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

Non-interventional Study in Allergic Patients Suffering from Grass Pollen Induced Rhinitis/ Rhinoconjunctivitis with or without Asthma.
Retrospective Assessment of the Efficacy of a Pre-seasonal Specific Immunotherapy on the Allergy Symptoms/Disease Activity during the Pollen Season

1.2. Protocol number

Depigoid Phleum – PRO 2013

1.3. EU trial number

EudraCT 2013-004920-12

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 PIP.

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.
Period of collection of data: October - December 2013

4. General information about clinical trial

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

Patient Reported Outcome (PRO) on the disease activity, intensity of allergic symptoms, intake of rescue medication and global assessment during the pollen season 2013 after 5 – 6 months of treatment with 4 different doses of Depigoid Phleum: 100, 1000, 5000 or 10000 DPP/ml.

The objectives to be assessed in this NIS were:

1. Patient Reported Outcome (PRO) of 5 – 6 months of pre-seasonal therapy with Depigoid Phleum by means of the Symptom and Rescue Medication Score (SMS).
2. PRO of 5 – 6 months of pre-seasonal therapy with Depigoid Phleum by means of the Visual Analogue Scale (VAS) for disease activity.
3. PRO of 5 – 6 months of pre-seasonal therapy with Depigoid Phleum on the allergy symptoms during the grass pollen season 2013 by means of the Symptom Score (SS).

4. PRO of 5 – 6 months of pre-seasonal therapy with Depigoid Phleum on the intake of rescue medication during the grass pollen season 2013 by means of the Rescue Medication Score (RMS).
5. PRO of 5 – 6 months of pre-seasonal therapy with Depigoid Phleum during the grass pollen season 2013 by means of global assessment.

4.2 Trial design

Overall 38 study sites in Germany, Poland and in the Czech Republic participated in this NIS for retrospective collection of patient outcome reports.

Patients who have been treated during the period October 2012 until April 2013 with one of the 4 concentrations of Depigoid Phleum (100, 1000, 5000 and 10000 DPP/ml) were contacted and asked if they were willing to complete a questionnaire about their personal assessment of their grass pollen allergy during the pollen season 2013.

The period for collection of these data was October until December 2013 when patients should still remember how they experienced the recent grass pollen season 2013. The completion of the questionnaire took approximately 15 minutes for a patient.

4.3 Scientific background

The 4 concentrations tested in the Depigoid Phleum dose-finding study showed a clear dose-response with respect to safety (see Tab 1) and immunological parameters (see Tab 2). However, in the Conjunctival Provocation Test (CPT) these results could not be confirmed (see Tab 3).

Table 1: Safety results in the dose-finding study Depigoid Phleum – Incidence of adverse drug reactions

	Total ADRs n (%)	Local Reactions n (%)	Severe LRs n	Systemic Reactions n (%)	Serious SR n	Premature discontinuation n
100 DPP N= 72	30 (41.7%)	21 (29.2%)	0	14 (19.4%)		1
1000 DPP N= 74	41 (55.4%)	38 (51.4%)	0	18 (24.3%)		3
5000 DPP N= 84	59 (70.2%)	55 (65.5%)	6	26 (31%)	1	6
10.000 DPP N= 78	67 (85.9%)	63 (80.8%)	3	34 (43.6%)	1	11

ADR: adverse drug reaction, LR: local reaction, N: number of patients, n: number of events, SR: systemic reaction

Table 2: Results for IgG_1 and IgG_4 in the dose-finding study Depigoid Phleum (ITT)

Concentration of Depigoid Phleum	IgG_1 (µg/ml) Mean difference V1 / V8	IgG_4 (µg/ml) Mean difference V1 / V8
100 DPP (N= 72)	2.5	27.0
1000 DPP (N= 74)	57.0	221.6
5000 DPP (N= 84)	157.4	393.2
10000 DPP (N= 78)	270.0	648.2

Ig: immune globulin, ITT: intention to treat population, N: number of patients, V: visit

Table 3: CPT results in dose-finding study Depigoid Phleum (different populations)

Concentration of Depigoid Phleum	CPT: Response rate	
	mITT*, Primary Endpoint N (%)	ITT** N (%)
100 DPP	70 (72.9%)	72 (69.4 %)
1000 DPP	70 (72.3 %)	74 (64.9 %)
5000 DPP	81 (75.3 %)	84 (67.9 %)
10000 DPP	76 (77.4 %)	78 (64.1 %)

*mITT: at least one post baseline CPT (CPT from early withdrawal is sufficient)

**ITT completer: patients in the ITT group who completed the study regularly

CPT: conjunctival provocation test, (m)ITT: (modified) intention to treat population, N: number of patients

This NIS aimed to gain further inside into patient's allergic disease status during the grass pollen season following the 5 – 6 months pre-seasonal Depigoid Phleum treatment. The patients were asked to report retrospectively their outcome by means of combined symptom – rescue medication score, disease activity and global assessment of the previous specific immunotherapy. The results of this NIS shall support the slope of efficacy of the following 4 concentrations of Depigoid Phleum 100, 1000, 5000 and 10000 DPP/ml in order to assess the effective dose range and the optimum dose as part of the clinical development program of Depigoid Phleum.

4.4 Measures of protection of subjects taken

Prior to participation in this NIS, each patient was informed by the physician on the purpose and extent of the documentation the patient provided by completing the questionnaire. A sample of the informed consent form can be found in Appendix 13.2.

No data provided by the patient in the questionnaire was forwarded to the sponsor without prior written informed consent by the patient. The consent was also necessary for possible verification of the identity of the patient though his patient clinic file (Source Data Verification, EUguideline 95/46/EC and – if applicable - national regulations on data protection). The informed consent procedure and date had to be documented in the patients' clinic files.

Protection of the patient‘s personal data was guaranteed. Data provided by the patient for this NIS were documented in pseudonymized form in the questionnaire, i.e. using a unique questionnaire number. Name, initials, date of birth or address of the patient was not collected.

In a publication, the data may be used in anonymized form only.

4.5 Background therapy

No background therapy as it was a NIS – questionnaire to collect retrospective data only.

4.6 Statistical methods

All endpoints were analysed descriptively overall and by treatment group. Summary statistics were determined for continuous variables (all scores, VAS) showing parameters for location and dispersion. For the global assessment, an ordinal variable, frequencies and percentages were calculated additionally.

Although the study was not powered to show differences between dose groups, statistical testing was carried out exploratorily. A non-parametric approach used the Kruskal–Wallis test for an overall investigation of differences between treatment groups. Subsequently, the Wilcoxon rank sum test was applied for a pairwise comparison in relation to the lowest dose group. Testing was done two-sided on an α-level of 5% for all parameters. Statistical analyses were carried out using SAS 9.2.

Efficacy was assessed by PRO of 5 – 6 months pre-seasonal therapy with Depigoid Phleum based on the following endpoints:

1. the symptom and rescue medication score (SMS).
2. the symptom score (SS).
3. the rescue medication score (RMS).
4. the VAS for disease activity.
5. the global assessment.

The SS was the sum score of all symptoms as documented in the Likert scale (none (0) – mild (1) – moderate (2) – severe (3)). The RMS was defined as the sum score of documented allergy (rescue) medications taken. Any rescue medication documented was taken into account and weighted as follows:

Medication	Recommendations for max. daily dose	Score per application	Max. daily score
Antihistamine nasal spray	2x2 puffs/day	1.5	3
Antihistamine eye drops	4x1 drop/eye	1.5	6
Oral Antihistamine tablets	1x5 mg	2	2
Nasal Corticosteroid	2 applications/day	2	4
Oral Corticosteroid tablets (e.g. Methylprednisolon 16mg/day)	1 tablet/day for 4 days	3	3
		Max. total	**18**
For asthmatic patients only:			
Medication	**Max. daily dose according to SmPC**	**Score per application**	**Max. daily score**
Short acting β_2-agonist	2 applications/day	2.0	4.0
Corticosteroid inhaler	2 applications/day	2.0	4.0
Oral Corticosteroid (lung symptoms) (e.g. Methyl-prednisolon 32-40mg/day)	1 tablet/day	3.0 – 4.0	3.0 – 4.0
		Max. total	**12**

Any other documented rescue medication was scored accordingly.
The SMS was defined as the sum of the SS and the RMS.

4.7 Population of subjects

4.7.1 Actual number of subjects included in the trial

Altogether 38 study sites in the Czech Republic, Germany and Poland enrolled 184 Patients into this NIS. Thereof, 89 female patients (48.4%) and 95 male patients (51.6%) were treated with one of 4 concentrations of Depigoid Phleum (100, 1000, 5000 or 10000 DPP/ml) between October 2012 and April 2013.

4.7.2 Age groups and gender breakdown

Number of patients by treatment group and gender

Treatment group	Gender	Number of patients (%)	N
100 DPP/ml	Female Male	23 (48.9) 24 (51.1)	47
1000 DPP/ml	Female Male	19 (39.6) 29 (60.4)	48
5000 DPP/ml	Female	27 (55.1)	49

	Male	22 (44.9)	
10000 DPP/ml	Female	20 (50.0)	40
	Male	20 (50.0)	
Total	Female	89 (48.4)	184
	Male	95 (51.6)	

N: number of patients

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

It was planned to enrol at least 250 patients into this NIS, actually 184 patients participated in this NIS.

1.2 Inclusion and exclusion criteria

Inclusion Criteria:

Participating patients had to fulfil all of the following inclusion criteria:

1. Written informed consent.
2. Allergic rhinitis/rhinoconjunctivitis with or without concomitant asthma due to grass pollen allergy.
3. Treatment with one of 4 concentrations of Depigoid Phleum (100, 1000, 5000 and 10000 DPP/ml) in the period from October 2012 until April 2013.

Exclusion Criteria:

1. Patients presenting the following exclusion criterion were not included in the study:
2. Less than 4 applications of 0.5 ml of one of 4 concentrations of Depigoid Phleum (100, 1000, 5000 and 10000 DPP/ml) between October 2012 and April 2013.

1.1 Randomization and blinding details

No randomization, no blinding

1.4 Investigational medicinal products used

No treatment.

2. Pre-assignment period

As this was a NIS aimed to collect retrospective data from eligible patients, no diagnostic and / or therapeutic measures were performed. Patients provided written informed consent before they documented their assessment of their grass pollen allergy during season 2013 in the questionnaire.

3. Post assignment periods

See 2.

C. BASELINE CHARACTERISTICS

1. Baseline characteristics – Age

Age: The age of all patients ranged from 19 to 70 years with a mean of 34.02 years.

2. Baseline characteristics – Gender

Gender: 184 Patients, 89 female patients (48.4%) and 95 male patients (51.6%)

D. END POINTS

1. End point definitions

Efficacy was assessed by PRO of 5 – 6 months pre-seasonal therapy with Depigoid Phleum based on the following endpoints:

1. the symptom and rescue medication score (SMS).
2. the symptom score (SS).
3. the rescue medication score (RMS).
4. the VAS for disease activity.
5. the global assessment.

2. End point #1 symptom and rescue medication score (SMS)

Patients filled in the questionnaire after 5 – 6 months of pre-seasonal therapy with Depigoid Phleum and assessed typical allergy symptoms on nose, eyes and lung with the help of a 4-point Likert scale (none-mild-moderate-severe). Additionally, patients documented their intake of allergy medication in the questionnaire after 5 – 6 months of pre-seasonal therapy with Depigoid Phleum.

As a primary efficacy endpoint, the scores regarding symptoms and rescue medication were combined. The combined SMS was defined as the sum of the SS and the RMS.

Treatment groups were compared overall using the Kruskal-Wallis test, a pairwise comparison of the groups in relation to the lowest dose group was performed using the Wilcoxon rank-sum test two-sided on an α-level of 5%.

The combined SMS regarding rhinitis/ rhinoconjunctivitis symptoms was lowest for the 1000 DPP/ml group with a median score of 8.0 (mean score: of 8.3). The difference compared to the 100 DPP/ml group missed statistical significance by only narrow margin ($p = 0.0513$).

The score was highest for the 100 DPP/ml group with a median score of 10.0 (median: 10.4) and for the 5000 DPP/ml group with a median score of 10.0 (median: 9.8).

The combined SMS regarding lung symptoms was lowest again for the 1000 DPP/ml dose group (median 8.5 and mean 9.8). However, the difference compared to the 100 DPP/ml group was not statistically significant ($p = 0.1091$).

As for the rhinitis/ rhinoconjunctivitis SMS, highest values were observed for the 100 DPP/ml dose group with a median score of 10.0 and a mean score of 11.9, followed by the 5000 DPP/ml group (median: 11.0; mean: 11.1).

3. **End point #2** symptom score (SS)

As a further endpoint of this NIS, efficacy was assessed by the SS based on the PRO.

Treatment groups were compared overall using the Kruskal-Wallis test, a pairwise comparison of the groups in relation to the lowest dose group was performed using the Wilcoxon rank-sum test two-sided on an α-level of 5%.

For the total population, the median SS regarding rhinitis/ rhinoconjunctivitis symptoms was 6.0.

Similar values were observed for the 1000, 5000 and 10000 DPP/ml group with median values of 6.0. The highest score was found for the 100 DPP/ml group with a median value of 7.0. The differences between the treatment groups were not statistically significant.

For the SS regarding lung symptoms slightly higher values compared to rhinitis/ rhinoconjunctivitis symptoms were found (total population, median: 7.0; mean: 8.1).

Median scores showed a dose-response relationship with lowest scores again for the 10000 DPP/ml dose group with 6.0 and in the 5000 DPP/ml group with 7.0, and highest for the 100 DPP/ml dose group (8.0). Mean values were also lowest for the 10000 DPP/ml group with a score of 7.2.

However, none of the tests revealed any statistically significant difference between the treatment groups.

4. **End point #3** rescue medication score (RMS)

In addition to the SS, efficacy was also assessed by the RMS based on the PRO.

Treatment groups were compared overall using the Kruskal-Wallis test, a pairwise comparison of the groups in relation to the lowest dose group was performed using the Wilcoxon rank-sum test two-sided on an α-level of 5%.

The RMS regarding rhinitis/ rhinoconjunctivitis and lung symptoms was lowest for the 1000 DPP/ml group with a median score of 1.5 and a mean score of 2.0. The difference compared to the 100 DPP/ml group was statistically significant with $p = 0.0387$.

The highest score was found for the 100 DPP/ml group with median 2.0 and mean 3.2.

Also for the 10000 DPP/ml group, high values were found (median: 3.0; mean: 2.9).

5. **End point #4** VAS for disease activity

The patients' perception of disease activity during the grass pollen season 2013 was assessed by means of a 10 cm VAS, ranging from "not present" to "extremely active". Patients were asked to document the mean intensity of their grass pollen allergy during the pollen season 2013.

Prior to the study, the disease activity was similar in all treatment groups, ranging from median 7.1 cm on the VAS for the 5000 DPP/ml group to 7.6 cm for the 10000 DPP/ml group.

In 2013, disease activity was lowest for the 1000 DPP/ml group with median 2.6 cm (mean: 3.1 cm) and for the 10000 DPP/ml group with median 2.7 cm (mean: 3.0 cm). For both

groups, the difference compared to the 100 DPP/ml group was statistically significant with p = 0.0375 and p = 0.0301, respectively.
According to these findings, the highest change in disease acitivity was found for the 1000 DPP/ml group (median change: -4.3; median change: -4.1; p = 0.0288) and for the 10000 DPP/ml group with a median change of -4.0 cm and a mean change of -4.2 (p = 0.0377), respectively.

6. **End point #5** global assessment

A further endpoint of this NIS was the patients' global assessment of the efficacy of the pre-seasonal immunotheraypy. Therefore, patients were asked to rate their overall impression as either "excellent", "good", (which was classified as "positive" assessment) or as "moderate", "poor" or "unacceptable" (classified as "negative").
Overall, most of the patients in this NIS rated the global efficacy of the therapy as "positive" (111 patients, 60.3%), only 4 patients (2.2%) rated the efficacy as "unacceptable".
The global assessment was best for the 10000 DPP/ml group, where 8 patients (20.0%) rated the efficacy of therapy as "excellent" and 20 patients (50.0%) as "good". No patient in this group assessed the efficacy as "unaccepatable". When classified into the two categories "positive" and "negative", 70% of the patients rated the efficacy as "positive".
Also, for the 1000 DPP/ml group, the global assessment was superior compared to the overall group and 62.5% of the patients rated the efficacy of therapy as "positive". "Excellent" efficacy was certified by 7 patients (14.6%) and "good" efficacy by 23 patients (47.9%); only 1 patient (2.1%) rated efficacy as "unacceptable" and 5 patients (10.4%) as "poor".
As for the previous endpoints, most negative results were obtained for the 100 DPP/ml group, where only 25 patients (53.2%) rated the efficacy of therapy as "positive". In addition, only 2 patients (4.3%) rated the efficacy as "excellent", compared to 10 patients (21.3%) rating efficacy as "poor" and 2 patients (4.3%) as "unacceptable".

E. ADVERSE EVENTS

1. Adverse Events information

n.a.

2. Adverse Event reporting group

n.a.

3. Serious Adverse event(s)

n.a.

1. Non-serious adverse event(s)

n.a.

F. ADDITIONAL INFORMATION

1. Global Substantial Modifications

This NIS started with Observational Plan Depigoid Phleum PRO-2013, version 1.0, 19-SEP-2013.
No changes.

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 Study Report.