Clinical trial results:
A multi-centre, randomized, double-blind, placebo-controlled, dose range finding study to identify the optimal (i.e. safe and effective) dose of PURETHAL® Mites SCIT in patients with house dust mites-induced persistent allergic rhinitis/rhinoconjunctivitis.

Summary

EudraCT number	2011-000393-61
Trial protocol	DE AT NL ES BE
Global end of trial date	15 May 2013

Results information

Result version number	v1 (current)
This version publication date	17 August 2017
First version publication date	17 August 2017
Summary attachment (see zip file)	CSR synopsis PM0037 EUdraCT (CSR synopsis PM0037 EUdraCT.pdf)

Trial information

Trial identification

Sponsor protocol code	PM/0037

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	HAL Allergy
Sponsor organisation address	J.H. Oortweg 15-17, Leiden, Netherlands, NL-2333 CH
Public contact	Head Department of Clinical Development & Pharmacovigilance, HAL Allergy, +31 88 195 9000, pjdkam@hal-allergy.com
Scientific contact	Head Department of Clinical Development & Pharmacovigilance, HAL Allergy, +31 88 195 9000, pjdkam@hal-allergy.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	31 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2013
Global end of trial reached?	Yes
Global end of trial date	15 May 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the present study is to characterize the dose-response relationship of PURETHAL® Mites (PM) with a nasal provocation test in order to identify the optimal dose in terms of highest clinical efficacy and safety.

Protection of trial subjects:

The trial is performed in accordance with GCP and with all applicable governmental regulations. Independent approval for the study conduct was obtained from the IECs. Informed consent was obtained from each subject participating in the trial after explanation of the aims, design, methods, benefits and potential hazards of the trial before any trial-specific procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2011
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: 28
Country: Number of subjects enrolled	Spain: 40
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Belgium: 30
Country: Number of subjects enrolled	Germany: 182
Worldwide total number of subjects	290
EEA total number of subjects	290

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)	290
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients visiting an outpatient clinic of a participating center fulfilling general in- and exclusion criteria, are informed about the study and requested to participate. Patient can also be recruited by means of advertisements. After their informed consent (IC) all inclusion and exclusion criteria were checked.

Pre-assignment

Screening details:

420 patients were screened, 130 were not randomized mainly because in- and/or exclusion criteria were not met.
Diagnosis and main criteria for inclusion: Persistent rhinitis or rhinoconjunctivitis, with or without concomitant asthma, related to house dust mites, age ≥ 18 years and ≤ 60 years.

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, Data analyst, Assessor

Blinding implementation details:

Purethal Mites and matching placebo was delivered to the participating sites in clearly marked blinded vials. To fully ensure the blinding the injections were prepared by an independent medically trained person. This person prepared the syringe with the correct volume shortly before injection and covered it with tinfoil, subsequently the injection was performed by the investigator.

Arms

Are arms mutually exclusive?	Yes
Arm title	PM 6,667 AUeq/ml

Arm description:

Active treatment

Arm type	Experimental
Investigational medicinal product name	PURETHAL Mites (PM)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6,6667 AUeq/ml.
Treatment started with an up-dosing phase lasting five weeks and six doses given at weekly intervals. After reaching the maintenance dose 10 monthly injections of 0.5 mL were administered. Dose: Weekly up-dosing of 0.05 mL, 0.1 mL, 0.2 mL, 0.3 mL, 0.4 mL, 0.5 mL. Followed by 4-weekly maintenance dose of 0.5 mL.

Arm title	PM 20,000 AUeq/ml

Arm description:

Active treatment

Arm type	Experimental
Investigational medicinal product name	PURETHAL Mites (PM)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

20,000 AUeq/ml.

Treatment started with an up-dosing phase lasting five weeks and six doses given at weekly intervals. After reaching the maintenance dose 10 monthly injections of 0.5 mL were administered. Dose: Weekly up-dosing of 0.05 mL, 0.1 mL, 0.2 mL, 0.3 mL, 0.4 mL, 0.5 mL. Followed by 4-weekly maintenance dose of 0.5 mL.

Arm title	PM 50,000 AUeq/ml

Arm description:

Active treatment

Arm type	Experimental
Investigational medicinal product name	PURETHAL Mites (PM)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

50,000 AUeq/ml.
Treatment started with an up-dosing phase lasting five weeks and six doses given at weekly intervals. After reaching the maintenance dose 10 monthly injections of 0.5 mL were administered. Dose: Weekly up-dosing of 0.05 mL, 0.1 mL, 0.2 mL, 0.3 mL, 0.4 mL, 0.5 mL. Followed by 4-weekly maintenance dose of 0.5 mL.

Arm title	PM 100,000 AUeq/ml

Arm description:

Active treatment

Arm type	Experimental
Investigational medicinal product name	PURETHAL Mites (PM)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

100,000 AUeq/ml.
Treatment started with an up-dosing phase lasting five weeks and six doses given at weekly intervals. After reaching the maintenance dose 10 monthly injections of 0.5 mL were administered. Dose: Weekly up-dosing of 0.05 mL, 0.1 mL, 0.2 mL, 0.3 mL, 0.4 mL, 0.5 mL. Followed by 4-weekly maintenance dose of 0.5 mL.

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0 AUeq/ml
Treatment started with an up-dosing phase lasting five weeks and six doses given at weekly intervals. After reaching the maintenance dose 10 monthly injections of 0.5 mL were administered. Dose: Weekly up-dosing of 0.05 mL, 0.1 mL, 0.2 mL, 0.3 mL, 0.4 mL, 0.5 mL. Followed by 4-weekly maintenance dose of 0.5 mL.

Number of subjects in period 1	PM 6,667 AUeq/ml	PM 20,000 AUeq/ml	PM 50,000 AUeq/ml
Started	57	59	59
Maintenance dose 4	47	53	49
Completed	47	52	46
Not completed	10	7	13
Consent withdrawn by subject	2	1	1
Adverse event, non-fatal	3	1	5
Other reasons	5	5	7

Number of subjects in period 1	PM 100,000 AUeq/ml	Placebo
Started	59	56
Maintenance dose 4	46	50
Completed	44	47
Not completed	15	9
Consent withdrawn by subject	-	2
Adverse event, non-fatal	7	2
Other reasons	8	5

Baseline characteristics

Reporting groups	
Reporting group title	PM 6,667 AUeq/ml
Reporting group description:	
Active treatment	
Reporting group title	PM 20,000 AUeq/ml
Reporting group description:	
Active treatment	
Reporting group title	PM 50,000 AUeq/ml
Reporting group description:	
Active treatment	
Reporting group title	PM 100,000 AUeq/ml
Reporting group description:	
Active treatment	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Reporting group values	PM 6,667 AUeq/ml	PM 20,000 AUeq/ml	PM 50,000 AUeq/ml
Number of subjects	57	59	59
Age categorical			
Units: Subjects			
In utero	0	0	0
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)	57	59	59
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	31.6	32.1	29.4
standard deviation	± 9.2	± 8.9	± 8.9
Gender categorical			
Units: Subjects			
Female	30	25	30
Male	27	34	29

Reporting group values	PM 100,000 AUeq/ml	Placebo	Total
Number of subjects	59	56	290
Age categorical			
Units: Subjects			
In utero	0	0	0

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)	59	56	290
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	30.5	30.2	
standard deviation	± 10.3	± 10.1	-
Gender categorical			
Units: Subjects			
Female	35	28	148
Male	24	28	142

End points

End points reporting groups	
Reporting group title	PM 6,667 AUeq/ml
Reporting group description: Active treatment	
Reporting group title	PM 20,000 AUeq/ml
Reporting group description: Active treatment	
Reporting group title	PM 50,000 AUeq/ml
Reporting group description: Active treatment	
Reporting group title	PM 100,000 AUeq/ml
Reporting group description: Active treatment	
Reporting group title	Placebo
Reporting group description: Placebo	

Primary: Change from baseline in mean Lebel score	
End point title	Change from baseline in mean Lebel score
End point description: Change from baseline in mean Lebel score in the Titrated Nasal Provocation Test (TNPT) at the end of study in ITT population.	
End point type	Primary
End point timeframe: At baseline and at end of study.	

End point values	PM 6,667 AUeq/ml	PM 20,000 AUeq/ml	PM 50,000 AUeq/ml	PM 100,000 AUeq/ml
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	59	59	59
Units: Lebel score				
least squares mean (standard error)	-2.28 (± 0.26)	-2.52 (± 0.25)	-2.57 (± 0.26)	-2.47 (± 0.27)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Lebel score				
least squares mean (standard error)	-1.74 (± 0.26)			

Statistical analyses

Statistical analysis title	Analysis of mean Lebel score: change from baseline
Comparison groups	PM 6,667 AUeq/ml v Placebo
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.26
upper limit	0.18

Statistical analysis title	Analysis of mean Lebel score: change from baseline
Comparison groups	Placebo v PM 20,000 AUeq/ml
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.44
upper limit	-0.04

Statistical analysis title	Analysis of mean Lebel score: change from baseline
Comparison groups	PM 50,000 AUeq/ml v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.58
upper limit	-0.13

Statistical analysis title	Analysis of mean Lebel score: change from baseline
Comparison groups	Placebo v PM 100,000 AUeq/ml
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.47
upper limit	0

Secondary: Change from baseline in mean Lebel score at maintenance visit 4	
End point title	Change from baseline in mean Lebel score at maintenance visit 4
End point description:	
Change from baseline in mean Lebel score in Titrated Nasal Provocation Test (TNPT) at Maintenance visit 4 in ITT population.	
End point type	Secondary
End point timeframe:	
At baseline and at maintenance visit 4 (approximately 22 weeks after study start).	

End point values	PM 6,667 AUeq/ml	PM 20,000 AUeq/ml	PM 50,000 AUeq/ml	PM 100,000 AUeq/ml
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47	53	49	49
Units: Lebel score				
least squares mean (standard error)	-1.43 (± 0.3)	-1.47 (± 0.28)	-1.83 (± 0.29)	-1.47 (± 0.3)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Lebel score				
least squares mean (standard error)	-1.42 (± 0.29)			

Statistical analyses

Statistical analysis title	Analysis of mean Lebel score at visit 4
Comparison groups	Placebo v PM 6,667 AUeq/ml
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.999
Method	ANCOVA

Statistical analysis title	Analysis of mean Lebel score at visit 4
Comparison groups	Placebo v PM 20,000 AUeq/ml
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9014
Method	ANCOVA

Statistical analysis title	Analysis of mean Lebel score at visit 4
Comparison groups	Placebo v PM 50,000 AUeq/ml
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3238
Method	ANCOVA

Statistical analysis title	Analysis of mean Lebel score at visit 4
Comparison groups	Placebo v PM 100,000 AUeq/ml
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9194
Method	ANCOVA

Secondary: Frequency counts of change in mean Lebel score in TNPT (EOS - baseline)

End point title	Frequency counts of change in mean Lebel score in TNPT (EOS - baseline)

End point description:

Frequency counts of change in mean Lebel score in titrated nasal provocation test (TNPT) between EOS and baseline (worsened, unchanged, improved) per treatment arm in ITT population.

End point type	Secondary

End point timeframe:

At baseline and at end of study.

End point values	PM 6,667 AUeq/ml	PM 20,000 AUeq/ml	PM 50,000 AUeq/ml	PM 100,000 AUeq/ml
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47	52	46	44
Units: Change in mean Lebel score in TNPT (n)				
number (not applicable)				
Worsened	6	6	4	3
Unchanged	2	4	2	1
Improved	39	42	40	40

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: Change in mean Lebel score in TNPT (n)				
number (not applicable)				
Worsened	7			
Unchanged	4			
Improved	36			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Peak Nasal Inspiratory Flow at the end of study

End point title	Change from baseline in Peak Nasal Inspiratory Flow at the end of study

End point description:

The change from baseline of mean of Peak Nasal Inspiratory Flow (PNIF) at end of study in the ITT population.

End point type	Secondary

End point timeframe:

At baseline and at end of study.

End point values	PM 6,667 AUeq/ml	PM 20,000 AUeq/ml	PM 50,000 AUeq/ml	PM 100,000 AUeq/ml
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47	52	46	44
Units: L/min				
least squares mean (standard error)	26.3 (± 5.9)	30.7 (± 5.8)	35.2 (± 6.1)	30.3 (± 6.1)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: L/min				
least squares mean (standard error)	28.5 (± 5.9)			

Statistical analyses

Statistical analysis title	Analysis of change from baseline of PNIF
Comparison groups	Placebo v PM 6,667 AUeq/ml
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.01
upper limit	14.61

Statistical analysis title	Analysis of change from baseline of PNIF
Comparison groups	Placebo v PM 20,000 AUeq/ml
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.788
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.4
upper limit	18.8

Statistical analysis title	Analysis of change from baseline of PNIF
Comparison groups	Placebo v PM 50,000 AUeq/ml
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.432
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.3
upper limit	23.7

Statistical analysis title	Analysis of change from baseline of PNIF
Comparison groups	Placebo v PM 100,000 AUeq/ml
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.828
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.2
upper limit	18.6

Secondary: Serum specific immunoglobulins EOS - baseline	
End point title	Serum specific immunoglobulins EOS - baseline[1]
End point description:	
Difference of active group vs. placebo of the change from baseline of serum specific immunoglobulins (in ITT population): ssIgG4 D. pteronyssinus, ssIgG4 D. farinae, ssIgG4 nDer p 1, ssIgG4 rDer p 2, ssIgG nDer p 1, ssIgG rDer p 2, ssIgE D.pteronyssinus, ssIgE nDer p 1, ssIgE rDer p 2. IgG levels were measured in mg/L, IgG4 levels were measured in µg/L, IgE levels were measured in KU/L.	
End point type	Secondary
End point timeframe:	
At baseline and end of study.	

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: No values were reported for the placebo treatment group because the presented values include the difference of LS means of the active treatment groups compared to placebo treatment group.

End point values	PM 6,667 AUeq/ml	PM 20,000 AUeq/ml	PM 50,000 AUeq/ml	PM 100,000 AUeq/ml
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	59	59	59
Units: concentration				
least squares mean (standard error)				
ssIgG4 D. pteronyssinus (µg/L)	377.3 (± 441.1)	806.6 (± 434.6)	1945.7 (± 444.1)	4213.6 (± 455.4)
ssIgG4 D. farinae (µg/L)	426.8 (± 493)	907.3 (± 485.6)	2492.8 (± 495.1)	4512.5 (± 508.3)
ssIgG4 nDer p 1 (µg/L)	268.1 (± 317.9)	531.9 (± 310.9)	1237.5 (± 138.8)	3256.6 (± 327.3)
ssIgG4 rDer p 2 (µg/L)	254 (± 140.3)	489.6 (± 139.3)	1005.6 (± 139)	1267.4 (± 146.2)
ssIgG nDer p 1 (mg/L)	0.34 (± 0.17)	0.57 (± 0.17)	1.34 (± 0.17)	2.34 (± 0.17)
ssIgG rDer p 2 (mg/L)	0.2 (± 0.17)	0.47 (± 0.16)	1 (± 0.16)	1.2 (± 0.17)
ssIgE D. pteronyssinus (KU/L)	-2.1 (± 6.5)	-7.9 (± 6.4)	-2.5 (± 6.6)	2.1 (± 6.7)
ssIgE nDer p 1 (KU/L)	1 (± 2.9)	-1.5 (± 2.8)	1.3 (± 2.9)	7.7 (± 2.9)
ssIgE rDer p 2 (KU/L)	-2.7 (± 2.9)	-3.1 (± 2.8)	3.7 (± 2.9)	1.1 (± 3)

Statistical analyses

No statistical analyses for this end point

Secondary: Average adjusted symptom score

End point title	Average adjusted symptom score

End point description:

Change from baseline of average adjusted symptom score (AAdSS) at the end of study in ITT population.

