Clinical trial results:
A Phase II, double-blind, placebo-controlled, Randomized, cross-over, dose-ranging study of oral PHA-022121 for Acute treatment of angioedema attacks in Patients with hereditary angioedema due to C1-Inhibitor Deficiency type I and II

Summary

EudraCT number	2020-003445-11
Trial protocol	FR ES HU NL PL DE CZ BG IT
Global end of trial date	01 March 2023

Results information

Result version number	v1 (current)
This version publication date	28 March 2024
First version publication date	28 March 2024

Trial information

Trial identification

Sponsor protocol code	PHA022121-C201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04618211
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharvaris Netherlands B.V.
Sponsor organisation address	J. H. Oortweg 21, Leiden, Netherlands, 2333 CH
Public contact	Pharvaris Clinical, Pharvaris Netherlands B.V., 31 712036410, clinical@pharvaris.com
Scientific contact	Pharvaris Clinical, Pharvaris Netherlands B.V., 31 712036410, clinical@pharvaris.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	Interim
Date of interim/final analysis	23 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2022
Global end of trial reached?	Yes
Global end of trial date	01 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of three different single doses of PHA-022121 (soft capsule formulation) versus placebo in achieving angioedema symptom reduction, defined as change in the 3-symptom composite visual analogue scale (VAS-3) score during hereditary angioedema (HAE) attacks in patients with HAE type 1/2.

Protection of trial subjects:

The study was conducted in accordance with this study protocol, the International Council for Harmonisation GCP (ICH GCP E6[R2]), and applicable local laws and regulations. Compliance with ICH-GCP provides public assurance that the rights, safety and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The Principal Investigator ensured that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the IEC/IRB, except where necessary to eliminate an immediate hazard to the patients. All relevant personnel involved in the conduct of this study have completed ICH GCP training.

Background therapy: -

Evidence for comparator:

Placebo consisted of matching placebo soft capsules for oral use.

Actual start date of recruitment	03 February 2021
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	Netherlands: 1
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Bulgaria: 9
Country: Number of subjects enrolled	Czechia: 5
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	United States: 7

Worldwide total number of subjects	74
EEA total number of subjects	51

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)	69
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multi-center study with a total of 36 sites in 13 countries (Bulgaria, Canada, Czechia, France, Germany, Hungary, Israel, Italy, Netherlands, Poland, Spain, United Kingdom, United States). A total of 89 participants were screened for the study, with 74 subjects enrolled into the study and received treatment.

Pre-assignment

Screening details:

All participants must have had a diagnosis of HAE-1/2 based upon all of the following:
Documented clinical history consistent with HAE
At least one of the following: age reported onset of first angioedema symptoms <= 40 years, family history consistent with HAE-1/2, C1q within normal range
Diagnostic testing results to confirm HAE Type 1 or 2

Period 1

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

Blinding implementation details:

All drug supplies were handled in a double-blinded manner. PHA-022121 capsules and placebo capsules were identical in appearance and each single dose consisted of 3 capsules. The contents of each wallet were blinded and the label on the wallet contained a unique code. Assignment of study drug in accordance with the randomized treatment assignment was managed by the IRT system.

Arms

Are arms mutually exclusive?	Yes
Arm title	Part I - PHA-022121 10 mg

Arm description:

Participants assigned to the PHA-022121 10 mg arm received a single dose of PHA-022121 (10 mg) during a quiescent non-attack state.

Arm type	Experimental
Investigational medicinal product name	PHA-022121
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The treatments to be administered in the study consist of 10 mg PHA-022121 soft capsules and matching placebo soft capsules for oral use:
• Low dose (10 mg): one capsule of 10 mg PHA-022121 and two placebo capsules

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo treatment consists of matching placebo soft capsules for oral use.

Arm title	Part I - PHA-022121 20 mg

Arm description:

Participants assigned to the PHA-022121 20 mg arm received a single dose of PHA-022121 (20 mg) during a quiescent non-attack state.

Arm type	Experimental
Investigational medicinal product name	PHA-022121
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The treatments to be administered in the study consist of 10 mg PHA-022121 soft capsules and matching placebo soft capsules for oral use:
• Medium dose (20 mg): two capsules of 10 mg PHA-022121 and one placebo capsule

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo treatment consists of matching placebo capsules for oral use.

Arm title	Part I - PHA-022121 30 mg

Arm description:

Participants assigned to the PHA-022121 30 mg arm received a single dose of PHA-022121 (30 mg) during a quiescent non-attack state.

Arm type	Experimental
Investigational medicinal product name	PHA-022121
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The treatments to be administered in the study consist of 10 mg PHA-022121 soft capsules for oral use:
• High dose (30 mg): three capsules of 10 mg PHA-022121

Number of subjects in period 1	Part I - PHA-022121 10 mg	Part I - PHA-022121 20 mg	Part I - PHA-022121 30 mg
Started	24	25	25
Completed	24	24	25
Not completed	0	1	0
Consent withdrawn by subject	-	1	-

Period 2

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

Blinding implementation details:

All drug supplies were handled in a double-blinded manner. PHA-022121 capsules and placebo capsules were identical in appearance and each single dose consisted of 3 capsules. The contents of each wallet were blinded and the label on the wallet contained a unique code. Assignment of study drug in accordance with the randomized treatment assignment was managed by the IRT system.

Arms

Are arms mutually exclusive?	No
Arm title	Part II - PHA-022121 10 mg

Arm description:

Participants were treated with 2 single doses of PHA-022121 (10 mg) and one single dose of placebo. Each participant self-administered the study drug at their randomly assigned dose level (10 mg, low dose) for each of the 3 qualifying HAE attacks according to 1 of the following randomly assigned treatment sequences (crossover design):
1. Low dose - Low dose - Placebo
2. Low dose - Placebo - Low dose
3. Placebo - Low dose - Low dose

Arm type	Experimental
Investigational medicinal product name	PHA-022121
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The treatments to be administered in the study consist of 10 mg PHA-022121 soft capsules and matching placebo soft capsules for oral use:
• Low dose (10 mg): one capsule of 10 mg PHA-022121 and two placebo capsules

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo treatment consists of matching placebo soft capsules for oral use.

Arm title	Part II - PHA-022121 20 mg

Arm description:

Participants will receive two single doses of PHA-022121 (20 mg) and one single dose of placebo. Each patient self-administers two single doses of PHA-022121 (20 mg, medium dose) and one single dose of placebo for each of the three qualifying HAE attacks according to one of the following sequences (cross-over design):
1. Medium dose - Medium dose - Placebo
2. Medium dose - Placebo - Medium dose
3. Placebo - Medium dose - Medium dose

Arm type	Experimental
Investigational medicinal product name	PHA-022121
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The treatments to be administered in the study consist of 10 mg PHA-022121 soft capsules and matching placebo soft capsules for oral use:
• Medium dose (20 mg): two capsules of 10 mg PHA-022121 and one placebo capsule

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo treatment consists of matching placebo capsules for oral use.

Arm title	Part II - PHA-022121 30 mg

Arm description:

Participants will receive two single doses of PHA-022121 (30 mg) and one single dose of placebo. Each patient self-administers two single doses of PHA-022121 (30 mg, high dose) and one single dose of placebo for each of the three qualifying HAE attacks according to one of the following sequences (cross-over design):
1. High dose - High dose - Placebo
2. High dose - Placebo - High dose
3. Placebo - High dose - High dose

Arm type	Experimental
Investigational medicinal product name	PHA-022121
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The treatments to be administered in the study consist of 10 mg PHA-022121 soft capsules for oral use:
• High dose (30 mg): three capsules of 10 mg PHA-022121

Arm title	Part II - Placebo

Arm description:

Participants will receive two single doses of PHA-022121 and one single dose of placebo. Each patient self-administers two single doses of PHA-022121 (10, 20 or 30 mg) and one single dose of placebo for each of the three qualifying HAE attacks according to one of the following sequences (cross-over design):
1. PHA-022121 dose - PHA-022121 dose - Placebo
2. PHA-022121 dose - Placebo - PHA-022121 dose
3. Placebo - PHA-022121 dose - PHA-022121 dose

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo treatment consists of matching placebo soft capsules for oral use.
- Placebo: 3 placebo capsules

Number of subjects in period 2	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg
Started	24	24	25
Completed	16	12	12
Not completed	8	12	13
Consent withdrawn by subject	2	3	5
Ongoing at Primary Analysis cutoff	6	9	8

Number of subjects in period 2	Part II - Placebo

Started	73
Completed	40
Not completed	33
Consent withdrawn by subject	10
Ongoing at Primary Analysis cutoff	23

Baseline characteristics

Reporting groups	
Reporting group title	Part I - PHA-022121 10 mg
Reporting group description:	
Participants assigned to the PHA-022121 10 mg arm received a single dose of PHA-022121 (10 mg) during a quiescent non-attack state.	
Reporting group title	Part I - PHA-022121 20 mg
Reporting group description:	
Participants assigned to the PHA-022121 20 mg arm received a single dose of PHA-022121 (20 mg) during a quiescent non-attack state.	
Reporting group title	Part I - PHA-022121 30 mg
Reporting group description:	
Participants assigned to the PHA-022121 30 mg arm received a single dose of PHA-022121 (30 mg) during a quiescent non-attack state.	

Reporting group values	Part I - PHA-022121 10 mg	Part I - PHA-022121 20 mg	Part I - PHA-022121 30 mg
Number of subjects	24	25	25
Age categorical Units: Subjects			
Adults (18-64 years)	22	24	23
From 65-84 years	2	1	2
Age continuous Units: years			
arithmetic mean	42.9	45.7	41.4
standard deviation	± 14.15	± 13.89	± 15.38
Gender categorical Units: Subjects			
Female	17	17	15
Male	7	8	10

Reporting group values	Total		
Number of subjects	74		
Age categorical Units: Subjects			
Adults (18-64 years)	69		
From 65-84 years	5		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	49		
Male	25		

Subject analysis sets	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS was defined as all participants enrolled and randomized in the study. Participants were analyzed based on the intention-to-treat principle, ie, according to their randomized treatment assignment regardless of actual treatment taken.

Subject analysis set title	Modified Intent-To-Treat (mITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified Intent-to-Treat (mITT) Analysis Set was defined as a subset of FAS including all randomized participants who had at least one study drug-treated (blinded PHA 022121 or placebo) HAE attack and who had non missing VAS results at both pre treatment and at least 1 post-treatment time point of that attack. Participants were analyzed based on the intention-to-treat principle, ie, according to their randomized treatment assignment regardless of actual treatment taken.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set was defined as a subset of FAS including all randomized participants who received any dose of study drug. Participants were analyzed according to their actual treatment taken.

Subject analysis set title	Per-Protocol Analysis Set
Subject analysis set type	Per protocol

Subject analysis set description:

The Per-Protocol (PP) Analysis Set was defined as a subset of the mITT Analysis Set, including all participants who had at least one attack satisfying mITT analysis set criteria, and also with no major protocol deviations or other non-compliance that could impact the key efficacy assessment. For participants in the PP Analysis Set, only such attacks satisfying the above criteria were included in the analyses performed on the PP Analysis Set. The PP Analysis Set was a secondary analysis set for analysis of the primary and key secondary efficacy endpoints. A list of participants with major protocol deviations or other non-compliance leading to exclusion from the PP Analysis Set was finalized prior to unblinding the randomized treatment assignments.

Reporting group values	Full Analysis Set (FAS)	Modified Intent-To-Treat (mITT)	Safety Analysis Set
Number of subjects	74	62	73
Age categorical Units: Subjects			
Adults (18-64 years)	69	57	68
From 65-84 years	5	5	5
Age continuous Units: years			
arithmetic mean	43.3	42.9	43.2
standard deviation	± 14.41	± 14.62	± 14.42
Gender categorical Units: Subjects			
Female	49	42	49
Male	25	20	24

Reporting group values	Per-Protocol Analysis Set		
Number of subjects	62		
Age categorical Units: Subjects			
Adults (18-64 years)	57		
From 65-84 years	5		

Age continuous Units: years			
arithmetic mean	42.9		
standard deviation	± 14.62		
Gender categorical Units: Subjects			
Female	42		
Male	20		

End points

End points reporting groups

Reporting group title	Part I - PHA-022121 10 mg

Reporting group description:

Participants assigned to the PHA-022121 10 mg arm received a single dose of PHA-022121 (10 mg) during a quiescent non-attack state.

Reporting group title	Part I - PHA-022121 20 mg

Reporting group description:

Participants assigned to the PHA-022121 20 mg arm received a single dose of PHA-022121 (20 mg) during a quiescent non-attack state.

Reporting group title	Part I - PHA-022121 30 mg

Reporting group description:

Participants assigned to the PHA-022121 30 mg arm received a single dose of PHA-022121 (30 mg) during a quiescent non-attack state.

Reporting group title	Part II - PHA-022121 10 mg

Reporting group description:

Participants were treated with 2 single doses of PHA-022121 (10 mg) and one single dose of placebo. Each participant self-administered the study drug at their randomly assigned dose level (10 mg, low dose) for each of the 3 qualifying HAE attacks according to 1 of the following randomly assigned treatment sequences (crossover design):
1. Low dose - Low dose - Placebo
2. Low dose - Placebo - Low dose
3. Placebo - Low dose - Low dose

Reporting group title	Part II - PHA-022121 20 mg

Reporting group description:

Participants will receive two single doses of PHA-022121 (20 mg) and one single dose of placebo. Each patient self-administers two single doses of PHA-022121 (20 mg, medium dose) and one single dose of placebo for each of the three qualifying HAE attacks according to one of the following sequences (cross-over design):
1. Medium dose - Medium dose - Placebo
2. Medium dose - Placebo - Medium dose
3. Placebo - Medium dose - Medium dose

Reporting group title	Part II - PHA-022121 30 mg

Reporting group description:

Participants will receive two single doses of PHA-022121 (30 mg) and one single dose of placebo. Each patient self-administers two single doses of PHA-022121 (30 mg, high dose) and one single dose of placebo for each of the three qualifying HAE attacks according to one of the following sequences (cross-over design):
1. High dose - High dose - Placebo
2. High dose - Placebo - High dose
3. Placebo - High dose - High dose

Reporting group title	Part II - Placebo

Reporting group description:

Participants will receive two single doses of PHA-022121 and one single dose of placebo. Each patient self-administers two single doses of PHA-022121 (10, 20 or 30 mg) and one single dose of placebo for each of the three qualifying HAE attacks according to one of the following sequences (cross-over design):
1. PHA-022121 dose - PHA-022121 dose - Placebo
2. PHA-022121 dose - Placebo - PHA-022121 dose
3. Placebo - PHA-022121 dose - PHA-022121 dose

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS was defined as all participants enrolled and randomized in the study. Participants were analyzed based on the intention-to-treat principle, ie, according to their randomized treatment assignment regardless of actual treatment taken.

Subject analysis set title	Modified Intent-To-Treat (mITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified Intent-to-Treat (mITT) Analysis Set was defined as a subset of FAS including all randomized participants who had at least one study drug-treated (blinded PHA 022121 or placebo) HAE attack and who had non missing VAS results at both pre treatment and at least 1 post-treatment time point of that attack. Participants were analyzed based on the intention-to-treat principle, ie, according to their randomized treatment assignment regardless of actual treatment taken.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set was defined as a subset of FAS including all randomized participants who received any dose of study drug. Participants were analyzed according to their actual treatment taken.

Subject analysis set title	Per-Protocol Analysis Set
Subject analysis set type	Per protocol

Subject analysis set description:

The Per-Protocol (PP) Analysis Set was defined as a subset of the mITT Analysis Set, including all participants who had at least one attack satisfying mITT analysis set criteria, and also with no major protocol deviations or other non-compliance that could impact the key efficacy assessment. For participants in the PP Analysis Set, only such attacks satisfying the above criteria were included in the analyses performed on the PP Analysis Set. The PP Analysis Set was a secondary analysis set for analysis of the primary and key secondary efficacy endpoints. A list of participants with major protocol deviations or other non-compliance leading to exclusion from the PP Analysis Set was finalized prior to unblinding the randomized treatment assignments.

Primary: Change of the VAS-3 Score from pre-treatment to 4 hours post-treatment

End point title	Change of the VAS-3 Score from pre-treatment to 4 hours post-treatment

End point description:

The primary endpoint of the study was the change of the VAS-3 (3-symptom composite visual analogue scale) score from pre-treatment to 4 hours post-treatment. The VAS-3 was calculated as the mean of the VAS scores of the 3 major HAE symptoms: skin swelling, skin pain, and abdominal pain. The VAS scores of the 3 major HAE symptoms (skin swelling, skin pain, and abdominal pain) could range between 0 (No swelling/No pain) and 100 (Extreme swelling/Excruciating pain).

