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

A Randomised, Double-Blind, Parallel Group, Multicentre Study to Assess the Efficacy and Safety of Four Concentrations of Depigoid® Phleum in Patients with Allergic Rhinitis and/or Rhinoconjunctivitis with or without Intermittent Asthma

1.2. Protocol number

6043-PG-PSC-192

1.3. EU trial number

2012-000416-28

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 part of a Paediatric Investigation Plan (EMEA-000795).

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 29-APR-2013 (LPLV).

4. General information about clinical trial

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

Depigoid Phleum (100/1000 DPP7mL) is since 2001 on the German market as NPP. To assess the optimal dose this study was designed to assess the efficacy and tolerability of a rush build-up titration scheme with 4 different doses of Depigoid® Phleum in grass-sensitised patients suffering from allergic rhinitis or rhinoconjunctivitis, as part of the clinical development program of Depigoid® Phleum. The proposed rush build-up scheme has been previously investigated with Depigoid® and its safety has been established.

4.2 Trial design

Multicenter, randomized, double-blind study with 4 parallel groups.

The study consisted of a 4-week screening period, an up to 20-week treatment period, and a follow-up visit at 2 weeks after the last treatment. The treatment period was entirely outside pollen season (i.e., patients were not treated during the grass pollen season).
Patients who met the selection criteria were randomly allocated to receive 1 of 4 concentrations of Depigoid® Phleum (100 DPP/mL, 1,000 DPP/mL, 5,000 DPP/mL and 10,000 DPP/mL).

On the first day of double-blind treatment (Visit 2), treatment began with a s.c. injection of 0.1 mL, followed by 0.2 mL after 30 minutes and 0.2 mL after an additional 30 minutes. From Visit 3 to Visit 7, treatment consisted of the administration of a single 0.5 mL injection at each visit.

During the treatment period (Visits 2 to 7), patients returned to the site every 4 weeks* (up to Week 20). Additionally, all patients had to keep a diary for 48 hours after every injection of the IMP in order to collect the occurrence of delayed local or systemic reactions. At the end of the treatment period, patients returned for a 2-week posttreatment follow-up visit (Visit 8). After screening, all visits had to be made within -5 days of scheduled visit.

* Patients randomized at a later point during the recruitment period, returned at approx. 3- week intervals to allow the application of 6 x 0.5 mL of IMP and the end of study visit prior to start of the pollen season for Phleum in 2013 (anticipated to start begin of April).

4.3 Scientific background

Despite advances in pharmacotherapy, the prevalence of allergic reactions resulting from sensitisation against pollen, dust mites and animal epithelium, especially epithelia from cats and dogs, has increased [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].

Pollens cause many allergic reactions in humans. A chemical and spectroscopic analysis of high molecular weight conventional allergenic extracts shows that a sizeable proportion of pigments (tannins, flavonoids, melanoidins, etc.) is not removed during dialysis and remains tightly adsorbed to the allergenic proteins [5-11]. These pigments have certain properties that make them clearly undesirable [12-18].

Depigmented proteins represent the preferred source material for the production of polymerized extracts, and their use minimizes the administration of undesirable, nonallergenic, foreign substances. Polymerization of depigmented allergens leads to a greatly improved 2nd generation of allergoids with considerably lower immunoglobulin E (IgE)-binding potencies than those observed in the 1st generation polymers based on non-depigmented source materials. However, no significant changes occur in the binding capacity for specific immunoglobulin G (IgG).

This study was designed to assess the efficacy and tolerability of a rush build-up titration scheme with 4 different doses of Depigoid® Phleum in grass-sensitised patients suffering from allergic rhinitis or rhinoconjunctivitis, as part of the clinical development programme of Depigoid® Phleum. The proposed rush build-up scheme has been previously investigated with Depigoid® and its safety has been established. Furthermore, Depigoid® has been available on the Spanish market since 2000 and on the German market since 2001.

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17. Middleton E, Kandaswami C. Effects of flavonoids on immune and inflammatory cell functions. Biochem Pharmacol 1992; 43: 1167-79.
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4.4 Measures of protection of subjects taken

Depigoid® *Phleum pratense* has been extensively used over the last years at both lower concentrations proposed in this study.

Efficacy and safety of the rush administration schedule (0.2 and 0.3 mL administered in the first day of treatment) of Depigoid® 1,000 DPP/mL has been extensively tested in one large post-marketing study in which 1,068 patients were included. In addition, the safety and tolerance of the rush versus the conventional build-up administration schedules with Depigoid® was investigated in a clinical study including 303 adult patients.

The results of this clinical study showed that although the absolute number of patients with local and systemic reactions was higher in the rush treatment arm than in the conventional treatment arm, the differences were not statistically significant.

In addition, stopping rules were implemented in this study in order to reduce the risk to participating patients. Patients who suffered from a systemic reaction ≥ Grade 2 or a severe local reaction or had a lung function test (LFT) result of ≤ 80% of predicted value (for forced expiratory volume in the first second [FEV1] or peak expiratory flow rate [PEFR]) after the administration of the investigational medicinal product (IMP) during the build-up phase were withdrawn. Patients who suffered from repeated systemic reactions ≥ Grade 2 or severe local reactions or had LFT results of ≤ 80% of predicted value prior to administration of the IMP during the maintenance phase were withdrawn at the discretion of the investigator. In general, the occurrence of systemic reactions Grades 3 or 4, or LFT results ≤ 80% of predicted value prior to administration of the IMP at 2 study visits, at any time during the course of the study, elicited the patient interruption of administration of IMP and withdrawal. Moreover, an independent Data Safety Monitoring Board (DSMB) was responsible for interrupting any treatment arm that met predefined criteria.

In addition, patients were observed for at least 30 minutes after administration of study medication. The LFT was performed before and 30 minutes after administration of study medication. The study medication was given only to patients with FEV1 or PEF value > 80% of the predicted normal value. If not, the patient was excluded from the study.

To summarize, the benefits of this study outweighed the potential risks, provided that these rules were implemented and study patients were monitored properly.

4.5 Background therapy

Any medication/therapy other than the IMP was defined as concomitant medication/therapy and was carefully documented in the eCRF together with the previous medication administered within the last 3 months prior to study begin.

