A. CLINICAL TRIAL INFORMATION

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

1.4 Name and contact of sponsor

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

2. Paediatric regulatory details

This clincial trial was not part of a Paediatric Investigation Plan.

3. Result stage (including information about intermediate data analysis date, interim or final analysis stage, date of global end of the clincial trial)

Final analysis stage. The trial was finished on 24-APR-2007 (LPLV).

4. General information about clinical trial

4.1 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 weeks rush treatment scheme with Depigoid® Grass Mix in patients with allergic rhinitis sensitized to grass pollen under standardized pollen chamber conditions.

This clinical trial was designed to evaluate in a prospective, controlled design the pre-seasonal rush treatment scheme with Depigoid® Grass Mix versus placebo in a subcutaneous immunotherapy in patients with allergic rhinitis and/or rhinoconjunctivitis with/without mild intermittent asthma caused by clinical relevant sensitization against grass pollen in an environmental chamber design at the Fraunhofer Institut in Hannover

4.2 Trial design

This trial was designed as a prospective placebo-controlled randomized, double-blind, mono-center study under standardized pollen chamber conditions.
It was planned to recruit approximately 60 eligible (ITT) patients meeting the inclusion/exclusion requirements into the study, in one study center in Germany.
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 initial build-up period of the rush regimen consisted of the IMP, labeled as Vial 2 with 1000 DPP/ml depigmented and polymerized allergenic extract of grass pollen. 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 recruitment time for patients started in January 2007. The trial consisted of 11 regular visits.

4.3 Scientific background

Despite advances in pharmacotherapy the prevalence of allergic reactions resulting from sensitization against pollen, dust mites and animal epithelium, especially epithelia from cats and dogs, has increased during the past [1, 2].
Although the use of topical nasal steroids and non-sedating antihistamines is highly effective in the treatment of allergic symptoms, e.g. rhinitis [3, 4], allergen immunotherapy is recommended for patients having poor response to this treatment [2].

Depigoid® is currently used for the treatment of allergic diseases of the immediate (IgE mediated) type as for example hay fever (allergic rhinitis), allergic conjunctivitis, allergic bronchial asthma caused by sensitization to allergic substances as pollen, mites and animal dander.

1. Stephen R, Durham S. Long-Term Clinical Efficacy of Grass-Pollen Immunotherapy New Engl. J. Med. 341, 7: 468-475 (1999)
2. Allergen immunotherapy: therapeutic vaccines for allergic diseases: Geneva: January 27-29, 1997 Allergy 53: Suppl: 1-42 (1998)
3. Illi S, von Mutius E, Lau S, Bergmann R, Niggemann B. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study BMJ 322:380-5 (2001)
4. The International Rhinitis Management Working Group. International consensus report on the diagnosis and management of rhinitis. Allergy 49: Suppl: 1-34 (1994)

4.4 Measures of protection of subjects taken

The medication used in this study is a pollen extract, which is available on the German market since 2001 and is dispensed upon named patient basis (information based upon German SPC, 2004). The efficacy and safety have been proven in former studies.
Patients were closely monitored during the course of the study.
As a summary, patients were treated and monitored appropriately, and the benefit outweighed potential risks for the patients.

4.5 Background therapy

Prior and Concomitant Therapy

The following therapy was not allowed within the specified time prior to screening as well as during the study:

- SIT within the last 5 years
- 7 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 will lead to the patient being withdrawn
- Treatment with substances interfering with the immune system were not allowed during the entire study and led to the patient being withdrawn.

No additional anti-allergic treatment was allowed for four weeks prior to randomization and during the study, apart from rescue medication right after each pollen chamber visit.

Rescue medication were nasal/ocular H1-blocking agents. The intake of rescue medication had to be documented in the respective section of the Case Record Form (CRF). Salbutamol was allowed if deemed necessary.

4.6 Statistical methods

Primary criterion

The primary criterion of this study was the Total Nasal Symptom Score (TNSS) for the symptoms rhinorrhea, nasal congestion sneezing and nasal itching. Each one of these symptoms was evaluated on a scale from 0 - 3 (none - severe).

The TNSS was documented at the baseline visit 3 (V3) during the pollen chamber test and at visit 10. Evaluation by the subject was done prior to and every 20 min during allergen challenges (every 15 min during screening).

The mean TNSS resulting from these values during allergen challenges were calculated at baseline visit 3 (V3) and at visit 10 (V10). Effect of treatment was investigated using the pre-post difference of these mean TNSS values.

According to the SAP the comparison of Depigoid® Grass Mix and placebo was based on the Wilcoxon rank sum test two-sided for the primary variable, the pre-post difference of mean TNSS values.

Due to different baseline values of the TNSS at visit 3 an ANCOVA model, including baseline severity as prognostic variable, was used according to the amended SAP for comparison of Depigoid® Grass Mix and placebo:

$$Y_{ij} = \mu + \alpha_j + \beta X_{ij} + \varepsilon_{ij}$$

With Y_{ij} observed value of dependent variable pre-post difference TNSS μ mean expected value

α_j effect of factor treatment

β regression coefficient for baseline TNSS

X_{ij} baseline TNSS

ε_{ij} randomly varying error term ~N (0, σ)

The baseline severity, i.e. the severity prior to the pollen chamber challenge was included in an ANCOVA analysis as a variable, which influenced the outcome.

Secondary criteria

The following secondary criteria were analyzed descriptively by treatment group and visit. For comparison of Depigoid® Grass Mix and Placebo an ANCOVA model was used analogously to the primary criterion.

- Change from baseline in the mean of the weight of paper tissues during four hours of allergen challenge was analyzed analogously to the primary criterion.
- Change from baseline in the mean nasal flow measured by anterior rhinomanometry during four hours of allergen challenge was analyzed analogously to the primary criterion.

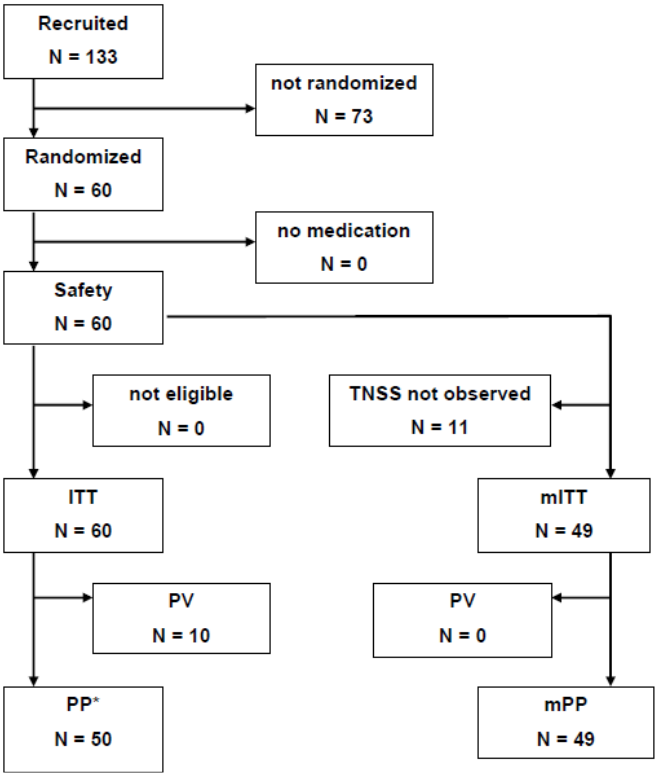
The following secondary criteria were analyzed descriptively by treatment group and visit:

- Adverse events
- Global evaluation of safety.

4.7 Population of subjects

4.7.1 Actual number of subjects included in the trial

One center in Germany recruited a total of 133 patients into the study.



N = number of patients; ITT = intention-to-treat; PP = per-protocol; mITT = modified intention-to-treat; mPP = modified per-protocol; PV = protocol violators; TNSS = Total Nasal Symptom Score
* including 1 patient classified as "dropout

4.7.2 Age groups and gender breakdown

The demographic data of the **ITT** set (N = 60) were as follows:

- Gender: 37 patients (61.7%) were male, 23 patients (38.3%) were female;
- Age: ranged from 18 to 54 years with a mean of 33.8 years;

The demographic data of the **mITT** set (N = 49) were as follows:

- Gender: 30 patients (61.2%) were male, 19 patients (38.8%) were female;
- Age: ranged from 19 to 54 years with a mean of 34.2 years;

B. SUBJECT DISPOSITION

1. Recruitment (incl. information on the number of subjects screened, recruited and withdrawn; inclusion and exclusion criteria, randomization and blinding details, investigational medicinal products used)

1.1 Number of subjects screened, recruited and withdrawn

See above.

1.2 Inclusion and exclusion criteria

Inclusion citeria

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)

1.3 Randomization and blinding details

60 patients were randomized into one of the two treatment groups in the ratio of 1:1 according to a randomization list:
• Treatment group A: Depigoid® Grass Mix
• Treatment group B: Placebo regimen

The treatment was conducted following a rush schedule:
• Initial build-up period: 1 day (day 1: 0.2 + 0.3 ml)
• Treatment period: 5 weeks (week 1-5: 0.5 ml/week)

The study medication was allocated according to the numeration in ascending order. This procedure had to be precisely adhered to, i.e. numbers should not be omitted or exchanged.

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.

1.4 Investigational medicinal products used

The used extract of Depigoid® Grass Mix consisted of depigmented and glutaraldehyde polymerized allergenic extract of the grass pollen *Dactylis glomerata*, *Festuca elatior, Lolium perenne, Phleum pratense* and *Poa pratensis* adsorbed onto aluminium hydroxide. Depigoid® Grass Mix with a concentration of 1000 DPP/ml, labeled as Vial 2 was used in this study. Excipients were sodium chloride 9 mg/ml, phenol 5 mg/ml, aluminium hydroxide 1.1 mg/ml and water for injection.

The placebo treatment was conducted with injections of Depigoid® vehicle consisting of sodium chloride 9 mg/ml, phenol 5 mg/ml, aluminium hydroxide 1.1 mg/ml and water for injection.

The study medication was administered by subcutaenous injection.

2. Pre-assignment period

Initial visit (V1)

The following examinations/procedures were performed:

- Patient information/Informed consent
- Inclusion/Exclusion criteria
- Demographic data
- Medical history
- Grass pollen allergy history
- Physical examination
- Vital signs
- 12-lead ECG
- Safety laboratory (including HIV and hepatitis B and C serology)
- Urine pregnancy test
- Spirometry
- Skin prick test
- 2 hour pollen chamber challenge
- Total Nasal Symptom Score (TNSS)
- Concomitant medication
- Adverse events

The patient was instructed to return to the study center 1 to 3 days after the initial visit (V1).

Visit 2

V2 was performed 1 to 3 days after V1. The following examinations/procedures were performed:

- Review of spirometry
- Concomitant medication
- Adverse events

The spirometry readings, patients had taken at home for the rest of the day after allergen challenge, were reviewed.

Visit 3 (V3) (Baseline)

The visit was performed on day 1, 1 to 4 weeks after visit 1. The following

examinations/procedures were performed:
• Urine pregnancy test
• Spirometry
• 4-hour pollen chamber challenge
• Total Nasal Symptom Score (TNSS)
• Tissue weight
• Rhinomanometry
• Concomitant medication
• Adverse events

3. Post assignment periods

Visit 4 (V4)
The visit was performed on day 3. A maximum deviation of ± 1 day was permitted. The following examinations/procedures were performed:
• Spirometry review
• Randomization
• Administration of study medication
• Concomitant medication
• Adverse events

Visit 5 to visit 9 (V5 to V9)
These visits were performed on day 10, day 17, day 24, day 31 and day 38. A maximum deviation of ± 1 day was permitted. The following examinations/procedures were performed:
• Administration of study medication
• Concomitant medication
• Adverse events

Visit 10 (V10)
The visit was performed on day 59. A maximum deviation of ± 3 days was permitted. The following examinations/procedures were performed:
• Spirometry
• 4 hour pollen chamber challenge
• Total Nasal Symptom Score (TNSS)
• Tissue weight
• Rhinomanometry
• Concomitant medication
• Adverse events

Final visit - visit 11 (V11)
The visit was performed between day 60 and 64. The following examinations/procedures were performed:
• Urine pregnancy test
• Spirometry review
• Global evaluation of safety by patient
• Concomitant medication
• Adverse events

Visit 11 was performed for all patients, irrespective whether they completed the study regularly, or terminated the study prematurely.

For patients who, at the final examination, showed signs of adverse events a further examination, the so-called *post-study-visit (PS)* was carried out.

Unscheduled visits (UV)
If the patient had to visit the investigator for any reason between scheduled study visits, then the reason for the visit was reported by completing the appropriate section (UV) in the CRF. In any case, patients were questioned about adverse events and changes in concomitant medication, additionally vital signs were recorded.

Premature Termination of the Study
The patient might have withdrawn from the study at any time without giving reasons and without any disadvantageous consequences for his subsequent medical care. Furthermore, the patient should have been withdrawn from the study if the investigator had the impression, it would have been to the patient's detriment to continue. In any case the investigator had to complete the discontinuation/termination report in the CRF. The reasons for withdrawal were described as detailed as possible.
In case of premature withdrawal from the study the investigator performed visit 11 (V11) as stated above. In summary, for patients discontinuing the trial the discontinuation/ termination report in the CRF as well as visit 11 had to be filled

C. BASELINE CHARACTERISTICS

No significant differences between the treatment groups were found for dichotomous parameter gender using Fisher's exact two-sided test on an α- level of 5% as well as for the ordinal parameters age and BMI, and height (in the case of the ITT set) using two-sided Wilcoxon rank sum test on an α-level of 5%. Significant differences between the treatment groups were concluded for the ordinal parameters weight and height (height only for the mITT set), since p-values for these parameters were below 0.05.

1. Baseline characteristics – Age

The demographic data of the **ITT** set (N = 60) were as follows:

	Overall (N = 60 (= Safety Set))	Depigoid® GrassMix (N = 30)	Placebo (N = 30)
Age (years)	33.8	34.7	32.9

The demographic data of the **mITT** set (N = 49) were as follows:

	Overall (N = 60)	Depigoid® GrassMix (N = 30)	Placebo (N = 30)
Age (years)	34.2	34.4	34.0

2. Baseline characteristics – Gender

The demographic data of the **ITT** set (N = 60) were as follows:

	Overall (N = 60(= Safety Set))	Depigoid® GrassMix (N = 30)	Placebo (N = 30)
male	37	16	21
female	23	14	9

The demographic data of the **mITT** set (N = 49) were as follows:

	Overall (N = 60)	Depigoid® GrassMix (N = 30)	Placebo (N = 30)
male	30	14	16
female	19	13	6

D. END POINTS

1. End point definitions

Evaluation was performed for the intention-to-treat set (N = 60) and for the modified intention-to-treat set (N = 49).

2. End point #1 Statistical analysis – primary criterion

A) Analysis Performed, Dated According to the SAP dated 30-May-2007

The primary criterion of this study was the Total Nasal Symptom Score (TNSS) assessed for the symptoms rhinorrhea, nasal congestion, sneezing and nasal itching. Each of the symptoms was evaluated on a scale ranging from 0 to 3 (0 = none, 1 = mild, 2 = moderate and 3 = severe).

The Wilcoxon rank sum test did not show any significant difference between the two treatment groups concerning the. However, the severity prior to the pollen chamber challenge (baseline severity) was identified as a possible confounding variable, which influenced the results.

B) Analysis Performed According to the SAP Amendment dated 01-Jun-2007

In order to evaluate the pre-post differences of the mean TNSS values with respect to baseline severity at visit 3 an ANCOVA model was employed including "TNSS severity at visit 3" and "treatment" as factors influencing the results. Analysis was based on the ITT set (N = 60).

<u>Pre-post difference of the mean TNSS in patients with a baseline mean TNSS value ≥ 6</u>

Patients were grouped according to their baseline severity: intervals [6, 7[, [7, 8[, [8, 9[and equal or above 9.

The pre-post difference of the mean TNSS for patients with a baseline mean TNSS between 6 and 7 was -2.15 (SD: 1.98) in Depigoid® Grass Mix treated patients and -1.76 (SD: 1.17) in the placebo group. For patients with a baseline mean TNSS below 5 no major difference in the pre-post TNSS values was observed between Depigoid® Grass Mix and placebo treated patients.

It was observed that the pre-post difference of the mean TNSS in Depigoid® Grass Mix treated patients increased coinciding with an increasing of the baseline severity.

A statistically significant influence ($p < 0.0001$) of the TNSS grade at baseline (for patients with the mean TNSS of 6 and higher) on the difference between the mean TNSS at visit 10 and visit 3 was observed. Together with the baseline TNSS the pre-post difference of mean TNSS increased upon treatment with Depigoid® Grass Mix in comparison to the placebo group.

<u>Pre-post difference of the mean TNSS in all patients with a baseline TNSS value of 6 and higher</u>

Additionally, the pre-post difference of the mean TNSS in all patients with a baseline TNSS of 6 and higher was analyzed. Patients were grouped according to their baseline severity: 6 and higher, 7 and higher, 8 and higher and 9 or above. The pre-post difference of the mean TNSS in patients with a baseline TNSS of 6 and higher was -2.57 (SD: 2.23) for Depigoid® treated group and -1.38 (SD: 1.25) for the placebo group.

A statistically significant influence ($p < 0.0001$) of the TNSS grade at baseline (for patients with the mean TNSS of 6 and higher) on the difference between the mean TNSS at visit 10 and visit 3 was observed. Together with the baseline TNSS the pre-post difference of mean TNSS increased upon treatment with Depigoid® Grass Mix in comparison to the placebo group.

3. End point #2 Statistical analysis – Secondary criterion – Change from Baseline in the Mean Weight of Paper Tissues

A) Analyzed According to the SAP dated 30-May-2007

A change in the mean weight of paper tissues from baseline (visit 3) during four hours of allergen challenge was analyzed for patients receiving Depigoid® Grass Mix or placebo.

The pre-post difference of the mean tissue weight indicating nasal secretion was -2.391 g in Depigoid® Grass Mix treated patients and -1.122 g in placebo group, respectively.
No significant difference between the treatment groups was observed according to the Wilcoxon rank sum test (p = 0.1044).

B) Analyzed According to the SAP Amendment dated 01-Jun-2007
Since baseline severity was identified as a possible confounding variable, it was included into analysis of the results. A change in the mean weight of paper tissues from baseline (visit 3) during four hours of allergen challenge was calculated.
The ANCOVA analysis showed that the difference between the mean tissue weights (reflecting nasal secretion) depends significantly (p < 0.001) on the baseline value. The p-value for the difference of mean weight of paper tissues between the treatment groups was 0.7256, thus no significant difference could be concluded.

4. End point #3 Statistical analysis – Secondary criterion – Change from Baseline in the Mean Nasal Flow

A) Analyzed According to the SAP, dated 30-May-2007
A change from baseline of mean nasal flow measured by anterior rhinomanometry during the four hours of allergen challenge was analyzed descriptively.
For both groups an increase in the mean nasal flow was observed. For Depigoid® Grass Mix treated patients the change between V3 and V10 of mean nasal flow was 3.6 cm3/sec and for the placebo group 13.6 cm3/sec, respectively.
No significant difference between the treatment groups was observed according to Wilcoxon rank sum test.

B) Analyzed According to the SAP Amendment, dated 01-Jun-2007
The baseline severity (the mean nasal flow at visit 3) was included into the analysis using an ANCOVA model.
For Depigoid® Grass Mix treated patients the change between V3 and V10 of mean nasal flow was 3.6 cm3/sec and for the placebo group 13.6 cm3/sec, respectively.
The ANCOVA model used for comparison of Depigoid® Grass Mix and placebo groups showed that the mean nasal flow at visit 10 (V10) depended significantly (p < 0.001) on the mean baseline nasal flow at V3.
No significant difference between treatment groups concerning the mean nasal flow was observed (p = 0.5720).

Efficacy Conclusion
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 included in an ANCOVA model, which was used

additionally to analyze the primary criterion. For TNSS severity of 5 and below at baseline no difference in the pre-post TNSS values was observed between Depigoid® Grass Mix and placebo treated patients. This might be due to the fact that the detected change was lying within the error range of the TNSS scale.
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.

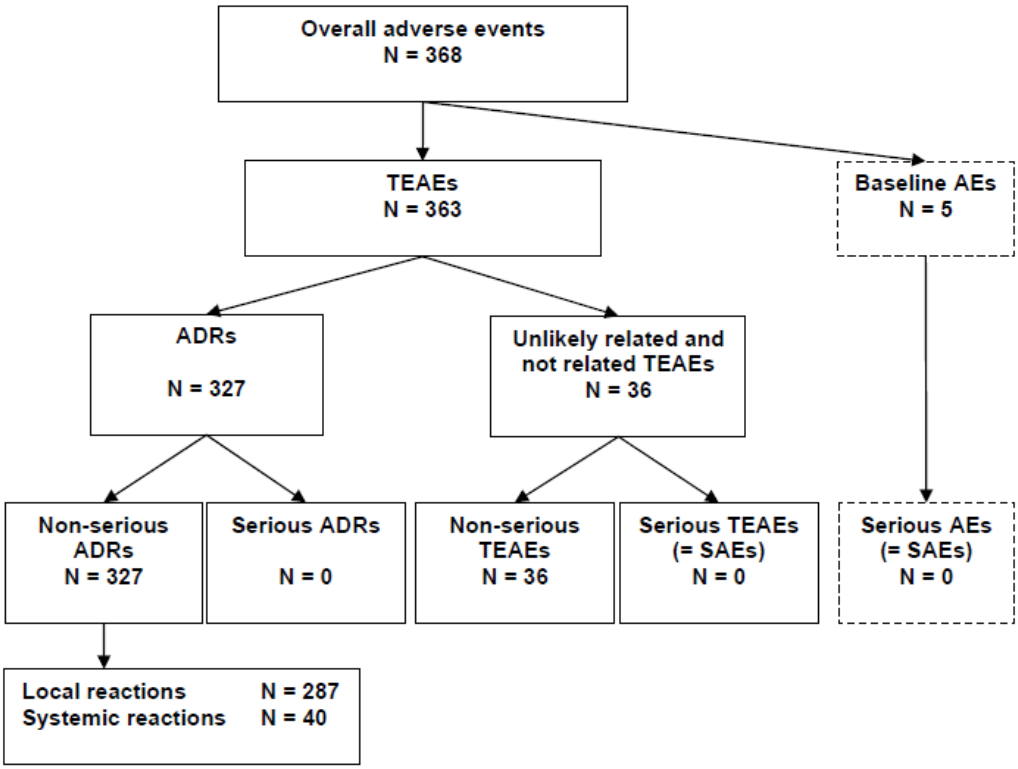
As a secondary criterion the change from baseline in the mean of the weight of paper tissues (measuring the nasal secretion) during the four hours of allergen challenge was evaluated. The pre-post difference in nasal secretion of Depigoid® Grass Mix treated patients was -2.391 g, whereas it was -1.122 g in placebo treated patients. The difference between treatment groups was not significant according to the two-sided Wilcoxon rank sum test ($p = 0.1044$).
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).