End point type	Secondary

End point timeframe:

At baseline and end of study.

End point values	PM 6,667 AUeq/ml	PM 20,000 AUeq/ml	PM 50,000 AUeq/ml	PM 100,000 AUeq/ml
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	52	47	44
Units: AadSS				
least squares mean (standard error)	-3 (± 0.3)	-2.7 (± 0.3)	-2.6 (± 0.3)	-3 (± 0.3)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: AadSS				
least squares mean (standard error)	-2.6 (± 0.3)			

Statistical analyses

Statistical analysis title	Analysis of change from baseline of AAdSS
Comparison groups	Placebo v PM 6,667 AUeq/ml
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.999
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	0.58

Statistical analysis title	Analysis of change from baseline of AAdSS
Comparison groups	Placebo v PM 20,000 AUeq/ml
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.86

Statistical analysis title	Analysis of change from baseline of AAdSS
Comparison groups	Placebo v PM 50,000 AUeq/ml

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.958
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	0.92

Statistical analysis title	Analysis of change from baseline of AAdSS
Comparison groups	Placebo v PM 100,000 AUeq/ml
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.473
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.23
upper limit	0.57

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events were collected throughout the study.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.2
Reporting groups	
Reporting group title	PM 6,667 AUeq/ml
Reporting group description: Active treatment	
Reporting group title	PM 20,000 AUeq/ml
Reporting group description: Active treatment	
Reporting group title	PM 50,000 AUeq/ml
Reporting group description: Active treatment	
Reporting group title	PM 100,000 AUeq/ml
Reporting group description: Active treatment	
Reporting group title	Placebo
Reporting group description: Placebo	

Serious adverse events	PM 6,667 AUeq/ml	PM 20,000 AUeq/ml	PM 50,000 AUeq/ml
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 57 (3.51%)	1 / 59 (1.69%)	3 / 59 (5.08%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	0 / 59 (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
Upper limb fracture			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	0 / 59 (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
jaw fracture			

subjects affected / exposed	0 / 57 (0.00%)	0 / 59 (0.00%)	0 / 59 (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
Surgical and medical procedures			
Hip surgery			
subjects affected / exposed	0 / 57 (0.00%)	0 / 59 (0.00%)	0 / 59 (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
Mammoplasty			
subjects affected / exposed	1 / 57 (1.75%)	0 / 59 (0.00%)	0 / 59 (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
Nervous system disorders			
Status epilepticus			
subjects affected / exposed	0 / 57 (0.00%)	0 / 59 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
syncope			
subjects affected / exposed	0 / 57 (0.00%)	0 / 59 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 57 (0.00%)	0 / 59 (0.00%)	0 / 59 (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
Injection site nodule			
subjects affected / exposed	0 / 57 (0.00%)	0 / 59 (0.00%)	0 / 59 (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
Gastrointestinal disorders			
Hiatus hernia			

subjects affected / exposed	0 / 57 (0.00%)	1 / 59 (1.69%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 57 (0.00%)	0 / 59 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 57 (0.00%)	0 / 59 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
arthralgia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 59 (0.00%)	0 / 59 (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
Infections and infestations			
Tonsillitis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 59 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	PM 100,000 AUeq/ml	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 59 (5.08%)	2 / 56 (3.57%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Upper limb fracture			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
jaw fracture			
subjects affected / exposed	0 / 59 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hip surgery			
subjects affected / exposed	1 / 59 (1.69%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mammoplasty			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Status epilepticus			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
syncope			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 59 (1.69%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site nodule			

subjects affected / exposed	1 / 59 (1.69%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Hiatus hernia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 59 (1.69%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 59 (0.00%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
arthralgia			
subjects affected / exposed	0 / 59 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Tonsillitis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	PM 6,667 AUeq/ml	PM 20,000 AUeq/ml	PM 50,000 AUeq/ml
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 57 (87.72%)	54 / 59 (91.53%)	53 / 59 (89.83%)
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 57 (29.82%)	22 / 59 (37.29%)	20 / 59 (33.90%)
occurrences (all)	23	44	36
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	18 / 57 (31.58%)	23 / 59 (38.98%)	23 / 59 (38.98%)
occurrences (all)	41	68	83
injection site pain			
subjects affected / exposed	5 / 57 (8.77%)	11 / 59 (18.64%)	3 / 59 (5.08%)
occurrences (all)	12	18	9
Injection site pruritus			
subjects affected / exposed	17 / 57 (29.82%)	26 / 59 (44.07%)	15 / 59 (25.42%)
occurrences (all)	52	73	56
Injection site swelling			
subjects affected / exposed	17 / 57 (29.82%)	26 / 59 (44.07%)	31 / 59 (52.54%)
occurrences (all)	51	72	112
injection site warmth			
subjects affected / exposed	3 / 57 (5.26%)	3 / 59 (5.08%)	2 / 59 (3.39%)
occurrences (all)	8	4	2
nasopharyngitis			
subjects affected / exposed	19 / 57 (33.33%)	22 / 59 (37.29%)	19 / 59 (32.20%)
occurrences (all)	23	27	27
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	5 / 57 (8.77%)	3 / 59 (5.08%)	3 / 59 (5.08%)
occurrences (all)	6	5	3
Eye disorders			
Eye pruritus			
subjects affected / exposed	3 / 57 (5.26%)	3 / 59 (5.08%)	2 / 59 (3.39%)
occurrences (all)	5	6	2
Lacrimation increased			
subjects affected / exposed	3 / 57 (5.26%)	5 / 59 (8.47%)	3 / 59 (5.08%)
occurrences (all)	8	16	4

Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	3 / 57 (5.26%)	3 / 59 (5.08%)	4 / 59 (6.78%)
occurrences (all)	3	3	4
Sneezing			
subjects affected / exposed	5 / 57 (8.77%)	6 / 59 (10.17%)	2 / 59 (3.39%)
occurrences (all)	8	19	10

Non-serious adverse events	PM 100,000 AUeq/ml	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 59 (94.92%)	50 / 56 (89.29%)	
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 59 (33.90%)	15 / 56 (26.79%)	
occurrences (all)	72	49	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	34 / 59 (57.63%)	1 / 56 (1.79%)	
occurrences (all)	142	1	
injection site pain			
subjects affected / exposed	8 / 59 (13.56%)	3 / 56 (5.36%)	
occurrences (all)	13	6	
Injection site pruritus			
subjects affected / exposed	18 / 59 (30.51%)	2 / 56 (3.57%)	
occurrences (all)	88	3	
Injection site swelling			
subjects affected / exposed	36 / 59 (61.02%)	0 / 56 (0.00%)	
occurrences (all)	155	0	
injection site warmth			
subjects affected / exposed	9 / 59 (15.25%)	0 / 56 (0.00%)	
occurrences (all)	58	0	
nasopharyngitis			
subjects affected / exposed	24 / 59 (40.68%)	19 / 56 (33.93%)	
occurrences (all)	32	28	
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	7 / 59 (11.86%)	4 / 56 (7.14%)	
occurrences (all)	9	6	
Eye disorders			
Eye pruritus			
subjects affected / exposed	5 / 59 (8.47%)	2 / 56 (3.57%)	
occurrences (all)	6	2	
Lacrimation increased			
subjects affected / exposed	6 / 59 (10.17%)	2 / 56 (3.57%)	
occurrences (all)	11	6	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	4 / 59 (6.78%)	3 / 56 (5.36%)	
occurrences (all)	5	7	
Sneezing			
subjects affected / exposed	5 / 59 (8.47%)	3 / 56 (5.36%)	
occurrences (all)	6	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2012	The following changes were implemented in the clinical trial protocol: • To adapt the symptom and medication score to the Adjusted Symptom Score • To give a justification for the use of the PNIF measurement.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported