Clinical trial results:
A randomized, double-blind, placebo-controlled (DBPC) parallel-group multi-centre study to assess the efficacy and safety of PM subcutaneous immunotherapy (SCIT) in patients with allergic rhinitis/rhinoconjunctivitis (ARC) caused by house dust mite (HDM) allergy

Summary

EudraCT number	2016-000051-27
Trial protocol	DE SK HU ES BE PT
Global end of trial date	23 April 2018
Results information	
Result version number	v2 (current)
This version publication date	17 February 2021
First version publication date	14 November 2020
Version creation reason	• Correction of full data set • Changes to summary attachments To reflect large, significant and clinically relevant decrease in the primary outcome measure CSMS(n) for moderate to severe HDM allergic subjects (dSS(n) ≥ 2 at baseline). Correct transcriptional errors and to update Sponsor's contact data

Trial information

Trial identification	
Sponsor protocol code	PM/0041
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	HAL Allergy B.V.
Sponsor organisation address	J.H. Oortweg 15-17, Leiden, Netherlands,
Public contact	Director Pre Clinical and Clinical Development, HAL Allergy B.V. , +31 881959 000, rverdonk@hal-allergy.com
Scientific contact	Director Pre Clinical and Clinical Development, HAL Allergy B.V. , +31 881959 000, rverdonk@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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess clinical efficacy of 50,000 AUeq/mL (0.5 mL) PM SCIT, compared to placebo, in patients suffering from HDM-induced ARC, measured by the nasal symptoms of the combined symptom and medication score (CSMS(n)) during the last 8 weeks of approximately 1 year treatment. For this primary readout parameter, the symptom score was based on nasal symptoms only (CSMS(n)).

Protection of trial subjects:

From signing of the informed consent form until the End of Study (EoS) visit, the subjects were instructed to take only the study treatments(s) described in the protocol and any other concomitant medications specifically allowed by the investigator (e.g., Rescue Medication). Aside from these, if the subject would take any other treatment during the study, the investigator would record the necessary information and notify the Sponsor, if judged to have a potential effect on study results. Rescue Medication was provided to the subjects as from Visit 1 until EoS. Rescue Medication was excluded from the prohibited medication list. During the period Rescue Medication use was recorded in the eCRF.

Background therapy:

See rescue medication.

Evidence for comparator:

This was a double-blind placebo-controlled study.

Actual start date of recruitment	26 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 91
Country: Number of subjects enrolled	Portugal: 15
Country: Number of subjects enrolled	Slovakia: 10
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Germany: 85
Country: Number of subjects enrolled	Hungary: 12
Worldwide total number of subjects	230
EEA total number of subjects	230

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)	230
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place in 7 countries in period 4 Oct 2016 (FPI) till 23 Apr2018 (LPI). Statistical analyses were performed for the study population of moderate to severe HDM allergic subjects with a daily symptom score equal or greater than 2 at baseline (dSS(n) ≥ 2 at baseline).

Pre-assignment

Screening details:

Patients (18-65 years) a history of allergic rhinitis or rhinoconjunctivitis; FEV1 (forced expiratory volume in the first second) >70% of the predicted value at screening for patients with concomitant asthma and FEV1 >70% or a PEF >80% of predicted value for patients without asthma; a positive SPT result for HDM D. pter or D. far.

Period 1

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

Blinding implementation details:

Since this was a double-blind study, neither the subjects, nor the investigators, monitors or the Sponsor knew to which treatment group a subject was randomized. The data manager responsible for creation and release of the randomization list was not involved in this study until after database lock and routine unblinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	PM (active)

Arm description: -

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

Dosage and administration details:

6 to 11 incremental weekly doses, depending on the occurrence of side effects, until reaching the maintenance dose (0.5 mL) which was given at 4-weekly intervals for up to approximately 1 year.

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

Placebo was administrated as 6 to 11 incremental weekly doses, depending on the occurrence of side effects, until reaching the maintenance dose (0.5 mL) which was given at 4-weekly intervals for up to approximately 1 year.

Number of subjects in period 1[1]	PM (active)	Placebo
Started	105	123
Completed	87	110
Not completed	18	13
Not able to reach the maintenance dose	1	-
Consent withdrawn by subject	8	6
Adverse event, non-fatal	2	2
Pregnancy	4	1
Lost to follow-up	1	3
Protocol deviation	1	1
other reason	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 230 subjects were included into Safety analysis. 228 subjects were included into Baseline characteristics and Efficacy analysis.

Baseline characteristics

Reporting groups

Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	228	228	
Age categorical Units: Subjects			
Adults (18-65)	228	228	
Age continuous Units: years			
arithmetic mean	31.62		
standard deviation	± 10.36	-	
Gender categorical Units: Subjects			
Female	138	138	
Male	90	90	
Concomitant asthma Units: Subjects			
Asthma Yes	102	102	
Asthma No	126	126	
Sensitization Units: Subjects			
Monosensitized	93	93	
Polysensitized	135	135	

Subject analysis sets

Subject analysis set title	Moderate to severe HDM allergic subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Analysis set of moderate to severe HDM allergic subjects defined as dSS(n) ≥ 2 at baseline

Reporting group values	Moderate to severe HDM allergic subjects		
Number of subjects	228		
Age categorical Units: Subjects			
Adults (18-65)	228		
Age continuous Units: years			
arithmetic mean	31.62		
standard deviation	± 10.36		
Gender categorical Units: Subjects			
Female	138		