End point type	Primary

End point timeframe:

Pre-treatment to 4 hours post-treatment.

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: 3-symptom composite analogue scale				
least squares mean (standard error)	-14.83 (± 1.833)	-13.10 (± 2.111)	-14.37 (± 1.975)	1.92 (± 1.596)

Statistical analyses

Statistical analysis title	MMRM 10mg versus placebo

Statistical analysis description:

mITT Analysis Set

Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	-16.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.52
upper limit	-11.97
Variability estimate	Standard error of the mean
Dispersion value	2.423

Notes:
[1] - Nominal P-value

Statistical analysis title	MMRM 20mg versus placebo
Statistical analysis description:	
mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	-15.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.22
upper limit	-9.81
Variability estimate	Standard error of the mean
Dispersion value	2.64

Statistical analysis title	MMRM 30mg versus placebo
Statistical analysis description:	
mITT Analysis Set	
Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	-16.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.27
upper limit	-11.29
Variability estimate	Standard error of the mean
Dispersion value	2.531

Secondary: Time to onset of symptom relief by ≥30% reduction in VAS-3 composite score from the pre-treatment score

End point title	Time to onset of symptom relief by ≥30% reduction in VAS-3 composite score from the pre-treatment score

End point description:

VAS-3 scores range between 0 and 100. Symptom relief is defined as a 30% or higher reduction of the VAS-3 score from the pre-treatment value.

End point type	Secondary

End point timeframe:

Assessed from pre-treatment to 48 hours post-treatment

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: Hours				
median (confidence interval 95%)	2.1 (1.5 to 2.9)	2.7 (1.9 to 3.5)	2.5 (1.9 to 3.8)	8.0 (7.6 to 48.0)

Statistical analyses

Statistical analysis title	Marginal Cox Proportional Analysis 10mg vs placebo

Statistical analysis description:

mITT Analysis Set

Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Cox proportional hazard
Point estimate	3.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.01
upper limit	7.2

Notes:
[2] - Nominal P-value

Statistical analysis title	Marginal Cox Proportional Analysis 20mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Cox proportional hazard
Point estimate	3.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	6.3

Statistical analysis title	Marginal Cox Proportional Analysis 30mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Cox proportional hazard
Point estimate	3.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	6.19

Secondary: Time to almost complete or complete symptom relief by VAS-3 score	
End point title	Time to almost complete or complete symptom relief by VAS-3 score
End point description:	

End point type	Secondary
End point timeframe: Up to 48 hours post-treatment of an attack	

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: Hours				
median (confidence interval 95%)	5.8 (3.6 to 7.5)	20.0 (4.5 to 20.0)	20.0 (6.0 to 20.1)	42.0 (22.0 to 48.0)

Statistical analyses

Statistical analysis title	Marginal Cox Proportional Analysis 10mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Cox proportional hazard
Point estimate	5.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.81
upper limit	9.22

Notes:
[3] - Nominal P-value

Statistical analysis title	Marginal Cox Proportional Analysis 20mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0127
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Cox proportional hazard
Point estimate	2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	4.27

Statistical analysis title	Marginal Cox Proportional Analysis 30mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Cox proportional hazard
Point estimate	2.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.61
upper limit	4.38

Secondary: Time to a ≥50% reduction in VAS-3 composite score from the pre-treatment score

End point title	Time to a ≥50% reduction in VAS-3 composite score from the pre-treatment score
End point description:	
End point type	Secondary
End point timeframe: Assessed from pre-treatment to 48 hours post-treatment	

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: Hours				
median (confidence interval 95%)	3.3 (2.4 to 3.9)	4.0 (2.9 to 6.0)	4.0 (3.3 to 5.8)	22.8 (20.0 to 24.1)

Statistical analyses

Statistical analysis title	Marginal Cox Proportional Analysis 10mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Cox proportional hazard
Point estimate	4.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.41
upper limit	8.59

Notes:

[4] - Nominal P-value

Statistical analysis title	Marginal Cox Proportional Analysis 20mg vs placebo
Statistical analysis description:	
mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Cox proportional hazard
Point estimate	3.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	7.38

Statistical analysis title	Marginal Cox Proportional Analysis 30mg vs placebo
Statistical analysis description:	
mITT Analysis Set	
Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Cox proportional hazard
Point estimate	3.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.26
upper limit	6.63

Secondary: Change in Mean Symptom Complex Severity score from pre-treatment to 4 hours post-treatment

End point title	Change in Mean Symptom Complex Severity score from pre-treatment to 4 hours post-treatment

End point description:

End point type	Secondary

End point timeframe:

Assessed at 4 hours post-treatment

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: Value				
least squares mean (confidence interval 95%)	-1.08 (-1.33 to -0.83)	-0.91 (-1.19 to -0.62)	-0.68 (-0.95 to -0.40)	-0.29 (-0.51 to -0.08)

Statistical analyses

Statistical analysis title	MMRM Analysis 10 mg versus placebo

Statistical analysis description:

mITT Analysis Set

Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	-0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.11
upper limit	-0.46
Variability estimate	Standard error of the mean
Dispersion value	0.164

Notes:

[5] - Nominal P-value

Statistical analysis title	MMRM Analysis 20 mg versus placebo

Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	-0.26
Variability estimate	Standard error of the mean
Dispersion value	0.178

Statistical analysis title	MMRM Analysis 30 mg versus placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0291
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.174

Secondary: TOS at 4 hours post-treatment

End point title	TOS at 4 hours post-treatment
End point description:	

End point type	Secondary
End point timeframe: Assessed until 4 hours post-treatment	

