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

2. Name and contact of sponsor

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

3. General information about clinical trial

3.1 Where the trial was conducted

The trial was conducted at 21 centers in Germany only.

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

The study started on 6th of March 2007 (FPFV) and was completed after 3 years on 2nd of July 2010. The study consisted of 2 phases, whereas the treatment was divided into 2 periods:

1. Screening phase: up to 2 weeks
2. Treatment phase:
    - o Initial up-dosing period: 3 weeks
    - o Maintenance treatment period: 17 months

3.3. 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.

The primary end points of the study were the assessments of the area under the curves of the total Severity Scoring Atopic Dermatitis (SCORAD) score and of the use of basic medication during the 18-month treatment period. Post hoc subgroup analyses were also performed.

4. Population of subjects

4.1. 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

4.2. Age groups and gender breakdown

• Gender:
  - o 90 male (62 Depigoid® MiteMix & 28 Placebo)
  - o 78 female (50 Depigoid® MiteMix & 28 Placebo)

• Age:
  - o 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

4.3. 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).

5. 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

6. Description of adverse reactions and their frequency

Side effects are unwanted medical events (e.g. headache) that happen during the study, and are reported because they are thought to be related to the treatments in the study. Not all the people [people/patients] in this study had side effects.
Common and serious side effects are listed here

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. Within the subpopulation, 96 ADRs occurred in 24 patients (31.8%) with 99 ADR symptoms.

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.

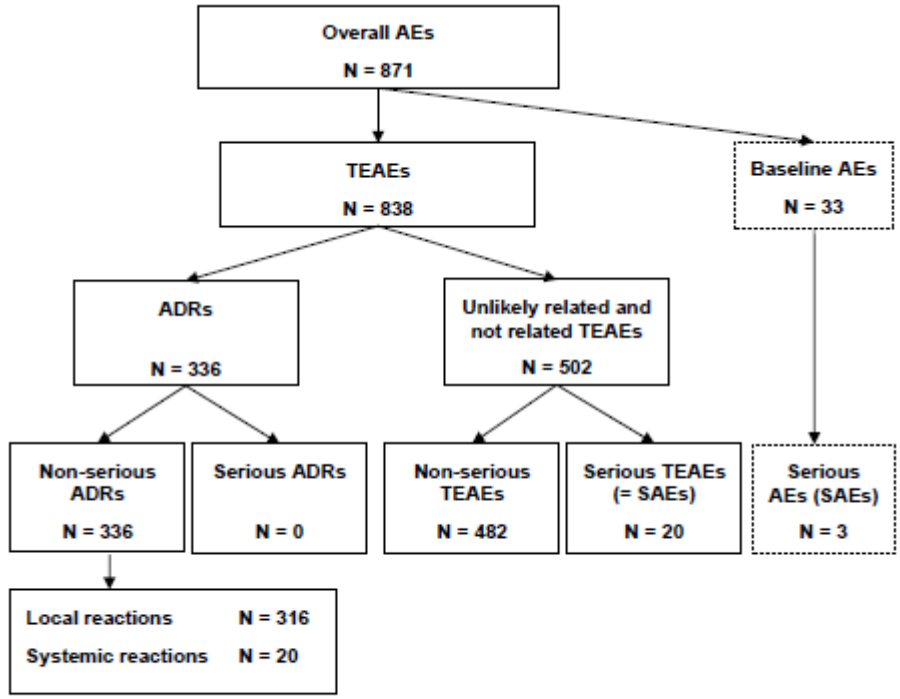
Under Depigoid® Mite Mix treatment, 229 local reactions with 232 symptoms were reported for 44 patients (39.3%) and 87 local reactions with 91 symptoms occurred in 20 patients (35.7%) receiving placebo.
213 local reactions (93.0%) in the Depigoid® Mite Mix-group and 83 local reactions (95.4%) in the Placebo-group were of 'mild' intensity. None of the local reactions was of 'severe' intensity.
Systemic reactions were documented in 9 patients (8.0%) of the Depigoid® Mite Mix-group and in 6 patients (10.7%) of the Placebogroup.
14 systemic reactions with 17 symptoms in the Depigoid® Mite Mix-group and 6 systemic reactions with 8 symptoms in the Placebogroup.
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.

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).

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.
Regarding treatment-emergent SAEs in the subpopulation, 3 SAEs were reported in 3 patients of the Depigoid® Mite Mix-group and 6 SAEs in 4 patients of the Placebo group.

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.



N: Number of episodes in the safety set.

ADR	Active treatment (n = 112)	Placebo (n = 56)
Local reactions, no. of patients (%)/no. of reactions	44 (39.3)/229	20 (35.7)/87
Systemic reactions, no. of patients (%)/no. of reactions	9 (8)/14	6 (10.7)/6
Atopic dermatitis, no. of patients/no. of reactions	8/8	6/6
Asthma, no. of patients/no. of reactions	—	1/1
Dry eye, no. of patients/no. of reactions	1/1	—
Rhinitis, no. of patients/no. of reactions	1/1	—
Throat irritation, no. of patients/no. of reactions	1/1	—
Headache, no. of patients/no. of reactions	1/1	—
Vesicular eczema, no. of patients/no. of reactions	1/1	—
Erythema, no. of patients/no. of reactions	1/1	—
Generalized pruritus, no. of patients/no. of reactions	1/1	—
Skin lesion, no. of patients/no. of reactions	1/1	—
Flatulence, no. of patients/no. of reactions	1/1	—
Sensation of foreign body, no. of patients/no. of reactions	—	1/1

ADR, Adverse drug reaction.

7. Overall results of the clinical trials

The objective of this study was the comparison of the efficacy and tolerability of an Add-on-Therapy of Depigoid® Mite Mix 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 clinically relevant IgE-mediated sensitization against HDM (house dust mites) leading to aggravation of patient's skin lesions.

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. The mean Total SCORAD over 18 months of treatment was similar in both treatment groups. Analyzing only patients who already had a high Total SCORAD (> = 50) before the treatment, a significantly higher Total SCORAD was found in patients treated with Placebo compared to patients receiving Depigoid® Mite Mix. 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 after treatment with Depigoid® Mite Mix compare 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. The respective results regarding the medication consumption over 18 months of treatment merely indicated similar tendencies. Patients being treated with Depigoid® Mite Mix seem to have numerically lower medication consumption than patients receiving placebo, albeit this result was not significant. Also for the subpopulation, similar results were.
A difference in atopic exacerbations and time to exacerbation could not be assessed between both treatment groups.
But in the subpopulation, patients in the Depigoid® Mite Mix-group tended 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. In the PP set, this difference became statistically significant.
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). 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).

During this study, 145 patients of the overall population experienced a total of 880 TEAE symptoms during 838 TEAE episodes. For 96 patients under Depigoid® Mite Mix treatment, 576 TEAEs with 602 TEAE symptoms were documented; whereas under placebo treatment, in 49 patients, overall 262 TEAEs with 278 symptoms occurred. According to the investigators' assessment, 502 TEAEs were reported as being 'not related' or 'unlikely related' to study medication. The other 336 TEAEs were 'likely' or 'definitely' related and therefore classified as ADRs.
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aggravated' (4 symptoms), and 'Eczema' (3 symptoms). 2 of the systemic reactions, one in each treatment group, were of 'severe' intensity but not serious.
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Altogether, 20 treatment-emergent SAEs were reported in 12 patients, 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.

8. Comments on the outcome of the clinical trial

This study was planned in 2006 and started in 2007. Since that time, several other studies with similar indications and objectives have been performed. During these studies, knowledge was gained regarding factors affecting the study results. One of these factors is the time of inclusion of patients into the study. In this study, patients were included over a period of two years throughout the whole year compromising the comparability of patient data due to variable conditions during different seasons. Another factor associated with the inclusion time is the pollen exposure and concentration of co-allergens such as grass or tree pollen during the different seasons.
Data from patients obtained during the so-called pollen season are often affected by symptoms caused by co-allergies, whereas data obtained during the winter season are more relevant for diseases affected by HDM exposure. Due to these facts, the conditions at the study visits were highly different for all patients. For some patients, the treatment started out of the pollen season and ended in the pollen season, whereas it was the other way around for other patients. Also, the disease activity of atopic eczema was identified to have an impact on the study results. Given all these considerations, the originally planned analysis was extended with an analysis of a special subpopulation comprising patients with high baseline Total SCORAD (>50) at the time of enrolment.
Due to all these restrictions, the overall efficacy results obtained in this study were mostly lacking significance as they might have shown when not being influenced by the factors listed above.
However, the efficacy of Depigoid® Mite Mix in patients with moderate to severe atopic eczema with or without rhinitis and/or conjunctivitis caused by clinically relevant IgE-mediated sensitization against HDM leading to aggravation of patient's skin lesions was indicated by the results of several parameters.
During the 18 months of treatment, the Total SCORAD decreased indicating an improvement in the extent of skin lesions and in subjective symptoms like pruritus and sleep loss. This reduction was observed under treatment with Depigoid® Mite Mix as well as under treatment with placebo. However, by limiting the analyses to a population of patients with high baseline Total SCORAD scores only, the difference between Depigoid® Mite Mix and placebo groups in the Total SCORAD changes over time became statistically significant.

Patients under Depigoid® Mite Mix treatment have up to 32% less skin lesions and less subjective symptoms than patients being treated with placebo. Patients under Depigoid® Mite Mix treatment also seemed to apply less medication compared to placebo, what was already merely indicated after the first 6 months of treatment.
The improvement in patients' quality of life was assessed using a questionnaire assessing the impact of atopic eczema and generalized pruritus on patients' quality of life. During the overall study duration of 18 months and also during the first year of treatment, the quality of life improved indicated by decreasing DLQI scores. This improvement was experienced by patients in both treatment groups, as indicated by the non-significant differences in the comparison of pre-post differences calculated for each treatment group. In the subpopulation of patients with a high baseline Total SCORAD patients in the Depigoid® Mite Mix-group had a lower DLQI score than patients in the Placebo-group, indicating a lower impairment of quality of life under Depigoid® Mite Mix treatment. Efficacy was also assessed based on immune response data. Total and specific IgE-values decreased and Der. pter. IgG4-values increased after treatment with Depigoid® Mite Mix compared to placebo. Also, these results underlined the success of the Depigoid® Mite Mix therapy vs. placebo. Depigoid® Mite Mix appeared to reduce allergenicity (reduced IgE-values) and provides greater or retained immunogenicity (increase of IgG4-values).
In summary, the treatment with Depigoid® Mite Mix proved to be safe and well tolerated with no significant differences compared to placebo, especially in terms of local and systemic reactions after application of the study medication.

Overall efficacy analysis of the intention-to-treat and per-protocol study populations showed no statistically significant differences between the active treatment and placebo
groups. However, the subgroup of patients with severe AD (SCORAD > 50) showed a statistically significant reduction of the median total SCORAD by 18% (P 5 .02) compared with placebo. The frequency of adverse reactions was similar in both groups, suggesting the safety of the active treatment.

9. Indication if follow up clinical trials are forseen not yet decided

10. Indication where additional information could be found

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*