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

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

603-PG-PSC-165

1.3. EU trial number

2007-004876-38

1.4. Name and contact of sponsor

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

2. Paediatric regulatory details

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

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

Final analysis stage. The trial was finished on 06-JAN-2009 (LPLV).

4. General information about clinical trial

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

The objective of the study was the 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.

4.2 Trial design

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.

4.3 Scientific background

House Dust Mites (HDM) such as *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, and birch pollen, are important indoor and outdoor allergen sources for patients with atopic eczema. Since allergen-reduction achieved by encasings and environmental control does not lead to significant improvement of the clinical symptoms in patients with atopic eczema, specific immunotherapy (SIT) with birch pollen extract might represent an attractive therapeutic option for a long-term treatment of these patients. However, studies on effectiveness of SIT in atopic eczema have provided controversial clinical results.

LETI has developed techniques for depigmentation of allergenic proteins leading to the ideal source for the production of polymerized extracts (allergoids).
Polymerization of depigmented allergens leads to a greatly improved 2nd generation of allergoids with considerably lower IgE-binding potencies than those observed in the 1st generation polymers based on non-depigmented source materials. Due to the considerable better tolerability of the Depigoid® product range this product seems to be the ideal candidate in the indication “atopic eczema”.

4.4 Measures of protection of subjects taken

Depigoid® is currently used for the treatment of allergic diseases of the immediate (IgE-mediated) type as for example hay fever (allergic rhinitis), allergic conjunctivitis, allergic bronchial asthma caused by sensitization to allergic substances as pollen, mites and animal dander.
To elucidate the specific risks for patients suffering from atopic eczema, reference is made to the pilot study of Depigoid® Mite Mix:
LETI investigated primarily the safety and also the efficacy of Depigoid® Mite Mix in 24 patients suffering from moderate to severe atopic eczema (mean subjective SCORAD 44.3 at baseline) in an open prospective pilot trial. Subjective and objective SCORAD improved significantly already after 4 weeks of treatment in >50% patients.
After 6 months of treatment clinically relevant and statistically highly ($p < 0.001$) significant improvement in the objective SCORAD of 48.6% and in the subjective SCORAD of 52% was documented.
Despite historical observations leading to pose atopic eczema as a contraindication for SIT, the good safety profile indicated by this study encourages to further pursue the therapy. Only one patient experienced an exacerbation of his skin lesions during SIT which could not be exclusively attributed to the therapy but also to the specific circumstances such as the compliance of the patient.
Patients were closely monitored during the course of the study. All patients received standard basic medication for atopic eczema.
As a summary, patients were treated and monitored appropriately and the potential benefit outweighed potential risks for the patients.

The patient could withdraw from the study at any time for any reason without disadvantageous consequences to his/her subsequent medical treatment. The patient was also withdrawn from the study at any time if the investigator had the impression that it would be to the patient’s detriment to continue.

4.5 Background therapy

Prior and Concomitant Therapy

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.

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.

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 other than the basic medication urbason,

- UV-therapy, tanning bed.

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.

Any medication/therapy other than the investigational medicinal product (IMP) was defined as concomitant medication/therapy and was carefully documented in the CRF together with the previous medication administered within the last 3 months prior to the beginning of the study. The dose of concomitant medication required for a chronic disease should have been kept as constant as possible throughout the study.

Basic Medication

The sponsor provided the patient with the following basic medication:

INN/composition	Trade name	Pharmaceutical form	Dose
Desloratadine	Aerius	Tablet	5 mg
Pimecrolismus	Elidel	Crème	1%
Betamethasone	Betnesol	Crème	0.1%
Prednicarbate	Dermatop	Crème	0.25%
Eucerin cum aqua	Eucerin cum aqua	Ointment	-
Glycerolmonostearate 60, cetyl alcohol, medium chain triglycerides, white Vaseline, Macrogol-1000-glycerolmonostearate, Propylene glycol, purified water	Basis crème DAC	Crème	-
Methylprednisolone	Urbason®	Tablet	40 mg
Fusidic acid	Fucidine crème	Crème	0.2%

It was at the discretion of the investigator to decide which of the above listed basic medications was given to the patient. Additionally, he had to decide the daily dose of basic medication for each patient individually.

Due to application of SIT and during birch pollen season in addition the following rescue medication was provided to each patient at the discretion of the investigator:

INN	Trade name	Pharmaceutical form	Dose
Mometasone	Nasonex®	Spray	50 µg
Levocabastin	Livocab®/-direkt Augentropfen	Drops	0.5 mg
Levocetirizin	Xusal®	Tablet	5 mg
Methylprednisolone	Urbason®	Tablet	40 mg
Salbutamolsulfat	Sultanol®	Spray	0.12 mg
Budenosid	Miflonide®	Spray	200 µg

Patients were advised that they could have taken rescue medication (oral antihistamines as step I) on an as-needed basis for symptoms of birch pollen allergic rhinitis and conjunctivitis:

Step I:

Oral antihistaminic (Xusal® 5 mg Filmtabletten)

If oral antihistamines as initial rescue medication did not result in adequate symptom control, the patient should have contacted the study center where the following step-up (“escalation”) co-medication (step II to III) was provided by the study physician:

Step II:
Nasal steroid (Nasonex® 50 µg/Spruehstoss Nasenspray) (usually in addition to step I therapy)
Livocab® Eye Drops (0.5 mg Levocabastin/ml)

If no symptom control was achieved:
Step III:
Oral corticosteroid (Urbason® 40 mg)

During birch pollen season, additional rescue medication for therapy of asthma was provided to patients at the discretion of the investigator. Patients were advised that they could have taken short acting β-2 agonist rescue medication as initial rescue medication (step I) for symptoms of intercurrent bronchospasm:
Step I:
Intermittent short acting beta-agonists (Sultanol® Dosieraerosol) as needed. If β-2 agonists as initial rescue medication (step I) did not result in adequate control of asthma, the patient should have contacted the study center where the following stepup ("escalation") co-medication (steps IIa/b to III, usually replacing previous rescue medication) was provided by the study physician:
Step IIa:
Low-dose inhaled corticosteroid (Miflonide® 200 µg o.d.)

If no symptom control was achieved:
Step IIb:
Medium-dose inhaled corticosteroid (Miflonide® 200 µg b.i.d.)

If no symptom control was achieved:
Step III:
Oral corticosteroid (Urbason® 40 mg)

If no symptom control was achieved after step III, patients had to be discontinued from the study. In this case, the responsible study physician needed to specifically optimize the patient's individual treatment regimen.
Use of rescue medication after start of study drug had to be recorded on the Concomitant medications/Significant non-drug therapies CRF pages.

After the end of the study the patients were treated following recommended standards and available treatment options in the respective study center.

4.6 Statistical methods

As this study constituted to be a non-confirmatory approach, both primary and secondary variables were analyzed descriptively using appropriate summary statistics (i.e. parameters for location and dispersion like mean, standard deviation, median, minimum, maximum and quartiles) and/or frequency tables depending on the type of parameter (continuous or discrete). The analysis of the primary variable was performed based upon the safety population. The analysis of the secondary variables was performed based upon the safety population (safety parameter) and the ITT population (efficacy parameter) depending on the type of the variable.

Primary Variable

For the evaluation of the tolerability of Depigoid® Birch Pollen in patients suffering from atopic eczema and clinical relevant IgE-mediated sensitization against birch pollen the type and frequency of AEs were investigated as primary variable.

For that purpose, AEs (coded according to MedDRA) were summarized by system organ class and preferred term. The number and percentage of affected patients was tabulated along with the number of events for each category.

Frequency tables were produced summarizing AEs by relationship to study medication and by intensity. The number and percentage of patients with at least one AE occurring after first administration of study medication was calculated.

All AEs occurring at baseline and throughout the study period were listed. AEs occurring between Visit 0 and Visit 1 (i.e. prior to first administration of study medication) were reported as baseline AEs.

Secondary Variables

- *Type and frequency of SAEs:*
  Frequency tables were produced summarizing SAEs by relationship to study medication and by intensity. The number and percentage of patients with at least one SAE occurring after first administration of study medication was calculated.
- *Type and frequency of exacerbations of atopic eczema:*
  Frequency tables were produced summarizing exacerbations of atopic eczema by relationship to study medication and by intensity. The number and percentage of patients with at least one exacerbation of atopic eczema occurring after first administration of study medication was calculated.
- *Type and frequency of adverse drug reactions (i.e. AEs with at least 'likely' relationship to study medication):*
  Frequency tables were produced summarizing adverse drug reactions by relationship to study medication and by intensity. The number and percentage of patients with at least one adverse drug reaction occurring after first administration of study medication were calculated.
- *Type and frequency of local and systemic adverse drug reactions:*
  Frequency tables were produced summarizing local adverse drug reactions by relationship to study medication and by intensity. The number and percentage of patients with at least one local adverse drug reaction occurring after first administration of study medication were calculated.
- *Withdrawal due to local and systemic adverse drug reactions:*
  The number and percentage of patients who withdrew the study due to local adverse drug reactions were calculated.
- *The number and percentage of patients with a positive patch test were evaluated.*
- *Total SCORAD over the time:*
  As the total SCORAD was investigated at baseline (Visit 1) and at all following visits, the total SCORAD was analyzed by means of summary statistics for all visits. Additionally, the pre-post difference of the total SCORAD between baseline (Visit 1) and after end of treatment Visit 7 (Week 17) was analyzed descriptively.
- *Medication consumption (of basic medication):*
  Basic medication was defined as any concomitant medication which was known to have an influence on the typical atopic eczema symptoms. It was documented in the patient's diary. The basic medication consisted of different medication types. The total medication consumption per medication type was investigated descriptively.
- *Quality of life using the DLQI:*

As the quality of life using the DLQI was investigated at baseline (Visit 1) and after end of treatment (Visit 6), the sum score of the quality of life questionnaire was analyzed by means of summary statistics for both visits.
Additionally, the pre-post difference of the sum score of the quality of life questionnaire between both visits/investigations was analyzed descriptively.

- *Overall tolerability of treatment as assessed by patient and investigator:*
  The overall tolerability of treatment was assessed by means of a 5-point Likert scale (1 = excellent, 2 = good, 3 = moderate, 4 = poor, 5 = unacceptable).
  Frequencies and percentages as well as summary statistics were given.
- *Overall efficacy of treatment as assessed by patient and investigator:*
  The overall efficacy of treatment was assessed by means of a 5-point Likert scale (1 = excellent, 2 = good, 3 = moderate, 4 = poor, 5 = ineffective).
  Frequencies and percentages as well as summary statistics were given.
- *Overall acceptance of treatment as assessed by patient and investigator:*
  The overall acceptance of treatment was assessed by means of a 5-point Likert scale (1 = excellent, 2 = good, 3 = moderate, 4 = poor, 5 = unacceptable). Frequencies and percentages as well as summary statistics were given.
- *Safety laboratory:*
  The safety laboratory was conducted at the Screening (V0), Baseline (V1) and Final Visit (V7). All laboratory parameters were listed and values outside the normal range were marked. Frequencies and percentages for all laboratory values with respect to normal ranges were given and shift analyses were performed. For each laboratory parameter and for each visit descriptive statistics were calculated. Pre-post differences for all laboratory parameters between baseline and end of treatment were analyzed descriptively.

Additional Analyses

According to the decisions reached on the meeting on 05-May-2009 an additional analysis was made. This additional analysis is presented as following:

- Days of treatment during and out of the birch pollen season,
- Number of patients with 'exacerbations of atopic eczema' within ADRs,
- Number of patients with systemic reactions without 'exacerbation of atopic eczema'.

4.7 Population of subjects

4.7.1 Actual 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. There was no limit to the number of patients included by each trial center.

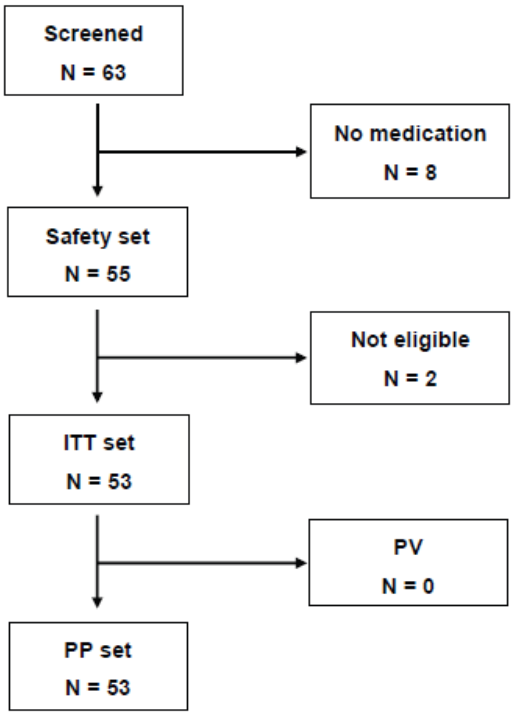
4.7.2 Age groups and gender breakdown

Demographic data (safety set, N = 55)
Gender: 20 patients were male, 35 patients were female.
Age: mean of 36.1 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



N: number of patients; ITT: intention-to-treat; PP: per protocol; PV: protocol violation

1.2 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).

1.3 Randomization and blinding details

n.a.

1.4 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.
Excipients were sodium chloride 9 mg/ml, phenol 5 mg/ml, aluminum hydroxide 1.1 mg/ml and water for injection.

2. Pre-assignment period

Initial Visit - Screening Visit (V0)

The following examinations/procedures were to be performed:
- Informed consent,
- Inclusion/exclusion criteria,
- Demographic data,
- Medical history,
- Atopic eczema history according to Hanifin and Rajka,
- Allergen history,
- Concomitant disease and/or additional medication,
- Physical examination,
- Lung function test,
- Vital signs,
- Safety laboratory,
- Pregnancy test,
- Specific IgE for birch pollen,
- Skin Prick Test (only if not performed within the last 3 month),
- Atopy Patch Test∗,
- Dispense basic medication,
- Total SCORAD.

The patient was instructed to return to study center within 2 weeks after Screening Visit (V0). V1 was mandatory within a minimum timeframe of 1 week after V0.

3. Post assignment periods

Visit 1 - Baseline Visit (V1)

The visit had to be performed at Week 0. A maximum deviation of ±3 days was permitted.
The following examinations/procedures were to be performed:
- AEs,
- Concomitant diseases and/or additional medication,

• Vital signs,
• Physical examination,
• Safety laboratory,
• Dispense basic medication,
• Issue patient diary cards,
• DLQI,
• Total SCORAD,
• Lung function test,
• Administration of study medication.

The patient was instructed to return to study center 1 week after Baseline Visit (V1).

Visit 2, 3, 4, 5, 6 (V2, V3, V4, V5, V6)

The visits had to be performed at Week 1, 2, 3, 9 and 15. A maximum deviation of ±3 days was permitted.

The following examinations/procedures were to be performed:

• AEs,
• Concomitant disease and/or additional medication,
• Lung function test,
• Vital signs,
• Atopy Patch Test (only at V6)*, * only in selected study centers, optional
• Issue patient diary cards,
• Collect and review of patient diary including control of used basic medication,
• DLQI,
• Total SCORAD,
• Administration of study medication.

The patient was instructed to return to the study center 1 week after V2 and V3, 6 weeks after V4 and V5 and 2 weeks after V6, respectively.

Visit 7 – Final Visit (V7)

The visit had to be performed at Week 15. A maximum deviation of ±3 days was permitted.

The following examinations/procedures were to be performed:

• AEs,
• Concomitant disease and/or additional medication,
• Physical examination,
• Lung function test,
• Vital signs,
• Safety laboratory,
• Pregnancy Test,
• Specific IgE,
• Collect and review of patient diary including control of used basic medication,
• Total SCORAD,
• DLQI,
• Assessment of overall tolerability of treatment by patient and investigator,
• Assessment of overall efficacy of treatment by patient and investigator,
• Assessment of overall acceptance by patient and investigator

Unscheduled Visits (UV), Unscheduled Administration of Study Medication (UAS)

If the patient had to visit the investigator for any reason except for rescheduled/unscheduled administration of study medication between scheduled study visits, then the reason for the visit had to be reported by completing the appropriate section (Unscheduled Visit [UV]) in the CRF.

In case that the reason for a UV was the administration of study medication due to dose-reduction, documentation had to be performed in section 'Unscheduled Administration of Study Medication' (UAS) in the CRF. UAS was also performed, if a patient presented with a forced expiration volume (FEV1) or peak expiratory flow (PEF) below 70% of the predicted normal value at the regular visit. In this case, the injection of study medication had to be omitted and the visit had to be rescheduled for a later date, 3 days ±1 day after. In any case, patients were questioned about AEs and changes in concomitant medication, additionally vital signs were recorded. At UAS, additional dose of study medication as well as the assessment of local reactions and assessment of lung function were documented.

Premature Termination of the Study

The patient was allowed to withdraw from the study at any time without giving reasons, and without any disadvantageous consequences for his/her subsequent medical care. The patient was to be withdrawn once the investigator had considered that his/her further participation would be detrimental. In case of premature termination of the study, the investigator had still to perform all examinations assigned for Visit 7.

C. BASELINE CHARACTERISTICS

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

1. Baseline characteristics – Age

Age: mean of 36.31 years

2. Baseline characteristics – Gender

Gender: 20 patients (36.4%) were male, 35 patients (63.6%) were female

D. END POINTS

1. End point definitions

Evaluation was performed for the safety set (N = 55), the ITT set (N = 53), and the PP set (N = 53).

Primary Variable

- Type and frequency of Adverse Events (AEs)

Secondary Variables

- Type and frequency of Serious Adverse Events (SAEs),
- Type and frequency of exacerbations of atopic eczema,
- Type and frequency of Adverse Drug Reactions (ADRs),
- Type and frequency of local and systemic ADRs,
- Withdrawal due to local and systemic ADRs,
- Percentage of subjects with a positive patch test,
- Total SCORAD over the time,
- Medication consumption,
- Quality of life using the Dermatology Life Quality Index (DLQI),
- Overall tolerability of treatment as assessed by patient, and by investigator,
- Overall efficacy of treatment as assessed by patient, and by investigator,
- Overall acceptance of treatment as assessed by patient, and by investigator,
- Safety laboratory.

Both primary and secondary variables were analyzed descriptively using appropriate summary statistics and/or frequency tables. The analysis was performed based upon the Safety and ITT population.

2. End point #1 Statistical analysis – Secondary variable – Total SCORAD

As the total SCORAD was investigated at baseline (V1) and at all following visits, the total SCORAD was analyzed by means of summary statistics for all visits. Additionally, the pre-post difference of the total SCORAD between baseline (V1) and end of treatment at Visit 7 was analyzed descriptively.

The change in the total SCORAD from V1 to V7 was significant ($p < 0.0001$). The median score of the total SCORAD decreased significantly by 42%. The intensity of skin lesions as well as the intensity of the symptoms 'itching' and 'insomnia' decreased during the treatment.

3. End point #2 Statistical analysis – Secondary variable – Quality of Life Questionnaire

The assessment of quality of life using the DLQI was performed at every visit (V1 - V7). The sum score of the questionnaire was analyzed by means of summary statistics for all visits. Additionally, the pre-post difference of the sum score of the questionnaire between Visit 1 and Visit 7 was analyzed descriptively. The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the stronger the negative impact on life quality is.

The change in the DLQI score from V1 to V7 was significant ($p < 0.0001$). The median score of life quality improved by 62%.

4. End point #3 Statistical analysis – Secondary variable – Overall Efficacy of Treatment as Assessed by Patient, and by Investigator

Subjective assessments of efficacy were independently collected from patients and investigators. All of them were asked to rate their overall impression of therapy success by selecting one option in the following statement: "My overall impression of the efficacy of the trial medication is:

1 = excellent
2 = good
3 = moderate
4 = poor
5 = ineffective"

Most of the assessors thought that the therapy outcome was 'excellent', 'good' or 'moderate'. Neither the patients nor investigators thought that the therapy was 'ineffective'.

On average, the overall assessment of efficacy was rated by both patients and investigators as 'good' (assessment by patients: mean: 2.31, SD: 0.829; assessment by investigators: mean: 2.15, SD: 0.886).

<u>Efficacy Conclusions</u>

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'.

5. End point #4 Statistical analysis – Secondary variable – Type and Frequency of Serious Adverse Events

During the study, altogether 2 SAEs were reported. These SAEs were all treatment emergent and occurred in 2 patients (3.6%). One SAE was stated as 'skin infection' (by MedDRA preferred term) and the other as 'atopic dermatitis' (by MedDRA preferred term). Both SAEs were of 'severe' intensity but assessed as being 'unlikely' related to the study medication. Only the patient with 'skin infection' withdrew from the study.
All SAEs were also reported as adverse events.

6. End point #5 Statistical analysis – Secondary variable – Type and Frequency of Adverse Drug Reactions

In total, 24 patients (43.6%) experienced 44 TEAEs that were assessed as being 'likely' or 'definitely' related to the study medication and thus fulfill the definition for ADRs. These ADRs were 2 exacerbations of atopic eczema, 6 systemic reactions, and 36 local reactions. None of the ADRs was of 'severe' intensity.

- *Type and frequency of exacerbation of atopic eczema*
  After administration of study medication, 2 patients (3.6%) experienced 2 'exacerbations of atopic eczema', both classified as 'atopic dermatitis'. For these 2 patients, the symptoms were assessed as being 'likely' related to the study medication.
- *Type and frequency of systemic reactions*
  Overall, 6 systemic reactions were recorded for 6 patients (10.9%). These were in detail: 2 'pruritus', 1 'procedural headache', 1 'rhinitis allergic', 1 'urticaria', and 1 'vertigo'. All systemic reactions were assessed as being 'likely' related to the study medication.
- *Type and frequency of local reactions*
  36 local reactions (with 36 symptoms classified as 'local reaction') after administration of study medication occurred in 19 patients (34.5%). They were all assessed as being 'definitely' related to the study medication by the investigator. 9 of the local reactions arose immediately with 'mild' (8 local reactions) or 'moderate' (1 local reaction) intensity. The other 27 local reactions occurred with delay. Most of them (25 local reactions) were of 'mild' intensity, 1 local reaction was of 'moderate' intensity. For 1 local reaction, the information regarding intensity is 'missing'.

There was no local or systemic reaction leading to premature discontinuation of the study.

7. End point #6 Statistical analysis – Secondary variable – Medication Consumption

Basic medication was defined as any concomitant medication which is known to have an influence on the typical atopic eczema symptoms. Their usage was documented in the patient's diary. Basic medication consisted of different medication. The total medication consumption per medication type during the study was investigated descriptively.

Additionally, a pre-post difference was assessed based on the calculated medication consumption during the week after Baseline Visit (V1) and the week before the Final Visit (V7). There was no change in the total medication consumption at the end of the treatment.

8. **End point #7 Statistical analysis – Secondary variable – Overall Tolerability of Treatment as Assessed by Patient, and by Investigator**

The patient and the investigator assessed the tolerability of the treatment at the Final Visit (V7), by selecting one option in the following statement: "My overall impression of the tolerability of the trial medication is:

1 = excellent
2 = good
3 = moderate
4 = poor
5 = unacceptable"

Overall tolerability was rated by both patients and investigators mostly as 'excellent' and 'good'. There was no case reported where the overall tolerability was rated as 'unacceptable'. On average, the overall assessment of tolerability was rated by both patients and investigators as 'good'.

9. **End point #8 Statistical analysis – Secondary variable – Overall Acceptance of Treatment as Assessed by Patient, and by Investigator**

The patient and the investigator gave their overall assessment of acceptance at the final visit (V7), by selecting one option in the following statement: "My overall impression of the acceptance of the trial medication is:

1 = excellent
2 = good
3 = moderate
4 = poor
5 = unacceptable"

Overall acceptance was rated by both patients and investigators mostly as 'excellent', 'good', and 'moderate'. There was 1 case reported where the overall acceptance was rated as 'unacceptable' by the investigator.

On average, the overall assessment of acceptance was rated by both patients and investigators as 'good' (assessment by patients: mean: 1.85, SD: 0.770; assessment by investigators: mean: 1.81, SD: 0.913).

10. **End point #9 Statistical analysis – Secondary variable – Safety Laboratory**

During the course of the study, analyses of laboratory parameters were performed at V0 (Screening Visit), V1, and V7 for safety purposes.

The analysis of laboratory parameters comprised hematology (hemoglobin, hematocrit, erythrocytes, leukocytes, and platelets) and clinical chemistry (creatinine, alkaline phosphatase, SGOT, SGPT, γ-GT, total bilirubin, and glucose), as well as the total and specific serum IgE levels.

Additionally, a pregnancy test (ß-HCG in serum) was carried out in all female patients of childbearing potential at V0 and V7.

For each parameter, mean values, standard deviation, and median values were calculated.

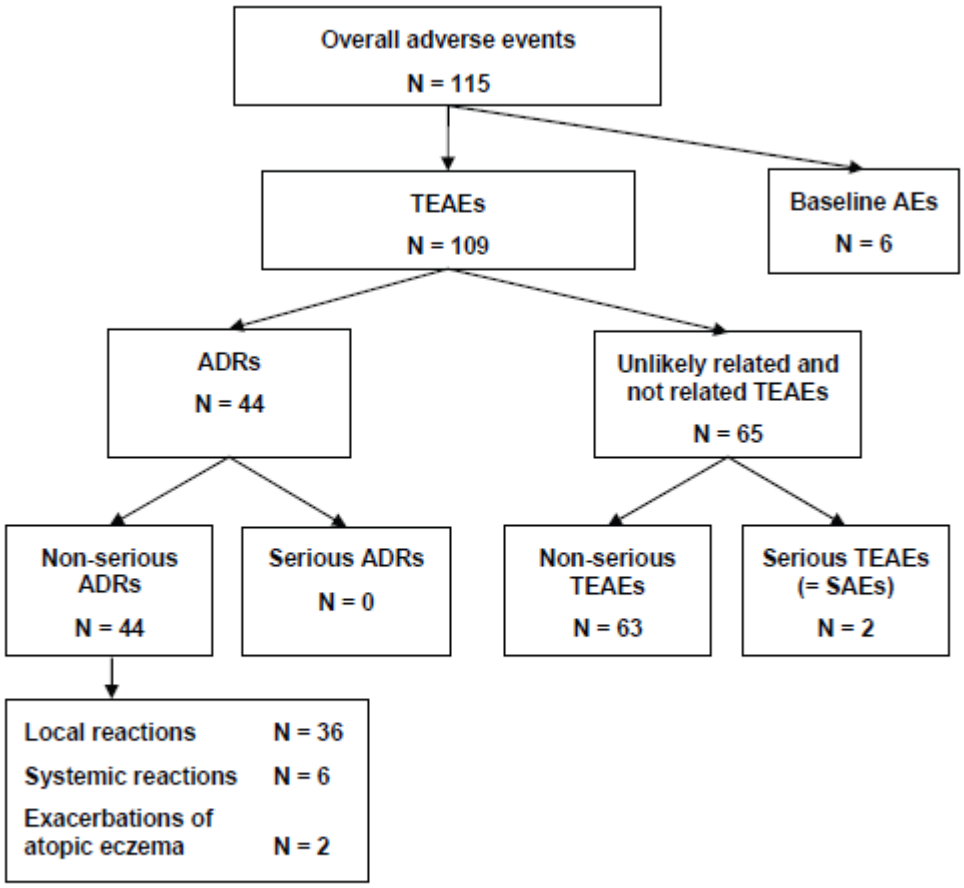
None of the assessed parameters showed relevant changes during the course of the study.

11. **End point #10 Statistical analysis – additional analysis – Days of treatment during and out of the birch pollen season**

This study started prior to the onset of the birch pollen season and lasted during the birch pollen season. For 33 patients (60%), the individual treatment period comprised at least one day within the birch pollen season. On average, every patient was treated with Depigoid® Birch Pollen for 19.2 days during the birch pollen season.

E. ADVERSE EVENTS

1. Adverse Events information



N: number of episodes

Adverse events were recorded and coded according to MedDRA (version 11.1).

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.

All local reactions were considered also as AEs. The overall amount of AEs includes all SAEs and ADRs (with ADRs comprising the subgroups 'exacerbations of atopic eczema', systemic reactions, and local reactions).

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.

Most of the TEAE symptoms were assigned to the following MedDRA SOC:

- 31 TEAE symptoms as MedDRA SOC 'infections and infestations' in 20 patients (36.4%) of the safety set,
- 36 TEAE symptoms as MedDRA SOC 'general disorders and administration site conditions' were documented in 19 patients (34.5%),
- 11 TEAE symptoms as MedDRA SOC 'skin and subcutaneous tissue disorders' were documented in 9 patients (16.4%),
- 5 TEAE symptoms as MedDRA SOC 'musculoskeletal and connective tissue disorders' were documented in 5 patients (9.1%).

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 (8 TEAEs with a likely relation and 36 TEAEs with a definite relation).

The incidences of TEAE symptoms by MedDRA preferred term and sorted by decreasing order of frequency are listed in the following table:

Symptom (MedDRA preferred term)[a)]	n1	%	n2
Local reaction	19	34.5	36
Nasopharyngitis	15	27.3	17
Pruritus	3	5.5	5
Headache	3	5.5	4
Dermatitis atopic	3	5.5	3
Conjunctivitis	2	3.6	2
Rhinitis allergic	2	3.6	2
Tonsillitis	2	3.6	2
Vulvovaginal mycotic infection	2	3.6	2
Anxiety	1	1.8	2
Asthma	1	1.8	2
Diarrhoea	1	1.8	2
Herpes simplex	1	1.8	2
Abscess drainage	1	1.8	1
Alopecia	1	1.8	1
Arthralgia	1	1.8	1
Bladder disorders	1	1.8	1
Eczema	1	1.8	1
Euphoric mood	1	1.8	1
Eyelid edema	1	1.8	1
Heart rate increased	1	1.8	1
Herpes dermatitis	1	1.8	1
Herpes simplex ophthalmic	1	1.8	1
Hypertension	1	1.8	1
Keratitis herpetic	1	1.8	1
Lymphadenopathy	1	1.8	1
Musculoskeletal pain	1	1.8	1
Nausea	1	1.8	1
Neck pain	1	1.8	1
Oral herpes	1	1.8	1
Pain in extremity	1	1.8	1
Procedural headache	1	1.8	1
Respiratory tract infection	1	1.8	1
Sinusitis	1	1.8	1
Skin infection	1	1.8	1
Sleep disorders	1	1.8	1
Sunburn	1	1.8	1
Tendonitis	1	1.8	1
Tic	1	1.8	1
Tooth abscess	1	1.8	1
Urticaria	1	1.8	1
Vertigo	1	1.8	1

a) coding according to MedDRA, version 11.1
n1: number of patients with at least one TEAE symptom; N: number of patients; %: calculation of percentages based on N; n2: number of TEAE symptoms

The most common **TEAE** symptoms summarized by MedDRA preferred term were 'local reaction' (number of symptoms = 36), 'nasopharyngitis' (number of symptoms = 17), 'pruritus' (number of symptoms = 5), and 'headache' (number of symptoms = 4).
Out of these 110 TEAE symptoms, 66 TEAE symptoms in 28 patients (50.9%) were assessed as being 'unlikely' or 'not' related to the study and 44 TEAE symptoms were assessed as being 'likely' or 'definitely' related to the study medication and therefore documented as **ADRs**.
2 symptoms were additionally reported as **SAEs** and 3 symptoms as 'exacerbations of atopic eczema'.
6 of the **ADR** symptoms were allergic reactions and for this reason documented as systemic reactions.
The 36 local reaction symptoms at the injection site were all 'definitely' related to the study medication and analyzed with regard to its onset.

Due to treatment-emergent adverse events, 4 patients of the safety set (N = 55) discontinued the study prematurely. One of these AEs was classified as SAE. All of these were assessed as being 'unlikely' related to the study medication.
There was no case of premature discontinuation due to an ADR or a local or systemic reaction symptom.

2. Adverse Event reporting group

The safety analysis was performed for the safety set (N = 55).

3. Serious Adverse event(s)

During this study, a total of 2 SAEs occurred in 2 different patients. These were assessed as being 'unlikely' related to the study medication.
See above.
No patient died in the course of this study.
No pregnancy was reported during the trial.

4. Non-serious adverse event(s)

See above

F. ADDITIONAL INFORMATION

1. Global Substantial Modifications

Modifications of the Study Protocol

The documentation of local reactions was to be performed on specific CRF data fields, which were separated from the areas for AE documentation. Nevertheless, local reactions were analyzed as AEs.

Additional Analyses

According to the decisions reached on the meeting on 05-May-2009 an additional analysis was made. This additional analysis is presented as following:

- Days of treatment during and out of the birch pollen season,
- Number of patients with 'exacerbations of atopic eczema' within ADRs,
- Number of patients with systemic reactions without 'exacerbation of atopic eczema',

Data Review Meeting (DRM), dated 16-Apr-2009

2. Global interruptions and re-starts

The trial was not interrupted nor re-started.

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.