NOVARTIS

Clinical Development

Depigoid® *D. pteronyssinus*
Depigoid® Milben-Mix (*D. pteronyssinus & D. farinae*)

Non-interventional Study Report

Specific immunotherapy with Depigoid® *D. pteronyssinus* and Depigoid® *Milben-Mix* under clinical routine conditions (DepiMilb / DepiMilb Kinder)

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ADR	Adverse Drug Reaction
AE	Adverse Event
AMG	German Medicinal Products Act (*Arzneimittelgesetz*)
CRF	Case Report Form
D.	*Dermatophagoides*
DPP	Biological Unit (1 DPP = 1 HEP_L, after Depigmentation and Polymerization). HEP_L = Histamine Equivalent Prick Test LETI
EPI	Epidemiological Analysis Set
FAS	Full Analysis Set
FPFV	First Patient First Visit
FSA	Freiwillige Selbstkontrolle für die Arzneimittelindustrie e.V. (Voluntary Self-Regulation for the Pharmaceutical Industry; registered association)
ICD-10	International Classification of Diseases, 10th Revision
IgE	Immunoglobulin E
L 13 …	Refers to listing no. … in Appendix Volume 1
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of Valid or Evaluable Cases
N/A	Not Applicable
nsADR	Non-serious Adverse Drug Reaction
nsAE	Non-serious Adverse Event
nsAEnr	Non-serious Adverse Event not related to drug treatment
PT	Preferred Term (MedDRA)
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SIT	Specific Immunotherapy
SmPC	Summary of Product Characteristics (*Fachinformation*)
SOC	System Organ Class (MedDRA)
T 13 …	Refers to table no. … in Appendix Volume 1
vfa	Verband forschender Arzneimittelhersteller (Association of Research-Based Pharmaceutical Companies)

1 Abstract

Title	Specific immunotherapy with Depigoid® *D. pteronyssinus* and Depigoid® Milben-Mix under clinical routine conditions (DepiMilb / DepiMilb Kinder)
Keywords	Specific immunotherapy
Rationale and background	The present non-interventional study was conducted to collect – under clinical routine conditions – information about the therapy with Depigoid® *D. pteronyssinus* and Depigoid® Milben-Mix in children and adults.
Research question and objectives	• Investigation of the effectiveness of the therapy by evaluating nose, eye and lung related symptoms, specific asthma symptoms, and the use of concomitant anti-allergic medication (at the start of the study, and after 1 and 2 years of treatment). • Physician's and patient's or parent's assessment of effectiveness and tolerability. • Evaluation of the patient's disease related quality of life. • Collection of data on the dose regimens used under clinical routine conditions, the occurrence of adverse events during therapy, and the patients' exposure to allergens. • Epidemiologic survey at the beginning of the study to gather information about the treatment of patients allergic to domestic mites.
Study design	This was a prospective, multi-center, non-interventional study. Individual patients were observed over a period of 2 years. Medical findings were documented at the start of treatment, and 1, 12 and 24 months later. The 2-year observation of patients treated with Depigoid® *D. pteronyssinus* or Depigoid® Milben-Mix was supplemented by a 3-month epidemiological survey at the beginning of the study to gather information about the treatment of patients allergic to domestic mites in general.
Setting	The study was conducted in the practices of allergists and dermatologists in Germany.
Subjects and study size, including dropouts	220 patients (117 adults and 103 children) were enrolled at 70 study centers. The following key inclusion criteria were applied: (1) patient ≥ 5 years of age; (2) confirmed IgE mediated immediate hypersensitivity (type 1) which – independently from the study – the patient's physician had decided to treat with Depigoid® *D. pteronyssinus* or Depigoid® Milben-Mix, and (3) positive skin test result, and if available, in vitro reactivity against domestic mite and possibly against other allergens.
Variables and data sources	Demographics, medical history, information on exposure to allergens (living situation and remedial measures taken), health-related quality of life assessed by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), rating of severity of allergy related symptoms and use of concomitant anti-allergic medication, details of therapy, physician's and patient's assessment of the tolerability and effectiveness of the therapy, occurrence of adverse events. The data were collected by means of paper case report forms.
Results	219 of the 220 patients enrolled (116 adults; 103 children) were included in the full analysis set (FAS) as they received Depigoid® D. pteronyssinus or Depigoid® MilbenMix and had at least one follow-up examination documented. Approximately 90% of the patients were documented 12 months after the start of therapy and approximately 75% after 24 months. The adult patients were, on average, 38 years old at study entry, the children 11 years. Approximately 50% of the adults and 60% of

the children were male. Almost all patients were treated with Depigoid® Milben-Mix.

During the course of the study, an improvement of the total sum score of symptoms was observed in the majority of patients; worsening of the sum score was rare:

Total sum score of symptoms: Changes over time (FAS; LOCF)

	Adults				
	Improved	No change	Worsened	Missing data	
Change …	N (%)	N (%)	N (%)	N (%)	p
12 mo. *vs.* baseline	83 (71.6)	10 (8.6)	5 (4.3)	18 (15.5)	*
24 mo. *vs.* baseline	88 (75.9)	11 (9.5)	0 (0.0)	17 (14.7)	*

	Children				
	Improved	No change	Worsened	Missing data	
Change …	N (%)	N (%)	N (%)	N (%)	p
12 mo. *vs.* baseline	81 (78.6)	6 (5.8)	6 (5.8)	10 (9.7)	*
24 mo. *vs.* baseline	82 (79.6)	6 (5.8)	6 (5.8)	9 (8.7)	*

* McNemar test (improved *vs.* worsened): $p < .0001$

On average, the total sum score of symptoms decreased by 4 – 5 points over the observation period from approximately 7 points at baseline to 3 – 4 points at 12 and 24 months (21-point scale: *0 = no symptoms; 21 = all 3 main symptoms and 4 specific asthma symptoms severe*). The median change from month 12 to month 24 was a decrease by 1 point in adults and in children ($N_{missing}$: 34% of the adults and 25% of the children due to premature discontinuations). The analysis of the data stratified by study completion status revealed no substantial differences in baseline values or change values (month 12 *vs.* baseline) between patients who discontinued therapy prematurely and patients who completed the full 24 months of therapy.

Both in adults and in children, the use of concomitant anti-allergic medications became less frequent during the observation period. An improvement (reduction) of the sum score of concomitant medications was observed in approximately 50% of the adults and 60% of the children at both assessments.

In the majority of cases (~ 80% of the adults; ~ 90% of the children at 12 months), the physician assessed the effectiveness and the tolerability of treatment with Depigoid® D. pteronyssinus or Depigoid® Milben-Mix as good or very good. Similarly positive assessments were obtained from the patients themselves.

The positive assessment of the tolerability of the treatments was supported by adverse event data: Two patients experienced adverse events that were classified as serious adverse drug reactions. One patient experienced an anaphylactic reaction after administration of the first dose of Depigoid® Milben-Mix (2 DPP), another patient experienced an exacerbation of an infection which was classified as *possibly related to treatment.* All other (possibly) treatment related adverse events (AEs) reported were transient, mild to moderate injection site conditions such as erythema, pain and swelling. Such conditions were observed in 1 adult and 6 children.

The RQLQ data collected indicate that, on average, the health-related quality of life improved during the course of the study. In adults and older children, the RQLQ total score as well as all RQLQ domain scores were improved (decreased) by more than 0.5 points, on average, at 12 months after baseline.

Discussion	In summary, the data collected in this study showed that treatment with Depigoid® Milben-Mix and Depigoid® *D. pteronyssinus* was effective, well tolerated and safe in adults as well as in children. However, the fact that all non-serious AEs reported were injection site conditions might suggest that other types of AEs, particularly AEs that were not serious and not obviously related to the administration Depigoid® Milben-Mix or Depigoid® *D. pteronyssinus w*ere under-reported. Thus, general conclusion regarding the safety of treatment with Depigoid® Milben-Mix or Depigoid® *D. pteronyssinus* may be drawn from the present data only with due reservation.
Conclusion	The data collected in this study showed that treatment with Depigoid® Milben-Mix and Depigoid® D. pteronyssinus was effective, well tolerated and safe in the patient population studied.
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A list of all collaborating institutions and investigators is available upon request.

4 Milestones

Table 4-1 gives an overview of the milestones of the study. There were no relevant discrepancies between planned and actual dates.

Table 4-1: Study milestones

Milestone	Planned date	Actual date
Start of data collection	March 2011 *	04 February 2011
End of patient enrollment	September 2011 *	17 October 2013
End of data collection	September 2013 *	31 December 2013
Deadline for submission of CRFs	31 October 2013 *	15 December 2013
Final report of study results	January 2014	25 September 2014

* according to study protocol v1.2, dated 17 Sep 2012
CRF = case report form

5 Rationale and background

Since 2005, Depigoid® *D. pteronyssinus* and Depigoid® Milben-Mix – a combination of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* extracts – have been approved in Germany for the subcutaneous specific immunotherapy (SIT; hyposensitization) of IgE[1] mediated allergic diseases caused by domestic mite[2] allergens. The clinical efficacy and safety of both products – as observed in clinical studies – is well documented.

The present non-interventional study was conducted to collect – under everyday conditions – information about the therapy with Depigoid® *D. pteronyssinus* and Depigoid® Milben-Mix in children and adults.

6 Research question and objectives

The present study was designed to collect information on the use of Depigoid® *D. pteronyssinus* and Depigoid® Milben-Mix under clinical routine conditions.

The following was planned:

- Investigation of the effectiveness of the therapy by evaluating nose, eye and lung related symptoms, specific asthma symptoms, and the use of concomitant anti-allergic medication (at the start of the study, and after 1 and 2 years of treatment).
- Physician's and patient's or parent's assessment of effectiveness and tolerability.
- Evaluation of the patient's health related quality of life (at the start of the study, and after 1 and 2 years of treatment).
- Documentation of adverse events occurring during the observation period.
- Acquisition of knowledge about the patients' exposure to allergens (living situation and related factors, remedial measures taken).
- Collection of epidemiologic and sociographic data to identify and characterize the patients.
- Documentation of the dose regimens used under clinical routine conditions.
- Supplementary epidemiological survey at the beginning of the study to gather information about the treatment of domestic mite allergies.

7 Amendments and updates to the protocol

The study was conducted according to the following documents:

- study protocol version 1.0, 25 May 2010,
- study protocol version 1.2, 17 September 2012,
- statistical analysis plan (SAP), version 1.0, 10 January 2013.

[1] Immunoglobulin E
[2] Referred to as "dust mite" in the tables of results in Appendix Volume 1.

Copies of these documents are provided in Appendix Volume 2 A.

8 Research methods

8.1 Study design

This was a prospective, multi-center, non-interventional study. In accordance with the German Medicinal Products Act (AMG), treatment, including the diagnosis and monitoring, followed current medical practice and not a predetermined trial protocol and the data collected in the study were analyzed using epidemiological methods.

Individual patients were observed over a period of 2 years. In accordance with medical routine under every day conditions, medical findings were documented at the start of treatment (start of observation period; baseline), and 4 weeks, 12 months, and 24 months after the start of treatment.

Treatment consisted of two phases: (1) the build-up phase, and (2) the maintenance phase; see also Section 8.2.

The 2-year observation of patients treated with Depigoid® *D. pteronyssinus* or Depigoid® Milben-Mix was supplemented by a 3-month epidemiological survey at the beginning of the study to gather information about the treatment of domestic mite allergies in general.

The study was conducted in compliance with internal standard operating procedures of Novartis Pharma GmbH and Winicker Norimed GmbH, which were based on the following laws, directives and guidelines:

- § 4 (23) 3rd sentence of the German Medicinal Products Act (Arzneimittelgesetz),
- § 67 (6) of the German Medicinal Products Act,
- § 63 b of the German Medicinal Products Act,
- Directive 2001/83/EC of the European Parliament and of the Council,
- Pharmacovigilance Guidelines of Volume 9A of 'The Rules Governing Medicinal Products in the European Union',
- the joint recommendations of the [German] Federal Institute for Drugs and Medical Devices and the Paul Ehrlich Institute on the planning, execution, and evaluation of observational studies (Bundesinstitut für Arzneimittel und Medizinprodukte & Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel 2010),
- the vfa[3] recommendations on improving the quality and transparency of non-interventional studies (Verband Forschender Arzneimittelhersteller e.V. 2007a, 2007b),
- the FSA[4] Code (Freiwillige Selbstkontrolle für die Arzneimittelindustrie e.V. (FSA) 2008).

[3] Verband Forschender Arzneimittelhersteller e.V. (Association of Research-Based Pharmaceutical Companies)

Before the start of the study, the ethics committee responsible for the medical leader of this study was consulted and a favorable vote was obtained.

Prior to inclusion of a patient in the study, the study objectives and the nature and the extent of the documentation were explained in writing to each patient or his/her legal representative by the treating physician. Written consent regarding the documentation of data in the context of this study and regarding the inspection of the patient's medical records for source data verification was a prerequisite for inclusion of the patient in the study.

8.2 Setting and treatments

The study was conducted as a multi-center study in the practices of allergists and dermatologists in Germany. Approximately 300, non-selected, regionally widely distributed study centers were planned to be recruited by sales representatives of Novartis Pharma GmbH.

The medications studied, Depigoid® *D. pteronyssinus* and Depigoid® MilbenMix, were prescribed in accordance with current routine practice and the recommendations in the summary of product characteristics (SmPC; *Fachinformation*) (Appendix Volume 2 D). Treatment was exclusively determined by medical therapeutic needs. The patients were treated with commercially available products.

For both Depigoid® *D. pteronyssinus* and Depigoid® MilbenMix, the same treatment regimen was recommended (see the respective SmPC), i.e., a 4-week build-up regimen with escalating doses (2 DPP[5], 5 DPP, 20 DPP, and 50 DPP) administered at weekly intervals followed by a maintenance regimen with administration of 50 DPP every 4 weeks.

This regimen could be modified as deemed appropriate by the physician and a "quick build-up regimen" could be applied instead of the above described conventional regimen.