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.

E. ADVERSE EVENTS

1. Adverse Events information

Adverse events were recorded and coded according to MedDRA Version 9.0.
For the analysis of AEs, all systemic and local reactions were included. They were documented either on the Drug Administration page or only on the AE page of the CRF.



N: number of episodes in the overall population

During this study, 57 (95.0%) of the patients of the safety set experienced **TEAEs**. A total of 363 TEAEs with 526 TEAE-symptoms altogether were reported for the overall population.
For the patients under Depigoid® Grass Mix treatment, 192 TEAEs with 283 TEAE-symptoms in total were documented. In the placebo treated patients, 171 TEAEs occurred with 243 TEAE-symptoms.
For the overall population, the most reported TEAE-symptoms by MedDRA preferred term were 'Pruritus' (163 TEAE-symptoms), 'Swelling' (149 TEAE symptoms), and 'Pain' (130 TEAE-symptoms).

Out of 363 TEAEs, 36 episodes were assessed by the investigators as being 'unrelated' or 'unlikely related' to study medication ('unrelated': 26 [7.2%] TEAEs, 'unlikely related': 10 [2.8%] TEAEs). The other 327 episodes were assessed as being 'likely' (30 [8.3%] TEAEs) or 'definitely related' (297 [81.8%] 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 (93.3%) 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 (96%) patients; in the placebo group, 201 symptoms were documented for 129 local reactions in 27 (90%) patients.
For the overall population, 8 (2.8%) local reactions were assessed as 'severe' (Depigoid® Grass Mix-group: 3 [1.9%] local reactions in 2 [6.7%] patients; placebo group: 5 [3.9%] local reactions in 4 [13.3%] patients).

The treatment groups did not differ significantly regarding the number of patients with at least one local reaction (p = 0.6120).
For the overall population, the most reported local reaction symptoms by MedDRA preferred term were 'Pruritus' (163 symptoms), 'Swelling' (149 symptoms), and 'Pain' (130 symptoms).

Overall, 40 episodes of **systemic reactions** were recorded for 14 (23.3%) 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'.
For both treatment groups, the most reported systemic reaction symptom by MedDRA preferred term was 'Rhinitis alergic' (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.

The intensity of 7 out of 40 systemic reactions was additionally assessed according to the *DGAKI criteria*. All these 7 reactions (recorded for 3 out of 14 patients with systemic reactions) were assessed with grade 1. The other 33 systemic reactions were documented by the investigator only in the AE page and for them no assessment according to the DGAKI criteria was available.

Out of 60 patients of the safety set, 11 (18.3%) patients **discontinued prematurely** the study due to TEAE (3 [10.0%] patients in the Depigoid® Grass Mix-group and 8 [26.7%] 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 (73.3%) 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.

2. Adverse Event reporting group

The safety analysis was performed for the safety set for both treatment groups.

3. Serious Adverse event(s)

See above

4. Non-serious adverse event(s)

See above

F. ADDITIONAL INFORMATION

1. Global Substantial Modifications

The final SAP dated 30-May-2007 was amended after unblinding of the data.
Initially planned number of patients had changed. It was planned to enroll 60 patients to receive data from 48 patients, 24 patients per treatment group (PP set). However finally 133 patients were enrolled into the study and out of them 60, 30 patients per treatment group were included into the PP set.
Minor changes from the original documents were made in order to correct wording errors.

2. Global interruptions and re-starts

The trial was not interrupted nor restarted.

3. Limitations, addressing sources of potential bias and imprecisions and Caveats

Not applicable.

4. Declaration by the submitting party on the accuracy of the submitted information

The information provided within this summary is based on the Clinical Trial Report.