The following concomitant medications were prohibited at any time during the study:

- Any rhinitis, rhinoconjunctivitis or asthma medications other than short-acting beta-2 agonists and topical or oral antihistamines, except when required as rescue medication,
- Systemic (oral or IV) or topical corticosteroids, except when required as rescue medication, ß-blockers (e.g. propanolol) and topical ß-blockers,
- Drugs interfering with the immune system,
- Tranquillizers and psychoactive drugs,
- Exposure to any investigational drug within one month or 6 half-lives (whichever is longer) prior to screening visit,
- Immunization with vaccines was not allowed within 7 days prior to and 14 days after study drug administration.

The study sites were provided with country specific rescue-medication (antihistamine, prednisolone and salbutamol) containing the following active substances:

- Levocabastine
- Olopatadine
- Azelastine
- Levocetirizine
- Desloratadine
- Salbutamol
- Prednisone
- Prednisolone
- Methylprednisolone

The patient got rescue medication only in case of emergency as evaluated by the respective investigator.

4.6 Statistical methods

Primary efficacy analysis:

The percentage of patients who required a clinically relevant increased amount of allergen to elicit a positive CPT was calculated for each Depigoid® Phleum dose group, comparing the results from Visit 8 (follow-up) with those at Visit 1 (baseline) together with the corresponding 95% confidence intervals. A difference of 1 log category in the tested allergen concentrations was considered clinically relevant.

The primary efficacy analysis was a hierarchical test procedure to compare the percentage of patients who required an increased amount of allergen to elicit a positive CPT between the 3 different Depigoid® Phleum dose groups and the lowest dose group of 100 DPP/mL in the mITT population. For each comparison, a Fisher's exact test was used.

In case, the Visit 8 CPT was missing for the primary analysis, results from the CPT performed at the early withdrawal visit were used and compared to those at baseline ("Last Observation Carried Forward").

Analysis of secondary endpoints:

The safety endpoints with the number and percentage of patients suffering from local or systemic reactions and those being withdrawn due to local or systemic reactions were presented in an AE summary table together with the corresponding 95% confidence intervals.

4.7 Population of subjects

4.7.1 Actual number of subjects included in the trial

In overall 45 study centers in Germany (28 centers), Poland (10 centers), Spain (3 centers), and the Czech Republic (4 centers) 466 patients were screened. Of these 308 patients were eligible and randomized.

4.7.2 Age groups and gender breakdown

The demographic data of the safety set (N = 308) were as follows:

- Gender: 160 patients (51.95%) were male, 148 patients (48.05%) were female
- Age: ranged from 18 to 69 years with a mean of 32.65 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

In overall 45 study centers in Germany (28 centers), Poland (10 centers), Spain (3 centers), and the Czech Republic (4 centers) 466 patients were screened. 158 patients were not randomized and therefore excluded from the safety set. As all randomized patients received IMP, the safety set comprized 308 patients. Out of these, 72 patients received Depigoid® Phleum 100 DPP/mL, 74 received 1,000 DPP/mL, 84 received 5,000 DPP/mL, and 78 received
10,000 DPP/mL.

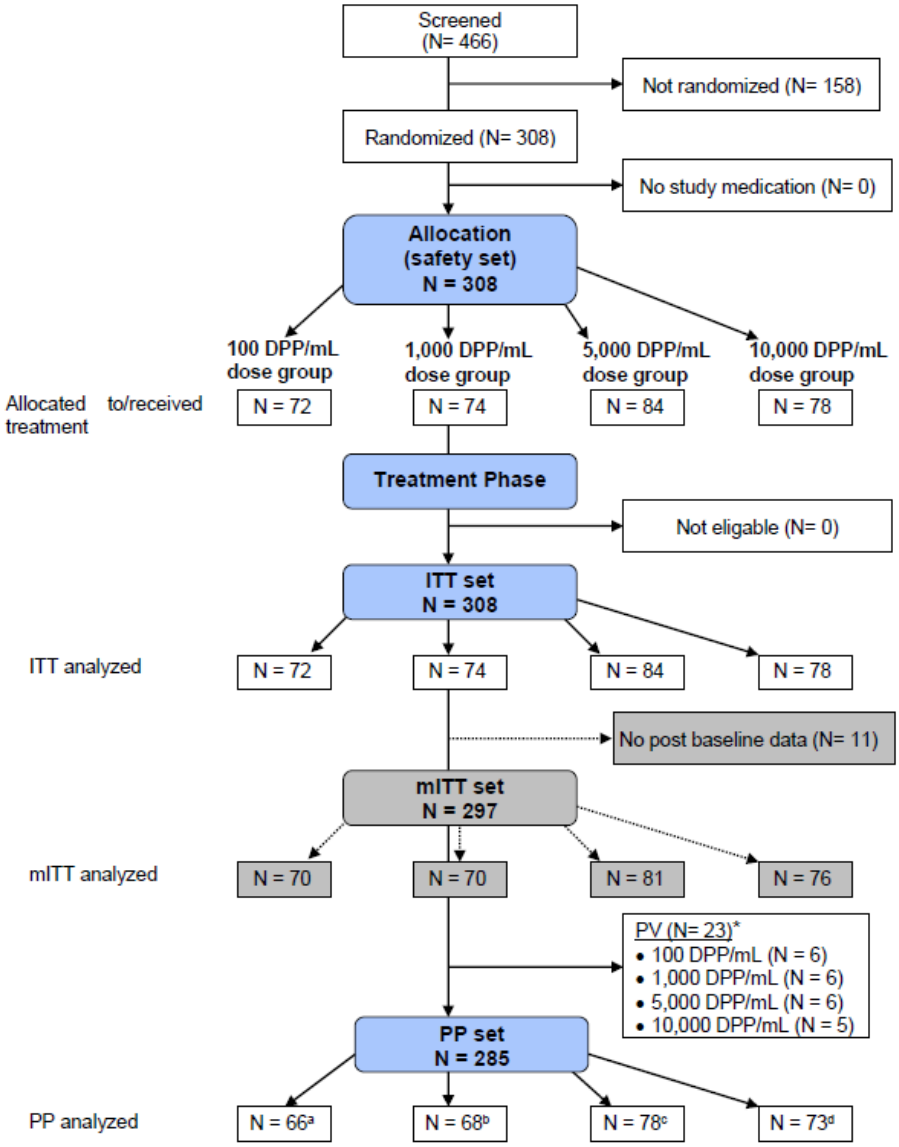
All 308 patients of the safety set were evaluated as eligible and therefore included in the ITT set. As for 11 patients no post-baseline data were available, the mITT set consists of 297 patients.

According to the decisions taken during the BDRM on 17- JUN-2013, 23 patients of the ITT set showed major deviations from the study protocol and were therefore excluded from the PP set. As a consequence, the PP set comprised 285 patients. Thereof, 66 patients received Depigoid® Phleum 100 DPP/mL, 68 received 1,000 DPP/mL, 78 received 5,000 DPP/mL, and 73 received 10,000 DPP/mL.

In addition, the PP set included 21 patients defined as dropouts, as they terminated the study due to AEs related to the IMP.

33 patients (100 DPP/mL: N = 3, 1,000 DPP/mL: N = 7, 5,000 DPP/mL: N = 10, 10,000 DPP/mL: N = 13) of the safety set discontinued the study prematurely.

No patient was prematurely withdrawn from the study due to ‘lack of efficacy’.



N: number of patients; ITT: intention-to-treat; mITT: modified ITT; PP: per-protocol
* more than 1 reason per patient possible, [a]including 1 patient classified as dropouts, [b] including 3 patients classified as dropouts, [c] including 6 patients classified as dropouts, [d] including 11 patients classified as dropouts

1.2 Inclusion and exclusion criteria

Patients had to meet ALL the following ***inclusion criteria*** to be considered for admission to the study:

1. Has provided appropriately signed and dated informed consent.
2. Is a male or female aged ≥ 18 years and ≤ 70 years of age at Visit 1.
3. Has a perception of disease activity of at least 30 mm on a 100 mm VAS.
4. Has an FEV1 or a PEFR value > 80% of predicted normal value.
5. Has complained about allergic rhinitis and/or rhinoconjunctivitis symptoms for at least 2 years, with or without intermittent asthma symptoms, caused by clinical sensitisation

against grass pollen. The IgE-mediated sensitization must be verified by the following: suggestive medical history AND specific IgE against grass pollen using an ImmunoCAP specific IgE radioallergosorbent test (CAP-RAST) ≥ 2 AND a positive SPT AND a positive CPT for grass pollen.

An SPT will be considered positive if the test results in a wheal diameter that is at least 3 mm.

A CPT will be considered positive if a score of 5 is achieved after treatment with any one of the following concentrations: 0.03, 0.1, 0.3, 1, or 3 HEP/mL.

Patients with co-allergies are allowed to enter the study:

- being asymptomatic against co-allergens such as tree or weed pollen,
- house dust mites, cat and dog, and other country specific allergens (e.g.
- but not limited to *Olea europaea* [olive tree], *Parietaria judaica* [wall
- pellitory], *Ambrosia elatior* [ragweed]),

 with specific IgE CAP-RAST and SPT co-allergen, as specified below:

- o Pollen co-allergen and house dust mites: specific IgE CAP-RAST < grass and an SPT wheal diameter co-allergen < grass,
- o Animal dander, only if exposed to: specific IgE CAP-RAST animal ≤ grass and an SPT wheal diameter co-allergen ≤ grass (for patients who are not exposed, no CAP-RAST limit applied.

Note: Alternatively a currently performed (up to 1 month prior to screening) negative Provocation Test (conjunctival or nasal) is acceptable and overrules a high CAP-RAST result and/or a positive SPT for the respective co-allergen.

6. If a female is of non-childbearing potential, the patient must be postmenopausal for at least 1 year or surgically sterile (e.g., bilateral tubal ligation, bilateral oophorectomy, or hysterectomy).
7. If a female is of childbearing potential, the patient must be non-lactating and non-pregnant (with a negative pregnancy test result at Visit 1) and must correctly use an effective method of contraception during the study. An effective method of contraception is defined as one that results in a failure rate of less than 1% per year. The following are allowed methods of contraception when used continuously and properly: hormonal contraceptives administered by implant, injection, or orally; complete abstinence; partner's vasectomy if the female has not more than one partner. Barrier methods (e.g., preservatives) are only considered effective if used together with one of the above.

Patients presenting any one of the following ***exclusion criteria*** were not included in the study:

1. Acute or chronic infectious conjunctivitis.
2. Has a history of significant clinical manifestations of allergy as a result of sensitisation against trees or weed pollen and perennial allergens (e.g., house dust mites).

Patients are not allowed to enter into the study:

- with typical symptoms against co-allergens such as tree or weed pollen, house dust mites, cat and dog, and other country specific allergens (e.g. but not limited to *Olea europaea* [olive tree], *Parietaria judaica* [wall pellitory], *Ambrosia elatior* [ragweed]),
- with CAP-RAST co-allergen ≥ grass, except anminal dander if not exposed CAP-RAST animal dander > grass.

3. Has persistent asthma, according to Global Initiative for Asthma (GINA) Guidelines32.
4. Has acute or chronic inflammatory or infectious airways diseases of the airways, sinuses or the conjunctiva.
5. Has chronic structural disease of the lung (e.g., emphysema or bronchiectasis).
6. Has an autoimmune and/or immune deficiency.
7. Has any disease that prohibits the use of adrenaline (e.g., hyperthyroidism).

8. Has a severe uncontrolled disease that could increase the risk to the patients while participating in the study, including but not limited to, the following: cardiovascular insufficiency, any severe or unstable lung diseases, endocrine diseases, clinically significant renal or hepatic diseases or hematological disorders.
9. Has had active malignant disease during the previous 5 years.
10. Has a significant abnormal laboratory parameter or alteration in vital signs that could increase the risk to the study patient.
11. Has abused alcohol, drugs or medications within the past year.
12. Has a severe psychiatric, psychological or neurological disorder.
13. Has used immunotherapy against grass pollen within the last 5 years.
14. Has used systemic and/or topical treatment with β-blockers within 1 week prior to Visit 2.
15. Is using any medication that may interfere with the immune system or has been using any medication which might still have an influence on the immune system at Visit 2.
16. Has used tranquilizer or psychoactive drugs within 1 week prior to Visit 1.
17. Has used systemic corticosteroids within 3 months prior to Visit 1.
18. Has been immunized with vaccines within 7 days prior to Visit 2.
19. Is expected to be non-compliant and/or not cooperative.
20. Has participated in another clinical study within 30 days prior to Visit 2.
21. Has already participated in this study.
22. Is an employee at the investigational center or first degree relative or partner of the investigator.
23. Plans to donate germ cells, blood, organs or bone marrow during the course of the study.
24. Is not contractually capable.
25. Has a positive pregnancy test at Visit 1.
26. Is jurisdictionally or governmentally institutionalized.

1.1 Randomization and blinding details

In this parallel group, randomized study, patients who met study entry criteria were randomly assigned in a 1:1:1:1 ratio to 1 of 4 concentrations of Depigoid®Phleum. The randomization schedule was computer generated using a permuted block algorithm and randomly allocated IMP to randomization numbers.

Study personnel was specifically instructed to handle IMP in a blinded manner to safeguard the integrity of the study blind to minimize bias in the conduct of the study.

1.4 Investigational medicinal products used

The study medication was Depigoid® Phleum (depigmented and glutaraldehyde polymerized grass allergen extract adsorbed to aluminum hydroxide), biologically standardized in HEPL/mL equivalent units (DPP).

Patients were randomly assigned to one of the 4 treatment groups according to the following scheme:

- Treatment group A: Depigoid® Phleum 100 DPP/mL regimen (n = 80),
- Treatment group B: Depigoid® Phleum 1,000 DPP/mL regimen (n = 80),
- Treatment group C: Depigoid® Phleum 5,000 DPP/mL regimen (n = 80),
- Treatment group D: Depigoid® Phleum 10,000 DPP/mL regimen (n = 80).

Patients were treated for a maximum of 6 dosing days over up to 20 weeks comprising 2 treatment phases:

1. Initial build-up phase: At Visit 2 (Week 0): a total of 0.5 mL Depigoid® suspension administered was administered as 3 s.c. injections (0.1 mL, 0.2 mL, and 0.2 mL with 30 minute intervals between administrations),

2. Maintenance-treatment phase: At Visits 3 to 7 (Week 4 to Week 20): a total of 0.5 mL Depigoid® suspension was administered at each visit as a single s.c. injection.

A LFT was performed prior to and 30 minutes after each injection of IMP. The IMP was given only to patients with LFT (FEV1 or PEFR) results > 80% of their predicted normal value.

2. Pre-assignment period

Screening - Visit 1 (Week -4)

The patient was screened within 4 weeks before Visit 2 (randomization/start of treatment with IMP). The following procedures were performed at screening:

1. Obtain written informed consent,
2. Review inclusion/exclusion criteria,
3. Collect demographic information.
4. Record medical history, including concomitant therapies (e.g., prescription and non-prescription medications). Smoking and alcohol consumption histories are also collected during the Screening Visit,
5. Perform a physical examination including weight, height and vital signs,
6. Perform SPT, perception of disease activity on a VAS, LFT (FEV1 or PEFR), laboratory assessments and urine pregnancy test (if applicable) to determine eligibility,
7. Perform the CPT. The test has to be performed 4 weeks after official end of the previous grass pollen season,
8. Dispense of rescue medication.

Once the results were made available by the central laboratory the confirmation of randomization was requested electronically (web-based).

3. Post assignment periods

Visit 2 (Week 0)

At Visit 2, patients who met the selection criteria were randomly allocated to receive one of the 4 concentrations of Depigoid® Phleum.

The following procedures were performed prior to randomization:

1. The confirmation for randomization must be available,
2. Review inclusion/exclusion criteria (e.g., exclusion criteria #14, 15, 18, 20),
3. Measure vital signs. If any alteration in the vital signs that could increase the risk to the patient is noted, the patient may be excluded,
4. Ask the patient for AEs and change in concomitant therapies since the last visit to the study center (V1),
5. Perform LFT (FEV1 or PEFR) before administration of 1st injection of IMP.

In case the result of the LFT was < 80% of the predicted value the visit was rescheduled within the next 5 days. In case the LFT again was < 80% at the rescheduled visit the patient was excluded from the study (screening failure).

The following procedures were performed after randomization if the patient was eligible to continue:

6. Assign randomization number,
7. Administer double-blind treatment: 3 s.c. injections (0.1 mL + 0.2 mL + 0.2 mL, administered at 30 minute intervals).
   Perform LFT 30 minutes after each of the 3 injections. Special early termination criteria need to be considered during this build-up treatment,

8. For safety reasons, the patient remained at the study center for at least 60 minutes after the last injection of IMP,
9. Dispense rescue medications, if applicable,
10. Dispense patient diaries.

Visit 3 to Visit 7 (Weeks 4, 8, 12, 16 and 20)

After Visit 2, patients returned to the study centre in 4-week intervals (-5 days). The following procedures were performed at Visits 3 to 7:

1. Collect and review patient diaries for documentation of symptoms and rescue medication intake and make corresponding entries to the patient file and eCRF if applicable,
2. Ask the patient for AEs and change in concomitant therapies since the previous visit to the study centre,
3. Measure vital signs,
4. Perform LFT (FEV1 or PEFR), before and 30 minutes after the administration of each injection. If the result of the LFT is < 80% of the predicted value, the visit can be rescheduled within the next 5 days. If the LFT again is < 80% at the rescheduled visit the patient has to be excluded from the study.
5. Administer double-blind treatment: a single s.c. injection (0.5 mL),
6. Dispense rescue medications, if applicable,
7. Dispense new patient diaries.

End of Study Visit - Visit 8 (Week 22)

This visit was performed 2 weeks (-5 days) after the last treatment.

The following procedures were performed at Follow-up Visit 8:

1. Collect and review patient diaries for documentation of symptoms and rescue medication intake and make corresponding entries to the patient file and eCRF if applicable,
2. Ask the patient for AEs and change in concomitant therapies since the previous visit to the study center,
3. Measure vital signs,
4. Perform laboratory assessments and urine pregnancy test (if applicable),
5. Perform a physical examination,
6. Perform the CPT. The test has to be performed prior to the anticipated begin of the grass pollen season,
7. Collect unused rescue medications,
8. Perform overall tolerability assessments (from patient and from physician).

Optional Visits

Post-Study Visit (PS)

For patients who experienced AEs or showed clinically relevant deviations regarding the laboratory analyses at V8, a PS visit for further examination was scheduled within reasonable time. The latest date for such a visit was 1 month after V8.

The following examinations/procedures were performed at PS visit:

1. Physical examination,
2. Measure vital signs,
3. Perform laboratory assessments (if feasible) and urine pregnancy test (if applicable),
4. Ask the patient for AEs and change in concomitant therapies since the previous visit to the study centre,
5. Collect and review patient diaries for documentation of symptoms and rescue medication intake and make corresponding entries to the patient file and eCRF if applicable.

Unscheduled Visit (UV)

If a patient had to consult the investigator for any reason and came to the study site between the scheduled study visits during the study, the reason for the visit had to be documented on the unscheduled visit (UV)-page of the eCRF.

The following examinations/procedures were performed:

1. Perform a physical examination,
2. Measure vital signs,
3. Perform laboratory assessments (if feasible) and urine pregnancy test (if applicable),
4. Ask the patient for AEs and change in concomitant therapies since the previous visit to the study centre,
5. Collect and review patient diaries for documentation of symptoms and rescue medication intake and make corresponding entries to the patient file and eCRF if applicable.

Re-scheduled Visit

A re-scheduled visit took place if at a scheduled visit the IMP was not administered because of FEV1 or PEF (peak expiratory flow) values ≤ 80% of the predicted normal value. It was allowed to reschedule Visit 2 once (RS V2) and up to 2 visits out of Visits 3-7 were also allowed to be rescheduled once (RS V3-7).

In case the result of the LFT was < 80% at more than 2 consecutive visits the patient was excluded from the study.

This visit has to be performed within 5 days after the originally scheduled visit.

The following examinations/procedures have to be performed:

1. Measure vital signs,
2. Perform LFT (prior to and 30 min after the application of study medication),
3. Administer study medication (V2: 0.1 mL injection followed by two injections of 0.2 mL each; V3-7: 0.5 mL injection),
4. Collect patient diaries,
5. Dispense patient diaries,
6. Dispense rescue medication if applicable,
7. Ask the patient for AEs and change in concomitant therapies since the previous visit to the study centre.

C. BASELINE CHARACTERISTICS

The demographic data of the safety set (N = 308) were raised as follows:

1. Baseline characteristics – Age

Age: ranged from 18 to 69 years with a mean of 32.65 years

2. Baseline characteristics – Gender

Gender: 160 patients (51.95%) were male, 148 patients (48.05%) were female

D. END POINTS

1. End point definitions

The primary endpoint (efficacy):

Percentage of patients who needed an increased amount of allergen to elicit a positive CPT performed after up to 20 weeks of treatment in comparison to baseline (i.e., comparing the results from follow-up Visit 8 with those at baseline, Visit 1).

The secondary endpoint (efficacy):

The individual results for allergen amount in the CPT were investigated supportive to the primary endpoint.

The secondary endpoints (safety):

- Patients (%) suffering from systemic reactions (Grades 1 to 4) during the treatment period,
- Patients (%) suffering from local reactions during the treatment period,
- Patients (%) withdrawn from the study due to systemic reactions (Grades 1 to 4) during the build-up phase,
- Patients (%) withdrawn from the study due to local reactions during the build-up phase,
- Patients (%) suffering from different severity levels of systemic reactions during the treatment period,
- Patients (%) suffering from different severity levels of local reactions during the treatment period,
- Patients (%) withdrawn from the study due to systemic reactions during the treatment period,
- Patients (%) withdrawn from the study due to local reactions during the treatment period,
- Patient's diary assessments of symptoms and rescue medication use for rhinitis/rhinoconjunctivitis and asthma,
- Change from baseline to the end of the treatment period in the clinical chemistry and haematological parameters,
- Change of lung function parameters before and after the administration of the IMP,
- Physician's overall tolerability assessment,
- Patient's overall tolerability assessment.

The exploratory endpoints:

- Immunology laboratory parameters: total and specific IgE, specific IgG1 and IgG4 and fragment antigen-binding (FAB) assay,
- Baseline vitamin D levels versus efficacy outcome.

Evaluation was performed for the safety set (N = 308), the ITT set (N = 308), the mITT set (N = 297), and the PP set (N = 285).

2. End point #1 Statistical analysis – efficacy – primary variable

The primary objective of this study was the comparison between patients treated with Depigoid® Phleum (100, 1,000, 5,000, or 10,000 DPP/mL) with regard to the percentage of patients who needed an increased amount of allergen to provoke a positive CPT at the end of the treatment period. A hierarchic test procedure considering the dose was used.
In decreasing order, the 3 higher doses were compared with the lowest dose group, i.e. 100 DPP/mL.
As result, responder rates were similar in 100 and 1000 DPP/mL dose groups but higher in the 5,000 DPP/mL (75.3%) and the 10,000 DPP/mL groups (77.4%). The responder rates in the 100 DPP/mL and the 1,000 DPP/mL groups were 72.9% and 72.3%, respectively (mITT).
The respective differences to the 100 DPP/mL group were -4.5% for the 10,000 DPP/mL group, -2.5% for the 5,000 DPP/mL group, and 0.6% for the 1,000 DPP/mL group (mITT).
No statistically significant difference was found. For the PP set, similar results were observed.

3. End point #2 Statistical analysis – efficacy – Conjunctival Provocation Test

As further secondary variable, individual results for allergen amount needed for a positive result of the CPT at V8 were compared to V1 and the respective pre-post differences were analyzed for each dose group.
The highest increase in the lowest concentration resulting in a positive CPT was found in the 5,000 DPP/mL indicated by a pre-post difference of 7.955 HEP/mL (V1: 1.273; V8: 9.244 HEP/mL [ITT set]). In the 10,000 DPP/mL group, the increase was only marginal lower, i.e. from 1.053 to 8.950 HEP/mL with a pre-post difference of 7.888 HEP/mL. In the 100 and the 1,000

DPP/mL group, the increase in the lowest concentration resulting in a positive CPT was almost identical but lower compared to the two higher dose groups. In the 100 DPP/mL group, it was from 1.104 at V1 to 7.133 HEP/mL at V8 (pre-post difference: 6.029 HEP/mL) and in the 1,000 DPP/mL group from 1.239 to 7.282 HEP/mL with a pre-post difference of 6.012 HEP/mL.
None of the tests revealed any statistically significant difference between treatment groups.

Similar values were found for the two subgroups, analyzing either data of patients with at least 20 weeks of treatment or data of those patients, included at a later point of time into the study and were therefore treated for less than 20 weeks.

4. End point #3 Statistical analysis – efficacy – Immunological Results

Immune-response data (total IgE, Phleum-specific IgE, IgG1, and IgG4) were obtained prior to the first injection of IMP at V1 and at the study end at V8.
Mean overall IgE values slightly decreased in all dose groups with the highest decrease observed in the 100 DPP/mL and 5,000 DPP/mL groups (-22.50 mg/L and -14.27 mg/L, respectively [ITT]).
Differences between the dose groups were found in the pre-post differences. However, these slight varieties correspond to normal fluctuations of Phleum-specific IgE.
For the mean values of Phleum-specific IgE, a minor decrease was found in the dose groups 100 DPP/mL with -3.78 kU/L and 1,000 DPP/mL with -1.98 kU/L. For the two higher dose groups, values increased slightly by 7.11 kU/L in the 5,000 DPP/mL group and 8.34 kU/L in the 10,000 DPP/mL group (ITT).
Regarding IgG4 mean values increased most in the 5,000 DPP/mL and 10,000 DPP/mL groups with a pre-post difference of 407.76 ng/mL and 648.61 ng/mL, respectively. In the 100 DPP/mL and 1,000 DPP/mL dose group, values also increased, but with less intensity (26.97 ng/mL in the 100 DPP/mL and 221.55 ng/mL in the 1,000 DPP/mL group [ITT]). At V8, the difference between the mean values of the groups was statistically significant between all dose groups (ITT and PP). This was further supported by the respective pre-post differences.
The same trend was observed for mean IgG1 values, i.e. the highest increase was found in the 5,000 DPP/mL and 10,000 DPP/mL groups with 157.45 and 270.18 U/mL. For the 100 and 1,000 DPP/mL groups, the increase was 2.48 U/mL and 57.00 U/mL, respectively. At V8, the difference between the mean values of the groups was statistically significant between all dose groups (ITT and PP). This was further supported by the respective pre-post differences.

5. End point #4 Statistical analysis – efficacy – Analyses of Safety Variables regarding the Patient Diary

For each symptom documented at different body regions/systems in the patient diary (i.e. injection site, skin, nose, eyes, lung/respiratory system, and others), frequencies and percentages were calculated.
For symptoms at all different body regions/systems, the percentage of affected patients decreased in most of the dose groups after the first application of IMP and showed similar values. However, in patients receiving the 1,000 DPP/mL dose, a marginal increase of the percentage of patients affected by symptoms at the body regions ‘nose’ and ‘eyes’ was found from V2 to V7 (‘nose’: from 5.56% to 6.45%; ‘eyes’: from 2.78% to 4.92%).
Highest values throughout the study were observed for ‘symptoms at the injection site’. However, the percentage of patients affected by symptoms at the injection site decreased during the course of the study, the number of affected patients was always higher in the dose groups with higher IMP concentrations at all visits.

Regarding frequencies and percentages of patients who used rescue medication, overall only few patients took rescue medication, and no relevant differences were observed between the dose groups.

E. ADVERSE EVENTS

1. Adverse Events information

AEs were coded according to MedDRA version 16.0.

During this study, 233 patients (75.6%) experienced 1045 **TEAEs** (treatment emergent adverse events).
Thereof, 121 TEAEs occurred in 42 patients (58.3%) of the 100 DPP/mL group, 194 TEAEs in 51 patients (68.9%) of the 1,000 DPP/mL group, 330 TEAEs in 67 patients (79.8%) of the 5,000 DPP/mL group, and 400 TEAEs in 73 patients (93.6%) of the 10,000 DPP/mL group.
According to the investigators, 840 TEAEs were 'related' to the IMP and 205 TEAEs were not.

Overall, most of the TEAE symptoms were assigned to the MedDRA SOC 'general disorders and administration site conditions' with 180 patients (58.4%) showing 649 TEAE symptoms. Furthermore, 60 patients (19.5%) had 114 TEAE symptoms classified as 'respiratory, thoracic and mediastinal disorders', followed by 66 patients (21.4%) with 82 TEAE symptoms classified as 'infections and infestations'. Overall, the most frequently reported TEAE symptoms by MedDRA PT were 'injection site reaction' (184 TEAE symptoms), 'injection site swelling' (141 TEAE symptoms), and 'injection site erythema' (95 TEAE symptoms).

Overall, 196 patients (63.6%) experienced 839 TEAEs that fulfilled the **ADR** (adverse drug reaction) criteria. The lowest number of ADR occurred in the 100 DPP/mL group (30 patients [41.7%] had 84 ADRs), the highest number of ADRs occurred in the 10,000 DPP/mL group (67 patients [85.9%] had 353 ADRs).
In this study, ADRs were subdivided into the subgroups 'local reaction' and 'systemic reaction'. Altogether, these ADRs comprised 621 LRs (local reactions) and 218 SRs (systemic reactions).

Local Reactions

LRs were documented as part of the AE documentation using the corresponding intensity assessment. The causal relation to the IMP was defined as 'related'. The LRs were analyzed descriptively (N and percentage) and compared between the dose groups using Fisher's exact test.

During the course of the study, 177 patients (57.5%) experienced 621 LRs after administration of IMP. Thereof, 203 LRs during the build-up and 418 LRs during the maintenance phase. The lowest number of LRs occurred in the 100 DPP/mL group (overall 51 LRs in 21 patients [29.2%]), the highest number of LRs occurred in the 10,000 DPP/mL group (overall 267 LRs in 63 patients [80.8%]).
According to investigators assessment, all LRs were 'related' to the IMP and 'not related' to the rescue medication.

Overall, the intensity of LRs was mostly 'mild' (495 [79.7%]) and 'moderate' (115 [18.5%]). 11 LR (1.8%) was of 'severe' intensity.
For the overall safety set, 11 LRs (1.8%) were of 'severe' intensity with higher frequency during the build-up phase. In all dose groups, most of the LRs were of 'mild' intensity (overall: 495 [79.7%]). None of the LRs was serious.

There was a statistically significant difference regarding the overall number of patients with LRs between the 100 DPP/mL and the 3 higher dose groups, between the 1,000DPP/mL and the 10,000 DPP/mL group and between the 5,000 DPP/mL and the 10,000 DPP/mL group.

However, during the build-up phase, all dose groups differed from each other regarding the number of patients with LRs (all p-values < 0.05). During the maintenance phase, statistical significant differences were found between 100 DPP/mL and 5,000 DPP/mL group and the 10,000 DPP/mL group and between the 1,000 DPP/mL and the 10,000 DPP/mL group. For each difference, the following applied: patients in the respective higher dose group had more LRs compared to the lower dose group.
Moreover, for 7 patients (2.3%) overall 7 LRs led to premature study termination; 1 in the 1,000 DPP/mL group, 2 in the 5,000 DPP/mL group and 4 in the 10,000 DPP/mL group. However, the difference was not statistically significant (p = 0.2113). All these LRs occurred during the build-up phase.
Even separated by the build-up and the maintenance phase, no differences between the dose groups were found (p-values > 0.05).

Systemic Reactions
All SRs were defined as AEs which were related to the IMP. For the evaluation of SRs the EAACI criteria were used (Grade 0 to Grade 4).

During the course of the study, 91 patients (29.5%) experienced 218 SRs after administration of IMP. Thereof, 114 SRs during the build-up and 104 SRs during the maintenance phase. The lowest number of SRs occurred in the 100 DPP/mL group (overall 14 patients [19.4%] with 33 SRs), the highest number occurred in the 10,000 DPP/mL group (overall 33 patients [42.3%] with 86 SRs).
According to investigators assessment, all SRs were 'related' to the IMP and 'not related' to the rescue medication.

Although, more SRs were reported during the maintenance phase, the frequency of patients suffering from SRs was higher during the build-up phase for the 100 DPP/mL, the 5,000 DPP/mL, and the 10,000 DPP/mL group. Only in the 1,000 DPP/mL group, more patients complained about SRs during the maintenance phase compared to the build-up phase.
In the 3 higher dose groups, most SRs were of 'Grade 1' intensity, however SRs of 'Grade 2' intensity were reported in 2 cases in the 1,000 DPP/mL and the 5,000 DPP/mL group, respectively and in 14 cases in the 10,000 DPP/mL group.
Moreover, there was one case, where the intensity of the SR was assessed as 'Grade 3'. It was a 'pharyngeal oedema' that led to premature study termination and was reported in a patient of the 100 DPP/mL group.
During the maintenance phase, the intensity was assessed as being 'Grade 0' or 'Grade 1' for all patients of the 100 DPP/mL, the 1,000 DPP/mL, and the 5,000 DPP/mL group. For the 10,000 DPP/mL group, 1 SR was assessed being 'Grade 2'. No reaction of 'Grade 3' or 'Grade 4' was documented.

In all dose groups, most of the SRs were of 'Grade 1' intensity (overall safety set:
173 [79.4%]). 19 SRs (8.7%) were assessed as 'Grade 2' and 1 SR (0.5%) as 'Grade 3' but not as serious. Except 1 SR with 'Grade 2' intensity, they all occurred during the build-up phase.
4 of the SRs were serious. They occurred in the 2 higher dose groups and were 'urticaria' and 'cardiovascular disorders' in the 5,000 DPP/mL and 'headache' and 'vomiting' in the 10,000 DPP/mL group.

There was a statistically significant difference regarding the overall number of patients with SRs between the 100 DPP/mL and the 10,000 DPP/mL group and the 1,000 DPP/mL and the 10,000 DPP/mL group with more patients experiencing SRs in the 10,000 DPP/mL group.
However, during the build-up phase, statistically significant difference was reached between the 100 DPP/mL and the 10,000 DPP/mL group and between the 1,000 DPP/mL and the two higher dose groups.
During the maintenance phase, a statistically significant difference was found between 100 DPP/mL and the 10,000 DPP/mL group only (p-value = 0.0398). For each difference the following applied: patients in the respective higher dose group had more SRs compared to the lower dose group.
Moreover for 14 patients (4.5%), a total of 18 SRs led to **premature study termination**; 1 SR in 1 patient of the 100 DPP/mL, 2 SRs in 2 patients of the 1,000 DPP/mL, 6 SRs in 4 patients of the 5,000 DPP/mL and 9 SRs in 7 patients of the 10,000 DPP/mL group. In the 5,000 DPP/mL group, 1 SR was recorded during the maintenance phase, in the 10,000 DPP/mL group, it were 3 SRs. All other SRs occurred during the build-up phase.

The difference regarding the number of patients for whom an SR led to premature study termination was not statistically significant (overall p = 0.1478). The same was found for the build-up and the maintenance phase (p-values > 0.05).
Similarly, as for local reactions, SRs were evaluated regarding the timing of their occurrence. Thus, immediate reactions are defined as SRs occurring within 30/60 minutes after the administration of the IMP and all SRs occurring later than 60 minutes as delayed reactions.
Out of the 218 SRs that were documented in the study, 37 SRs occurred within 60 mins after administration of the IMP, 24 SRs already within the first 30 mins.
168 SRs were defined as being delayed and for 13 SRs no time assessment was made.

In all dose groups, the most often reported SR by MedDRA PT was ‘rhinitis allergic’ (overall 36 symptoms in 18 patients [5.8%,).
With regard to respiratory symptoms, only ‘cough’ was documented in the 100 DPP/mL group (1 symptom). In the 1,000 DPP/mL group ‘asthma’ (1 symptom) and ‘peak expiratory flow rate decreased’ (2 symptoms) occurred and in the 5,000 DPP/mL group, ‘asthma’ (2 symptoms), ‘cough’, ‘chest discomfort, and ‘allergic cough’ (1 symptom each) was documented. Most respiratory symptoms were recorded in the 10,000 DPP/mL group, i.e. ‘asthma’ (5 symptoms), ‘cough’ and ‘allergic cough’ (1 symptom each), and ‘chest discomfort’ (2 symptoms).

No death and **no pregnancy** were reported during the study.