8.3 Subjects

Approximately 900 patients (3 patients per practice) were planned to be included.

Patients fulfilling the following criteria were eligible:

- Male or female patient ≥ 5 years of age.
- Confirmed IgE mediated immediate hypersensitivity (type 1) which – independently from the study – the patient's physician had decided to treat with Depigoid® *D. pteronyssinus* or Depigoid® Milben-Mix.
- Positive skin test and, if available, *in vitro* reactivity against domestic mite and possibly against other allergens.

[4] Freiwillige Selbstkontrolle für die Arzneimittelindustrie e.V. (Voluntary Self-Regulation for the Pharmaceutical Industry; registered association)
[5] DPP = biological unit (1 DPP = 1 HEP_L, after depigmentation and polymerization). HEP_L = histamine equivalent prick test LETI

- Informed consent by patient or legal representative.

There were no exclusion criteria apart from the contraindications listed in the SmPC.

The aimed-at ratio of children and adolescents (< 18 years of age)[6] to adults (≥ 18 years of age) was 1 : 1.

8.4 Variables

The following information was documented during the course of the study (see the sample case report form in Appendix Volume 2 C):

At start of therapy (baseline):

- Demographics:
  - age or date of birth,[7]
  - height,
  - body weight,
  - gender.
- Information on exposure to allergens:
  - living situation (city center, suburban, rural),
  - remedial measures taken to reduce the allergen load due to domestic mite,
  - grading of domestic mite exposure due to living situation (low, moderate, high, unclear).
- Diagnosis and history of domestic mite allergy:
  - IgE mediated immediate type allergy (to be ticked),
  - ICD-10[8] code,
  - time of first diagnosis,
  - other known sensitizations in addition to domestic mite,
  - symptoms (allergic rhinitis, allergic conjunctivitis, allergic asthma, atopic eczema, other).
- Severity of domestic mite allergy related symptoms during the previous 2 months
  - main symptoms (eye, nose and lung related symptoms)[9],
  - specific asthma symptoms (shortness of breath, chest tightness, wheezing, productive cough).

[6] For simplicity, all patients below 18 years of age will be referred to as "children" in the following sections.
[7] Year and month of birth for children
[8] International Classification of Diseases, 10th Revision
[9] Referred to as "cardinal symptoms" in the tables of results in Appendix Volume 1 and in the SAP.

- Anti-allergic medication during the previous 2 months (local antihistamines, systemic antihistamines, inhalative corticosteroids, oral corticosteroids, local corticosteroids for the nose, local corticosteroids for the eyes, inhalative beta-2-agonists).
- Prior treatment of domestic mite allergy (symptomatic or SIT treatment, time of first and last treatment, medications).
- Prescription of SIT with Depigoid® (extract to be used, planned start of SIT).
- Health-related quality of life assessed by means of the age-appropriate version of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (Juniper and Guyatt, 1991; Juniper *et al.*, 1994; Juniper *et al.*, 1996; Juniper *et al.*, 1998; Juniper and Styles, no year). For further details, Section 9.1.4.9.

1 month after start of therapy:

- Date and time of injections with Depigoid® *D. pteronyssinus* or Depigoid® Milben-Mix.
- Current treatment regimen.
- Occurrence of adverse events.
- Documentation of date and reasons for premature discontinuation of SIT, if applicable.
- Anti-allergic medication during the therapy (local antihistamines, systemic antihistamines, etc.; see above).
- Acceptance of treatment regimen.
- Physician's assessment of the tolerability of the therapy with Depigoid® *D. pteronyssinus* or Depigoid® Milben Mix.
- Patient's assessment of the tolerability of the therapy with Depigoid® *D. pteronyssinus* or Depigoid® Milben Mix.

12 months after start of therapy:

- Date and time of injections with Depigoid® *D. pteronyssinus* or Depigoid® Milben-Mix during the previous 11 months.
- Current treatment regimen.
- Occurrence of adverse events.
- Documentation of date and reasons for premature discontinuation of SIT, if applicable.
- Concomitant anti-allergic medication during the previous 2 months (local antihistamines, systemic antihistamines, etc.; see above).
- RQLQ (age-appropriate version).
- Severity of domestic mite allergy related symptoms during the previous 2 months:

  - main symptoms (eye, nose and lung related symptoms),
  - specific asthma symptoms (shortness of breath, chest tightness, wheezing, productive cough).
- Physician's assessment of the tolerability and effectiveness of the therapy with Depigoid® *D. pteronyssinus* or Depigoid® Milben Mix.
- Patient's assessment of the tolerability and effectiveness of the therapy with Depigoid® *D. pteronyssinus* or Depigoid® Milben Mix.
- Review of exposure to allergens:
  - living situation (inner city, outskirts, country),
  - remedial measures taken in the meantime to reduce the allergen load,
  - grading of domestic mite exposure due to living situation (low, moderate, high, unknown).

Final examination (24 months after start of therapy):

- Date and time of injections with Depigoid® *D. pteronyssinus* or Depigoid® Milben-Mix during the previous 12 months.
- Current treatment regimen.
- Occurrence of adverse events.
- Documentation of date and reasons for premature discontinuation of SIT, if applicable.
- Concomitant anti-allergic medication during the previous 2 months (local antihistamines, systemic antihistamines, etc., see above).
- RQLQ (age-appropriate version).
- Severity of domestic mite allergy related symptoms during the previous 2 months:
  - main symptoms (eye, nose and lung related symptoms),
  - specific asthma symptoms (shortness of breath, chest tightness, wheezing, productive cough).
- Physician's assessment of the tolerability and effectiveness of the therapy with Depigoid® *D. pteronyssinus* or Depigoid® Milben Mix.
- Patient's assessment of the tolerability and effectiveness of the therapy with Depigoid® *D. pteronyssinus* or Depigoid® Milben Mix.
- Review of exposure to allergens:
  - living situation (inner city, outskirts, country),
  - remedial measures taken in the meantime to reduce the allergen load,
  - grading of domestic mite exposure due to living situation (low, moderate, high, unknown).

8.5 Data sources and measurements

8.5.1 Case report forms

All data collected during the observational part of the study – except for health-related quality of life data – were documented in pseudonymized form in case report forms (CRFs; paper versions). There were two CRF versions, one for adults and one for children.

Health-related quality of life data were obtained by means of the RQLQ (age appropriate paper version[10]). The questionnaires were completed by the patients themselves or by their parents, if appropriate.

For the epidemiological survey, a separate report form, the physician's questionnaire ("*Praxisfragebogen*"), was used.

Sample copies of the CRFs, the RQLQs, and the physician's questionnaire are provided in Appendix Volume 2 C.

8.5.2 Documentation of adverse events

Definition: An "adverse event" (AE) is defined as any untoward medical occurrence in a subject to whom a medicinal product was administered, irrespective of whether the event was suspected to be causally related to a medicinal product.

The details of all adverse events that occurred during the study were documented in the CRF.

Serious adverse events

It was differentiated between non-serious and serious adverse events. Serious adverse events (SAE) were all events that

- were fatal,
- were life-threatening,
- resulted in inpatient hospitalization or a prolongation of existing hospitalization,
- resulted in inability to work[11], persistent or significant disability[12], or invalidity,
- resulted in a congenital anomaly or a birth defect,
- were medically relevant, i.e., affected the patient considerably, but did not meet any of the above criteria.

For further details, see the study protocol section 7.2 (Appendix Volume 2 A; both protocol versions).

[10] Three different versions of the RQLQ were used: a version for adults, a version for adolescents (12 – 17 years of age), and a version for young children (5 – 12 years of age); see Appendix Volume 2 C.
[11] The inability to work was understood as the consequence of persisting injury to health.
[12] Disability meant considerable disability or permanent damage.

8.5.3 Reporting of SAEs and pregnancies

The physicians were asked to report all SAEs and pregnancies directly to the sponsor; see the study protocol sections 7.2 and 7.3 (Appendix Volume 2 A; protocol version 1.2). Non-serious adverse events were directly reported to the involved CRO who informed the sponsor in regular terms on the occurrence of the respective events.

8.6 Bias

No particular measures to assess and address potential sources of bias were planned.

8.7 Study size

The study was planned to be performed with a representative sample of 5% of all office-based physicians practicing allergology in Germany. Assuming that there were approximately 6000 office-based allergologists in Germany in 2008[13], 300 practices/study centers were planned to be recruited. With 3 patients to be documented per center, a total of 900 patients were aimed for.

8.8 Data transformation

All data were analyzed without transformation.

For the definitions of derived variables such as the age (children only), refer to the SAP or the footnotes of the respective tables of results in Appendix Volume 1.

8.9 Statistical methods

SAS version 9.2 was used for all statistical analyses. Details of the analyses were specified in a statistical analysis plan (SAP). The SAP was finalized before data base lock for final analysis. Any deviations from the SAP in the final analysis are described in Section 8.9.3.

8.9.1 Data analysis

All data were analyzed descriptively using epidemiological methods. Therefore, all results, including *p*-values, were interpreted only descriptively. No adjustment for multiple testing was performed.

All analyses were performed by treatment (Depigoid® *D. pteronyssinus* or Depigoid® Milben-Mix) and by age class (adult or child). Patients were classified by age according to their age at

[13] http://www.schwarzeck.de/adressen/

study entry (<18 years *vs.* ≥18 years) and not by the CRF version used. An exception was made only for the analysis of RQLQ data, where the patients were classified according to the RQLQ version used. Classification by treatment was done according to the product documented first during the buildup phase (1st follow-up visit) or maintenance phase (2nd and 3rd follow-up visit). Potential later switches were not considered.

Descriptive analyses of numeric variables (interval or higher scale) comprised the number of valid or evaluable cases (N), mean, standard deviation (SD), minimum, 5% percentile, 1st quartile, median, 3rd quartile, 95% percentile, and maximum. Categorical variables (nominal or ordinal scale) were presented by absolute and relative frequencies.

Missing values were generally not replaced. However, some of the key analyses were repeated using the last observation carried forward (LOCF) approach for replacement of missing data; see Section 8.9.3. Implausibilities appearing during the analysis were treated adequately by changing the analysis and/or the analysis datasets; details are given in the SAP.

8.9.2 Analysis sets

The **safety population** included all patients enrolled who received at least one dose of Depigoid® *D. pteronyssinus* or Depigoid® Milben-Mix.

The **full analysis set (FAS)** included all patients of the safety population for whom at least one follow-up documentation was available. All analyses of the 2-year observational part of the study were based on the FAS.

The **epidemiological analysis set (EPI)** included all patients who were documented for the epidemiological survey ("*Praxisfragebogen*").

8.9.3 Any amendments to the plan of data analysis included in the study protocol with a rationale for the change

Except for the following deviations, the statistical analyses were carried out according to the study protocol, version 1.2, dated 17 September 2012, and the SAP, version 1.0, dated 10 January 2013:

- Relative frequencies were reported as non-adjusted frequencies, not as adjusted frequencies. Non-adjusted frequencies were preferred over adjusted frequencies because a substantial number of patients had missing values at 24 months after the baseline documentation.
- A safety population was defined in addition to the FAS in order to be able to consider patients with safety information but without any CRF follow-up documentation in the safety analysis.
- The variable *time interval between diagnosis and start of therapy* was calculated in addition to the variable *time interval between diagnosis and 1st visit*.
- A number of additional analyses were carried out:
  - Shift tables (baseline *vs.* 12 months or 24 months) were prepared to describe changes in the severity of main symptoms and specific asthma symptoms and the frequency of use of concomitant anti-allergic medication.
  - Spearman correlation coefficients were calculated to investigate the relationship between the length of the time interval between diagnosis and start of therapy on the one hand and the severity of main and specific asthma symptoms on the other hand.
  - McNemar tests were used to compare the frequency of improvements and worsening of symptoms.
  - The analyses of sum scores of main symptoms, specific asthma symptoms and concomitant anti-allergic medications at baseline and 12 months were repeated stratified by study completion status in order to gather information about patients who discontinued therapy and/or the study.
  - The key analyses of main symptoms, specific asthma symptoms and concomitant anti-allergic medications were repeated after replacement of missing data using the last observation carried forward (LOCF) approach. Observations were carried forward only from month 12 onwards. Missing observations at or before month 12 were not replaced.

8.10 Quality control

- All data management quality assurance measures were set out in a data management plan specific to the project and specified for the individual stages of data management:
  - check of the CRFs before data capture,
  - plausibility checks in the context of data capture,
  - data query plan with a catalogue of questions that led to queries at the study center,
  - implementation of an audit trail as per US Food and Drug Administration CFR21. Part 11 Standard,
  - comparison of CRFs and the database in the context of a database audit,
  - ensuring data integrity by recorded database closure,
  - data handling report for dealing with inconsistent data still existing after closure of the database.
- Data collection and data queries:

  All CRFs received at the clinical research organization responsible for data management (SIMW GmbH and Winicker Norimed GmbH) were registered in the study database and promptly checked for (S)AEs and/or hidden (S)AEs.

  Data were manually entered into an audit trail controlled database (single data entry).

  After data entry, defined basic data regarding demographics and course of the study was electronically verified on the basis of a previously defined query logic. Queries to the study centers for verification and amendment of the data were generated and sent to the sites. If there was no response, a written reminder was sent after about 2 weeks. Incompletely recorded AEs or hidden AEs were followed in the context of the data query according to the relevant standard operating procedures of Winicker Norimed GmbH.
- On-site monitoring was not conducted.

9 Results

9.1 2-year observation of patients treated with Depigoid® *D. pteronyssinus* or Depigoid® Milben-Mix

9.1.1 Participants

A total of 225 patients were enrolled in the 2-year observation part of this study (Table 9-1). 220 of these patients (117 adults, 103 children[14]) received Depigoid® *D. pteronyssinus* or Depigoid® MilbenMix (safety population). 219 of the 220 patients in the safety population had at least one follow-up examination documented and qualified therefore for the FAS. The 220th patient (012/01) was withdrawn from the study immediately after the first injection of Depigoid® MilbenMix. This patient was excluded from the FAS, since the SAE form was the only study document that was completed for this patient. For details of the adverse event that led to withdrawal of the patient, see Section 9.1.5.2.

Almost all patients were treated with Depigoid® Milben-Mix[15]. Only 7 patients (2 adults, 5 children) received Depigoid® *D. pteronyssinus*. Therefore, the following description of results does not differentiate between the two treatments. Please refer to the corresponding tables of results in Appendix Volume 1 for results by treatment group.

Table 9-1: Study population

	Enrolled	Safety population	FAS	12 months documented		24 months documented	
	N	N	N	N	%	N	%
Total	225	220	219	196	(87.1)	169	(75.1)
Adults total	120	117	116	101	(84.2)	86	(71.7)
Adults Mite mix	118	115	114	100	(84.7)	85	(72.0)
Adults *D. pteronyssinus*	2	2	2	1	(50.0)	1	(50.0)
Children total	105	103	103	95	(90.5)	83	(79.0)
Children Mite mix	100	98	98	90	(90.0)	79	(79.0)
Children *D. pteronyssinus*	5	5	5	5	(100.0)	4	(80.0)

Source: T 13.1-1.1

The patients were documented at 70 study centers in total between January 2011 and December 2013. 40 centers documented adults and 36 centers documented children. On average, 3.1 ± 1.87 patients (mean ± SD) were documented per center (safety population) (T 13.1-1.2[16]).

[14] For simplicity, all study participants < 18 years of age are referred to as "children".
[15] Referred to as "Mite mix" in the tables of results in Appendix Volume 1.
[16] "T 13…" refers to table no. … in Appendix Volume 1. "L 13…" refers to listing no. … in Appendix Volume 1.

Approximately 90% of the patients were documented 12 months after the start of therapy and approximately 75% after 24 months (Table 9-1). An overview of the patient disposition is given in T 13.1-1.3. The most common reasons given for discontinuing therapy were "patient lost to follow-up" and "patient's own request". None of the patients was reported to have discontinued therapy due to an adverse drug reaction. One patient was reported to have discontinued therapy due to lack of therapy adherence. However, for most of the patients with missing information at 12 or 24 months, no reason for therapy discontinuation was documented as the respective visits were missing completely.

9.1.2 Descriptive data

The following subsections give an overview of the demographic and baseline characteristics of the patients in the FAS. Demographic data for the safety population can be found in T 13.1-3.1-2.

9.1.2.1 Demographics

An overview of the demographic characteristics of the study population is given in Table 9-2 and Table 9-3. The male to female ratio was approximately 50:50 among the adults and 60:40 among the children. The adult patients were on average 38 years old, the children on average 11 years.

Table 9-2: Demographic characteristics (1) (FAS)

		Adults N = 116		**Children** N = 103	
		N	**(%)**	**N**	**(%)**
Sex	Male	55	(47.4)	60	(58.3)
	Female	60	(51.7)	43	(41.7)
	Missing	1	(0.9)	-	-

Source: T 13.1-3.1-1

Table 9-3: Demographic characteristics (2) (FAS)

		Adults N = 116	Children N = 103
Age [years] #	Mean ± SD	37.8 ± 15.1	11.2 ± 3.1
	Median (range)	36 (18– 82)	10.3 (5.4 – 18)
	Missing	1	-
Height [cm]	Mean ± SD	172.1 ± 9.0	146.2 ± 17.4
	Median (range)	171 (155 – 194)	146 (110 – 190)
	Missing	5	4
Weight [kg]	Mean ± SD	75.4 ± 14.6	43.6 ± 17.2
	Median (range)	75 (50 – 136)	39.5 (19 – 98)
	Missing	7	4
BMI [kg/m2]	Mean ± SD	25.4 ± 4.4	19.5 ± 4.0
	Median (range)	25.0 (16.8 – 43.9)	18.7 (12.8 – 30.2)
	Missing	7	4

Source: T 13.1-3.1-1
The children's ages were calculated in relation to the date of the 1st visit.

9.1.2.2 Allergen exposure at baseline

Table 9-4 gives an overview of the patients' allergen exposure at baseline. Roughly the same fraction of patients lived in the center of a city, a suburban region, and a rural region. Pre-study remedial measures[17] taken to reduce the domestic mite related allergen exposure were documented for approximately 50% of the adult patients and for approximately 80% the children. The most frequently documented measures in both groups were – in decreasing order – encasing of the mattress, anti-allergy bedclothes and anti-allergy mattress.

The overall exposure to domestic mites was judged to be *moderate* in approximately 60% of the adults and 50% of the children (physician's assessment based on information regarding the patient's living situation and remedial measures taken). *High* exposure was documented for approximately every seventh patient in both groups.

[17] Referred to as "remedial actions" in the tables of results in Appendix Volume 1.

Table 9-4: Allergen exposure at baseline (FAS)

		Adults N = 116		Children N = 103	
		N	**(%)**	**N**	**(%)**
Living situation	City center	41	(35.3)	38	(36.9)
	Suburban	32	(27.6)	27	(26.2)
	Rural	30	(25.9)	32	(31.1)
	Missing	13	(11.2)	6	(5.8)
Have any remedial measures already been taken to reduce allergen exposure due to domestic mites?	No	40	(34.5)	14	(13.6)
	Yes	62	(53.4)	87	(84.5)
	Unknown	10	(8.6)	1	(1.0)
	Missing	4	(3.4)	1	(1.0)
Remedial measures taken #	Anti-allergy mattress	23	(19.8)	24	(23.3)
	Anti-allergy bedclothes	32	(27.6)	47	(45.6)
	Mattress encasing	38	(32.8)	70	(68.0)
	Mattress vacuum cleaner	4	(3.4)	1	(1.0)
	Special filter for vacuum cleaner	5	(4.3)	17	(16.5)
	Air purifier (electronic or physical)	-	-	-	-
Physician's assessment of exposure to domestic mites resulting from living situation	Low	11	(9.5)	20	(19.4)
	Moderate	66	(56.9)	49	(47.6)
	High	15	(12.9)	16	(15.5)
	Unclear	20	(17.2)	14	(13.6)
	Missing	4	(3.4)	4	(3.9)

Source: T 13.1-3.2
multiple answers were possible.

9.1.2.3 Diagnosis of domestic mite allergy

The interval between the first diagnosis of domestic mite allergy and start of therapy varied between 0 and 23 years in adults and 0 and 13 years in children (Table 9-5). Worth noticing is that the mean interval between diagnosis and start of therapy was similar in adults and children, whereas the median interval was considerably shorter in adults than in children (0.6 years *vs.* 2.2 years).

Table 9-5: Interval between diagnosis and start of therapy (FAS)

		Adults N = 116	Children N = 103
Interval between diagnosis and start of therapy [years]	Mean ± SD	2.2 ± 4.0	2.8 ± 2.7
	Median (range)	0.6 (0.0 – 22.7)	2.2 (0.0 – 12.7)
	Missing	- -	- -

Source: T 13.1-3.3 - add

In adults, but not in children, the length of the time interval between diagnosis and start of therapy was weakly negatively correlated with the severity of the following main symptoms at baseline: symptoms affecting the nose, symptoms affecting the eyes, and sum score of main symptoms (Spearman correlation coefficients between -0.17 and -0.18; $p < 0.10$) (T 13.1-3.3 - add). In addition to that, a weak positive correlation between the length of the interval and the severity of the specific asthma symptom chest tightness was observed in adults (Spearman correlation coefficient = 0.20; $p < 0.10$). In children, only a weak positive correlation was observed between the length of the interval and the severity of the asthma symptom productive cough (Spearman correlation coefficient = 0.17; $p < 0.10$).[18]

The presence of an IgE mediated immediate type allergic disease was confirmed for approximately 90% of the patients in both groups (T 13.1-3.3). For approximately 10% of the patients, this information was not explicitly given (missing tick mark).

An overview of the ICD-10 codes documented for more than 10% of the patients in a group is given in Table 9-6. The code most frequently documented in both groups was *J30.3 – Other allergic rhinitis / perennial allergic rhinitis*.

Table 9-6: Diagnosis of domestic mite allergy: ICD-10 codes (FAS)

ICD-10 code		Adults N = 116		Children N = 103	
		N	(%)	N	(%)
J30.3	Other allergic rhinitis / perennial allergic rhinitis	64	(55.2)	51	(49.5)
J30.4	Allergic rhinitis, unspecified	17	(14.7)	10	(9.7)
J45.0	Predominantly allergic asthma	17	(14.7)	22	(21.4)
T78.4	Allergy, unspecified	2	(1.7)	17	(16.5)

Source: T 13.1-3.4
For this in-text table, confirmed ICD codes, which are marked with "G" in T 13.1-3.4, and codes without such a specification were aggregated.

9.1.2.4 Prior treatment of domestic mite allergy

Approximately every second child and 3 out of 4 adults had not received any treatment for their domestic mite allergy before the therapy with Depigoid® *D. pteronyssinus* or Depigoid® MilbenMix was started (Table 9-7). Among the patients who had received any prior treatment, symptomatic treatment dominated. On average, they received their first symptomatic treatment 3 years (adults: 3.17 ± 3.46 years, N = 22; children: 3.25 ± 2.41 years, N = 39) and their last symptomatic treatment 1 – 2 months before the baseline documentation (adults: 0.18 ± 0.37 years, N = 13; children: 0.09 ± 0.16 years, N = 30) (T 13.1-3.6).

A few patients had previously received multiannual SIT. The interval between the first multiannual SIT[19] and the baseline documentation varied between approximately 0.1 and 22 years in adults and between 3 and 7 years in children (T 13.1-3.6).

[18] Similar results were obtained when the correlation analyses were performed with the variable *interval between diagnosis and 1st visit* instead of the variable *interval between diagnosis and start of therapy* (T 13.1-3.3).
[19] The date of the last SIT was documented only in a few cases.

Details of prior anti-allergic medication were documented for none of the patients (T 13.1-3.7).

Table 9-7: Prior treatment of domestic mite allergy (FAS)

		Adults N = 116		Children N = 103	
		N	**(%)**	**N**	**(%)**
Has the domestic mite allergy been treated yet?	No	87	(75.0)	56	(54.4)
	Yes	28	(24.1)	47	(45.6)
	Symptomatic treatment	24	(20.7)	45	(43.7)
	Multiannual SIT	6	(5.2)	3	(2.9)
	Missing	1	(0.9)	-	-

Source: T 13.1-3.6

9.1.2.5 Domestic mite allergy symptoms at baseline

Table 9-8 gives an overview of the main symptoms of domestic mite allergy at baseline. Most patients suffered from allergy symptoms affecting the nose (adults: 99.2%; children: 92.2%); and often, these symptoms were graded as *severe* (adults: 29.3%; children: 25.2%). Symptoms affecting the eyes or the lung were less common (adults: 84.5% and 62.9%, respectively; children: 60.2% and 63.2%, respectively). The most common specific asthma symptoms were productive cough and shortness of breath (Table 9-9).

The corresponding mean sum scores were all in the lower halves of the respective measurement scales[20]: The mean sum score of main symptoms was 4.7 ± 1.8 in adults and 4.0 ± 1.7 in children (9-point scale) (Table 9-10). The mean sum score of specific asthma symptoms was 2.8 ± 2.8 in adults and 3.2 ± 3.2 in children (12-point scale) (Table 9-11) and the mean total sum score of symptoms was 7.5 ± 4.0 in adults and 7.2 ± 4.4 in children (21-point scale) (Table 9-12).

[20] The severity of main symptoms and specific asthma symptoms was graded using a 4-point scale ranging from 0 = *not at all* to 3 = *severe*.

Sum scores of main symptoms could range from *0 = no symptoms* to *9 = all three main symptoms severe*. Sum scores of specific asthma symptoms could range from *0 = no symptoms* to *12 = all four specific asthma symptoms severe*. Total sum scores of symptoms could range from *0 = no symptoms* to *21 = all 3 main symptoms and 4 specific asthma symptoms severe*.

Table 9-8: Main symptoms of domestic mite allergy at baseline (FAS)

Symptoms affecting the …	Severity *	Adults N = 116		Children N = 103	
		N	**(%)**	**N**	**(%)**
Nose	0 Not at all	1	(0.9)	7	(6.8)
	1 Mild	22	(19.0)	22	(21.4)
	2 Moderate	59	(50.9)	47	(45.6)
	3 Severe	34	(29.3)	26	(25.2)
	Missing	-	-	1	(1.0)
	Median score	**2.0**		**2.0**	
Eyes	0 Not at all	17	(14.7)	40	(38.8)
	1 Mild	29	(25.0)	29	(28.2)
	2 Moderate	53	(45.7)	27	(26.2)
	3 Severe	16	(13.8)	6	(5.8)
	Missing	1	(0.9)	1	(1.0)
	Median score	**2.0**		**1.0**	
Lung	0 Not at all	43	(37.1)	37	(35.9)
	1 Mild	36	(31.0)	24	(23.3)
	2 Moderate	31	(26.7)	29	(28.2)
	3 Severe	6	(5.2)	12	(11.7)
	Missing	-	-	1	(1.0)
	Median score	**1.0**		**1.0**	

Source: T 13.2-1.1.1, T 13.2-1.2.1, T 13.2-1.3.1
* Definitions according to CRF:
Mild ≈ present but not annoying (*leicht ≈ vorhanden, aber nicht störend*); moderate ≈ annoying but not disabling or unbearable (*mäßig ≈ störend, aber nicht behindernd oder unerträglich*); severe ≈ disabling and/or unbearable (*schwer ≈ behindernd und/oder unerträglich*).

Table 9-9: Specific asthma symptoms at baseline (FAS)

Symptom	Severity *	Adults N = 116		Children N = 103	
		N	**(%)**	**N**	**(%)**
Shortness of breath	0 Not at all	52	(44.8)	52	(50.5)
	1 Mild	32	(27.6)	24	(23.3)
	2 Moderate	24	(20.7)	22	(21.4)
	3 Severe	6	(5.2)	4	(3.9)
	Missing	2	(1.7)	1	(1.0)
	Median score	**1.0**		**0.0**	
Chest tightness	0 Not at all	64	(55.2)	66	(64.1)
	1 Mild	31	(26.7)	21	(20.4)
	2 Moderate	19	(16.4)	13	(12.6)
	3 Severe	0	(0.0)	2	(1.9)
	Missing	2	(1.7)	1	(1.0)
	Median score	**0.0**		**0.0**	
Wheezing	0 Not at all	75	(64.7)	56	(54.4)
	1 Mild	28	(24.1)	17	(16.5)
	2 Moderate	9	(7.8)	23	(22.3)
	3 Severe	2	(1.7)	6	(5.8)
	Missing	2	(1.7)	1	(1.0)
	Median score	**0.0**		**0.0**	
Productive cough	0 Not at all	48	(41.4)	36	(35.0)
	1 Mild	38	(32.8)	31	(30.1)
	2 Moderate	22	(19.0)	26	(25.2)
	3 Severe	6	(5.2)	9	(8.7)
	Missing	2	(1.7)	1	(1.0)
	Median score	**1.0**		**1.0**	

Source: T 13.2-2.1.1, T 13.2-2.2.1, T 13.2-2.3.1, and T 13.2-2.4.1
* Definitions according to CRF:
Mild ≈ present but not annoying (*leicht ≈ vorhanden, aber nicht störend*); moderate ≈ annoying but not disabling or unbearable (*mäßig ≈ störend, aber nicht behindernd oder unerträglich*); severe ≈ disabling and/or unbearable (*schwer ≈ behindernd und/oder unerträglich*).

Table 9-10: Sum score of main symptoms at baseline (FAS)

		Adults N = 116	Children N = 103
Sum score of main symptoms #	Mean ± SD	4.7 ± 1.8	4.0 ± 1.7
	Median (range)	5.0 (0 – 9)	4.0 (0 – 9)
	Missing	- -	1 -

Source: T 13.2-1.4
Sum scores of main symptoms could range from *0 = no symptoms* to *9 = all three main symptoms severe*.

Table 9-11: Sum score of specific asthma symptoms at baseline (FAS)

		Adults N = 116	Children N = 103
Sum score of specific asthma symptoms #	Mean ± SD	2.8 ± 2.8	3.2 ± 3.2
	Median (range)	2.0 (0 – 11)	2.0 (0 – 11)
	Missing	2	1

Source: T 13.2-2.5
Sum scores of specific asthma symptoms could range from *0 = no symptoms* to *12 = all four specific asthma symptoms severe*.

Table 9-12: Total sum score of symptoms at baseline (FAS)

		Adults N = 116	Children N = 103
Sum score of all symptoms #	Mean ± SD	7.5 ± 4.0	7.2 ± 4.4
	Median (range)	7.0 (0 – 19)	6.0 (0 – 20)
	Missing	0	1

Source: T 13.2-3
Total sum scores of symptoms could range from *0 = no symptoms* to *21 = all 3 main symptoms and 4 specific asthma symptoms severe*.

9.1.2.6 Other allergies

A large proportion of patients was allergic not only to domestic mites but also to other allergens (adults: 57%; children: 72%), mainly trees and grasses (Table 9-13). An overview of the symptoms associated with these other allergies is given in Table 9-14. The majority of patients affected suffered from mild or moderate rhinitis, conjunctivitis, and/or asthma. Atopic eczema was less common. In single cases other symptoms such as fever or urticaria were documented (T 13.1-3.5). However, the data presented in Table 9-14 and T 13.1-3.5 must be interpreted with reservation: the discrepancy between the total number of children suffering from any other allergy (74 children) and the number of children suffering from allergic rhinitis (89 children), for example, raises doubts as to the physicians' interpretations of the respective questions in the CRF.

Table 9-13: Allergy diagnoses in addition to domestic mite allergy (FAS)

Allergens documented for ≥ 5% of the patients in a group

Allergen	Adults N = 116		Children N = 103	
	N	(%)	N	(%)
Any other allergen	66	(56.9)	74	(71.8)
Trees	39	(33.6)	52	(50.5)
Grasses	45	(38.8)	51	(49.5)
Animal epithelia	25	(21.6)	39	(37.9)
Herbs	22	(19.0)	17	(16.5)
Mold		< 5%	12	(11.7)

Source: T 13.1-3.5

Table 9-14: Severity of other allergies (FAS)

		Adults N = 116		Children N = 103	
		N	(%)	N	(%)
Rhinitis allergic	1 Mild	12	(10.3)	11	(10.7)
	2 Moderate	59	(50.9)	55	(53.4)
	3 Severe	39	(33.6)	23	(22.3)
	Unknown	5	(4.3)	6	(5.8)
Conjunctivitis allergic	1 Mild	22	(19.0)	33	(32.0)
	2 Moderate	50	(43.1)	32	(31.1)
	3 Severe	17	(14.7)	3	(2.9)
	Unknown	2	(1.7)	3	(2.9)
Allergic asthma	1 Mild	23	(19.8)	28	(27.2)
	2 Moderate	34	(29.3)	29	(28.2)
	3 Severe	5	(4.3)	13	(12.6)
	Unknown	2	(1.7)	1	(1.0)
Atopic eczema	1 Mild	23	(19.8)	18	(17.5)
	2 Moderate	11	(9.5)	7	(6.8)
	3 Severe	-	-	4	(3.9)
	Unknown	4	(3.4)	-	-

Source: T 13.1-3.5
For details of "other symptoms", see T 13.1-3.5.

9.1.2.7 Anti-allergic medication at baseline

Table 9-15 and Table 9-16 show the use of anti-allergic medication at baseline. Anti-allergic medication was used by the majority of patients at least on rare occasions. The 1st quartile of the sum score of anti-allergic medications[21] was 2.0 both in adults and children, indicating that either one class of medication was used *occasionally* or drugs from two classes were used *rarely* (T 13.2-4.8). The only medications used by more than 50% of the patients in a group were systemic antihistamines, which were used by 53.4% of the adults, and inhaled corticosteroids, which were used by 52.5% of the children. Medications *frequently* used by more than 10% of the adult patients were (in decreasing order) local corticosteroids for the nose, inhaled corticosteroids, and systemic antihistamines. Medications *frequently* used by more than 10% of the children were inhaled corticosteroids, systemic antihistamines, inhaled beta-2 agonists, and local corticosteroids for the nose.

In both groups, the median sum score of anti-allergic medications was in the lower range of the 21-point scale (adults: 4.0; children; 5.0) (Table 9-15).

Table 9-15: Sum score of anti-allergic medications at baseline (FAS)

		Adults N = 116	**Children** N = 103
Sum score of anti-allergic medications #	Mean ± SD	5.1 ± 4.4	5.5 ± 4.4
	Median (range)	4.0 (0 – 18)	5.0 (0 – 19)
	Missing	3	2

Source: T 13.2-4.8

Sum scores of anti-allergic medications could range from *0 = no medication* to *21 = all seven types of medication used frequently*.

[21] Sum scores of anti-allergic medications could range from *0 = no medication* to *21 = all seven types of medication used frequently*.

Table 9-16: Anti-allergic medication at baseline (FAS)

		Adults N = 116		Children N = 103	
		N	**(%)**	**N**	**(%)**
Topic antihistamines	0 Never	66	(56.9)	69	(67.0)
	1 Rarely	18	(15.5)	10	(9.7)
	2 Occasionally	22	(19.0)	13	(12.6)
	3 Frequently	8	(6.9)	10	(9.7)
	Missing	2	(1.7)	1	(1.0)
Systemic antihistamines	0 Never	52	(44.8)	55	(53.4)
	1 Rarely	13	(11.2)	8	(7.8)
	2 Occasionally	29	(25.0)	18	(17.5)
	3 Frequently	20	(17.2)	21	(20.4)
	Missing	2	(1.7)	1	(1.0)
Inhaled corticosteroids	0 Never	72	(62.1)	47	(45.6)
	1 Rarely	7	(6.0)	4	(3.9)
	2 Occasionally	14	(12.1)	11	(10.7)
	3 Frequently	21	(18.1)	39	(37.9)
	Missing	2	(1.7)	2	(1.9)
Oral corticosteroids	0 Never	92	(79.3)	90	(87.4)
	1 Rarely	7	(6.0)	4	(3.9)
	2 Occasionally	11	(9.5)	5	(4.9)
	3 Frequently	4	(3.4)	2	(1.9)
	Missing	2	(1.7)	2	(1.9)
Local corticosteroids for the nose	0 Never	61	(52.6)	62	(60.2)
	1 Rarely	13	(11.2)	10	(9.7)
	2 Occasionally	19	(16.4)	10	(9.7)
	3 Frequently	22	(19.0)	19	(18.4)
	Missing	1	(0.9)	2	(1.9)
Local corticosteroids for the eyes	0 Never	86	(74.1)	88	(85.4)
	1 Rarely	11	(9.5)	6	(5.8)
	2 Occasionally	13	(11.2)	1	(1.0)
	3 Frequently	4	(3.4)	6	(5.8)
	Missing	2	(1.7)	2	(1.9)
Inhaled beta-2 agonists	0 Never	84	(72.4)	52	(50.5)
	1 Rarely	5	(4.3)	8	(7.8)
	2 Occasionally	13	(11.2)	21	(20.4)
	3 Frequently	12	(10.3)	20	(19.4)
	Missing	2	(1.7)	2	(1.9)

Source: T 13.2-4.1.1, T 13.2-4.2.1, T 13.2-4.3.1, T 13.2-4.4.1, T 13.2-4.5.1, T 13.2-4.6.1, T 13.2-4.7.1

9.1.2.8 Depigoid® *D. pteronyssinus* or Depigoid® Milben Mix therapy regimens

Almost all patients were treated with Depigoid® Milben-Mix. Only 7 patients (2 adults, 5 children) received Depigoid® *D. pteronyssinus* (T 13.3-1.1-1).

Table 9-17 and Table 9-18 show the doses administered and the intervals between administrations during the build-up phase and during the maintenance phase (current

regimens at 12 and 24 months)[22]. The maintenance regimens generally followed the recommendations of the SmPC. Build-up regimens, in contrast, frequently deviated from the recommended scheme. The average mean dose administered to adults was higher than the recommended dose (mean and median: approx. 30 DPP as compared to approx. 20 DPP) and the average mean interval between administrations was approx. 2 weeks instead of 1 week. The build-up regimens used for children deviated less from the recommended regimen. However, when interpreting these data, it has to be taken into account that the time on therapy (T 13.3-1.6), the number of injections per phase (T 13.3-1.5), and the duration of the time period during which a regimen was constantly applied (T 13.3-1.4) varied considerably between patients.

Table 9-17: Doses administered [DPP] / current regimen (FAS)

Depigoid® Milben-Mix or Depigoid® *D. pteronyssinus*		**Adults** N = 116	**Children** N = 103
4 weeks (build-up phase) #	Mean ± SD	28.5 ± 10.6	22.2 ± 7.9
	Median	29.5	19.3
	5% perc. – 95% perc.	18 – 50.0	7.2 – 34.0
	Missing	1	2
12 months	Mean ± SD	50.0 ± 0.0	50.1 ± 1.0
	Median	50.0	50.0
	5% perc. – 95% perc	50.0 – 50.0	50.0 – 50.0
	Missing	17	11
24 months	Mean ± SD	49.4 ± 5.2	50.0 ± 0.0
	Median	50.0	50.0
	5% perc. – 95% perc	50.0 – 50.0	50.0 – 50.0
	Missing	40	25

Source: T 13.3-1.2.1
Mean of individual build-up injections during the past 4 weeks as documented at this visit. Note that in case of premature termination of therapy or documentation only the first few build-up injections are considered.
Ranges from the 5% percentile to the 95% percentile are presented in this in-text table to avoid the confusion possibly caused by single very low values the genuineness of which is uncertain.

[22] For means of injections in the months 2 to 12 and 13 to 24, see T 13.3-1.2.1 and T 13.3-1.3.

Table 9-18: Intervals between injections [days] / current regimen (FAS)

Depigoid® Milben-Mix or Depigoid® *D. pteronyssinus*		**Adults** N = 116	**Children** N = 103
4 weeks (build-up phase) #	Mean ± SD	16.0 ± 7.5	11.8 ± 8.0
	Median	15.4	9.3
	5% perc. – 95% perc.	7.0 – 31.2	7.0 – 25.1
	Missing	2	1
12 months	Mean ± SD	29.2 ± 3.0	29.4 ± 5.7
	Median	30.0	28.0
	5% perc. – 95% perc	28.0 – 30.0	20.0 – 40.0
	Missing	17	11
24 months	Mean ± SD	29.9 ± 4.1	29.5 ± 3.1
	Median	30.0	28.0
	5% perc. – 95% perc	28.0 – 39.0	28.0 – 35.0
	Missing	39	25

Source: T 13.3-1.3
: Mean of individual build-up injections during the past 4 weeks as documented at this visit. Note that in case of premature termination of therapy or of documentation only the first few build-up injections are considered.
Ranges from the 5% percentile to the 95% percentile are presented in this in-text table for consistency with the preceding in-text table.

9.1.3 Outcome data

Table 9-19 shows the number of evaluable patients for the key study variables. Please note that the number of evaluable patients decreased considerably during the course of the study (T 13.1-1.1).

Table 9-19: Key study variables – number of evaluable patients

Variables	**FAS**		**Safety population**	
	Adults	**Children**	**Adults**	**Children**
Main symptoms	116	103	-	-
Adverse events	-	-	117	103

Source: T 13.1-1.1; T 13.1-2.1

9.1.4 Main results

Note: The main focus of this study was on changes from baseline based on data as observed, i.e., without replacement of missing data. Therefore, primarily changes between baseline and month 12 or month 24 based on non-LOCF data are described below. These results are supplemented by the key results of LOCF-based analyses.

9.1.4.1 Main symptoms

9.1.4.1.1 Symptoms affecting the nose

Table 9-20 and Table 9-21 show the changes in the severity of allergy symptoms affecting the nose. An overview of the severity of such symptoms at baseline is given in Table 9-8. For further details, see T 13.2-1.1.1. Detailed shift tables are provided in T 13.2-1.1.2.

An improvement of symptoms affecting the nose was observed in approximately 50 – 60% of the patients (adults and children) at both assessments. Worsening of symptoms was rare – in particular in adults – and if it happened, it was of minor extent (1 point); see also shift table T 13.2-1.1.2.

The average (median) change was an improvement by 1 point[23] in both groups and at both assessments.

Table 9-20: Changes in the severity of allergy symptoms affecting the nose (overview) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	69	(59.5)	25	(21.6)	4	(3.4)	18	(15.5)	***
24 mo. *vs.* baseline	56	(48.3)	18	(15.5)	2	(1.7)	40	(34.5)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	58	(56.3)	32	(31.1)	3	(2.9)	10	(9.7)	***
24 mo. *vs.* baseline	53	(51.5)	17	(16.5)	8	(7.8)	26	(25.2)	***

Source: T 13.2-1.1.1
*** McNemar test (improved *vs.* worsened): $p < 0.001$.

[23] Note: Negative median "change scores" as tabulated for example in Table 9-21 indicate an improvement of the respective symptom. For simplicity this is described in the text as "improvement by … points" and not as a "change of +/- … points". The same applies – *mutatis mutandis* – to worsening of symptoms.

Table 9-21: Changes in the severity of allergy symptoms affecting the nose (details) (FAS)

	Change of …. grades	Adults N = 116		Children N = 103	
		N	**(%)**	**N**	**(%)**
12 months after baseline	-3	4	(3.4)	4	(3.9)
	-2	14	(12.1)	18	(17.5)
	-1	51	(44.0)	36	(35.0)
	0	**25**	**(21.6)**	**32**	**(31.1)**
	1	4	(3.4)	3	(2.9)
	2	-	-	-	-
	3	-	-	-	-
	Missing	18	(15.5)	10	(9.7)
	Median change	-1.0	***	-1.0	***
24 months after baseline	-3	8	(6.9)	5	(4.9)
	-2	16	(13.8)	15	(14.6)
	-1	32	(27.6)	32	(31.1)
	0	**18**	**(15.5)**	**17**	**(16.5)**
	1	2	(1.7)	8	(7.8)
	2	-	-	-	-
	3	-	-	-	-
	Missing	40	(34.5)	26	(25.2)
	Median change	-1.0	***	-1.0	***

Source: T 13.2-1.1.1
*** Wilcoxon signed rank test: $p < 0.001$.
The severity of main symptoms was graded using a 4-category scale ranging from *0 = not at all* to *3 = severe*. Negative "change scores" indicate an improvement of the symptom.

For adults, the analysis of LOCF data showed similar improvement rates in month 12 and month 24 (Table 9-22). The same applied to deterioration rates. In children, the improvement rate was slightly higher in month 24 than in month 12. For further details, see T 13.2-1.1.1 - addB.

Table 9-22: Changes in the severity of allergy symptoms affecting the nose (overview) (FAS; LOCF)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	69	(59.5)	25	(21.6)	4	(3.4)	18	(15.5)	***
24 mo. *vs.* baseline	72	(62.1)	23	(19.8)	3	(2.6)	18	(15.5)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	58	(56.3)	32	(31.1)	3	(2.9)	10	(9.7)	***
24 mo. *vs.* baseline	67	(65.0)	19	(18.4)	8	(7.8)	10	(9.7)	***

Source: T 13.2-1.1.1 – addB
*** McNemar test (improved *vs.* worsened): $p < 0.001$.

9.1.4.1.2 Symptoms affecting the eyes

Table 9-23 and Table 9-24 show the changes in the severity of allergy symptoms affecting the eyes. For further details, see T 13.2-1.2.1. Detailed shift tables are provided in T 13.2-1.2.2.

An improvement of symptoms affecting the eyes was observed in approximately 40 – 50% of the patients (adults and children) at both assessments.

Worsening of symptoms was rare – in particular in adults – and if it happened, it was generally of minor extent (1 point); see also shift table T 13.2-1.2.2.

In adults, the average (median) change was an improvement of 1.0 points at both assessments. In children, there was no change, on average, at both assessments.

Table 9-23: Changes in the severity of allergy symptoms affecting the eyes (overview) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	58	(50.0)	**31**	**(26.7)**	8	(6.9)	19	(16.4)	***
24 mo. *vs.* baseline	52	(44.8)	**19**	**(16.4)**	4	(3.4)	41	(35.3)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	42	(40.8)	**41**	**(39.8)**	10	(9.7)	10	(9.7)	***
24 mo. *vs.* baseline	37	(35.9)	**30**	**(29.1)**	11	(10.7)	26	(25.2)	***

Source: T 13.2-1.2.1
*** McNemar test (improved *vs.* worsened): p < 0.001.

Table 9-24: Changes in the severity of allergy symptoms affecting the eyes (details) (FAS)

	Change of …. grades	**Adults** N = 116		**Children** N = 103	
		N	**(%)**	**N**	**(%)**
12 months after baseline	-3	4	(3.4)	1	(1.0)
	-2	18	(15.5)	11	(10.7)
	-1	36	(31.0)	30	(29.1)
	0	**31**	**(26.7)**	**41**	**(39.8)**
	1	8	(6.9)	9	(8.7)
	2	-	-	1	(1.0)
	3	-	-	-	-
	Missing	19	(16.4)	10	(9.7)
	Median change	-1.0	***	-0.0	***
24 months after baseline	-3	4	(3.4)	1	(1.0)
	-2	19	(16.4)	13	(12.6)
	-1	29	(25.0)	22	(21.4)
	0	**19**	**(16.4)**	**30**	**(29.1)**
	1	4	(3.4)	10	(9.7)
	2	-	-	1	(1.0)
	3	-	-	-	-
	Missing	41	(35.3)	26	(25.2)
	Median change	-1.0	***	0.0	***

Source: T 13.2-1.2.1
*** Wilcoxon signed rank test: p < 0.001.
The severity of main symptoms was graded using a 4-category scale ranging from *0 = not at all* to *3 = severe*. Negative "change scores" indicate an improvement of the symptom.

For both adults and children, the analysis of LOCF data showed largely similar improvement rates in month 12 and month 24 (Table 9-25). The same applied to deterioration rates. For further details, see T 13.2-1.2.1 addB.

Table 9-25: Changes in the severity of allergy symptoms affecting the eyes (overview) (FAS; LOCF)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	58	(50.0)	31	(26.7)	8	(6.9)	19	(16.4)	***
24 mo. *vs.* baseline	65	(56.0)	27	(23.3)	5	(4.3)	19	(16.4)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	42	(40.8)	41	(39.8)	10	(9.7)	10	(9.7)	***
24 mo. *vs.* baseline	47	(45.6)	36	(35.0)	11	(10.7)	10	(9.7)	***

Source: T 13.2-1.2.1 - addB
*** McNemar test (improved *vs.* worsened): $p < 0.001$.

9.1.4.1.3 Symptoms affecting the lung

Table 9-26 and Table 9-27 show the changes in the severity of allergy symptoms affecting the lung. For further details, see T 13.2-1.3.1. Detailed shift tables are provided in T 13.2-1.3.2.

An improvement of symptoms affecting the lung was observed in approximately 40 – 50% of the patients (adults and children) at both assessments.

Worsening of symptoms was rare and if it happened, it was generally of minor extent (1 point); see also shift table T 13.2-1.3.2.

The symptom severity scores showed an improvement of 1.0 points, on average (medians), in adults at 24 months, and in children at 12 and 24 months after the baseline documentation. At 12 months, there was no change in the median symptom severity in adults.

Table 9-26: Changes in the severity of allergy symptoms affecting the lung (overview) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	47	(40.5)	43	(37.1)	8	(6.9)	18	(15.5)	***
24 mo. *vs.* baseline	42	(36.2)	32	(27.6)	2	(1.7)	40	(34.5)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	47	(45.6)	41	(39.8)	5	(4.9)	10	(9.7)	***
24 mo. *vs.* baseline	44	(42.7)	31	(30.1)	2	(1.9)	26	(25.2)	***

Source: T 13.2-1.3.1
*** McNemar test (improved *vs.* worsened): p < 0.001.

Table 9-27: Changes in the severity of allergy symptoms affecting the lung (details) (FAS)

	Change of …. grades	**Adults** N = 116		**Children** N = 103	
		N	**(%)**	**N**	**(%)**
12 months after baseline	-3	4	(3.4)	5	(4.9)
	-2	9	(7.8)	14	(13.6)
	-1	34	(29.3)	28	(27.2)
	0	**43**	**(37.1)**	**41**	**(39.8)**
	1	8	(6.9)	5	(4.9)
	2	-		-	
	3	-		-	
	Missing	18	(15.5)	10	(9.7)
	Median change	0.0 ***		-1.0 ***	
24 months after baseline	-3	1	(0.9)	5	(4.9)
	-2	10	(8.6)	19	(18.4)
	-1	31	(26.7)	20	(19.4)
	0	**32**	**(27.6)**	**31**	**(30.1)**
	1	2	(1.7)	2	(1.9)
	2	-		-	
	3	-		-	
	Missing	40	(34.5)	26	(25.2)
	Median change	-1.0 ***		-1.0 ***	

Source: T 13.2-1.3.1
*** Wilcoxon signed rank test: p < 0.001.
The severity of main symptoms was graded using a 4-category scale ranging from *0 = not at all* to *3 = severe*. Negative "change scores" indicate an improvement of the symptom.

For both adults and children, the analysis of LOCF data showed largely similar improvement rates in month 12 and month 24 (Table 9-28). The same applied to deterioration rates. For further details, see T 13.2-1.3.1 -addB.

Table 9-28: Changes in the severity of allergy symptoms affecting the lung (overview) (FAS; LOCF)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	47	(40.5)	43	(37.1)	8	(6.9)	18	(15.5)	***
24 mo. *vs.* baseline	52	(44.8)	44	(37.9)	2	(1.7)	18	(15.5)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	47	(45.6)	41	(39.8)	5	(4.9)	10	(9.7)	***
24 mo. *vs.* baseline	50	(48.5)	40	(38.8)	3	(2.9)	10	(9.7)	***

Source: T 13.2-1.3.1 - addB
*** McNemar test (improved *vs.* worsened): $p < 0.001$.

9.1.4.1.4 Sum score of main symptoms

Table 9-29 and Table 9-30 show the changes in the sum score of main symptoms. For further details, see T 13.2-1.4.

An improvement of the sum score of main symptoms was observed in approximately 60 – 70% of the patients (adults and children) at both assessments. Worsening of the sum score was rare (≤ 7%).

On average, the sum score decreased, i.e., improved, by 2 – 3 points over the observation period from 4 – 5 points at baseline to 2 – 3 points at 12 and 24 months.

An improvement of the sum score in the interval between 12 months and 24 months after the baseline documentation was observed in approximately 30% of the adults and children; worsening was observed in 10% of the adults and approximately 15% of the children.

Table 9-29: Sum score of main symptoms: Changes over time (frequency table) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	76	(65.5)	14	(12.1)	8	(6.9)	18	(15.5)	***
24 mo. *vs.* baseline	66	(56.9)	9	(7.8)	2	(1.7)	39	(33.6)	***
24 mo. *vs.* 12 mo.	40	(34.5)	24	(20.7)	12	(10.3)	40	(34.5)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	72	(69.9)	18	(17.5)	3	(2.9)	10	(9.7)	***
24 mo. *vs.* baseline	62	(60.2)	11	(10.7)	5	(4.9)	25	(24.3)	***
24 mo. *vs.* 12 mo.	35	(34.0)	26	(25.2)	16	(15.5)	26	(25.2)	*

Source: T 13.2-1.4
*** McNemar test (improved *vs.* worsened): $p < 0.001$.
* McNemar test (improved *vs.* worsened): $p < 0.05$

Table 9-30: Sum score of main symptoms: Changes over time (descriptive statistics) (FAS)

		Adults N = 116	Children N = 103
Baseline	Mean ± SD	4.7 ± 1.8	4.0 ± 1.7
	Median (range)	5.0 (0 – 9)	4.0 (0 – 9)
	Missing	0	1
Change 12 months *vs.* baseline	Mean ± SD	-2.3 ± 2.1	-2.1 ± 1.8
	Median (range)	-2.0 *** (-9 – 1)	-2.0 *** (-7 – 1)
	Missing	18	10
Change 24 months *vs.* baseline	Mean ± SD	-2.8 ± 2.0	-2.3 ± 2.0
	Median (range)	-3.0 *** (-9 – 1)	-2.0 *** (-7 – 1)
	Missing	39	25
Change 24 months *vs.* 12 months	Mean ± SD	-0.7 ± 1.5	-0.4 ± 1.6
	Median (range)	-1.0 *** (-4 – 4)	0.0 * (-4 – 3)
	Missing	40	26

Source: T 13.2-1.4
*** Wilcoxon signed rank test: $p < 0.001$.
* Wilcoxon signed rank test: $p < 0.05$.
Sum scores of main symptoms could range from *0 = no main symptoms* to *9 = all three main symptoms severe*. Negative "change scores" indicate an improvement of the symptom.

For both adults and children, the analysis of LOCF data showed similar improvement rates in month 12 and month 24 (Table 9-31). The same applied to deterioration rates. The degrees of change were also similar, on average, at both assessments (T 13.2-1.4 – addB).

Table 9-31: Sum score of main symptoms: Changes over time (frequency table) (FAS; LOCF)

	Adults N = 116				
Change …	**Improved N (%)**	**No change N (%)**	**Worsened N (%)**	**Missing data N (%)**	**p**
12 mo. *vs.* baseline	76 (65.5)	14 (12.1)	8 (6.9)	18 (15.5)	***
24 mo. *vs.* baseline	84 (72.4)	12 (10.3)	3 (2.6)	17 (14.7)	***

	Children N = 103				
Change …	**Improved N (%)**	**No change N (%)**	**Worsened N (%)**	**Missing data N (%)**	**p**
12 mo. *vs.* baseline	72 (69.9)	18 (17.5)	3 (2.9)	10 (9.7)	***
24 mo. *vs.* baseline	77 (74.8)	12 (11.7)	5 (4.9)	9 (8.7)	***

Source: T 13.2-1.4 - addB
*** McNemar test (improved *vs.* worsened): $p < 0.001$.

9.1.4.2 Specific asthma symptoms

9.1.4.2.1 Shortness of breath

Table 9-32 and Table 9-33 show the changes in shortness of breath. For further details, see T 13.2-2.1.1.

Approximately 40% of the adults and 50% of the children did not suffer from shortness of breath at baseline (Table 9-9). Accordingly, no changes in shortness of breath were observed in approximately 50% of the patients at 12 months after baseline and in 30 – 40% of the patients at 24 months after baseline. In most patients who suffered from this symptom at baseline, the symptom improved by 1 or 2 points over time; see also shift table T 13.2-2.1.2. Worsening of this symptom was rare and if it happened, it was of minor extent (1 point) in most cases.

Table 9-32: Changes in shortness of breath (overview) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	35	(30.2)	58	(50.0)	2	(1.7)	21	(18.1)	***
24 mo. *vs.* baseline	32	(27.6)	39	(33.6)	4	(3.4)	42	(36.2)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**P**
12 mo. *vs.* baseline	38	(36.9)	52	(50.5)	3	(2.9)	10	(9.7)	***
24 mo. *vs.* baseline	35	(34.0)	37	(35.9)	5	(4.9)	26	(25.2)	***

Source: T 13.2-2.1.1
*** McNemar test (improved *vs.* worsened): p < 0.001.

Table 9-33: Changes in shortness of breath (details) (FAS)

	Change of …. grades	**Adults** N = 116		**Children** N = 103	
		N	**(%)**	**N**	**(%)**
12 months after baseline	-3	2	(1.7)	1	(1.0)
	-2	11	(9.5)	15	(14.6)
	-1	22	(19.0)	22	(21.4)
	0	58	(50.0)	52	(50.5)
	1	2	(1.7)	3	(2.9)
	2	-	-	-	-
	3	-	-	-	-
	Missing	21	(18.1)	10	(9.7)
	Median change	0.0	***	0.0	***
24 months after baseline	-3	2	(1.7)	3	(2.9)
	-2	11	(9.5)	15	(14.6)
	-1	18	(15.5)	17	(16.5)
	0	39	(33.6)	37	(35.9)
	1	4	(3.4)	4	(3.9)
	2	-	-	1	(1.0)
	3	-	-	-	-
	Missing	42	(36.2)	26	(25.2)
	Median change	0.0	***	0.0	***

Source: T 13.2-2.1.1
*** Wilcoxon signed rank test: p < 0.001
The severity of specific asthma symptoms was graded using a 4-category scale ranging from *0 = not at all* to *3 = severe*. Negative "change scores" indicate an improvement of the symptom.

The analysis of LOCF data showed largely similar improvement rates in month 12 and month 24 (Table 9-34). The same applied to deterioration rates. For further details, see T 13.2-2.1.1 - addB.

Table 9-34: Changes in shortness of breath (overview) (FAS; LOCF)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	35	(30.2)	58	(50.0)	2	(1.7)	21	(18.1)	***
24 mo. *vs.* baseline	41	(35.3)	51	(44.0)	5	(4.3)	21	(18.1)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	38	(36.9)	52	(50.5)	3	(2.9)	10	(9.7)	***
24 mo. *vs.* baseline	42	(40.8)	46	(44.7)	5	(4.9)	10	(9.7)	***

Source: T 13.2-2.1.1 - addB
*** McNemar test (improved *vs.* worsened): $p < 0.001$.

9.1.4.2.2 Chest tightness

Table 9-35 and Table 9-36 show the changes in chest tightness. For further details, see T 13.2-2.2.1.

Approximately 60% of the patients did not suffer from chest tightness at baseline (Table 9-9). Accordingly, no changes in chest tightness were observed in 50 – 60% of the patients at 12 months after baseline and in 40 – 50% of the patients at 24 months after baseline. In most patients who suffered from this symptom at baseline, the symptom improved by 1 or 2 points over time; see also shift table T 13.2-2.2.2. Worsening of this symptom was rare and if it happened, it was of minor extent (1 point) in most cases.

Table 9-35: Changes in chest tightness (overview) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	36	(31.0)	57	(49.1)	2	(1.7)	21	(18.1)	***
24 mo. *vs.* baseline	30	(25.9)	44	(37.9)	0	(0.0)	42	(36.2)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**P**
12 mo. *vs.* baseline	26	(25.2)	64	(62.1)	3	(2.9)	10	(9.7)	***
24 mo. *vs.* baseline	28	(27.2)	46	(44.7)	3	(2.9)	26	(25.2)	***

Source: T 13.2-2.2.1
*** McNemar test (improved *vs.* worsened): p < 0.001.

Table 9-36: Changes in chest tightness (details) (FAS)

	Change of …. grades	**Adults** N = 116		**Children** N = 103	
		N	**(%)**	**N**	**(%)**
12 months after baseline	-3	-	-	1	(1.0)
	-2	10	(8.6)	8	(7.8)
	-1	26	(22.4)	17	(16.5)
	0	57	(49.1)	64	(62.1)
	1	2	(1.7)	3	(2.9)
	2	-	-	-	-
	3	-	-	-	-
	Missing	21	(18.1)	10	(9.7)
	Median change	0.0	***	0.0	***
24 months after baseline	-3	-	-	2	(1.9)
	-2	10	(8.6)	9	(8.7)
	-1	20	(17.2)	17	(16.5)
	0	44	(37.9)	46	(44.7)
	1	-	-	2	(1.9)
	2	-	-	1	(1.0)
	3	-	-	-	-
	Missing	42	(36.2)	26	(25.2)
	Median change	0.0	***	0.0	***

Source: T 13.2-2.2.1
*** Wilcoxon signed rank test: p < 0.001.
The severity of specific asthma symptoms was graded using a 4-category scale ranging from *0 = not at all* to *3 = severe*. Negative "change scores" indicate an improvement of the symptom.

The analyses of LOCF data showed largely similar improvement rates in month 12 and month 24 (Table 9-37). The same applied to deterioration rates. For further details, see T 13.2-2.2.1 - addB.

Table 9-37: Changes in chest tightness (overview) (FAS; LOCF)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	36	(31.0)	57	(49.1)	2	(1.7)	21	(18.1)	***
24 mo. *vs.* baseline	38	(32.8)	58	(50.0)	0	(0.0)	21	(18.1)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	26	(25.2)	64	(62.1)	3	(2.9)	10	(9.7)	***
24 mo. *vs.* baseline	32	(31.1)	57	(55.3)	4	(3.9)	10	(9.7)	***

Source: T 13.2-2.2.1 - addB
*** McNemar test (improved *vs.* worsened): $p < 0.001$.

9.1.4.2.3 Wheezing

Table 9-38 and Table 9-39 show the changes in wheezing (determined by auscultation). For further details, see T 13.2-2.3.1.

Approximately 50 - 60% of the patients did not present with wheezing at baseline (Table 9-9). Accordingly, no changes in wheezing were observed in approximately 50% of the patients at 12 months after baseline and in approximately 40% of the patients at 24 months after baseline. In most patients who suffered from this symptom at baseline, the symptom improved by 1 or 2 points over time; see also shift table T 13.2-2.3.2. Worsening of this symptom was rare and if it happened, it was of minor extent (1 point) in most cases.

Table 9-38: Changes in wheezing (overview) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	32	(27.6)	61	(52.6)	2	(1.7)	21	(18.1)	***
24 mo. *vs.* baseline	25	(21.6)	46	(39.7)	3	(2.6)	42	(36.2)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	38	(36.9)	52	(50.5)	3	(2.9)	10	(9.7)	***
24 mo. *vs.* baseline	35	(34.0)	40	(38.8)	2	(1.9)	26	(25.2)	***

Source: T 13.2-2.3.1
*** McNemar test (improved *vs.* worsened): p < 0.001.

Table 9-39: Changes in wheezing (details) (FAS)

	Change of …. grades	**Adults** N = 116	**Children** N = 103
		N (%)	**N (%)**
12 months after baseline	-3	1 (0.9)	4 (3.9)
	-2	4 (3.4)	10 (9.7)
	-1	27 (23.3)	24 (23.3)
	0	61 (52.6)	52 (50.5)
	1	2 (1.7)	2 (1.9)
	2	- -	1 (1.0)
	3	- -	- -
	Missing	21 (18.1)	10 (9.7)
	Median change	0.0 ***	0.0 ***
24 months after baseline	-3	1 (0.9)	4 (3.9)
	-2	6 (5.2)	16 (15.5)
	-1	18 (15.5)	15 (14.6)
	0	46 (39.7)	40 (38.8)
	1	3 (2.6)	2 (1.9)
	2	- -	- -
	3	- -	- -
	Missing	42 (36.2)	26 (25.2)
	Median change	0.0 ***	0.0 ***

Source: T 13.2-2.3.1
*** Wilcoxon signed rank test: p < 0.001.
The severity of specific asthma symptoms was graded using a 4-category scale ranging from *0 = not at all* to *3 = severe*. Negative "change scores" indicate an improvement of the symptom.

The analyses of LOCF data showed largely similar improvement rates in month 12 and month 24 (Table 9-40). The same applied to deterioration rates. For further details, see T 13.2-2.3.1 - addB.

Table 9-40: Changes in wheezing (overview) (FAS; LOCF)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	N	(%)	N	(%)	N	(%)	N	(%)	p
12 mo. *vs.* baseline	32	(27.6)	61	(52.6)	2	(1.7)	21	(18.1)	***
24 mo. *vs.* baseline	31	(26.7)	62	(53.4)	3	(2.6)	21	(18.1)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	N	(%)	N	(%)	N	(%)	N	(%)	P
12 mo. *vs.* baseline	38	(36.9)	52	(50.5)	3	(2.9)	10	(9.7)	***
24 mo. *vs.* baseline	40	(38.8)	51	(49.5)	2	(1.9)	10	(9.7)	***

Source: T 13.2-2.3.1 - addB
*** McNemar test (improved *vs.* worsened): $p < 0.001$.

9.1.4.2.4 Productive cough

Table 9-41 and Table 9-42 show the changes in productive coughing. For further details, see T 13.2-2.4.1.

Approximately 40% of the patients did not present with productive cough at baseline (Table 9-9). Accordingly, no changes in cough were observed in 30 - 40% of the patients at 12 and 24 months after baseline. In most patients who suffered from this symptom at baseline, the symptom improved by 1 or 2 points over time; see also shift table T 13.2-2.4.2. Worsening of this symptom was rare and if it happened, it was of minor extent (1 point) in most cases.

Table 9-41: Changes in productive cough (overview) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	46	(39.7)	46	(39.7)	3	(2.6)	21	(18.1)	***
24 mo. *vs.* baseline	40	(34.5)	32	(27.6)	2	(1.7)	42	(36.2)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	45	(43.7)	42	(40.8)	6	(5.8)	10	(9.7)	***
24 mo. *vs.* baseline	46	(44.7)	30	(29.1)	1	(1.0)	26	(25.2)	***

Source: T 13.2-2.4.1
*** McNemar test (improved *vs.* worsened): p < 0.001.

Table 9-42: Changes in productive cough (details) (FAS)

	Change of …. grades	**Adults** N = 116		**Children** N = 103	
		N	**(%)**	**N**	**(%)**
12 months after baseline	-3	2	(1.7)	3	(2.9)
	-2	8	(6.9)	16	(15.5)
	-1	36	(31.0)	26	(25.2)
	0	46	(39.7)	42	(40.8)
	1	2	(1.7)	6	(5.8)
	2	1	(0.9)	-	-
	3	-	-	-	-
	Missing	21	(18.1)	10	(9.7)
	Median change	0.0	***	0.0	***
24 months after baseline	-3	1	(0.9)	5	(4.9)
	-2	11	(9.5)	14	(13.6)
	-1	28	(24.1)	27	(26.2)
	0	32	(27.6)	30	(29.1)
	1	2	(1.7)	1	(1.0)
	2	-	-	-	-
	3	-	-	-	-
	Missing	42	(36.2)	26	(25.2)
	Median change	-1.0	***	-1.0	***

Source: T 13.2-2.4.1
*** Wilcoxon signed rank test: p < 0.001.
The severity of specific asthma symptoms was graded using a 4-category scale ranging from *0 = not at all* to *3 = severe*. Negative "change scores" indicate an improvement of the symptom.

For adults, the analysis of LOCF data showed largely similar improvement rates in month 12 and month 24 (Table 9-43). The same applied to deterioration rates. In children, the improvement rate was slightly higher in month 24 than in month 12. For further details, see T 13.2-2.4.1 addB.

Table 9-43: Changes in productive cough (overview) (FAS; LOCF)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	46	(39.7)	46	(39.7)	3	(2.6)	21	(18.1)	***
24 mo. *vs.* baseline	52	(44.8)	41	(35.3)	3	(2.6)	21	(18.1)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	45	(43.7)	42	(40.8)	6	(5.8)	10	(9.7)	***
24 mo. *vs.* baseline	54	(52.4)	37	(35.9)	2	(1.9)	10	(9.7)	***

Source: T 13.2-2.4.1 - addB
*** McNemar test (improved *vs.* worsened): $p < 0.001$.

9.1.4.2.5 Sum score of specific asthma symptoms

Table 9-44 and Table 9-45 show the changes in the sum score of specific asthma symptoms. For further details, see T 13.2-2.5.

An improvement of the sum score of specific asthma symptoms was observed in approximately 40 – 50% of the patients (adults and children) at both assessments. Worsening of the sum score was rare (< 7%).

On average, the sum score decreased, i.e., improved, by 2 – 3 points over the observation period from approximately 3 points at baseline to approximately 1 point at 12 and 24 months (means).

An improvement of the sum score in the interval between 12 months and 24 months after the baseline documentation was observed in approximately 20% of the adults and 30% of the children; worsening was observed in < 10% of the adults and children.

Table 9-44: Sum score of specific asthma symptoms: Changes over time (frequency table) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	60	(51.7)	32	(27.6)	3	(2.6)	21	(18.1)	***
24 mo. *vs.* baseline	48	(41.4)	24	(20.7)	3	(2.6)	41	(35.3)	***
24 mo. *vs.* 12 mo.	20	(17.2)	46	(39.7)	9	(7.8)	41	(35.3)	+

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	54	(52.4)	32	(31.1)	7	(6.8)	10	(9.7)	***
24 mo. *vs.* baseline	53	(51.5)	22	(21.4)	3	(2.9)	25	(24.3)	***
24 mo. *vs.* 12 mo.	29	(28.2)	40	(38.8)	8	(7.8)	26	(25.2)	***

Source: T 13.2-2.5
*** McNemar test (improved *vs.* worsened): $p < 0.001$.
+ McNemar test (improved *vs.* worsened): $p \geq 0.05$.

Table 9-45: Sum score of specific asthma symptoms: Changes over time (descriptive statistics) (FAS)

		Adults N = 116	Children N = 103
Baseline	Mean ± SD	2.8 ± 2.8	3.2 ± 3.2
	Median	2.0 (0 – 11)	2.0 (0 – 11)
	Missing	2	1
Change 12 months *vs.* baseline	Mean ± SD	-1.9 ± 2.4	-2.1 ± 2.8
	Median	-1.0 *** (-10 – 3)	-1.0 *** (-10 – 2)
	Missing	21	10
Change 24 months *vs.* baseline	Mean ± SD	-2.2 ± 2.6	-2.7 ± 3.1
	Median	-1.0 *** (-10 – 1)	-2.0 *** (-11 – 3)
	Missing	41	25
Change 24 months *vs.* 12 months	Mean ± SD	-0.2 ± 1.5	-0.6 ± 1.6
	Median	0.0 + (-4 – 6)	0.0 *** (-7 – 4)
	Missing	41	26

Source: T 13.2-2.5
*** Wilcoxon signed rank test: $p < 0.001$.
+ Wilcoxon signed rank test: $p \geq 0.05$.
Sum scores of specific asthma symptoms could range *from 0 = no specific asthma symptoms* to *12 = all four specific asthma symptoms severe*. Negative "change scores" indicate an improvement of the symptom.

For adults, the analysis of LOCF data showed similar improvement rates in month 12 and month 24 (Table 9-46). The same applied to deterioration rates. In children, the improvement rate was slightly higher in month 24 than in month 12. The degrees of change were similar, on average, at both assessments (T 13.2-2.5 – addB).

Table 9-46: Sum score of specific asthma symptoms: Changes over time (frequency table) (FAS; LOCF)

	Adults N = 116				
	Improved	No change	Worsened	Missing data	
Change …	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**p**
12 mo. *vs.* baseline	60 (51.7)	32 (27.6)	3 (2.6)	21 (18.1)	***
24 mo. *vs.* baseline	63 (54.3)	31 (26.7)	3 (2.6)	19 (16.4)	***

	Children N = 103				
	Improved	No change	Worsened	Missing data	
Change …	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**p**
12 mo. *vs.* baseline	54 (52.4)	32 (31.1)	7 (6.8)	10 (9.7)	***
24 mo. *vs.* baseline	62 (60.2)	28 (27.2)	4 (3.9)	9 (8.7)	***

Source: T 13.2-2.5 - addB
*** McNemar test (improved *vs.* worsened): $p < 0.001$.

9.1.4.3 Total sum score of symptoms

Table 9-47 and Table 9-48 show the changes in the total sum score of symptoms. For further details, see T 13.2-3.

An improvement of the total sum score of symptoms was observed in 60 – 80% of the patients (adults and children; both assessments). Worsening of the sum score was rare (< 6%).

On average, the total sum score decreased by 4 – 5 points over the observation period from approximately 7 points at baseline to 3 – 4 points at 12 and 24 months.

An improvement of the total sum score in the interval between 12 months and 24 months after the baseline documentation was observed in approximately 40% of the adults and children; worsening was observed in < 20% of the adults and children.

Table 9-47: Total sum score of symptoms: Changes over time (frequency table) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	83	(71.6)	10	(8.6)	5	(4.3)	18	(15.5)	***
24 mo. *vs.* baseline	69	(59.5)	8	(6.9)	0	(0.0)	39	(33.6)	***
24 mo. *vs.* 12 mo.	42	(36.2)	19	(16.4)	15	(12.9)	40	(34.5)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	81	(78.6)	6	(5.8)	6	(5.8)	10	(9.7)	***
24 mo. *vs.* baseline	67	(65.0)	6	(5.8)	5	(4.9)	25	(24.3)	***
24 mo. *vs.* 12 mo.	42	(40.8)	18	(17.5)	17	(16.5)	26	(25.2)	**

Source: T 13.2-3
*** McNemar test (improved *vs.* worsened): $p < 0.001$.
** McNemar test (improved *vs.* worsened): $p < 0.01$.

Table 9-48: Total sum score of symptoms: Changes over time (descriptive statistics) (FAS)

		Adults N = 116	Children N = 103
Baseline	Mean ± SD	7.5 ± 4.0	7.2 ± 4.4
	Median (range)	7.0 (0 – 19)	6.0 (0 – 20)
	Missing	0	1
Change 12 months *vs.* baseline	Mean ± SD	-4.2 ± 4.0	-4.2 ± 3.9
	Median (range)	-3.0 *** (-17 – 4)	-3.0 *** (-16 – 1)
	Missing	18	10
Change 24 months vs. baseline	Mean ± SD	-5.0 ± 3.9	-5.1 ± 4.4
	Median (range)	-4.0 *** (-18 – 0)	-4.5 *** (-18 – 4)
	Missing	39	25
Change 24 months *vs.* 12 months	Mean ± SD	-0.9 ± 2.2	-1.1 ± 2.6
	Median (range)	-1.0 *** (-5 – 7)	-1.0 *** (-10 – 6)
	Missing	40	26

Source: T 13.2-3
*** Wilcoxon signed rank test: $p < 0.001$.
Total sum scores of symptoms could range *from 0 = no symptoms* to 21 = *all seven symptoms severe*.
Negative "change scores" indicate an improvement of the symptom.

For both adults and children, the analysis of LOCF data showed similar improvement rates in month 12 and month 24 (Table 9-49; Figure 10-1). The same applied to deterioration rates. The degrees of change were also similar, on average, at both assessments (T 13.2-2.5 –addB).

Table 9-49: Total sum score of symptoms: Changes over time (frequency table) (FAS; LOCF)

	Adults N = 116				
	Improved	No change	Worsened	Missing data	
Change …	N (%)	N (%)	N (%)	N (%)	p
12 mo. *vs.* baseline	83 (71.6)	10 (8.6)	5 (4.3)	18 (15.5)	***
24 mo. *vs.* baseline	88 (75.9)	11 (9.5)	0 (0.0)	17 (14.7)	***

	Children N = 103				
	Improved	No change	Worsened	Missing data	
Change …	N (%)	N (%)	N (%)	N (%)	p
12 mo. *vs.* baseline	81 (78.6)	6 (5.8)	6 (5.8)	10 (9.7)	***
24 mo. *vs.* baseline	82 (79.6)	6 (5.8)	6 (5.8)	9 (8.7)	***

Source: T 13.2-3 - addB
*** McNemar test (improved *vs.* worsened): $p < 0.001$.

9.1.4.4 Anti-allergic concomitant medication

9.1.4.4.1 Topic antihistamines

Table 9-50 and Table 9-51 show the changes in the concomitant use of topic antihistamines. For further details, see T 13.2-4.1.1.

Approximately 60% of the adults and 70% of the children did not use any topic antihistamines at baseline (T 13.2-4.1.1). No changes in the use of this type of medication were observed in 50 – 60% of the patients at 12 months and in approximately 40% at 24 months after baseline. In most other patients, the use of this type of medication became less frequent over time. More frequent use was rare and if it occurred, the frequency of use was only slightly increased, except for one child who had never used topic antihistamines at baseline, but used them frequently at 24 months; see shift table T 13.2-4.1.2.

Table 9-50: Changes in concomitant use of topic antihistamines (overview) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	27	(23.3)	62	(53.4)	6	(5.2)	21	(18.1)	***
24 mo. *vs.* baseline	27	(23.3)	44	(37.9)	4	(3.4)	42	(36.2)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	28	(27.2)	63	(61.2)	2	(1.9)	10	(9.7)	***
24 mo. *vs.* baseline	26	(25.2)	45	(43.7)	5	(4.9)	27	(26.2)	***

Source: T 13.2-4.1.1
*** McNemar test (improved *vs.* worsened): p < 0.001.

Table 9-51: Changes in concomitant use of topic antihistamines (details) (FAS)

	Change of …. grades	**Adults** N = 116		**Children** N = 103	
		N	**(%)**	**N**	**(%)**
12 months after baseline	-3	1	(0.9)	5	(4.9)
	-2	11	(9.5)	12	(11.7)
	-1	15	(12.9)	11	(10.7)
	0	62	(53.4)	63	(61.2)
	1	6	(5.2)	2	(1.9)
	2	-	-	-	-
	3	-	-	-	-
	Missing	21	(18.1)	10	(9.7)
	Median change	0.0	***	0.0	***
24 months after baseline	-3	2	(1.7)	5	(4.9)
	-2	9	(7.8)	10	(9.7)
	-1	15	(12.9)	11	(10.7)
	0	44	(37.9)	45	(43.7)
	1	4	(3.4)	4	(3.9)
	2	-	-	-	-
	3	-	-	1	(1.0)
	Missing	42	(36.2)	27	(26.2)
	Median change	0.0	***	0.0	***

Source: T 13.2-4.1.1
*** Wilcoxon signed rank test: p < 0.001.
The use of concomitant medication was documented as follows: *0 = never, 1 = rarely, 2 = occasionally, and 3 = frequently*.
Negative "change scores" indicate that this type of medication was used less frequently by the patient.

For both adults and children, the analysis of LOCF data showed similar improvement rates in month 12 and month 24 (Table 9-52). The same applied to deterioration rates. For further details, see T 13.2-4.1.1 - addB.

Table 9-52: Changes in concomitant use of topic antihistamines (overview) (FAS; LOCF)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	27	(23.3)	62	(53.4)	6	(5.2)	21	(18.1)	***
24 mo. *vs.* baseline	32	(27.6)	59	(50.9)	5	(4.3)	21	(18.1)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	28	(27.2)	63	(61.2)	2	(1.9)	10	(9.7)	***
24 mo. *vs.* baseline	28	(27.2)	60	(58.3)	5	(4.9)	10	(9.7)	***

Source: T 13.2-4.1.1 - addB
*** McNemar test (improved *vs.* worsened): $p < 0.001$.

9.1.4.4.2 Systemic antihistamines

Table 9-53 and Table 9-54 show the changes in the concomitant use of systemic antihistamines. For further details, see T 13.2-4.2.1.

Approximately 40% of the adults and 50% of the children did not use any systemic antihistamines at baseline (T 13.2-4.2.1). No changes in the use of this type of medication were observed in 50% of the patients at 12 months and in 30 - 40% at 24 months after baseline. In most other patients, the use of this type of medication became less frequent over time.

Table 9-53: Changes in concomitant use of systemic antihistamines (overview) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	34	(29.3)	53	(45.7)	9	(7.8)	20	(17.2)	***
24 mo. *vs.* baseline	32	(27.6)	34	(29.3)	8	(6.9)	42	(36.2)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	37	(35.9)	49	(47.6)	7	(6.8)	10	(9.7)	***
24 mo. *vs.* baseline	35	(34.0)	37	(35.9)	5	(4.9)	27	(26.2)	***

Source: T 13.2-4.2.1
*** McNemar test (improved *vs.* worsened): p < 0.001.

Table 9-54: Changes in concomitant use of systemic antihistamines (FAS)

	Change of …. grades	**Adults** N = 116		**Children** N = 103	
		N	**(%)**	**N**	**(%)**
12 months after baseline	-3	5	(4.3)	7	(6.8)
	-2	11	(9.5)	14	(13.6)
	-1	18	(15.5)	16	(15.5)
	0	53	(45.7)	49	(47.6)
	1	7	(6.0)	4	(3.9)
	2	1	(0.9)	3	(2.9)
	3	1	(0.9)	-	-
	Missing	20	(17.2)	10	(9.7)
	Median change	0.0	***	0.0	***
24 months after baseline	-3	8	(6.9)	7	(6.8)
	-2	13	(11.2)	15	(14.6)
	-1	11	(9.5)	13	(12.6)
	0	34	(29.3)	37	(35.9)
	1	6	(5.2)	3	(2.9)
	2	-	-	1	(1.0)
	3	2	(1.7)	1	(1.0)
	Missing	42	(36.2)	27	(26.2)
	Median change	0.0	***	0.0	***

Source: T 13.2-4.2.1
* Wilcoxon signed rank test: p < 0.001.
Negative "change scores" indicate that this type of medication was used less frequently by the patient.

For both adults and children, the analysis of LOCF data showed similar improvement rates in month 12 and month 24 (Table 9-55). The same applied to deterioration rates. For further details, see T 13.2-4.2.1 - addB.

Table 9-55: Changes in concomitant use of systemic antihistamines (overview) (FAS; LOCF)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	34	(29.3)	53	(45.7)	9	(7.8)	20	(17.2)	***
24 mo. *vs.* baseline	37	(31.9)	48	(41.4)	11	(9.5)	20	(17.2)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	37	(35.9)	49	(47.6)	7	(6.8)	10	(9.7)	***
24 mo. *vs.* baseline	41	(39.8)	47	(45.6)	6	(5.8)	10	(9.7)	***

Source: T 13.2-4.2.1 – addB
*** McNemar test (improved *vs.* worsened): $p < 0.001$.