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: Value				
least squares mean (confidence interval 95%)	60.52 (41.74 to 79.29)	59.08 (37.58 to 80.57)	67.44 (47.15 to 87.74)	-3.62 (-19.68 to 12.45)

Statistical analyses

Statistical analysis title	MMRM Analysis 10 mg versus placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	64.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	40.35
upper limit	87.91
Variability estimate	Standard error of the mean
Dispersion value	12.016

Notes:
[6] - Nominal P-value

Statistical analysis title	MMRM Analysis 20 mg versus placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	62.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	36.71
upper limit	88.67
Variability estimate	Standard error of the mean
Dispersion value	13.128

Statistical analysis title	MMRM Analysis 30 mg versus placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	71.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	46.09
upper limit	96.03
Variability estimate	Standard error of the mean
Dispersion value	12.613

Secondary: Time to onset of primary symptom relief assessed by a 30% reduction in the VAS for the primary symptom

End point title	Time to onset of primary symptom relief assessed by a 30% reduction in the VAS for the primary symptom
End point description:	
End point type	Secondary
End point timeframe: Within 48 hours post-treatment	

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: Hours				
median (confidence interval 95%)	2.0 (1.4 to 2.4)	3.0 (1.9 to 4.1)	2.9 (1.9 to 3.9)	23.3 (6.1 to 48.0)

Statistical analyses

Statistical analysis title	Cox Proportional Hazard Model 10 mg versus placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Cox proportional hazard
Point estimate	3.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.99
upper limit	7.15

Notes:
[7] - Nominal P-value

Statistical analysis title	Cox Proportional Hazard Model 20 mg versus placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [8]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Cox proportional hazard
Point estimate	3.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.84
upper limit	6.34

Notes:
[8] - Nominal P-value

Statistical analysis title	Cox Proportional Hazard Model 30 mg versus placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Cox proportional hazard
Point estimate	3.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.06
upper limit	6.16

Notes:

[9] - Nominal P-value

Secondary: Proportion of study drug-treated attacks requiring HAE rescue medication within 12 hours

End point title	Proportion of study drug-treated attacks requiring HAE rescue medication within 12 hours

End point description:

End point type	Secondary

End point timeframe:

Proportion of blinded study drug treated attacks requiring HAE rescue medication within 12 hours post-treatment

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: Attacks requiring HAE rescue medication				
number (not applicable)	7	3	2	31

Statistical analyses

Statistical analysis title	HAE rescue medication at 12 hr - 10 mg vs placebo

Statistical analysis description:

mITT Analysis Set

Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Generalized estimating equation
Parameter estimate	Odds ratio (OR)
Point estimate	0.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.37

Notes:

[10] - Nominal P-value

Statistical analysis title	HAE rescue medication at 12 hr - 20 mg vs placebo
Statistical analysis description:	
mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
Method	Generalized estimating equation
Parameter estimate	Odds ratio (OR)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.35

Statistical analysis title	HAE rescue medication at 12 hr - 30 mg vs placebo
Statistical analysis description:	
mITT Analysis Set	
Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Generalized estimating equation
Parameter estimate	Odds ratio (OR)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.18

Notes:

[11] - Nominal P-value

Secondary: Time to first HAE rescue medication use for study drug-treated attacks within 48 hours post-treatment

End point title	Time to first HAE rescue medication use for study drug-treated attacks within 48 hours post-treatment

End point description:

End point type	Secondary

End point timeframe:

The proportion of treated attacks with first use of HAE rescue medication within 48 hours post-treatment with PHA-022121

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: Number of treated attacks				
number (not applicable)	9	4	5	37

Statistical analyses

Statistical analysis title	Time to first use of rescue meds 10 mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.43

Notes:

[12] - Nominal P-value

Statistical analysis title	Time to first use of rescue meds 20 mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.0001 [14]
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.33

Notes:
[13] - Nominal P-value
[14] - Nominal P-value

Statistical analysis title	Time to first use of rescue meds 30 mg vs placebo

Statistical analysis description:
mITT Analysis Set

Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.31

Notes:
[15] - Nominal P-value

Secondary: Time to change in the VAS score for Skin Pain Score - 30% reduction

End point title	Time to change in the VAS score for Skin Pain Score - 30% reduction

End point description:

End point type	Secondary

End point timeframe:
Within 48 Hours post-treatment

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	10	17	34
Units: Hours				
median (inter-quartile range (Q1-Q3))	2.9 (1.9 to 5.7)	3.40 (1.9 to 6.0)	2.7 (1.9 to 3.9)	22.8 (8.7 to 46.9)

Statistical analyses

Statistical analysis title	Marginal Cox Proportional Analysis 10mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [16]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	4.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.98
upper limit	9.19

Notes:
[16] - Nominal P-value

Statistical analysis title	Marginal Cox Proportional Analysis 20mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	5.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.38
upper limit	11.43

Notes:
[17] - Nominal P-value

Statistical analysis title	Marginal Cox Proportional Analysis 30mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	6.34

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.06
upper limit	13.12

Notes:

[18] - Nominal P-value

Secondary: Change in Mean Symptom Complex Severity score from pre-treatment to 24 hours post-treatment

End point title	Change in Mean Symptom Complex Severity score from pre-treatment to 24 hours post-treatment

End point description:

End point type	Secondary

End point timeframe:

24 hours post-treatment

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: Change in MSCS score				
least squares mean (standard error)	-1.65 (± 0.117)	-1.50 (± 0.123)	-1.68 (± 0.122)	-1.20 (± 0.163)

Statistical analyses

Statistical analysis title	MMRM Analysis 10 mg versus placebo
Statistical analysis description:	
mITT Analysis Set	
Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0267 [19]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.2

Notes:
[19] - Nominal P-value

Statistical analysis title	MMRM Analysis 20 mg versus placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1497 [20]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.204

Notes:
[20] - Nominal P-value

Statistical analysis title	MMRM Analysis 30 mg versus placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0211 [21]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	-0.07
Variability estimate	Standard error of the mean
Dispersion value	0.0211

Notes:
[21] - Nominal P-value

Secondary: TOS at 24 hours post-treatment

End point title	TOS at 24 hours post-treatment

End point description:

End point type	Secondary

End point timeframe:
24 Hours post-treatment

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: TOS Score Change				
least squares mean (standard error)	89.51 (± 5.511)	88.54 (± 5.997)	92.21 (± 5.703)	61.78 (± 6.776)

Statistical analyses

Statistical analysis title	MMRM Analysis 10 mg versus placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015 [22]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	27.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.93
upper limit	44.53
Variability estimate	Standard error of the mean
Dispersion value	8.452

Notes:
[22] - Nominal P-value

Statistical analysis title	MMRM Analysis 20 mg versus placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [23]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	26.76

Confidence interval	
level	95 %
sides	2-sided
lower limit	9.35
upper limit	44.17
Variability estimate	Standard error of the mean
Dispersion value	8.764

Notes:

[23] - Nominal P-value

Statistical analysis title	MMRM Analysis 30 mg versus placebo

Statistical analysis description:

mITT Analysis Set

Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 [24]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	30.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.6
upper limit	47.26
Variability estimate	Standard error of the mean
Dispersion value	8.464

Notes:

[24] - Nominal P-value

Secondary: Treatment Satisfaction Questionnaire for Medication scores at 48 hours post-treatment - Effectiveness Domain Score

End point title	Treatment Satisfaction Questionnaire for Medication scores at 48 hours post-treatment - Effectiveness Domain Score

End point description:

End point type	Secondary

End point timeframe:

MMRM analysis of Treatment Satisfaction Questionnaire for Medication (TSQM) at 48 hours post-treatment

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: TSQM Scores				
arithmetic mean (standard deviation)	79.17 (± 23.179)	70.45 (± 30.290)	72.92 (± 23.085)	65.38 (± 23.532)

Statistical analyses

Statistical analysis title	TSQM Effectiveness Domain Score 10 mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0906 [25]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	18.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.96
upper limit	39.31
Variability estimate	Standard error of the mean
Dispersion value	10.568

Notes:
[25] - Nominal P-value

Statistical analysis title	TSQM Effectiveness Domain Score 20mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.755 [26]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	3.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.59
upper limit	24.14
Variability estimate	Standard error of the mean
Dispersion value	10.442

Notes:
[26] - Nominal P-value

Statistical analysis title	TSQM Effectiveness Domain Score 30mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3879 [27]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	8.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.62
upper limit	29.53
Variability estimate	Standard error of the mean
Dispersion value	10.296

Notes:
[27] - Nominal P-value

Secondary: Time to Onset of Primary Symptom Relief by 50% Reduction in VAS Score

End point title	Time to Onset of Primary Symptom Relief by 50% Reduction in VAS Score
End point description:	
End point type	Secondary
End point timeframe: Within 48 hours post-treatment	

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: Hours				
median (confidence interval 95%)	2.9 (2.4 to 3.9)	4.5 (2.9 to 8.5)	4.0 (2.5 to 5.8)	22.8 (5.8 to 24.1)

Statistical analyses

Statistical analysis title	Marginal Cox Proportional Analysis 10mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [28]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Cox proportional hazard
Point estimate	3.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.16
upper limit	7.09

Notes:
[28] - Nominal P-value

Statistical analysis title	Marginal Cox Proportional Analysis 20mg vs placebo
Statistical analysis description:	
mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0024 [29]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Cox proportional hazard
Point estimate	3.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.48
upper limit	6.15

Notes:
[29] - Nominal P-value

Statistical analysis title	Marginal Cox Proportional Analysis 30mg vs placebo
Statistical analysis description:	
mITT Analysis Set	
Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [30]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Cox proportional hazard
Point estimate	3.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.71
upper limit	5.31

Notes:

[30] - Nominal P-value

Secondary: Proportion of study drug-treated attacks requiring HAE rescue medication within 24 hours

End point title	Proportion of study drug-treated attacks requiring HAE rescue medication within 24 hours

End point description:

End point type	Secondary

End point timeframe:

Proportion of blinded study drug treated attacks requiring HAE rescue medication within 24 hours post-treatment.

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: Attacks requiring HAE rescue medication				
number (not applicable)	9	3	4	37

Statistical analyses

Statistical analysis title	HAE rescue medication at 24 hr - 10 mg vs placebo

Statistical analysis description:

mITT Analysis Set

Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [31]
Method	Generalized estimating equation
Parameter estimate	Odds ratio (OR)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.29

Notes:

[31] - Nominal Analysis Set

Statistical analysis title	HAE rescue medication at 24 hr - 20 mg vs placebo

Statistical analysis description:

mITT Analysis Set

Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [32]
Method	Generalized estimating equation
Parameter estimate	Odds ratio (OR)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.19

Notes:

[32] - Nominal P-value

Statistical analysis title	HAE rescue medication at 24 hr - 30 mg vs placebo

Statistical analysis description:

mITT Analysis Set

Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [33]
Method	Generalized estimating equation
Parameter estimate	Odds ratio (OR)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.18

Notes:

[33] - Nominal P-value

Secondary: Proportion of study drug-treated attacks requiring HAE rescue medication within 48 hours

End point title	Proportion of study drug-treated attacks requiring HAE rescue medication within 48 hours

End point description:

End point type	Secondary

End point timeframe:

Proportion of blinded study drug treated attacks requiring HAE rescue medication within 48 hours post-treatment.

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: Attacks requiring HAE rescue medication				
number (not applicable)	9	4	5	37

Statistical analyses

Statistical analysis title	HAE rescue medication at 48 hr - 10 mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [34]
Method	Generalized estimating equation
Parameter estimate	Odds ratio (OR)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.29

Notes:
[34] - Nominal P-value

Statistical analysis title	HAE rescue medication at 48 hr - 20 mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [35]
Method	Generalized estimating equation
Parameter estimate	Odds ratio (OR)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.24

Notes:
[35] - Nominal P-value

Statistical analysis title	HAE rescue medication at 48 hr - 30 mg vs placebo

Statistical analysis description:	
mITT Analysis Set	
Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [36]
Method	Generalized estimating equation
Parameter estimate	Odds ratio (OR)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.22

Notes:

[36] - Nominal P-value

Secondary: Treatment Satisfaction Questionnaire for Medication scores at 48 hours post-treatment - Convenience Domain Score

End point title	Treatment Satisfaction Questionnaire for Medication scores at 48 hours post-treatment - Convenience Domain Score
End point description:	
End point type	Secondary
End point timeframe:	
MMRM analysis of Treatment Satisfaction Questionnaire for Medication (TSQM) at 48 hours post-treatment	

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: TSQM Scores				
arithmetic mean (standard deviation)	80.56 (± 16.569)	83.08 (± 23.096)	77.55 (± 20.229)	76.07 (± 27.441)

Statistical analyses

Statistical analysis title	TSQM Convenience Domain Score 10 mg vs placebo
Statistical analysis description:	
mITT Analysis Set	
Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4602 [37]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.51
upper limit	7.3
Variability estimate	Standard error of the mean
Dispersion value	5.444

Notes:
[37] - Nominal P-value

Statistical analysis title	TSQM Convenience Domain Score 20 mg vs placebo
Statistical analysis description:	
mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9053 [38]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	-0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.43
upper limit	11.07
Variability estimate	Standard error of the mean
Dispersion value	5.659

Notes:
[38] - Nominal P-value

Statistical analysis title	TSQM Convenience Domain Score 30 mg vs placebo
Statistical analysis description:	
mITT Analysis Set	
Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0223 [39]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	-13.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.02
upper limit	-2.1
Variability estimate	Standard error of the mean
Dispersion value	5.187

Notes:

[39] - Nominal P-value

Secondary: Treatment Satisfaction Questionnaire for Medication scores at 48 hours post-treatment - Satisfaction Domain Score

End point title	Treatment Satisfaction Questionnaire for Medication scores at 48 hours post-treatment - Satisfaction Domain Score

End point description:

End point type	Secondary

End point timeframe:

MMRM analysis of Treatment Satisfaction Questionnaire for Medication (TSQM) at 48 hours post-treatment

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	16	20	51
Units: TSQM Scores				
arithmetic mean (standard deviation)	82.50 (± 18.907)	80.68 (± 29.702)	76.74 (± 22.113)	64.10 (± 24.623)

Statistical analyses

Statistical analysis title	TSQM Satisfaction Domain Score 10 mg vs placebo

Statistical analysis description:

mITT Analysis Set

Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1339 [40]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	14.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.62
upper limit	33.64

Variability estimate	Standard error of the mean
Dispersion value	9.525

Notes:
[40] - Nominal P-value

Statistical analysis title	TSQM Satisfaction Domain Score 20 mg vs placebo

Statistical analysis description:
mITT Analysis Set

Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2406 [41]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	11.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.65
upper limit	29.76
Variability estimate	Standard error of the mean
Dispersion value	9.308

Notes:
[41] - Nominal P-value

Statistical analysis title	TSQM Satisfaction Domain Score 30 mg vs placebo

Statistical analysis description:
mITT Analysis Set

Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46 [42]
Method	Mixed model repeated measures
Parameter estimate	Least Squares mean difference
Point estimate	6.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.45
upper limit	24.92
Variability estimate	Standard error of the mean
Dispersion value	9.035

Notes:
[42] - Nominal P-value

Secondary: Time to change in the VAS score for Skin Swelling Score - 30% reduction

End point title	Time to change in the VAS score for Skin Swelling Score - 30% reduction

End point description:

End point type	Secondary

End point timeframe:

Within 48 hours post-treatment

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	9	9	14
Units: Hours				
median (inter-quartile range (Q1-Q3))	3.4 (1.9 to 20.0)	2.9 (1.9 to 4.9)	2.9 (1.9 to 3.9)	23.3 (5.8 to 24.1)

Statistical analyses

Statistical analysis title	Marginal Cox Proportional Analysis 10mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0013 [43]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	3.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.56
upper limit	6.2

Notes:

[43] - Nominal P-value

Statistical analysis title	Marginal Cox Proportional Analysis 20mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0023 [44]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	2.82

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.45
upper limit	5.5

Notes:

[44] - Nominal P-value

Statistical analysis title	Marginal Cox Proportional Analysis 30mg vs placebo

Statistical analysis description:

mITT Analysis Set

Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [45]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	3.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.78
upper limit	5.93

Notes:

[45] - Nominal P-value

Secondary: Time to change in the VAS score for Abdominal Pain Score - 30% reduction

End point title	Time to change in the VAS score for Abdominal Pain Score - 30% reduction

End point description:

End point type	Secondary

End point timeframe:

Within 48 hours pst-treatment

End point values	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg	Part II - Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	4	7	5
Units: Hours				
median (inter-quartile range (Q1-Q3))	1.4 (0.9 to 1.9)	1.9 (1.2 to 3.6)	3.8 (2.5 to 7.5)	2.9 (2.9 to 2.9)

Statistical analyses

Statistical analysis title	Marginal Cox Proportional Analysis 10mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 10 mg v Part II - Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [46]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	8.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.92
upper limit	23.77

Notes:
[46] - Nominal P-value

Statistical analysis title	Marginal Cox Proportional Analysis 20mg vs placebo
Statistical analysis description: mITT Analysis Set	
Comparison groups	Part II - PHA-022121 20 mg v Part II - Placebo
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [47]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	7.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.36
upper limit	23.2

Notes:
[47] - Nominal P-value

Statistical analysis title	Marginal Cox Proportional Analysis 30mg vs placebo
Comparison groups	Part II - PHA-022121 30 mg v Part II - Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0143 [48]
Method	Marginal Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	3.45

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.28
upper limit	9.29

Notes:

[48] - Nominal P-value

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Five (5) days post treatment.	
Adverse event reporting additional description:	
Adverse events were reported for the Safety Analysis Set	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Part I - PHA-022121 10 mg
Reporting group description: -	
Reporting group title	Part I - PHA-022121 20 mg
Reporting group description: -	
Reporting group title	Part I - PHA-022121 30 mg
Reporting group description: -	
Reporting group title	Part II - PHA-022121 10 mg
Reporting group description: -	
Reporting group title	Part II - PHA-022121 20 mg
Reporting group description: -	
Reporting group title	Part II - PHA-022121 30 mg
Reporting group description: -	
Reporting group title	Part II - Placebo
Reporting group description: -	

Serious adverse events	Part I - PHA-022121 10 mg	Part I - PHA-022121 20 mg	Part I - PHA-022121 30 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 25 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma	Additional description: On Study Day 221, subject reported a one-year history of double vision and was diagnosed with a brain tumor with optic nerve compression. On Study Day 238, subject underwent surgery for tumor resection, SAE unrelated to drug was considered resolved.		
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 16 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma	Additional description: On Study Day 221, subject reported a one-year history of double vision and was diagnosed with a brain tumor with optic nerve compression. On Study Day 238, subject underwent surgery for tumor resection, SAE unrelated to drug was considered resolved.		
subjects affected / exposed	0 / 16 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part II - Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 53 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma	Additional description: On Study Day 221, subject reported a one-year history of double vision and was diagnosed with a brain tumor with optic nerve compression. On Study Day 238, subject underwent surgery for tumor resection, SAE unrelated to drug was considered resolved.		
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part I - PHA-022121 10 mg	Part I - PHA-022121 20 mg	Part I - PHA-022121 30 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 23 (8.70%)	2 / 24 (8.33%)	4 / 25 (16.00%)
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	2 / 25 (8.00%)
occurrences (all)	0	1	2
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Dental caries			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Lower urinary tract symptoms			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Infections and infestations			
Gastrointestinal infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Viral infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Part II - PHA-022121 10 mg	Part II - PHA-022121 20 mg	Part II - PHA-022121 30 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 16 (18.75%)	1 / 19 (5.26%)	2 / 16 (12.50%)
Investigations			

Blood bilirubin increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 16 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 16 (6.25%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 16 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 16 (0.00%)	0 / 19 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Dental caries			
subjects affected / exposed	0 / 16 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Lower urinary tract symptoms			
subjects affected / exposed	0 / 16 (0.00%)	1 / 19 (5.26%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Gastrointestinal infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Viral infection			

subjects affected / exposed	0 / 16 (0.00%)	0 / 19 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part II - Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 53 (0.00%)		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Dental caries			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Lower urinary tract symptoms			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Infections and infestations			

Gastrointestinal infection			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2021	• The sample size was increased to 72 participants, and the number of participating countries and sites were increased. • Added further specification for the randomization process with stratification for willingness to participate in full PK sampling in Part I (non-attack) of the study (Yes/No). • The criteria for study drug intake and number of capsules to be taken in Part II of the study were clarified. • Added text regarding the handling of HAE attacks that occurred prior to the Part I (non-attack) for clarification. • In addition to metabolite M2-D, other metabolites could be analysed. • The time points for coagulation testing were clarified. • The duration of home treatment (Part II) was clarified. • The risk of airway involvement in case of laryngeal and pharyngeal attacks was specified. • The Schedule of Events was modified to distinguish between the study activities at the on-site screening visit and the remote screening visit. • Time periods were linked to groups of prohibited concomitant medications. • Updated SAE reporting procedures. • Minor errors, inconsistencies and unclarities were corrected.
25 April 2022	• Added brief results from the most recent non-clinical and clinical studies. • Modified the secondary efficacy endpoints and updated the statistical methods. • Changed the AE causality text per a request by a regulatory authority. • Incorporated changes from Amendment 6 (France only). • Waived the end-of-study visit if participants continued in another clinical study with PHA 022121 conducted by the Sponsor. • Extended the duration of participation and overall study if some participants needed longer than 24 weeks to complete assessments for 3 qualifying HAE attacks. • Allowed inclusion of participants with positive hepatitis B serology if they had normal liver function tests and no signs of active liver disease. • Allowed bilirubin elevation at screening if elevation was due to Gilbert's syndrome. • Removed the prohibition on concomitant medications that are metabolized by CYP3A4. • Defined clinically significant as it pertained to abnormal findings from safety assessments. • Indicated that Part II was subject to the same stopping rules as Part I (non-attack). • Clarified the use of the ePRO device for recording HAE attacks. • Added a new section for "Study Analyses" describing the plan for conducting a Primary Analysis and a Final Analysis of the study data.

Notes:

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.

Primary analysis is presented. Nominal P-values are listed for 10 mg dose for the primary and key secondary endpoints as tests for 10 mg dose weren't multiplicity controlled. P-values of other secondary endpoints are nominal for all doses.

Notes: