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.

Published: 30-05-2011
Last updated: 29-04-2024

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.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Allergic conditions
Study type	Interventional

Summary

ID

NL-OMON38151

Source
ToetsingOnline

Brief title
PURETHAL® Mites Dose Range Finding study

Condition

- Allergic conditions

Synonym
house dust mites-induced persistent allergic rhinitis/rhinoconjunctivitis; persistent allergy

against house dust mites

Research involving
Human

Sponsors and support

Primary sponsor: HAL Allergy BV
Source(s) of monetary or material Support: vanuit de industrie

Intervention

Keyword: Allergic rhinitis, Allergic rhinoconjunctivitis, House dust mites, Immunotherapy

Outcome measures

Primary outcome

The primary endpoint is the absolute difference in mean symptom score in the

TNPT between one year of treatment and baseline, among the different PM dose

groups versus placebo.

Secondary outcome

TNPT after 6 months of treatment, Average Adjusted Symptom Score (AdSS), Peak

Nasal Inspiratory Flow (PNIF), Serum immunoglobulin levels.

Study description

Background summary

In order to comply with the EMA guidelines on the development of specific immunotherapy (SIT) - products (EMA Guideline, 2008), the current study is designed to identify the optimal, safe and effective dose in HDM-sensitive allergic rhinitis/rhinoconjunctivitis with or without concomitant asthma.
Due to the need of at least 4 active study arms in a DRF study (EMA Guideline, 2008), the use of a classical endpoint (symptom & medication score) as primary parameter is not feasible because of the necessity of large sample sizes. We have selected the titrated nasal provocation test (TNPT) as the primary parameter. The TNPT is a reproducible exacerbation model of allergic rhinitis often applied to evaluate the efficacy of anti-allergy medications (Proud, 2010).

Furthermore, the response to nasal allergen challenges is correlated to symptom-medication scores during the relevant season and is an accepted endpoint in DRF studies (Bousquet 1988, EMA Guideline, 2008). Previous studies have found a significant effect of allergen specific immunotherapy on allergen provocations in combination with clinical improvement (Branco Ferreira 2005, Haugaard, 1993).
The optimal dose obtained from the DRF will be implemented in a 1-year randomized, placebocontrolled, pivotal study in patients with HDM-induced allergic rhinitis/ rhinoconjunctivitis.

Study objective

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.

Study design

Multi-centre, randomized, double-blind, placebo-controlled, 5 arms parallel-group, dose range finding study. Phase II.

Intervention

Patients are trested with one of the following strengths of PURETHAL® Mites: 3.333 , 10.000 , 25.000 or 50.000 AUeq/dose or Placebo by subcutaneous injection. The treatment duration is approximately one year.

Study burden and risks

The burden for the patient is comparable with the burden of regular immunotherapy (e.g. the weekly visits to the physician during up-dosing and the monthly visits during maintenance)
During the study the following additional assessments are performed:
- During one year the patient will visit the clinic 18 times. The visits will last 1 - 4 hours, depending on the assessment schedule.
- At screening and at the final visit, a physical examination and ECG is performed.
- In total, there will be tree blood draws (venapuncture) of approximately 15 ml per draw to assess safety laboratory parameters and immunoglobulin levels. Additionally, there will be urine samples collected at these time points for assessment of safety laboratory parameters.
- For asthmatic patients a PEF will also be measured during the study before each injection. The injection will be postponed if the value is below 80%.
- The patient will undergo three nasal provocation tests (TNPT) during the study (baseline, 6 months, one year). The patient will be dosed with increasing

concentrations of allergens per nasal spray and symptom scores and nasal obstruction will be measured during approximately one hour.
- At every visit, the nasal inhalation flow will be measured with a peak inhalation flow device.
- During screening a skin prick test will be performed and a pulmonary assessment will be done (FEV1 of PEF).
- The patient will use a diary to record allergy symptoms, adverse events and medication use.

Adverse drug reactions that can occur are considered to be mild, like redness, swelling, or itching at the site of the injection. Hardly ever, skin reactions or generalized itching can occur. These adverse events mostly resolve quickly and need no further treatment.

Intensified systemic reactions (shortness of breath, urticaria or angioedema) might occur in very rare cases. During the last five years only 5 of these serious reactions have been reported. Life-threatening adverse events have never been reported with the subcutaneous immunotherapy that is used in this study.

By testing higher doses of PURETHAL® Mites adverse reactions can be expected and there may be risks involved in this therapy that have not been identified in studies done so far. In a previous study a dose of 4-time the dose that is on the market was tested and defined as safe.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Signed informed consent;2. Patients (male or female) must be >= 18 and <= 60 years at screening;3. Patients with allergic rhinitis or rhinoconjunctivitis for at least 1 year; allergic symptoms related to HDM, with or without concomitant clinically stable controlled mild to moderate asthma (according to GINA classification) (Koshak, 2007) ;4. Patients with a history of concomitant asthma should have a FEV1 > 70% at inclusion. Patients without a history of asthma should have a FEV1 > 70% or a PEF > 80%.;5. Positive SPT to HDM D. pter and/or D. far (mean wheal diameter >= 3mm compared to negative control and negative control should be negative, assessed within 1 year before randomization) ;6. Serum specific IgE-test (ssIgE) level for HDM D. pter or D. far at screening (> 0.7 U/ml);7. Positive TNPT for HDM D. pter extract at screening (Lebel score >= 6 at or below 10,000 AU/ml)

Exclusion criteria

1. Current clinically relevant symptoms of seasonal rhinitis/rhinoconjunctivitis caused by other allergen(s) than HDM (with a demonstrated positive SPT for this allergen) at the time of inclusion (to avoid interference with TNPT at inclusion);2. Patients sensitized to animals should not be included if they are symptomatic upon exposure and regularly exposed to animals ;3. Completed allergen-specific immunotherapy (SCIT or SLIT) with HDM within the last 5 years;4. Completed unsuccessful allergen-specific immunotherapy (SCIT or SLIT) in the past 5 years ;5. Allergen-specific immunotherapy (SCIT or SLIT) with other allergens than HDM during the study period;6. Any vaccination one week before start of therapy and during the up-dosing phase ;7. Any anti-IgE therapy within the last 6 months prior to inclusion and during study ;8. Severe immune disorders (including auto-immune diseases) and/or diseases requiring immunosuppressive drugs;9. Active malignancies or any malignant disease in the past 5 years;10. A chronic or acute disease that in the opinion of the investigator might place the patient at an additional risk, including but not limited to the following: cardiovascular insufficiency, any severe or unstable lung diseases, endocrine disorders, clinically significant renal or hepatic diseases, or hematological disorders ;11. Moderate to severe nasal obstructive diseases such as polyps, septal deviations etc.;12. Clinically significant chronic sinusitis or ocular infection;13. Diseases with a contra-indication for the use of adrenaline (e.g. hyperthyroidism, glaucoma);14. Use of systemic corticosteroids within 4 weeks of

screening;15. Treatment with systemic or local beta-blockers;16. Participation in a clinical study with a new investigational drug within the last 3 months or a biological within the last 6 months prior to the study or during the study;17. Pregnancy, lactation or inadequate contraceptive measures (contraceptive measures considered as adequate include appropriate use of oral contraception, i.m. contraception or a contraceptive device);18. Alcohol, drug, or medication abuse within the past year and during study;19. Any abnormal laboratory parameter at screening that in the opinion of the investigator is considered clinically relevant;20. Lack of co-operation or compliance;21. Severe psychiatric, psychological, or neurological disorders;22. Patients who are employees of the department, 1st grade relatives, or partners of the investigator;23. Expected changes in HDM exposure during the study (avoidance measures, move, etc.)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-10-2011
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PURETHAL® Mites
Generic name:	Mixture of 50% Dermatophagoides pteronyssinus and 50% Dermatophagoides farinae.
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	30-05-2011
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-06-2011
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-09-2011
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-11-2011
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-01-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-02-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-07-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	10-07-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-000393-61-NL
CCMO	NL36879.056.11