

**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 | <ul style="list-style-type: none">• 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 |

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) \geq 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 standard deviation | 31.62 ± 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 standard deviation | 31.62 ± 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) \geq 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: PLATTENEPIITHELKARZINOM | | |
| 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: <ul style="list-style-type: none">- 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: <ul style="list-style-type: none">- 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 up dosing 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: <ul style="list-style-type: none">- 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