Male	90		

Concomitant asthma Units: Subjects			
Asthma Yes	102		
Asthma No	126		
Sensitization Units: Subjects			
Monosensitized	93		
Polysensitized	135		

End points

End points reporting groups

Reporting group title	PM (active)
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Moderate to severe HDM allergic subjects
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Analysis set of moderate to severe HDM allergic subjects defined as dSS(n) ≥ 2 at baseline	

Primary: mean CSMS(n) score during the last 8 weeks of treatment

End point title	mean CSMS(n) score during the last 8 weeks of treatment
End point description:	
End point type	Primary
End point timeframe:	
Last 8 weeks of treatment	

End point values	PM (active)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	123		
Units: point				
number (not applicable)	1.14	1.49		

Statistical analyses

Statistical analysis title	Analysis of primary endpoint
Statistical analysis description:	
The analysis of CSMS(n) involved a mixed model with the mean CSMS(n) during the last 8 weeks of the approximately 1-year treatment period. The treatment effect was much higher than the pre-specified minimal clinically relevant difference of 0.25 points and was highly statistically significant, which is proof of efficacy of PM in subjects with HDM-induced allergic rhinitis/rhinoconjunctivitis.	
Comparison groups	PM (active) v Placebo
Number of subjects included in analysis	228
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0065
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected and reported starting at visit 1 after signing the Informed Consent Form until the final End of Study visit.

Adverse event reporting additional description:

During the course of the study, both immediate and delayed local and systemic reactions have been reported, collected and reported in this section. The safety results show that treatment with PM is safe and well tolerated in subjects with HDM-induced allergic rhinitis/rhinoconjunctivitis (ARC).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Treatment Emergent AE's - PM

Reporting group description:

After unblinding, the total amount of Adverse Events in the PM group are reported in this section.

Reporting group title	Treatment Emergent AE's - Placebo

Reporting group description:

After unblinding, the total amount of Adverse Events in the PM group are reported in this section.

Serious adverse events	Treatment Emergent AE's - PM	Treatment Emergent AE's - Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 106 (3.77%)	5 / 124 (4.03%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive breast carcinoma	Additional description: RIGHT BREAST INVASIVE CACER (G2)		
subjects affected / exposed	0 / 106 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the cervix	Additional description: PLATTENEPITHELKARZINOM		
subjects affected / exposed	1 / 106 (0.94%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Bone contusion	Additional description: CONTUSION OF THE SPINE		

subjects affected / exposed	0 / 106 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture	Additional description: FRACTURE OF THE RIST RIGHT ARM		
subjects affected / exposed	0 / 106 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose	Additional description: INTENTIONAL OVERDOSE AFOBAM, PAROGEN		
subjects affected / exposed	1 / 106 (0.94%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia	Additional description: FEVER		
subjects affected / exposed	0 / 106 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: CHRONIC COUGH		
subjects affected / exposed	1 / 106 (0.94%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute	Additional description: ACUTE CHOLECYSTITIS		
subjects affected / exposed	1 / 106 (0.94%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder disorder			
subjects affected / exposed	0 / 106 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression	Additional description: SEVERE DEPRESSION		

subjects affected / exposed	1 / 106 (0.94%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 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	Treatment Emergent AE's - PM	Treatment Emergent AE's - Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 106 (64.15%)	31 / 124 (25.00%)	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	53 / 106 (50.00%)	11 / 124 (8.87%)	
occurrences (all)	158	13	
Injection site pain			
subjects affected / exposed	10 / 106 (9.43%)	20 / 124 (16.13%)	
occurrences (all)	17	53	
Injection site pruritus			
subjects affected / exposed	8 / 106 (7.55%)	2 / 124 (1.61%)	
occurrences (all)	13	3	
Injection site swelling			
subjects affected / exposed	51 / 106 (48.11%)	7 / 124 (5.65%)	
occurrences (all)	126	8	
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	6 / 106 (5.66%)	2 / 124 (1.61%)	
occurrences (all)	11	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2016	V4.0 This version includes updates since version 3.0, based on input during Site Initiation Visits: - According to the inclusion criterion 3, patients for whom asthma is controlled with LABA can be included according to the referred GINA criteria. Therefore, LABA was removed as prohibited medication from Table 4 - Clarification is provided on dosing rules in case dosing is scheduled out of the pre-defined visit window (Section 6.6.2). - The criteria for a negative control test were added to the NPT procedure, allowing a maximum score of 3 points (Appendix 1) - The statistical analysis approach was described in more detail (Section 10) - Some minor textual were added to the protocol for clarification
10 July 2017	V5.0 This version includes updates since version 4.0: - Addition of asthma related parameters for the subgroup of patients diagnosed with asthma - Better description of SPT and NPT definitions of negative controls used to determine inclusion criteria. - More detailed description of dose administration (section 6.6) including the possibility to limit study duration in case of an extended duration of the updosing phase or out of window visits. This possibility has been included in the protocol in order to ensure collection of the primary outcome data within the mite peak season. - Discarding the negative control measurement of the NPT measurement at the end of the study, as this measurement is not relevant for analysis. - Clarification that local reactions with a diameter of more than 50 mm should be recorded as AE - More detailed description of statistical analysis in section 10.
08 March 2018	V6.0 This version includes updates since version 5.0: - Updates on sponsor representatives - Change the analysis of the key secondary endpoints to the same analysis as the other secondary endpoints, specify all secondary endpoints are supportive. - Change of analysis for aluminium, from exploratory efficacy endpoint to safety endpoint - Clarification on QoL analysis - Clarification on analyses for study parameters

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported