A. CLINICAL TRIAL INFORMATION

1. Clinical trial identification

Researchers look at the results of many studies to decide which drugs work best and are safest for patients. It takes participants in many studies all around the world to advance medical science. This summary only shows the results from this one study. Other studies may find different results.

1.1. Title of the trial

A randomized, double blinded, placebo controlled multicenter study for the efficacy and safety of an Add-on-Therapy of Depigoid® House dust mites (HDM) in patients suffering from moderate to severe atopic eczema.

1.2. Protocol number

101-PG-PSC-150

1.3. EU trial number

2006-003066-34

1.4 Name and contact of sponsor

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

1. 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 ended on 02nd of July 2010.

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 comparison of the efficacy and tolerability of an Add-on-Therapy of Depigoid® Mite Mix (*Dermatophagoides pteronyssinus* [*Der. pter.*] and *Dermatophagoides farinae* [*Der. far.*]) extract versus placebo in a subcutaneous immunotherapy over 18 months in patients with moderate to severe atopic eczema with or without rhinitis and/or conjunctivitis caused by clinical relevant IgE-mediated sensitization against HDM leading to aggravation of patient's skin lesions.

4.2 Trial design

Randomized, double blinded, placebo controlled, multicenter, two parallel groups.

After a screening phase of up to 2 weeks, patients were randomly allocated to either verum or placebo and afterwards treated for 76 weeks.
The treatment phase was divided into two periods: the initial up-dosing period (3 weeks) and the maintenance treatment period (73 weeks). The overall study duration for an individual patient was 18 months, i.e. 78 weeks.

4.3 Scientific background

House dust mites (HDM) such as *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* are important indoor 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, specific immunotherapy (SIT) against HDM 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.

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.
Depigoid® Mite Mix is already on the German market since 2001 (information based upon German SmPC, 2004). The efficacy and safety have been proven in former studies.

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.

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

Concomitant Medication/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 HDM.

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,
- UV-therapy, tanning.

The following medications and therapies were not allowed during the entire study and led to the patient being withdrawn:

- β-blocker,
- Treatment with substances interfering with the immune system.

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
Any concomitant medication which is known to have an influence on the typical atopic eczema symptoms was defined as basic medication. The intake or application of any other medication

to treat atopic eczema symptoms was prohibited. Every basic medication intake/application was taken into account for the calculation of the total medication consumption. The following basic medication was recorded in the patient's diary and weighted at every study visit. The following basic medication was provided by the sponsor, dispensed and counted as follows:

- Aerius (each intake was counted, 1 tablet was counted as 1 point),
- Elidel (consumption was weighted, 5 g was counted as 2 points),
- Dermatop (Betnesol) (consumption was weighted, 5 g was counted as 2 points),
- Eucerin cum aqua (consumption was weighted, 5 g was counted as 1 point),
- Basic crème DAC (consumption was weighted, 5 g was counted as 1 point),
- Urbason 40 mg Tablets (each intake was counted, 0.5 mg per kg body weight was counted as 3 points),
- Fucidine crème (each application was weighted; 2 g was counted as 1 point).

The use of medication as documented in the CRF was added up to a medication score and evaluated as a primary criterion.
Due to the application of SIT, the following concomitant medication was provided in addition but only descriptively analyzed:

- Nasonex nasal spray,
- Livocab eye drops.

This medication was provided but not taken into account for the calculation of the patients' compliance.
The investigator was responsible for an accurate instruction of the patient including an appropriate documentation of the drug account. Basic medication was provided to the patient during the study period as needed. Between V0 and V1, only Eucerin cum aqua and basic crème DAC was allowed.

4.6 Statistical methods

Primary Variables

The primary criteria in this study were the Total SCORAD and basic medication consumption/application during the treatment period. Both were analyzed as the AUC, first of the Total SCORAD and second of the basic medication consumption.
For patients who had discontinued treatment due to medical reasons, the worst case was assumed, i.e. the maximum Total SCORAD and basic medication consumption were carried forward until the end of the study for analysis purposes. For patients who had discontinued treatment due to non medical reasons, the Total SCORAD and basic medication consumption were not carried forward.
Within a hierarchical test procedure with a global α-level of 2.5% the following system of hypotheses was investigated:
In the first step of the hierarchical test procedure the Total SCORAD was compared between an Add-on-Therapy of Depigoid® Mite Mix and placebo, i.e. the median of the AUC over the 18 months of treatment was investigated.

Statistical Hypotheses

H0: There is no difference for the median of the AUC Total SCORAD between the two treatment groups.
H1: There is a difference for the median Total SCORAD between the two treatment groups i.e. median Total SCORAD in the Placebo-group is larger than in the Depigoid® Mite Mix-group.
The one-tailed Wilcoxon rank-sum test was used for the treatment comparison with a significance level of $\alpha = 0.025$. Only if a significant difference between treatment groups was

shown, i.e. the p-value was below 0.025 and H0 could be rejected, the test procedure was continued with the following second step.
In the second step of the hierarchical test procedure the basic medication consumption was compared between Depigoid® Mite Mix and placebo, i.e. the median of cumulative intake, as counted in the medication score, over the 18 months time of treatment was investigated.

Statistical Hypotheses
H0: There is no difference for the median cumulative application between the two treatment groups.
H1: There is a difference for the median cumulative application between the two treatment groups, i.e. the consumption is larger in the Placebo-group than in the Depigoid® Mite Mix group.
The one-tailed Wilcoxon rank-sum test was used for the treatment comparison with a significance level of $\alpha = 0.025$.

Evaluation of secondary efficacy and safety variables
Adverse events (AEs) were documented and a causality assessment was made.
Laboratory parameters were listed and values outside the normal range were marked.
For the quality of life, the relative pre-post difference was calculated. The data of the questionnaire were compared between the two treatment groups using the Wilcoxon rank-sum test. Descriptive analyses were performed for all other parameters.

4.7 Population of subjects

4.7.1 The number of subjects included in the trial

195 patients were planned to be randomized in 30 centers in Germany.

Screened: 204
Randomized: 168

Intention-to-treat (ITT): Total: 162
- Depigoid® Mite Mix : 107
- Placebo: 55

Per protocol (PP): Total: 115
- Depigoid® MITE Mix : 76
- Placebo: 39

4.7.2 Age groups and gender breakdown

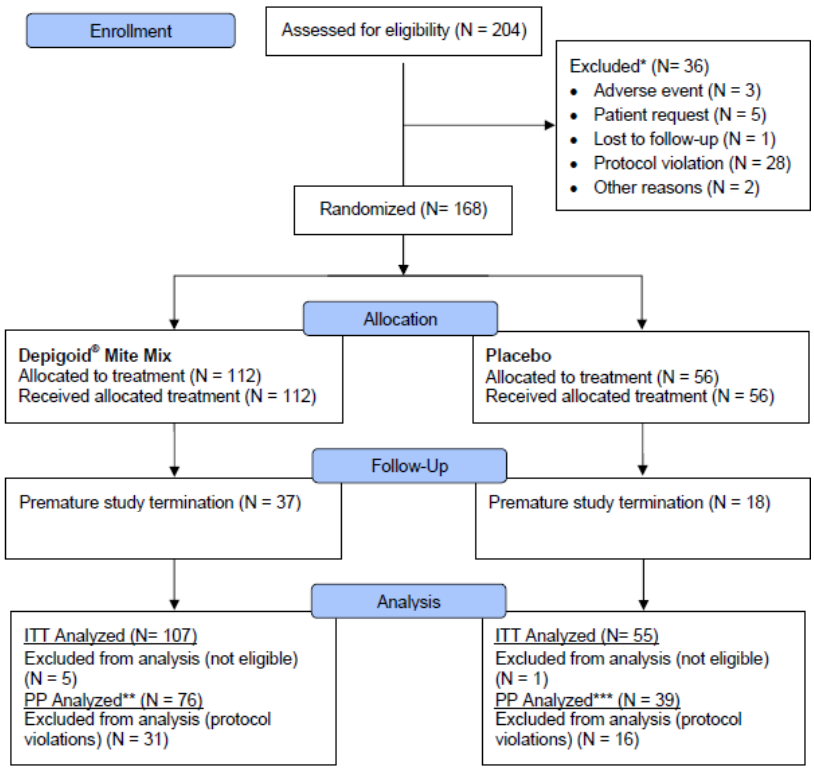
- Gender:
  - 90 male (62 Depigoid® MiteMix & 28 Placebo)
  - 78 female (50 Depigoid® MiteMix & 28 Placebo)
- Age:
  - ranged from 18 to 65 years with a mean of 34.2 years in the Depigoid® MiteMix group and 32.9 in the Placebo group

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

21 active centers in Germany enrolled a total of 204 patients into the study.



N: number of patients; ITT: intention-to-treat; PP: per-protocol; PV: protocol violation
* More than one reason per patient was possible, ** including 4 dropouts; *** including 1 dropout

1.2 Inclusion and exclusion criteria

Inclusion Criteria:

1. Patients of both gender aged from 18 up to 65 years,
2. Prior to study specific examinations, the patient had to give his/her written informed consent,
3. At least 2 exacerbations of eczema or permanent skin lesions during the last 2 months,
4. Patients had to suffer from atopic eczema (with or without rhinitis and/or conjunctivitis) impaired by clinical sensitization against HDM leading to an aggravation of skin lesions. The sensitization against HDM had to be verified by*
   - Symptom aggravation of skin lesions by exposure to HDM and during winter season,
   - A positive skin prick test for Der. pter. and/or Der. far., resulting in a wheal diameter of at least 4 mm > negative control reaction,
   - Specific IgE for Der. pter. or Der. far. CAP-RAST ≥3,

5. The diagnosis atopic eczema had to be verified according to the criteria of Hanifin and Rajka,
6. Duration of atopic eczema > 2 years,
7. Encasings of bedding and mattress for more than 6 months (or stable environmental control).

∗ Additionally, an atopy patch test with Der. pter. and Der. far. was performed in selected study sites but not be used as inclusion criterion.

Exclusion Criteria:

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 HDM,
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,
   - Treatment with substances interfering with the immune system,
5. Total SCORAD < 30 at screening,
6. Patients with therapeutically uncontrolled atopic eczema or erythrodermia,
7. Patients with 3 consecutive exacerbations within 12 - 24 hours after immunotherapy,

Patients with other Known Concomitant Diseases/Treatments

8. Active tuberculosis,
9. Acute and chronic inflammatory or infectious diseases at the target organ,
10. Advanced secondary changes at the target organ (e.g. emphysema or bronchiectasis),
11. Immunopathological diseases (e.g. of the liver, kidney, the nervous system, thyroid gland, rheumatic diseases) in which autoimmune mechanisms played a role,
12. Immune deficiencies,
13. Uncontrolled asthma, defined as Forced Expiration Volume in one second (FEV1) or Peak Expiratory Flow (PEF) ≤ 70% of predicted normal value,
14. Any disease which prohibited the use of adrenaline (e.g. hyperthyroidism),
15. 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,
16. Malignant disease of any kind during the previous 5 years,
17. Abnormal laboratory parameters and vital signs that could have increased the risk to the study participant,
18. Alcohol, drug, or medication abuse within the past year,
19. Severe psychiatric or neurologic disorders,

Others

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

Special Restrictions for Female Patients

26. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation,
27. 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 levels >40 mIU/m 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: Intrauterine device, male or female condom with spermicidal gel, diaphragm, sponge, cervical cap).

1.3 Randomization and blinding details

A 2:1 randomization was used, in order to expose more patients to Depigoid® Mite Mix for collection of safety data and to give the patients a higher chance to receive active immunotherapy on top of conventional pharmacotherapy.
The number of the study medication was predetermined by a computer-generated randomization procedure.

1.4 Investigational medicinal products used

The patients were randomized into 2 groups at a ratio of 2:1. Group A: Depigoid®, group B: placebo. This study was also “double blinded” – this means that neither patients nor doctors knew who was given which treatment/drug. This was done to make sure that the study results were not influenced in any way.

Investigational Medicinal Product: Depigoid® Mite Mix vial 1 (10 DPP/mL) and Depigoid® Mite Mix vial 2 (100 DPP/mL)

Dose/dosage:
- Up-dosing phase (Visit 1 – Visit 4):
  - 0.2 mL of vial 1, 0.5 mL of vial 1,
  - 0.2 mL of vial 2, and 0.5 mL of vial 2 in weekly intervals
- maintenance treatment phase (Visit 5 – Visit 15):
  - 0.5 mL of vial 2 in 6-week intervals
- Administration: Subcutaneously

Placebo: Identical solution as IMP without active ingredients

- Dose/dosage: Identical application scheme as IMP
- Administration: Subcutaneously

The study medication was injected subcutaneously additionally to a basic medication (see above).

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 (serum),
• Specific IgE and IgG4 (CAP-RAST) for *Der p* and *Der f*,
• Skin Prick Test (only if not performed within the last 3 months),
• Total SCORAD.
The patient was instructed to return to the study center within 2 weeks after the Screening Visit (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,

• Randomization,

• Dispense basic medication,

• Issue patient diary cards,

• Quality of life (DLQI),

• Total SCORAD,

• Digital photography (at selected study sites only),

• Atopy patch test (at selected study sites only),

• Lung function test,

• Administration of study medication.

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

Visit 2 and Visit 3 (V2 and V3)
The visits had to be performed at Week 1 and 2. A maximum deviation of ±3 days was permitted. The following examinations/procedures were to be performed:

• AEs,

• Concomitant disease and/or additional medication,

• Vital signs,

• Issue patient diary cards,

• Collection and review of patient diary including control of used basic medication,

• Lung function test,

• Administration of medication,

• Transfer of diary to data management.

The patient was instructed to return to the study center 1 week after V2 and V3, respectively.

Visit 4 (V4)
The visit had to be performed at Week 3. A maximum deviation of ±3 days was permitted. The following examinations/procedures were to be performed:

• AEs,

• Concomitant disease and/or additional medication,

• Vital signs,

• Issue patient diary cards,

• Collection and review of patient diary including control of used basic medication,

• Total SCORAD,

• Lung function test,

• Administration of medication,

• Transfer of diary to data management.

Visits 5, 6 (V5, V6)
The visits had to be performed at Week 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,

• Vital signs,

• Issue patient diary cards,

• Collection and review of patient diary including control of used basic medication,

• Total SCORAD,

• Lung function test,

• Administration of medication,

• Transfer of diary to data management.

Visits 7, 8, 9 (V7, V8, V9)
The visits had to be performed at Week 21, 27, and 33. A maximum deviation of ±3 days was permitted. The following examinations/procedures were to be performed:

• AEs,

• Concomitant disease and/or additional medication,

• Vital signs,

• Pregnancy test (only at V7),

• Dispense of basic medication (only at V8),

• Issue patient diary cards,

• Collection and review of patient diary including control of used basic medication,

• Quality of life (DLQI - only at V8),

• Total SCORAD,

• Lung function test,

• Administration of medication,

• Transfer of diary to data management.

Visits 10, 11, 12, 13, 14, 15 (V10 – V15)
The visits had to be performed at Week 39, 45, 52, 58, 64, and 70. A maximum deviation of ±3 days was permitted. The following examinations/procedures were to be performed:

• AEs,

• Concomitant disease and/or additional medication,

• Vital signs,

• Pregnancy test (only at V11),

• Dispense of basic medication (only at V12),

• Issue patient diary cards,

• Collection and review of patient diary including control of used basic medication,

• Quality of life (DLQI - only at V11),

• Total SCORAD,

• Lung function test,

• Administration of medication,

• Transfer of diary to data management.

Visit 16 - Final Visit (V16)
Visit 16 had to be performed for all patients, irrespective whether they completed the study regularly, or terminated the study prematurely. It had to be performed at Week 76, if the study was terminated regularly, or as soon as possible in case of a premature termination. 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,

• Vital signs,

• Safety laboratory,

• Specific IgE and IgG4 (CAP) for Der. pter. and Der. far.,

• Pregnancy test,

• Skin Prick Test,

• Collection and review of patient diary including control of used basic medication,

• Quality of life (DLQI),

• Total SCORAD,

• Digital photography (at selected study sites only),

• Atopy patch test (at selected study sites only),

• Transfer of diary to data management,

• Global evaluation of safety by patient and investigator.

For patients who showed signs of AEs or clinically relevant deviations from laboratory values at the final examination, a further examination, the so called Post-study Visit (PS) had to be carried out.

Unscheduled Visits

If the patient had to visit the investigator for any reason 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 any case, patients were questioned about AEs and changes in concomitant medication, additionally vital signs were recorded.

Premature Termination of the Study

Premature Termination of the Study on Patient Request

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. Furthermore, the patient was to be withdrawn from the study once the investigator had considered that his/her further participation would be detrimental.

Discontinuation of the Study on Investigator and/or Sponsor Request

The Coordinating Investigator could have terminated the study at any time for safety reasons. The sponsor could have ended the study for safety, ethical, or administrative reasons at any time. In such cases, all investigators had to be notified in writing, outlining reasons for the termination.

In particular cases, the study could have been terminated at a single investigational site, if the sponsor had relevant reasons, e.g. suspicion of a deceit or conduct of the study, which was not in accordance with the guidelines for GCP or no recruitment of patients 2 months after the start of the clinical study.

It was at the discretion and responsibility of the investigator to decide in individual cases on the patient's withdrawal from the study due to medical reasons.

C. BASELINE CHARACTERISTICS

The demographic data collected for the overall safety set (N 0 168):

1. Baseline characteristics – Age

Age: ranged with a mean of 34.23 years in the Verum group and 32.88 in the Placebo group.

2. Baseline characteristics – Gender

Gender: 90 (62 Verum + 28 Placebo) patients were male, 78 (50 Verum + 26 Placebo) patients were female.

D. END POINTS

1. End point definitions

Evaluation was performed for the overall safety set (N = 168), the ITT set (N = 162), and the PP set (N = 115). For the analyses of the subpopulation 'patients with Total SCORAD >50 at V0', the evaluated sizes of the sets were as follows: $N_{subpopulation}$ = 85 (subpopulation safety set), $N_{subpopulation}$ = 80 (subpopulation ITT set), and $N_{subpopulation}$ = 52 (subpopulation PP set).

Efficacy

Primary Variable:

For the comparison of efficacy between an Add-on-Therapy Depigoid® Mite Mix and placebo, a hierarchical test procedure was used. The primary objective was evaluated by assessment of the following criteria:

1. The AUC (area under the Total SCORAD curve) over the 18 months of treatment,
2. The medication consumption/basic medication (cumulative application) over the 18 month time of treatment.

Secondary Variables:

- Onset of efficacy,
- Number of atopic exacerbations,
- Time to and severity of atopic exacerbations,
- Quality of life questionnaire using the Dermatology Life Quality Index (DLQI),
- Specific IgG4 and IgE against *Der. pter.* and *Der. far.*

Safety: Adverse events reported by the patient/subject or noted by the investigator. Standard hematology and blood chemistry values, as well as vital signs and global safety were evaluated.

2. End point #1 Statistical analysis – primary variables

For both variables, analysis was performed based on the ITT and PP set. A sub-analysis was carried out for the subpopulation 'patients with Total SCORAD >50 at V0'. The AUCs were compared between the treatment groups using one-sided Wilcoxon rank-sum test.

The primary criterion was evaluated by two variables: The AUC of the Total SCORAD and the medication consumption, both over 18 months of treatment. Regarding the Total SCORAD, no difference between patients treated with Depigoid® Mite Mix or with placebo could be found (ITT set: p = 0.2441, PP set: p = 0.3342). The mean Total SCORAD over 18 months of treatment was similar in both treatment groups (Depigoid® Mite Mix: 17,802.7, placebo: 19,093.1; ITT set).

Analyzing only patients who already had a high Total SCORAD before the treatment (subpopulation 'patients with Total SCORAD >50 at V0'), a significantly higher Total SCORAD (ITT set: p = 0.0237) was found in patients treated with placebo (mean score of 23,215.6) compared to patients receiving Depigoid® Mite Mix (mean score of 19,452.0).

Additionally, post hoc analyses were performed for the subpopulation. During winter season with predominant HDM exposure, patients with a high SCORAD at inclusion had a lower Total SCORAD (ITT set: p = 0.0223) after treatment with Depigoid® Mite Mix compared to patients receiving placebo. The median Total SCORAD was reduced by 18% (ITT set) in the Depigoid® Mite Mix-group compared to placebo. Similar results were found within the analysis of different time-periods during treatment. During the last 12 months of treatment, the median of the Total SCORAD was reduced by 25% (ITT set) in patients receiving Depigoid® Mite Mix compared to placebo. During the last 6 months of treatment, the reduction in the Depigoid® Mite Mix-group compared to placebo was 30%, and for the last 3 months it was even 32%.
All these differences were statistically significant (all p-values < 0.025).

The respective results regarding the medication consumption over 18 months of treatment merely indicated similar tendencies. Patients being treated with Depigoid® Mite Mix (overall population: mean medication score of 31,648.0; ITT set) seem to have numerically lower medication consumption than patients receiving placebo (overall population: mean medication score of 41,828.7; ITT set), albeit this result was not significant (ITT set: p = 0.0754, PP set: 0.0563). Also for the subpopulation, similar results were found (ITT set: p = 0.2675, PP set: p = 0.0598).

3. **End point #2 Statistical analysis – onset of efficacy**
The onset of efficacy was originally defined as the first time-point the atopic dermatitis at visit has better classification than the one at V 1, but this definition was found to be t general and revealed not reliable results.

4. **End point #3 Statistical analysis – Number of atopic exacerbations**
Several variables regarding atopic exacerbations were evaluated to investigate the efficacy of Depigoid® Mite Mix compared to placebo:
First of all, the number of atopic exacerbations per patient was assessed. Based on patients' documentation in the diaries, a mean of 77.58 atopic exacerbations per patients was calculated for the Depigoid® Mite Mix-group and a mean of 75.47 for the Placebo group.
Also, similarly high mean values were calculated for the two treatment groups of the subpopulation (ITT set: 82.17 [Depigoid® Mite Mix] vs. 55.18 [placebo]). Since the patient's self-assessment of skin lesions documented rather the permanent skin affection than exacerbations of atopic dermatitis a reassessment of relevant exacerbations documented as AE was performed, i.e., the number of atopic exacerbations per patient was evaluated on basis of the AE documentation of the investigator only. The results revealed totally different numbers of atopic exacerbations: For both treatment groups, less than one atopic exacerbation per patient was reported (ITT set: Depigoid® Mite Mix: 0.20, placebo: 0.24). The results of the subpopulation were very similar (ITT set: Depigoid® Mite Mix: 0.19, placebo: 0.21). However, the number of atopic exacerbations based on patients' documentation in the diary or based on AE documentation by the investigator did not differ significantly between the treatment groups (all p-values > 0.05).

5. **End point #4 Statistical analysis** – Time to and severity of atopic exacerbations
Other variables concerning exacerbation of the skin lesions were the time to the first atopic exacerbation and its severity. Also for these two variables, no differences between Depigoid® Mite Mix and placebo could be found, neither in the overall population nor in the subpopulation comprising patients with a Total SCORAD >50 at V0 (all p-values > 0.05). The time to the first atopic exacerbation was numerically longer in the Placebo-group when based on mean values (ITT set; 5.8 days [Depigoid® Mite Mix] vs. 17.9 days [placebo]), or the same

as in the Depigoid® Mite Mix-group when based on median values (ITT set: 2.0 days [Depigoid® Mite Mix] vs. 2.0 days [placebo]).
This applied also to the subpopulation (ITT set, mean: 7.2 days [Depigoid® Mite Mix] vs. 24.7 days [placebo]; median: 1.0 days [Depigoid® Mite Mix] vs. 1.5 days [placebo]). In 81.3% of the patients (ITT set) in the Depigoid® Mite Mix-group and in 72.7% of the patients (ITT set) in the Placebo-group, no severity of the atopic exacerbations was assessed as most of the records in patients' diaries were not considered AE by the investigators. In all patients of the overall population as well as of the subpopulation for whom an intensity assessment of the atopic exacerbation existed, a 'moderate' atopic exacerbation was the most reported intensity. Regarding this variable, no difference between the treatment groups could also be found (all p-values > 0.05). All these calculations apply for atopic exacerbations based on patient's self-assessment of skin lesions. Taking only exacerbations into account that were documented as AE, different results in terms of extension of duration until first apotic exacerbation were obtained. In the Depigoid® Mite Mix-group, the first atopic exacerbation appeared after a mean of 144.3 days (ITT set), whereas it was after a mean of 192.8 days (ITT set) in the Placebo-group.
For the subpopulation, the respective mean values were 156.5 days (ITT set; Depigoid® Mite Mix) and 184.5 days (ITT set, placebo).
However, no statistically significant differences between Depigoid® Mite Mix and placebo treatment were found (all p-values > 0.05). Regarding the severity of atopic exacerbation, similar results were obtained in the post hoc analysis, as the intensity was only assessed for exacerbations that were documented as AE.

6. **End point #5 Statistical** analysis **– Quality of life questionnaire using the Dermatology Life Quality Index (DLQI)**

At different time points during the study, the quality of life was assessed using the DLQI. The calculated pre-post differences did not differ between the treatment groups (all p-vales > 0.05). However, they were negative for both Depigoid® Mite Mix and placebo groups for the overall study duration (V16 - V1) and during the first year (V11 – V1), indicating an improvement in quality of life. During the last 6 months of treatment (V16 – V11), no further improvement was achieved. These results apply also to the subpopulation 'patients with Total SCORAD >50 at V0'. To exclude symptoms of co-allergies on quality of life, the mean and median DLQI was also evaluated during a time-period from September to February predominated by HDM exposure. For the overall population, a difference between the treatment groups was found neither in the mean nor in the median DLQI score (all p-values > 0.05). But in the subpopulation, patients in the Depigoid® Mite Mix-group tended (two-sided p-values > 0.05 but < 0.1) to have a lower DLQI score than patients in the Placebo-group, indicating less impairment of quality of life under the Depigoid® Mite Mix treatment (ITT set: p = 0.0568). In the PP set, this difference became statistically significant (p = 0.0384).
Further post hoc analyses during the winter season were made concerning quality of life by classification of DLQI scores in different categories describing the impact of symptoms caused by the disease on patient's life.
Therefore, DLQI scores assessed during winter season were classified in 5 different categories for a detailed analysis and afterwards additionally in 2 different categories for a more general analysis. For both analyses, it was found that more patients under Depigoid® Mite Mix treatment were classified in those categories revealing less impairment of quality of life compared to placebo (overall ITT: p = 0.0329 and p = 0.0183; subpopulation ITT: p = 0.0276 and p = 0.0080).

7. **End point #6 Statistical analysis – Specific IgG4 and IgE against *Der. pter.* and *Der. far.***

Effects on immune response were also assessed. Immune response data (IgE and IgG4) were obtained prior to the first application of study medication at inclusion (V0) and at the end of the study (V16).

The mean values of total and specific IgE decreased in the Depigoid® Mite Mix-group from V0 to V16 (total IgE: -2.98 mg/L, IgE Der. pter.: - 8.46 mg/L, IgE Der. far.: -11.20 mg/L; ITT set) and slightly decreased in the Placebo-group (total IgE: -0.42 mg/L, IgE Der. far. -0.77 mg/L; ITT set). Only the mean value of IgE Der. pter. slightly increased (0.69 mg/L; ITT set). For the overall population, the pre-post differences in the total IgE and the two specific IgEs (Der. pter. And Der. far.) were statistically significant between the treatment groups (total IgE: p = 0.0262, IgE Der. pter.: 0.0090, IgE Der. far.: 0.0095; ITT set).

In the overall population as well as in the subpopulation, a statistically significant difference between the treatment groups regarding IgG4 Der. pter. could be concluded (all p-values < 0.0001). Under Depigoid® Mite Mix treatment, IgG4 Der. pter. increased during the course of the study by a mean of 140.50 mg/L in the overall population (ITT set) and by a mean of 182.31 mg/L in the subpopulation (ITT set), but decreased in the Placebo-group by a mean of -8.95 mg/L in the overall population (ITT set) and by a mean of -25.55 mg/L in the subpopulation (ITT set). Regarding IgG4 Der. far., all p-values were > 0.05, indicating no statistical difference in the values between Depigoid® Mite Mix and placebo treatment. In the Depigoid® Mite Mix-group, values of IgG4 Der. far. decreased by a mean of -8.70 mg/L in the overall population (ITT set) and by a mean of -37.25 mg/L in the subpopulation (ITT set). Respectively, the mean values in the Placebo-group decreased by -8.63 mg/L in the overall population (ITT set) and slightly increased by 0.45 mg/L in the subpopulation.

Finally, a responder analysis was performed post hoc evaluating the efficacy of the study medication as improvement of Total SCORAD values during the study compared to baseline values. For that reason, cut-off values were defined indicating the reduction (%) of Total SCORAD compared to baseline Total SCORAD. A cut-off value of 60% means that the Total SCORAD was reduced to 60% related to the baseline Total SCORAD (cut-off value of 100% means no reduction). No differences in the response rates were found between the treatment groups in the overall population (all p-values > 0.05), but for the subpopulation. Between cut-off values of 15% and 100% of baseline Total SCORAD for any total SCORAD during the study time window, the percentage of patients who could be defined as responders was higher under Depigoid® Mite Mix treatment, indicated by higher responder rates in the Depigoid® Mite Mix-group compared to placebo. In the range of 66% and 69% of baseline Total SCORAD, this difference was statistically significant. Therefore, it can be concluded that for more patients being treated with Depigoid® Mite Mix efficacy in terms of improvement of skin lesions could be assessed compared to placebo.

8. **End point #7 Statistical analysis – Safety**

Adverse Events were recorded and coded according to MedDRA 12.1. The rate of patients with at least one AE was compared between treatment groups using Fisher's exact test.

During this study, 145 patients (86.3%) of the overall population experienced a total of 880 TEAE symptoms during 838 TEAE episodes. For 96 patients (85.7%) under Depigoid® Mite Mix treatment, 576 TEAEs with 602 TEAE symptoms were documented; whereas under placebo treatment, in 49 patients (87.5%), overall 262 TEAEs with 278 symptoms occurred. According

to the investigators' assessment, 502 TEAEs were reported as being 'not related' (385 TEAEs [45.9%]) or 'unlikely related' (117 TEAEs [14.0%]) to study medication. The other 336 TEAEs were 'likely' or 'definitely' related and therefore classified as ADRs.
336 ADRs of the overall population occurred in 74 patients (44.0%) with 348 ADR symptoms, indicating that one patient could have suffered from more than one ADR.
All ADRs were subdivided into two subgroups: local reaction and systemic reaction. Out of the 336 ADRs reported during the study, 316 were local reactions and 20 systemic reactions. Under Depigoid® Mite Mix treatment, 229 local reactions with 232 symptoms were reported for 44 patients (39.3%) and 87 local reactions with 91 symptoms occurred in 20 patients (35.7%) receiving placebo.

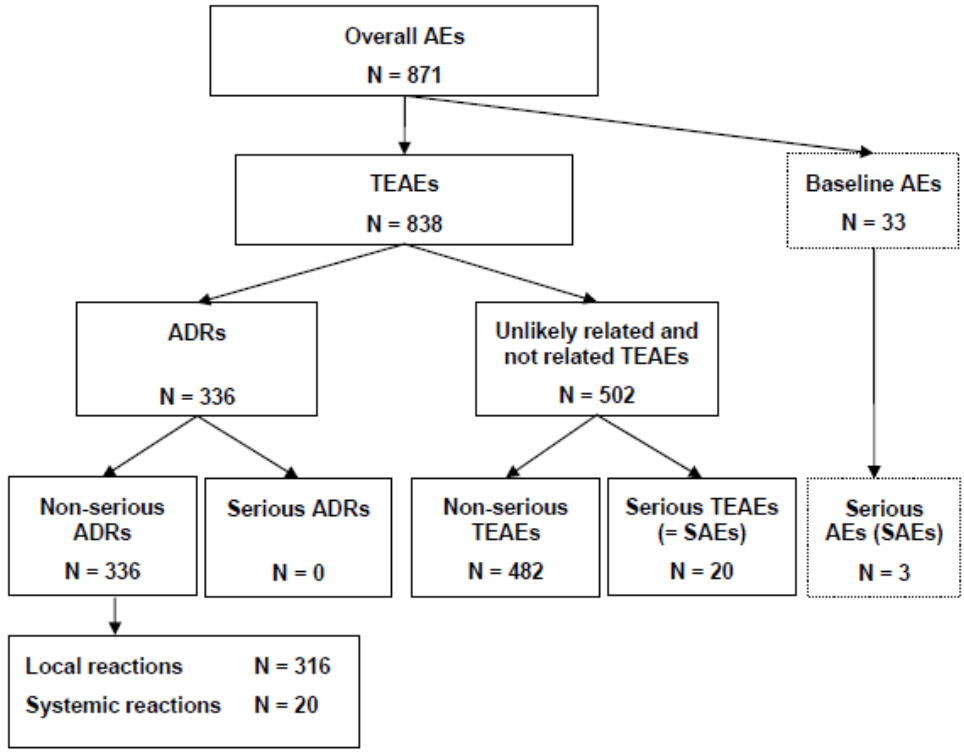
213 local reactions (93.0%) in the Depigoid® Mite Mix-group and 83 local reactions (95.4%) in the Placebo-group were of 'mild' intensity. None of the local reactions was of 'severe' intensity. All local reactions were considered as AEs.
Systemic reactions were documented in 9 patients (8.0%) of the Depigoid® Mite Mix-group and in 6 patients (10.7%) of the Placebo group.
14 systemic reactions with 17 symptoms in the Depigoid® Mite Mix-group and 6 systemic reactions with 8 symptoms in the Placebo group.
The most often reported systemic reaction symptoms were 'Dermatitis atopic' (7 symptoms), 'Condition aggravated' (4 symptoms), and 'Eczema' (3 symptoms). 2 of the systemic reactions, one in each treatment group, were of 'severe' intensity but not serious.
In the subpopulation 'patients with Total SCORAD >50 at V0', a total of 91 local reactions was reported. 66 local reactions occurred with 68 symptoms in 16 patients (28.6%) of the Depigoid® Mite Mix-group and 25 local reactions with 25 symptoms were recorded for 6 patients (20.7%) of the Placebo-group. Systemic reactions were only documented once in the Depigoid® Mite Mix-group. The patient (1.8%) in this treatment group experienced 'Dermatitis atopic'. Under placebo treatment, 4 systemic reactions with 5 symptoms were reported in 4 patients (13.8%). The symptoms were 'Dermatitis atopic' (3 symptoms), 'Condition aggravated' (1 symptom), and 'Sensation of foreign body' (1 symptom).

No death was reported during the course of the study.

Due to TEAEs, 13 patients (7.7%) discontinued the study prematurely, 10 patients of the Depigoid® Mite Mix-group and 3 patients of the Placebo-group. None of these TEAEs was assessed by the investigators as being 'definitely related' to study medication but 5 TEAEs were 'likely related' (4 TEAEs in the Depigoid® Mite Mixgroup and 1 TEAE in the Placebo-group). 4 of the patients in the Depigoid® Mite Mix-group who discontinued the study prematurely due to a TEAE belonged also to the subpopulation 'patients with Total SCORAD >50 at V0'. In the Placebo-group, there was 1 patient who discontinued the study prematurely due to a TEAE.
Altogether, 20 treatment-emergent SAEs were reported in 12 patients (7.1%), 6 patients in each treatment group. They all were assessed as being 'not related' to study medication. 4 of the 20 SAEs led to premature discontinuation of the study. They all occurred in patients receiving Depigoid® Mite Mix treatment. 3 of them were of 'severe' and 1 of 'moderate' intensity.
There were 2 abnormal findings in patients treated with Depigoid® Mite Mix. Both patients showed increased values of total bilirubin after treatment with Depigoid® Mite Mix but it was not causally related to study medication. Regarding vital signs, physical examination, and lung function test, no abnormal findings of clinical significance were found.
Significant differences between Depigoid® Mite Mix and placebo were not found in any of the assessed parameters relevant to drug safety.
Therefore, it can be concluded that in general Depigoid® Mite Mix was well tolerated and safe.

E. ADVERSE EVENTS

1. Adverse Events information



N: Number of episodes in the safety set.

2. Adverse Event reporting group

Adverse events were evaluated for the overall population and for the subpopulation 'patients with Total SCORAD >50 at V0'.

3. Serious Adverse event(s)

See above

4. Non-serious adverse event(s)

See above

F. ADDITIONAL INFORMATION

1. Global Substantial Modifications

The study was started and conducted according to the final Study Protocol (version 3.0), dated 01-Feb-2007. A change in the Sponsor's address, a renaming of the CRO and other corrective actions and additional information for clarification required the Amendment No. 1 (dated 12-Jul-2010), which is included in the final Study Protocol (version 4.0), dated 12-Jul-2010.

Thus, the clinical study was analyzed according to Study Protocol version 4.0.

Changes to the final Study Protocol regarding the patient status made during the Blinded Data Review Meeting (BDRM) on September 16, 2010 and changes of the statistical analysis are described in the BDRM protocol and the Statistical Analysis Plan (SAP), respectively.

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

Not applicable.

4. Declaration by the submitting party on the accuracy of the submitted information

The information provided within this summary is based on the Clinical Trial Report.

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

- *Natalija Novak, MD,Thomas Bieber, MD, PhD, MDRA, Matthias Hoffmann, MD, Regina Fölster-Holst, MD, Bernhard Homey, MD, Thomas Werfel, MD, Angelika Sager, MD, and Torsten Zuberbier, MDg,* Efficacy and safety of subcutaneous allergen-specific immunotherapy with depigmented polymerized mite extract in atopic dermatitis, *2012, J Allergy Clin Immunol 130:925-931*