1 / 21 (4.76%)	0 / 3 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 21 (9.52%)	0 / 3 (0.00%)	2 / 16 (12.50%)
occurrences (all)	2	0	2
Dizziness			
subjects affected / exposed	1 / 21 (4.76%)	0 / 3 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Migraine			
subjects affected / exposed	1 / 21 (4.76%)	0 / 3 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	1 / 21 (4.76%)	0 / 3 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 21 (0.00%)	1 / 3 (33.33%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2017	This amendment is issued to introduce changes in the conduct or management of the trial including updating the XML file with changes realted to the tasks and functions transfered by the sponsor to other organizations, as well as to the decision of the sponsor to reject the participation of the center planned in the Czech Republic to ensure timely completion of the clinical trial; To present an updated version of the IMPD; And to submit a new version of the Informed Consent Form/Patient Information Document (CI/IP) adapted with the new information.
28 March 2017	This amendment was issued to introduce changes in the conduct or management of the trial, including updating the XML file with changes relatet to the organization and person of contact of the legal representative of the Sponsor. In addition, it is agreed to notify the re-labeling of the medication in accordance with the specifications of the updated IMPD (version 8.0, dated 17 January 2017).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported