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

An open-label, multicenter, phase 2 study, for the initial evaluation of the tolerability of Birch pollen extract in patients suffering from atopic eczema and clinical relevant IgE-mediated sensitization against birch pollen.

1.2. Protocol number

6078-PG-PSC-165

1.3. EU trial number

2007-004876-38

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

This trial was an open-label, multicenter, phase 2 study. The treatment was divided into two periods: the initial build-up period (3 weeks) and the maintenance treatment period (12 weeks) which was continued by a follow-up period until the Final Visit. The overall study duration for an individual patient was 19 weeks.

3.1 Where the trial was conducted

This trial was conducted at 9 sites in Germany only.

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

The duration of the study for the individual patient was estimated to last 4 to 5 months. The study started on 11-JAN-2008 (FPFV) and was completed on 06-JAN-2009 (LPLV).

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

The objective of the study was the initial evaluation of the tolerability of Depigoid® Birch Pollen in a subcutaneous immunotherapy over 3 months in patients with atopic eczema and clinical relevant IgE-mediated sensitization against birch pollen.
The present clinical trial was designed to evaluate in an open-label design the tolerability of an initial add-on therapy with Depigoid® Birch Pollen, applied in a subcutaneous immunotherapy in patients with atopic eczema, sensitized against birch pollen causing aggravation of their underlying disease.

4. Population of subjects

4.1. The number of subjects included in the trial

A total of 9 active study centers in Germany screened a total of 63 patients. Out of these, 8 patients did not receive or take any study medication. Thus, the safety set comprised 55 patients. As 2 patients were not eligible, 53 patients were included into the intention-to-treat (ITT) set. None of the patients was classified as a protocol violator. Therefore, the per protocol (PP) set comprised also 53 patients.

4.2. Age groups and gender breakdown

The demographic data of the safety population (N = 55) were as follows:

- Gender: 20 patients were male (36.4%), 35 patients were female (6%).
- Age: mean of 36.1 years.

4.3. Inclusion and exclusion criteria

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

1. Patients of both genders aged from 18 up to 65 years,
2. Prior to study specific examinations the patient had to give his/her written informed consent,
3. Women of child-bearing age employing sufficient contraceptive measurements,
4. Patients had to suffer from atopic eczema,
5. Patients had to suffer from clinical relevant IgE-mediated sensitization against birch pollen assessed by:
   - specific IgE against birch pollen CAP radioallergoabsorbent test (CAPRAST) ≥3,
   - positive atopy patch test for birch pollen*,
   - positive skin prick test for birch pollen**,
6. The diagnosis AE had to be verified according to the criteria of Hanifin and Rajka,
7. Duration of atopic eczema ≥2 years,
8. Total SCORAD >25 at Screening Visit.

* only in selected study centers, optional but not used as inclusion criterion
** if not performed within 3 months prior to Screening Visit

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

Disease Specific Criteria

1. The following therapy was not allowed within the last 5 years prior to screening as well as during the study, and prevented the patient from being included into the study:
   - SIT with birch pollen,
2. The following therapy was not allowed within 3 months prior to screening as well as during the study, and prevented the patient from being included into the study:
   - Photopheresis,
3. The following medications and therapies were not allowed within the last month prior to screening as well as during the study, and prevented the patient from being included into the study:
   - Immunosuppressive agents (cyclosporins, mycophenolates),
   - Systemic corticosteroids others than basic medication Urbason®,
   - UV-therapy, tanning,
4. The following medications and therapies were not allowed during the entire study and led to the patient being withdrawn:
   - β-blocker (locally and systematically),
   - Treatment with substances interfering with the immune system,
   - Treatment with tranquillizer or psychoactive drugs,
5. Patients with therapeutically uncontrolled atopic eczema or erythrodermia, Patients with other Known Concomitant Diseases/Treatments
6. Active tuberculosis,
7. Acute and chronic inflammatory or infectious diseases at the target organ,
8. Advanced secondary changes at the target organ (e.g. emphysema or bronchiectasis),
9. Immunopathological diseases (e.g. of the liver, kidney, the nervous system, thyroid gland, rheumatic diseases) in which autoimmune mechanisms played a role,
10. Immune deficiencies,
11. Uncontrolled asthma, defined as FEV1 or PEF ≤ 70% of predicted normal value,

12. Any disease which prohibited the use of adrenaline (e.g. hyperthyroidism),
13. Cardiovascular insufficiency or any severe or unstable pulmonary condition, or endocrine disease; clinically significant renal or hepatic disease or dysfunction; hematologic disorder; any other clinically significant medical condition that could have increased the risk to the study participant,
14. Malignant disease of any kind during the previous 5 years,
15. Abnormal laboratory parameters and vital signs that could have increased the risk to the study participant,
16. Alcohol, drug or medication abuse within the past year,
17. Severe psychiatric or neurologic disorders,

Others

18. Patients who were expected to be non-compliant and/or not co-operative,
19. Participation in any other clinical study within the last 30 days prior to the start of the study,
20. Patients who had already participated in this study,
21. Patients who were employees at the investigational site, relatives or spouses of the investigator,
22. Any donation of germ cells, blood, organs, or bone marrow during the course of the study,
23. Patients who were not contractually capable,
24. Patients who were detained in an institution due to regulatory notice or judicial instruction,

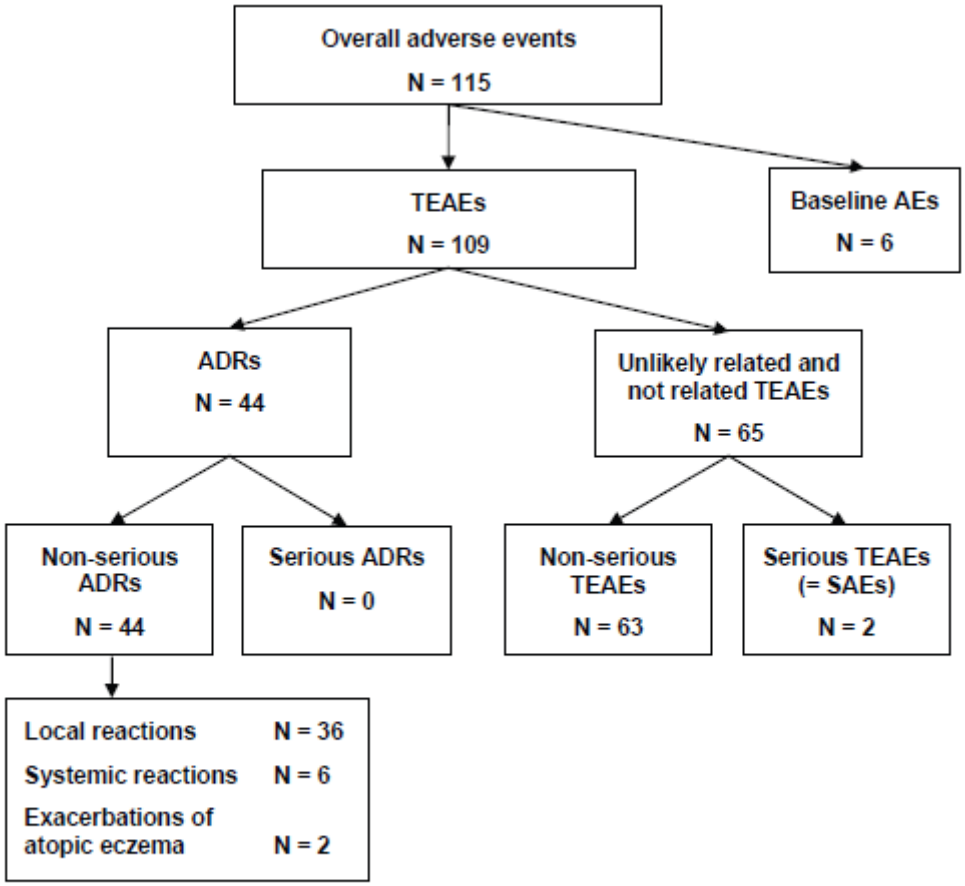
Special Restrictions for Female Patients

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

5. Investigational medicinal products used

Depigoid® Birch Pollen consisted of depigmented and glutaraldehyde polymerized allergenic extract of 100% birch pollen adsorbed onto aluminum hydroxide. Vial 1 had a concentration of 100 DPP/ml and vial 2 a concentration of 1000 DPP/ml.
Additional ingredients were sodium chloride 9 mg/ml, phenol 5 mg/ml, aluminum hydroxide 1.1 mg/ml and water for injection.

6. Description of adverse reactions and their frequency (primary variable)



N: number of episodes

The primary variable of the study was the type and frequency of AEs during a subcutaneous immunotherapy over 3 months in patients with atopic eczema and clinically relevant IgE-mediated sensitization against birch pollen.

In total, 109 TEAE episodes with 110 symptoms were reported in 37 patients (67.3%) on the safety set. Thus, throughout the study one patient could have suffered from more than one AE symptom.
The most frequently reported TEAE symptom was 'local reaction' (36 in 19 patients [34.5%]) and 'nasopharyngitis' (17 in 15 patients [27.3%]), followed by 'pruritus' (5 in 3 patients [5.5%]), 'headache' (4 in 3 patients [5.5%]), and 'atopic dermatitis' (3 in 3 patients [5.5%]).
In regard to the causality assessment, 30 out of the 109 TEAEs were assessed as not having relation with the study medication, 35 TEAEs as having an unlikely relation, and 44 TEAEs as being related ADRs: 36 local reactions, 6 systemic reactions and 2 exacerbations of atopic eczema.

7. Overall results of the clinical trials

Efficacy summary

As the objective of the study was the initial evaluation of the tolerability of Depigoid®Birch Pollen in a subcutaneous immunotherapy over 3 months in patients with atopic eczema and

clinical relevant IgE-mediated sensitization against birch pollen, the analyses focused mainly on safety aspects.
For the analysis of efficacy, 3 independent variables were investigated: Overall, there was a change in the total SCORAD from baseline to the end of treatment. The total SCORAD decreased by a median of 42%. This change was significant ($p < 0.0001$).
The second variable that evaluated the efficacy was the score index of dermatology life quality. From baseline to end of the study, there was a significant decrease ($p < 0.0001$) in the DLQI score. Patients' quality of life improved by 62%.
At the end of the study, patients as well as investigators evaluated the overall efficacy of the treatment. On average, both patients and investigators assessed the overall efficacy as 'good'. There was no case reported where the overall efficacy was rated as 'ineffective'.

Safety summary
During this study, 37 patients (67.3%) experienced a total of 110 TEAE symptoms during 109 TEAE episodes. Out of these, 65 TEAE episodes in 28 patients (50.9%) were assessed by the investigator as having been 'unlikely' or 'not' related to the study medication. The other 44 TEAE episodes were 'likely' or 'definitely' related and therefore classified as ADRs.
These 44 ADRs occurred in 24 patients (43.6%), reflecting that one patient could have suffered from more than one ADR.
The ADRs were subdivided into three subgroups: LR (36 ADRs in 19 patients [34.5% of patients of the safety set]), SR (6 ADRs in 6 patients [10.9% of patients]), and exacerbation of 'atopic dermatitis' (2 ADRs in 2 patients [3.6% of patients]).
The systemic reactions were 'pruritus' (2 ADRs), 'procedural headache' (1 ADR), 'rhinitis allergic' (1 ADR), 'urticaria' (1 ADR), and 'vertigo' (1 ADR).
No death and no pregnancy were reported during the course of the study.
Due to TEAEs, 4 patients discontinued the study prematurely. All of these TEAEs were assessed by the investigators as having been 'unlikely' related to the study medication. One of them was rated as serious and therefore documented as SAE (AE symptom 'skin infection').
Altogether, 2 SAEs were reported in 2 different patients. One SAE was the above mentioned 'skin infection' and the other one was 'atopic dermatitis'. These 2 SAEs were of 'severe' intensity but assessed as being 'unlikely' related to the study medication. The patient with 'skin infection' withdrew from the study; the patient with SAE 'atopic dermatitis' continued the study.
There were no abnormal findings of clinical significance in the laboratory values, vital signs, physical examination, and in the lung function test as assessed by the investigators.

8. Comments on the outcome of the clinical trial

The objective of the study was the initial evaluation of the tolerability of Depigoid®Birch Pollen in a subcutaneous immunotherapy over 3 months in patients with atopic eczema and clinically relevant IgE-mediated sensitization against birch pollen.
As the study started prior to the onset of the birch pollen season and lasted throughout the birch pollen season, every patient was treated with Depigoid® Birch Pollen for nearly 3 weeks during the birch pollen season. During the season, patients were exposed to birch pollen but also to other pollen that might have elicited hypersensitivity. This fact has to be considered for evaluation of all measured efficacy and safety parameters.

The efficacy of Depigoid® Birch Pollen therapy was demonstrated by several measurements. Compared to baseline, patients had a significant decrease of 42% in the total SCORAD at the end of the treatment. Also their quality of life improved significantly, indicated by a decrease

of 62% in the DLQI score from baseline to end of the treatment. These results were supported by the overall assessment of efficacy of the treatment, rated as 'good' by both patients and investigators. These results gain in importance, as the reduction of the total SCORAD and the DLQI score was significant and the efficacy was assessed as 'good', despite the high concentration of pollen during the season.
This applies also for the basic medication. At the end of the treatment period, patients were more often exposed to birch pollen as well as to other pollen. Despite the high pollen concentration, there was no increase in the basic medication from baseline to the end of the treatment.
From a total of 55 patients included in the safety set, 109 TEAEs (including all SAEs and ADRs) were reported in 37 patients (67.3%). Most of them were of mild or moderate intensity.
44 out of 109 TEAEs were classified as ADRs, subdivided in 36 LRs, 6 SRs, and 2 exacerbations of atopic eczema in patients suffering from recurrent episodes of exacerbations of atopic eczema also prior to study participation. The 44 ADRs were reported in 24 patients (43.6%). None of them was of severe intensity or rated as serious.
From the data presented, we conclude that therapy with Depigoid® Birch Pollen showed in this study a good efficacy and safety in patients with atopic eczema and clinical relevant IgE-mediated sensitization against birch pollen. The overall frequency of exacerbations of atopic eczema observed during the 15 weeks of treatment with Depigoid® Birch was considerably lower than generally expected for this patient population.

9. Indication if follow up clinical trials are foreseen

Not applicable

10. Indication where additional information could be found

Not applicable