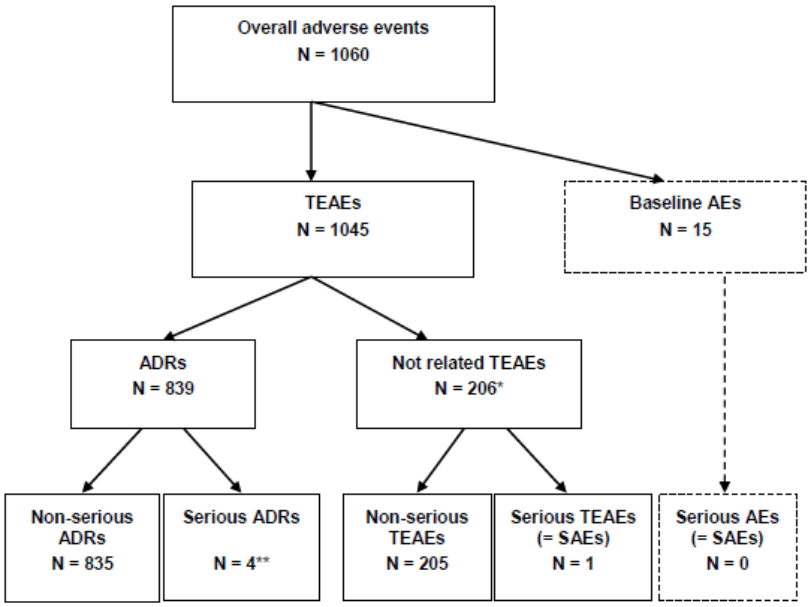
Overall, 23 patients (7.5%) of the safety set had 28 TEAEs leading to **premature termination** of the study. Thereof, 23 TEAEs occurred in 20 patients during the buildup phase and 5 TEAEs in 3 patients during the maintenance phase. Most of these TEAEs were assessed to be related to the IMP (25 [89.3%]) and were of ‘moderate’ intensity (6 [60.0% of all 10 TEAEs]) or of ‘Grade 2’ intensity (8 [44.4% of all 18 systemic reactions]).
The only TEAE leading to premature termination of Grade 3 (‘pharyngeal oedema’) occurred during the build-up phase in the 100 DPP/mL group and was assessed as related to IMP but not serious.
One of the 3 TEAEs assessed as ‘severe’ intensity occurred in a patient included in the 5,000 DPP/mL group (‘injection site induration’) and was assessed to have a relation to IMP. The symptom disappeared and was not serious. The other 2 ‘severe’ TEAEs that led to premature termination were reported during the build-up phase in 2 patients of the 10,000 DPP/mL group. One was related to IMP, the other was not.
Nevertheless, they were both not serious.

In the 100 DPP/mL group, 2 patients (2.8%) had 2 TEAEs, thereof 1 ADR, leading to premature discontinuation, none was serious.
In the 1,000 DPP/mL group, 3 patients (4.1%) had 3 TEAEs leading to premature discontinuation, all of them were ADRs and none serious.
In the 5,000 DPP/mL group, 6 patients (7.1%) had 8 TEAEs leading to premature discontinuation, all of them were ADRs and 1 serious.
In the 10,000 DPP/mL group, 12 patients (15.4%) had 15 TEAEs, thereof 13 ADRs including 1 serious ADR.
The dose groups were compared using Fisher's exact test and significant difference could be concluded (patients with TEAEs leading to premature termination: p = 0.0216; patients with treatment emergent ADRs leading to premature termination p = 0.0163). Regarding patients with TEAEs leading to premature termination, more patients in the 10,000 DPP/mL group terminated the study prematurely due to a TEAE compared to the 100 DPP/mL group (p = 0.0100) and compared to the 1,000 DPP/mL group (p = 0.0276). The same applied for the number of patients with premature termination due to an ADR (p = 0.0050 between 100 and 10,000 DPP/mL and p = 0.0474 between 1,000 and 10,000 DPP/mL).

Only small changes in **vital signs** in relation to the values at V1 were observed at study end. No substantial differences between the 4 dose groups were found.

Regarding the **PFTs** (pulmonary function test), no deterioration in the course of the study was found. 3 TEAEs related with a decreased pulmonary function were recorded during the study. For 1 patient of the 10,000 DPP/mL, the FEV1 decreased and for 2 patients of the 1,000 DPP/ml group, it was the PEFR.

The majority of patients and investigators rated the **global safety** as 'excellent' or 'good' in all dose groups. Overall, there was no case of 'unacceptable' global safety assessment.
Notably, in the 100 DPP/mL and 1,000 DPP/mL group, no patient or investigator rated the global safety as 'poor'.



N: number of AEs in the safety set (for overall AEs, TEAEs and baseline AEs: number of AEs in the total set)
* including 1 patient, for whom a related TEAE was reported that was neither a local nor a systemic reaction and occurred >72 hours after administration of IMP and that was therefore not evaluated as an ADR.
** all serious ADRs were systemic reactions

2. Adverse Event reporting group

The safety analysis was performed for the safety set.

3. Serious Adverse event(s)

Overall, 5 treatment emergent SAEs were reported for 3 patients (1.0%) of the safety set. Thereof, 1 treatment emergent SAE, that was not related to study medication, occurred in 1 patient (1.4%) of the 100 DPP/mL group, further 2 events were observed in 1 patient (1.2%) of the 5,000 DPP/mL group and were both assessed to be related to study medication, and also for 1 patient (1.3%) of the 10,000 DPP/mL group, 2 events with causal relationship to the study medication were reported.
No SAE was of 'severe' intensity or classified with Grade 3 or 4.
Notably, all SAEs occurred during the build-up phase.
The dose groups were compared regarding the number of patients with treatment emergent SAEs using the Fisher's exact test, but no significant difference could be concluded (p = 0.8995).

1. Non-serious adverse event(s)

See above

F. ADDITIONAL INFORMATION

1. Global Substantial Modifications

The clinical study was started according to study protocol version 3.0, dated 24-AUG-2012. Afterwards, changes concerning the inclusion of patients with co-allergies and the extension of the recruitment period by 3 weeks were implemented. As due to the shortening of intervals between treatments not all of the patients were treated for 20 weeks, a subgroup analyses was considered to be performed. These adaptations were contained in amended study protocol version 5.0, dated 17-DEC-2012.

2. Global interruptions and re-starts

n.a.

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

n.a.

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.

Further information on this trial can be found in the respective publications:

- Dose optimizing study of a depigmented polymerized allergen extract of phleum pollen by means of conjunctival provocation test (CPT), Sager A, Pfaar O Poster 3111, WAO, 16.10.2015, Seoul