1. Clinical trial identification

Researchers look at the results of many studies to decide which drugs work best and are safest for patients. It takes participants in many studies all around the world to advance medical science. This summary only shows the results from this one study. Other studies may find different results.

1.1. Title of the trial

Randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy of Depigoid® Grass Mix as a rush immunotherapy in patients with allergic rhinitis using an environmental exposure unit

1.2. Protocol number

6078-PG-PSC-158

1.3. EU trial number

2006-005269-20

2. Name and contact of sponsor

LETI Pharma GmbH, Stockumer Str. 28, 58453 Witten, Germany
Phone +49 2302 202860

3. General information about clinical trial

3.1 Where the trial was conducted

The trial was conducted at the Fraunhofer Institute of Toxicology and Experimental Medicine (ITEM), Hannover.

3.2 When the trial was conducted (start & stop dates)

The trial was conducted from 22-Jan-2007 (first patient in) to 24-Apr-2007 (last patient out).

3.3. The main objectives of the trial and explanation of the reasons for conducting it

The objective of the study was the investigation of the safety and efficacy of a pre-seasonal, 5 week rush treatment scheme with Depigoid® Grass Mix in patients with allergic rhinitis sensitized to grass pollen under standardized pollen chamber conditions.
A pollen chamber design was used for assessing the effectiveness of specific immunotherapy.

Population of subjects

3.1. The number of subjects included in the trial

60 patients were planned to be enrolled in one center in Germany to achieve data for at least 48 patients (24 active and 24 placebo) per protocol (PP).
A number of 133 patients were screened from which 60 were randomized. 73 patients were not randomized, because they did not meet conditions defined by the inclusion or exclusion criteria.

3.2. Age groups and gender breakdown

The demographic and baseline characteristics (safety set, N = 60) were raised as follows:

Gender: 37 patients were male (16 male patients in Verum group, 21 in Placebo group) and 23 patients were female (14 female patients in Verum group, 9 in Placebo group)
Age: The mean in Verum group was 34.7 years, in Placebo group 32.9 years

3.3. Inclusion and exclusion criteria

Inclusion criteria

Patients were enrolled into the study only if the following criteria were met:

- Prior to study specific examinations the patient had to give his/her written informed consent
- Patients ≥ 18 years old
- History of allergic rhinitis to grass pollen and a positive skin prick test for *Dactylis glomerata* pollen at or within 12 months prior to the screening visit
- Symptoms more than 2 years prior to study start
- Subject must exhibit a moderate response upon 4000 *Dactylis glomerata* pollen grains/m3 within 2 hours in the Environmental Challenge Chamber at the screening visit, which is defined as a Total Nasal Symptom Score (TNSS) of at least 6 on at least one of eight evaluation records during the pollen exposure
- Total Nasal Symptom Score (TNSS) of ≤ 3 and a score < 2 for each single symptom, i.e. obstruction, rhinorrhea, itch, and sneeze prior to the screening allergen challenge
- FEV1 ≥ 80% predicted and FEV1/FVC ≥ 70% predicted at screening
- Absence of any structural nasal abnormalities or nasal polyps, absence of a history of frequent nose bleeding or recent nasal surgery
- Absence of conditions or factors, which would have been made the subject unlikely to be able to stay in the Fraunhofer EEC for 4 hours
- Non-smokers or smokers with a history of less than 10 pack years
- Able and willing to give written informed consent to take part in the study
- Available to complete all study measurements.

Exclusion Criteria

Patients were excluded from the study if any of the following applied:

Disease specific criteria

- History of significant clinical manifestations of allergy as a result of sensitization against tree pollen allergens, weed allergens and perennial allergens (e.g. Aspergillus spores, animal dander, house dust mite)
- Persistent asthma (GINA ≥ II)
- History of a respiratory tract infection and/or exacerbation of asthma within 4 weeks before the screening and during the study
- Any history of life-threatening asthma, defined as an asthma episode that required intubation and/or was associated with apnea, respiratory arrest or hypoxic seizures.

Patients with other known previous/concomitant diseases

- Active tuberculosis
- Acute and chronic inflammatory or infectious diseases at the target organ (not including asthma)
- Advanced secondary changes at the target organ (e.g. emphysema or bronchiectasis)
- Autoimmune disorders (e.g. of the liver, kidney, the nervous system, thyroid gland, rheumatic diseases)
- Immune deficiencies
- Any disease which prohibited the use of adrenaline (e.g. hyperthyroidism)
- Cardiovascular insufficiency or any severe or unstable pulmonary, or endocrine disease; clinically significant renal or hepatic disease or dysfunction; hematologic disorder; any other clinically significant medical condition that could have been increase the risk to the study participant
- Malignant disease of any kind during the previous 5 years
- Abnormal laboratory parameters and vital signs that could have increased

- the risk to the study participant
- Alcohol, drug or medication abuse within the past year
- Severe psychiatric/psychological or neurologic disorders

Patients with other known previous/concomitant treatments
The following therapies were not allowed within the specified period prior to screening as well as during the study and prevented the patient from being included into the study:
- SIT within the last 5 years
- Seven days prior and 14 days post an immunization with vaccines
- Anti-allergic treatment within the last 4 weeks prior to screening
- β-blocker were not allowed during the entire study and led to the patient being withdrawn
- Treatments with substances interfering with the immune system were not allowed during the entire study and led to the patient being withdrawn

Others
- Patients who were expected to be non-compliant and/or not cooperative
- Participation in the treatment phase of any other clinical study within the last 30 days prior to the start of the study
- Patients who had already participated in this study
- Patients who were employees at the investigational site, relatives or spouses of the investigator
- Any donation of germ cells, blood, organs, or bone marrow during the course of the study
- Patients who were not contractually capable

Special restrictions for female patients
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation.
- Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precluded intercourse with a male partner and women whose partners had been sterilized by vasectomy or other means, unless they met the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/m or 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy or hysterectomy or were using one or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation, vasectomy), hormonal contraception (implantable, patch, oral), and double-barrier methods (any double combination of: IUD, male or female condom with spermicidal gel, diaphragm, sponge, cervical cap)

4. Investigational medicinal products used

After a screening period of 1-4 weeks at V4 patients were randomly allocated to receive Depigoid® Grass Mix or placebo followed by an initial build-up period (1 day), a treatment period (5 weeks) and a post-treatment period (3 weeks) prior to the grass season (May - August). Consequently, therapy commenced on day 3 at V4. The duration of the study was 9 to 12 weeks for the individual patient.
The rush treatment began with 0.2 ml followed by 0.3 ml after 30 minutes at day 3 (V4) and followed by 0.5 ml/week at weeks 1-5 (V5-V9). The treatment of the placebo regimen consisted of injections of Depigoid® vehicle with 0.2 ml followed by 0.3 ml at day 3 (V4) and followed by 0.5 ml/week at weeks 1-5 (V5-V9).
The medication was injected subcutaneously.

This study was also “double blinded” – this means that neither patients nor doctors knew who was given which treatment/drug. This was done to make sure that the study results were not influenced in any way.

5. Description of adverse reactions and their frequency

Side effects are unwanted medical events (e.g. headache) that happen during the study, and are reported because they are thought to be related to the treatments in the study. Not all the people [people/patients] in this study had side effects.
Common and serious side effects are listed here:

In total, 57 (95.0%) patients of the safety set experienced adverse events (368 AE episodes with a total of 531 AE symptoms).
At baseline, before the application of study medication, 5 AEs with 5 symptoms, respectively, occurred in 5 patients (8.3%) of the safety set (N = 60).
A total of 363 TEAEs with altogether 526 TEAE-symptoms were documented for the safety set. The number of patients reporting at least one TEAE (57 patients) was compared between the treatment groups using the two-sided Fisher’s exact test. The comparison revealed no statistically significant difference between Depigoid® Grass Mix and placebo group.

For both treatment groups, altogether 327 TEAEs (including local and systemic reactions) were assessed as being ‘likely’ or ‘definitely’ related to study medication. The other 36 TEAEs were assessed as being ‘unrelated’ or ‘unlikely related’ to study medication.
The intensity of the TEAEs was mostly ‘mild’ and ‘moderate’). For the Depigoid® Grass Mix-group, the intensity of 7 TEAEs were ‘severe’.
In the placebo group, 10 TEAEs were of ‘severe’ intensity.
Out of 60 patients of the safety set, 11 (18.3%) terminated the study prematurely (3 and 8 patients of the Depigoid® Grass Mix and placebo groups, respectively) due to TEAE.

An ADR is defined as an AE with at least ‘likely’ relation to study medication.
Altogether, 327 TEAEs fulfilled the criteria for an ADR, which were reported in total with 490 symptoms in 56 (93.3%) patients of the safety set. No significant difference was found between the treatment groups with regard to the proportion of patients with at least one ADR.
For both treatment groups, most of the ADR symptoms belonged to the MedDRA SOC ‘General disorders and administration site conditions’. None of the ADRs was rated serious, therefore the number of non-serious ADRs is 327.
In this study, ADRs were subdivided into the subgroups ‘local reactions’ and ‘systemic reactions’.
During the study, 56 patients experienced **local reactions** after administration of study medication. For the overall population, 287 local reactions with a total of 450 symptoms were documented. For the Depigoid® Grass Mix-group, 158 local reactions with 249 symptoms were documented; in the placebo group, 201 symptoms occurred in 129 local reactions.
No significant difference between the treatment groups was found regarding the number of patients with at least one local reaction).
In the Depigoid® Grass Mix-group, 2 patients experienced a local reaction of ‘severe’ intensity. In the placebo group, ‘severe’ local reactions were documented for 4 patients. Based on comparison of the treatment groups by the Fisher’s exact test, no significant difference regarding the number of patients with local reactions was concluded.

Overall, 40 **systemic reactions** with 40 symptoms were recorded for 14 patients. In the Depigoid® Grass Mix-group, 7 patients experienced 21 systemic reactions with 21 symptoms; in the placebo group, 7 patients experienced 19 systemic reactions with 19 symptoms. No

significant difference between the treatment groups was found regarding the number of patients with at least one systemic reaction.
For both treatment groups, the most reported systemic reaction symptom by MedDRA preferred term was 'Rhinitis allergic' (Depigoid® Grass Mix-group: 5 symptoms, placebo group: 5 symptoms). 'Nausea' (4 symptoms), 'Headache' (2 symptoms) and 'Asthenia' (1 symptom) were documented only in the Depigoid® Grass Mix-group.

No deaths and no SAEs were reported during the course of the study.

6. Overall results of the clinical trials

Efficacy Results

The primary criterion of this study was the Total Nasal Symptom Score (TNSS) evaluated for the symptoms rhinorrhea, nasal congestion, sneezing and nasal itching recorded during the allergen exposition in the pollen chamber. Effect of treatment was investigated using the pre-post difference of the mean TNSS values (i.e. the difference between values measured at visit 10 and at visit 3).
For the ITT set (N = 60) the mean TNSS at visit 3 was 6.02 (SD: 1.34) and at visit 10 4.30 (SD: 1.86) for the Depigoid® Grass Mix group and 6.08 (SD: 1.45) at visit 3 and 4.64 (SD: 2.04) at visit 10 for the placebo group. The mean pre-post difference calculated for the Depigoid® Grass Mix group was –1.72 (SD: 2.01) and for placebo group –1.44 (SD: 1.31). The analysis performed by means of the two-sided Wilcoxon rank sum test did not reveal any statistically significant difference between Depigoid® Grass Mix and placebo groups concerning the treatment effect. However, the influence of TNSS prior to the pollen chamber challenge, i.e. severity at baseline (visit 3) was identified as a possible confounding variable, which affected the results. Therefore, the "baseline severity" variable was to analyze the primary criterion.
The baseline severity affected the treatment effect. For Depigoid® Grass Mix patients with the baseline mean TNSS of 6 and higher a statistically significant influence ($p < 0.0001$) of the TNSS grade at baseline on
the mean pre-post differences of TNSS was observed. The pre-post difference of the mean TNSS was –2.57 (SD: 2.23) for Depigoid® treated patients and – 1.38 (SD: 1.25) for the placebo treated patients. The mean pre-post difference of the TNSS increased upon treatment with Depigoid® Grass Mix in comparison to the placebo group for patients with the mean baseline TNSS of 6 and higher.
As a secondary criterion the change from baseline in the mean of the weight of paper tissues (measuring the nasal secretion) during the four hours of allergen challenge was evaluated
However, also for this variable the baseline severity was considered as an important factor, which had an influence on the outcomes. Thus, the change from baseline in the mean nasal flow was evaluated with respect to the baseline severity treatment using the ANCOVA model. The pre-post difference in the nasal secretion was significantly dependent ($p < 0.0001$) on the nasal secretion at baseline visit 3 (V3).
The change from baseline of mean nasal flow measured by anterior rhinomanometry during the four hours of allergen challenge was also analyzed.
In Depigoid® Grass Mix treated patients a slight increase of the mean nasal flow (3.6 cm3/sec) was observed. Placebo treated patients showed a much stronger increase in the mean nasal flow (13.6 cm3/sec) between V3 and V10. Analysis of the mean nasal flow did not show a significant difference between the treatment groups. It was shown that the change from baseline in the mean nasal flow was significantly dependent ($p < 0.0001$) on the baseline nasal flow.
In summary, without considering the baseline TNSS, no statistically significant difference between Depigoid® Grass Mix and placebo treatment for the analysis of the primary and

secondary criteria was observed. However, including the baseline TNSS as a confounding factor, a Depigoid® effect on the primary and secondary criteria was revealed

Safety Results

During this study, 57 (95.0%) of the patients experienced TEAEs. A total of 363 TEAEs with 526 TEAE-symptoms altogether were reported for the overall population.

Out of 363 TEAEs, 36 episodes were assessed by the investigators as being 'unrelated' or 'unlikely related' to study medication ('unrelated': 26 TEAEs, 'unlikely related': 10 TEAEs). The other 327 episodes were assessed as being 'likely' (30 [8.3%] TEAEs) or 'definitely related' (297 TEAEs) to study medication and therefore fulfilled the criteria for an ADR (local and systemic reactions). The ADRs comprised 287 local reactions and 40 systemic reactions.

During this study, 56 of the patients experienced local reactions after administration of study medication. In the Depigoid® Grass Mix-group, 158 local reactions with 249 symptoms were recorded in 29 patients; in the placebo group, 201 symptoms were documented for 129 local reactions in 27 patients. For the overall population, 8 local reactions were assessed as 'severe' (Depigoid® Grass Mix-group: 3 local reactions in 2 patients; placebo group: 5 local reactions in 4 patients).

The treatment groups did not differ significantly regarding the number of patients with at least one local reaction.

Overall, 40 episodes of systemic reactions were recorded for 14 patients: 7 patients in the Depigoid® Grass Mix-group and 7 placebo patients.

The intensity of the systemic reactions was mostly 'mild' (30 episodes: 19 in the Depigoid® Grass Mix-group and 11 in the placebo group). The other 10 episodes of systemic reactions (2 in the Depigoid® Grass Mix-group and 8 in the placebo group) were assessed as 'moderate'.

Out of 60 patients of the safety set, 11 patients discontinued prematurely the study due to TEAE (3 patients in the Depigoid® Grass Mix-group and 8 in the placebo group). One of the TEAEs was assessed as 'definitely related' and two as 'unlikely related' to study medication.

The other TEAEs leading to premature discontinuation were assessed as 'unrelated' to study medication.

No SAE occurred and no death was reported in the course of the study.

The global safety of treatment was evaluated at the final visit (visit 11) by the investigator and the patient. Global safety was rated as 'excellent' or 'good' by the investigator in 26 (86.7%) of Depigoid® Grass Mix patients and in 22 of placebo patients. According to the patients' evaluation, 73.3% and 80.0% of patients treated with Depigoid® Grass Mix and placebo, respectively, assessed the global safety of treatment as 'excellent' or 'good'.

In general, the treatment of Depigoid® Grass Mix as a rush immunotherapy was well tolerated and did not reveal any suspicious of hitherto unknown risks.

7. Comments on the outcome of the clinical trial

This study demonstrated a superior efficacy of a short-term immunotherapy with quickly up-titrated Depigoid® Grass Mix compared to the placebo, which could only be shown after taking into account the different baseline values of the Total Nasal Symptom Score.

No relevant findings and no relevant differences in tolerability and safety between Depigoid® Grass Mix and placebo were observed.

A 5 weeks rush treatment scheme with Depigoid® Grass Mix in patients with allergic rhinitis sensitized to grass pollen under standardized pollen chamber conditions was shown to be well tolerated and safe.

8. Indication if follow up clinical trials are foreseen

Unknown at this timepoint.