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

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 study took place at 45 study centres in 4 countries (Germany, Poland, Spain and the Czech Republic). The minimum expected recruitment per site was 6 (-8) patients, but the study recruitment was competitive; a study centre that had a high recruitment rate was allowed to recruit more patients if other study centres had slow enrolment.

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

The study started in September 2012 and was completed prior to the grass pollen season in April 2013. The total duration of the study was 7 months.
First patient first visit: 25-SEP-2012
Last patient last visit: 29-APR-2013

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

Primary Objective:

To assess the effective dose range and the optimum dose of Depigoid® Phleum administered subcutaneously in adult patients with allergic rhinitis and/or rhinoconjunctivitis with or without intermittent asthma.

Secondary Objective(s):

To assess the safety and tolerability of 4 concentrations of Depigoid® Phleum administered subcutaneously during an up to 20-week treatment period.

Exploratory Objectives:

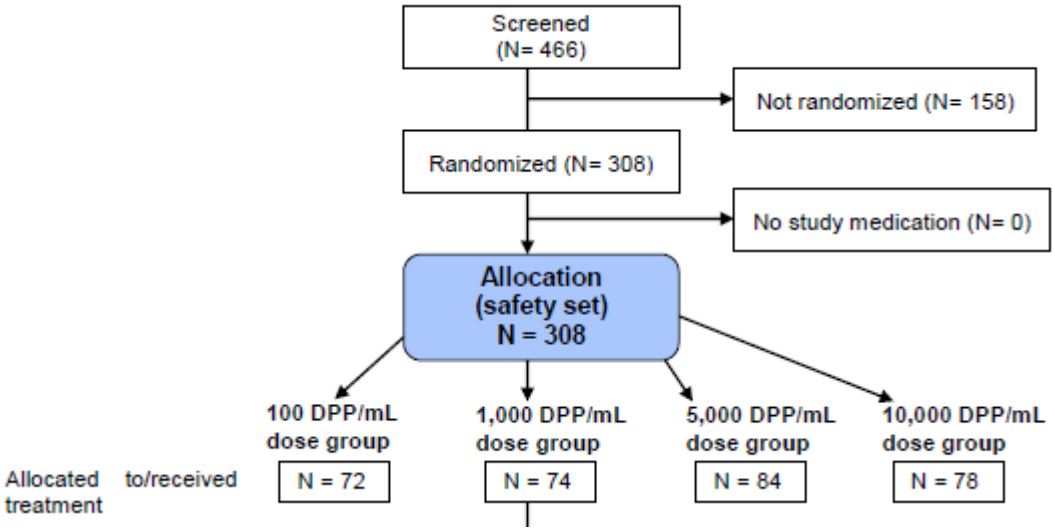
- To gain some insight on the mechanism of action of the treatment with Depigoid® Phleum administered subcutaneously by measuring immunology laboratory parameters in patients with allergic rhinitis and/or rhinoconjunctivitis with or without intermittent asthma.

This study was designed to assess the efficacy and tolerability of a rush build-up titration scheme followed by maintenance treatment 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. Furthermore, Depigoid® has been available on the Spanish market since 2000 and on the German market since 2001.

4. Population of subjects

4.1. The 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.



4.2. Age groups and gender breakdown

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

4.3. 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.

5. Investigational medicinal products used

The study medication was Depigoid® Phleum (depigmented and glutaraldehyde polymerized grass allergen extract adsorbed to aluminum hydroxide).
A total of 0.5 mL/day of 1 of 4 concentrations of Depigoid® Phleum was administered by s.c. injection on 6 days at 4-week intervals during the double-blind treatment period (from Week 0 to Week 20).
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.

6. Description of adverse reactions and their frequency

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 '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 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.

For the overall population, the most reported LR symptoms were 'injection site reaction' (184 symptoms), 'injection site swelling' (141 symptoms), and 'injection site erythema' (95 symptoms). For the 100 DPP/mL group, the most reported LR symptom was 'injection site swelling' (18 symptoms), for the other groups, it was 'injection site reaction' (1,000 DPP/mL: 34 symptoms; 5,000 DPP/mL: 52 symptoms; 10,000 DPP/mL: 83 symptoms.

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.

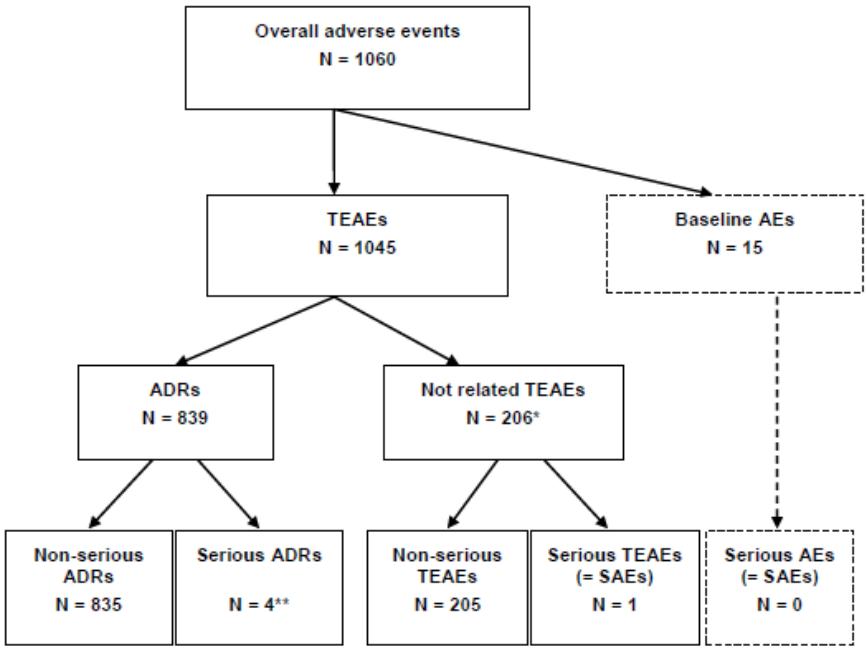
In all dose groups, most of the SRs were of 'Grade 1' intensity (overall safety set:
173 [79.4%]). 19 SRs (8.7%) were assessed as 'Grade 2' and 1 SR (0.5%) as 'Grade 3' but not as serious. Except 1 SR with 'Grade 2' intensity, they all occurred during the build-up phase.
4 of the SRs were serious. They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



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

7. Overall results of the clinical trials

The objective of the study was to assess the efficacy and safety of 4 doses of depigmented and glutaraldehyde polymerized allergenic extract of 100% Phleum pollen (Depigoid® Phleum) in patients suffering from grass pollen-induced allergic rhinitis and/or rhinoconjunctivitis with or without intermittent asthma.
The comparison between the 4 different doses of Depigoid® Phleum considering the percentage of patients who needed an increased amount of allergen to provoke a positive CPT at the end of treatment was carried out using a hierarchic test procedure. The 3 higher doses were compared with the lowest dose group (100 DPP/mL). As result, responder rates were very similar in all dose groups with 72.9% in the lowest and 77.4% in the highest dose group.

Although, highest responder rates were obtained in the 5,000 DPP/mL with 75.3% and the 10,000 DPP/mL group with 77.4%, the differences between the 4 dose groups did not reach statistical significance.
Also, the analyses of CPT data supported the beneficial effect of the 5,000 DPP/mL and the 10,000 DPP/mL group to some extent. In these dose groups, the highest mean increase regarding the lowest concentration resulting in a positive CPT was observed. However,
the differences to the 100 DPP/mL group was not statistically significant for any dose group.
Additionally, immune-response data were analysed. Obtained results suggested to provide greater induction of IgG4 and IgG1 antibodies for all four doses of Depigoid® Phleum. Mean IgG4 values increased in all dose groups until the end of the study but mostly 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. Results for the 100 DPP/mL and 1,000 DPP/mL dose group were similar 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). The differences were statistically significant between all dose groups (p value < 0.05). This was further supported by statistical significance between all dose groups regarding the pre-post differences (p-value < 0.05).
The same results were obtained 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. Similar to IgG4, the difference between the mean values at V8 and the pre-post differences was statistically significant between all dose groups (p-value < 0.05).
Results of total and Phleum-specific IgE values indicate minor immunological changes after treatment with Depigoid® Phleum shown by reduced total IgE values in the 100 DPP/mL and
1,000 DPP/mL groups but increased values in the 5,000 DPP/mL and 10,000 DPP/mL group. The differences at V8 did not reach statistical significance.
Regarding symptoms documented in the patient diary, the number and percentages of affected patients decreased in 3 of the 4 dose groups in the course of the study. In the 1,000 DPP/mL group, a marginal increase of symptoms affecting the nose and the eyes was found. Numbers were nearly identical in all groups regarding the single symptoms at study end. The only exception was ‘symptoms at the injection site’, where the number of affected patients was higher in the dose groups with higher concentrations of allergen.
There was a statistically significant difference regarding the number of patients affected by an LR between the 100 DPP/mL and the 3 higher dose groups, between the 1,000 DPP/mL and the 10,000 DPP/mL group, and between the 5,000 DPP/mL and the 10,000 DPP/mL group with more patients experiencing LRs in the higher dose group. Results were clearer during the build-up phase.
Severe LR occurred mainly during the build-up phase but in rare cases only.
No significant difference between the dose groups was found. No patient died during the study.
For all dose groups, global safety was mostly assessed as excellent and/or good but never as ‘unacceptable’.

8. Comments on the outcome of the clinical trial

In summary, Depigoid® Phleum increased allergen threshold in CPT and induced immunological changes by IgG4 antibody production.
A possible reason why there were no differences in the three active doses (1,000, 5,000 and 10,000 DPP/mL) compared to the pseudo placebo (100 DPP/mL) may be a methodology issue, as for the CPT different batches with different major allergen amount were used. Despite this unexpected effect, 5,000 and 10,000DPP/mL groups showed slight dose response relationship which was further underlined by the linear increase of immunological parameters. The safety profile of the 5,000 DPP/mL group with only 2 immediate grade 2 reactions (urticaria,

circulatory complaints) occurring in one patient supports this dose to be used for further long-term studies. Especially, since there was a correlation between the doses applied and the incidences of adverse events, such as local and systemic reactions, which does not suggest 10,000 DPP/mL for further investigations.

9. Indication if follow up clinical trials are foreseen

Since the results are inconclusive the dose-finding study Depigoid Phleum will be repeated in protocol number: 6043-PG-PSC-206.

10. Indication where additional information could be found

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