9.1.4.4.3 Inhaled corticosteroids

Table 9-56 and Table 9-57 show the changes in the concomitant use of inhaled corticosteroids. For further details, see T 13.2-4.3.1.

Approximately 60% of the adults and 50% of the children did not use any inhaled corticosteroids at baseline (T 13.2-4.3.1). No changes in the use of this type of medication were observed in approximately 60% of the patients at 12 months and in approximately 40% of the patients at 24 months after baseline. In most other patients, the use of this type of medication became less frequent over time. In two cases, however, a patient who had never used this type of medication started to use it frequently.

Table 9-56: Changes in concomitant use of inhaled corticosteroids (overview) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	25	(21.6)	64	(55.2)	6	(5.2)	21	(18.1)	***
24 mo. *vs.* baseline	21	(18.1)	52	(44.8)	2	(1.7)	42	(36.2)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	24	(23.3)	63	(61.2)	5	(4.9)	11	(10.7)	***
24 mo. *vs.* baseline	27	(26.2)	46	(44.7)	4	(3.9)	27	(26.2)	***

Source: T 13.2-4.3.1
*** McNemar test (improved *vs.* worsened): p < 0.001.

Table 9-57: Changes in concomitant use of inhaled corticosteroids (FAS)

	Change of …. grades	**Adults** N = 116		**Children** N = 103	
		N	**(%)**	**N**	**(%)**
12 months after baseline	-3	7	(6.0)	6	(5.8)
	-2	8	(6.9)	10	(9.7)
	-1	10	(8.6)	8	(7.8)
	0	64	(55.2)	63	(61.2)
	1	5	(4.3)	4	(3.9)
	2	1	(0.9)	-	-
	3	-	-	1	(1.0)
	Missing	21	(18.1)	11	(10.7)
	Median change	0.0	***	0.0	***
24 months after baseline	-3	4	(3.4)	11	(10.7)
	-2	9	(7.8)	8	(7.8)
	-1	7	(6.0)	7	(6.8)
	0	52	(44.8)	46	(44.7)
	1	1	(0.9)	2	(1.9)
	2	1	(0.9)	-	-
	3	-	-	2	(1.9)
	Missing	42	(36.2)	27	(26.2)
	Median change	0.0	***	0.0	***

Source: T 13.2-4.3.1
* Wilcoxon signed rank test: p < 0.001.
Negative "change scores" indicate that this type of medication was used less frequently by the patient.

For both adults and children, the analysis of LOCF data showed similar improvement rates in month 12 and month 24 (Table 9-58). The same applied to deterioration rates. For further details, see T 13.2-4.3.1 - addB.

Table 9-58: Changes in concomitant use of inhaled corticosteroids (overview) (FAS; LOCF)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	25	(21.6)	64	(55.2)	6	(5.2)	21	(18.1)	***
24 mo. *vs.* baseline	26	(22.4)	67	(57.8)	3	(2.6)	21	(18.1)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	24	(23.3)	63	(61.2)	5	(4.9)	11	(10.7)	***
24 mo. *vs.* baseline	30	(29.1)	58	(56.3)	5	(4.9)	11	(10.7)	***

Source: T 13.2-4.3.1 - addB
*** McNemar test (improved *vs.* worsened): $p < 0.001$.

9.1.4.4.4 Oral corticosteroids

Table 9-59 and Table 9-60 show the changes in the concomitant use of oral corticosteroids. For further details, see T 13.2-4.4.1.

Approximately 80% of the adults and 90% of the children did not use any oral corticosteroids at baseline (T 13.2-4.4.1). Accordingly, no changes in the use of this type of medication were observed in a high number of patients. In most other patients, the use of this type of medication became less frequent over time. In two cases, however, a patient who had never used this type of medication started to use it frequently.

Table 9-59: Changes in concomitant use of oral corticosteroids (overview) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	16	(13.8)	76	(65.5)	3	(2.6)	21	(18.1)	**
24 mo. *vs.* baseline	13	(11.2)	60	(51.7)	2	(1.7)	42	(36.2)	*

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	8	(7.8)	82	(79.6)	2	(1.9)	11	(10.7)	+
24 mo. *vs.* baseline	9	(8.7)	64	(62.1)	4	(3.9)	26	(25.2)	+

Source: T 13.2-4.4.1
** McNemar test (improved *vs.* worsened): p < 0.01
* McNemar test (improved *vs.* worsened): p < 0.05
+ McNemar test (improved *vs.* worsened): p ≥ 0.05

Table 9-60: Changes in concomitant use of oral corticosteroids (FAS)

	Change of …. grades	**Adults** N = 116	**Children** N = 103
		N (%)	**N (%)**
12 months after baseline	-3	2 (1.7)	2 (1.9)
	-2	9 (7.8)	3 (2.9)
	-1	5 (4.3)	3 (2.9)
	0	76 (65.5)	82 (79.6)
	1	2 (1.7)	1 (1.0)
	2	1 (0.9)	- -
	3	- -	1 (1.0)
	Missing	21 (18.1)	11 (10.7)
	Median change	0.0 **	0.0 +
24 months after baseline	-3	2 (1.7)	1 (1.0)
	-2	5 (4.3)	5 (4.9)
	-1	5 (4.3)	3 (2.9)
	0	60 (51.7)	64 (62.1)
	1	1 (0.9)	3 (2.9)
	2	- -	1 (1.0)
	3	1 (0.9)	- -
	Missing	42 (36.2)	26 (25.2)
	Median change	0.0 *	0.0 +

Source: T 13.2-4.4.1
** Wilcoxon signed rank test: p < 0.01
* Wilcoxon signed rank test: p < 0.05
+ Wilcoxon signed rank test: p ≥ 0.05
Negative "change scores" indicate that this type of medication was used less frequently by the patient.

For both adults and children, the analysis of LOCF data showed similar improvement rates in month 12 and month 24 (Table 9-61). The same applied to deterioration rates. For further details, see T 13.2-4.4.1 - addB.

Table 9-61: Changes in concomitant use of oral corticosteroids (overview) (FAS; LOCF)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	16	(13.8)	76	(65.5)	3	(2.6)	21	(18.1)	**
24 mo. *vs.* baseline	17	(14.7)	76	(65.5)	3	(2.6)	21	(18.1)	**

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	8	(7.8)	82	(79.6)	2	(1.9)	11	(10.7)	#
24 mo. *vs.* baseline	10	(9.7)	78	(75.7)	4	(3.9)	11	(10.7)	#

Source: T 13.2-4.4.1 - addB
** McNemar test (improved *vs.* worsened): $p < 0.01$.
# McNemar test (improved *vs.* worsened): $p \geq 0.05$.

9.1.4.4.5 Local corticosteroids for the nose

Table 9-62 and Table 9-63 show the changes in the concomitant use of local corticosteroids for the nose. For further details, see T 13.2-4.5.1.

Approximately 50% of the adults and 60% of the children did not use any local corticosteroids for the nose at baseline (T 13.2-4.5.1). No changes in the use of this type of medication were observed in 50 – 60% of the patients at 12 months and in approximately 40% at 24 months after baseline. In most other patients, the use of this type of medication became less frequent over time. In two cases, a patient who had never used this type of medication started to use it frequently (T 13.2-4.5.2).

Table 9-62: Changes in concomitant use of local corticosteroids for the nose (overview) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	34	(29.3)	57	(49.1)	6	(5.2)	19	(16.4)	***
24 mo. *vs.* baseline	29	(25.0)	43	(37.1)	3	(2.6)	41	(35.3)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	24	(23.3)	62	(60.2)	6	(5.8)	11	(10.7)	**
24 mo. *vs.* baseline	28	(27.2)	44	(42.7)	4	(3.9)	27	(26.2)	***

Source: T 13.2-4.5.1
*** McNemar test (improved *vs.* worsened): p < 0.001.
** McNemar test (improved *vs.* worsened): p < 0.01.

Table 9-63: Changes in concomitant use of local corticosteroids for the nose (FAS)

	Change of …. grades	**Adults** N = 116		**Children** N = 103	
		N	**(%)**	**N**	**(%)**
12 months after baseline	-3	7	(6.0)	4	(3.9)
	-2	16	(13.8)	7	(6.8)
	-1	11	(9.5)	13	(12.6)
	0	57	(49.1)	62	(60.2)
	1	5	(4.3)	4	(3.9)
	2	1	(0.9)	2	(1.9)
	3	0	(0.0)	0	(0.0)
	Missing	19	(16.4)	11	(10.7)
	Median change	0.0	***	0.0	***
24 months after baseline	-3	5	(4.3)	5	(4.9)
	-2	15	(12.9)	11	(10.7)
	-1	9	(7.8)	12	(11.7)
	0	43	(37.1)	44	(42.7)
	1	2	(1.7)	1	(1.0)
	2	0	(0.0)	2	(1.9)
	3	1	(0.9)	1	(1.0)
	Missing	41	(35.3)	27	(26.2)
	Median change	0.0	***	0.0	***

Source: T 13.2-4.5.1
* Wilcoxon signed rank test: p < 0.001.
Negative "change scores" indicate that this type of medication was used less frequently by the patient.

For both adults and children, the analysis of LOCF data showed similar improvement rates in month 12 and month 24 (Table 9-64). The same applied to deterioration rates. For further details, see T 13.2-4.5.1 - addB.

Table 9-64: Changes in concomitant use of local corticosteroids for the nose (overview) (FAS; LOCF)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	34	(29.3)	57	(49.1)	6	(5.2)	19	(16.4)	***
24 mo. *vs.* baseline	35	(30.2)	57	(49.1)	5	(4.3)	19	(16.4)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	24	(23.3)	62	(60.2)	6	(5.8)	11	(10.7)	**
24 mo. *vs.* baseline	30	(29.1)	57	(55.3)	5	(4.9)	11	(10.7)	***

Source: T 13.2-4.5.1 - addB
*** McNemar test (improved *vs.* worsened): $p < 0.001$.
** McNemar test (improved *vs.* worsened): $p < 0.01$.

9.1.4.4.6 Local corticosteroids for the eyes

Table 9-65 and Table 9-66 show the changes in the concomitant use of local corticosteroids for the eyes. For further details, see T 13.2-4.6.1.

Approximately 70% of the adults and 80% of the children did not use any local corticosteroids for the eyes at baseline (T 13.2-4.6.1). Accordingly, no changes in the use of this type of medication were observed in approximately 60% of the adults and 80% of the children at 12 months and in approximately 50% of the adults and 70% of the children at 24 months after baseline. In most other patients, the use of this type of medication became less frequent over time.

Table 9-65: Changes in concomitant use of local corticosteroids for the eyes (overview) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	22	(19.0)	71	(61.2)	3	(2.6)	20	(17.2)	***
24 mo. *vs.* baseline	18	(15.5)	55	(47.4)	1	(0.9)	42	(36.2)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p ***
12 mo. *vs.* baseline	8	(7.8)	82	(79.6)	2	(1.9)	11	(10.7)	+
24 mo. *vs.* baseline	8	(7.8)	68	(66.0)	0	(0.0)	27	(26.2)	**

Source: T 13.2-4.6.1
*** McNemar test (improved *vs.* worsened): $p < 0.001$.
** McNemar test (improved *vs.* worsened): $p < 0.01$.
+ McNemar test (improved *vs.* worsened): $p \geq 0.05$.

Table 9-66: Changes in concomitant use of local corticosteroids for the eyes (FAS)

	Change of …. grades	Adults N = 116		Children N = 103	
		N	**(%)**	**N**	**(%)**
12 months after baseline	-3	3	(2.6)	3	(2.9)
	-2	8	(6.9)	1	(1.0)
	-1	11	(9.5)	4	(3.9)
	0	71	(61.2)	82	(79.6)
	1	2	(1.7)	1	(1.0)
	2	1	(0.9)	1	(1.0)
	3	-	-	-	-
	Missing	20	(17.2)	11	(10.7)
	Median change	0.0 ***		0.0 +	
24 months after baseline	-3	3	(2.6)	-	-
	-2	9	(7.8)	4	(3.9)
	-1	6	(5.2)	4	(3.9)
	0	55	(47.4)	68	(66.0)
	1	1	(0.9)	-	-
	2	-	-	-	-
	3	-	-	-	-
	Missing	42	(36.2)	27	(26.2)
	Median change	0.0 ***		0.0 **	

Source: T 13.2-4.6.1
*** Wilcoxon signed rank test: $p < 0.001$.
** Wilcoxon signed rank test: $p < 0.01$.
+ Wilcoxon signed rank test: $p \geq 0.05$.
Negative "change scores" indicate that this type of medication was used less frequently by the patient.

For both adults and children, the analysis of LOCF data showed similar improvement rates in month 12 and month 24 (Table 9-67). The same applied to deterioration rates. For further details, see T 13.2-4.6.1 - addB.

Table 9-67: Changes in concomitant use of local corticosteroids for the eyes (overview) (FAS; LOCF)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	N	(%)	N	(%)	N	(%)	N	(%)	p
12 mo. *vs.* baseline	22	(19.0)	71	(61.2)	3	(2.6)	20	(17.2)	***
24 mo. *vs.* baseline	24	(20.7)	70	(60.3)	2	(1.7)	20	(17.2)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	N	(%)	N	(%)	N	(%)	N	(%)	p
12 mo. *vs.* baseline	8	(7.8)	82	(79.6)	2	(1.9)	11	(10.7)	+
24 mo. *vs.* baseline	11	(10.7)	81	(78.6)	0	(0.0)	11	(10.7)	**

Source: T 13.2-4.6.1 – addB
*** McNemar test (improved *vs.* worsened): $p < 0.001$.
** McNemar test (improved *vs.* worsened): $p < 0.01$.
+ McNemar test (improved *vs.* worsened): $p \geq 0.05$.

9.1.4.4.7 Inhaled beta-2 agonists

Table 9-68 and Table 9-69 show the changes in the concomitant use of inhaled beta-2 agonists. For further details, see T 13.2-4.7.1.

Approximately 70% of the adults and 50% of the children did not use any inhaled beta-2 agonists at baseline (T 13.2-4.7.1). Accordingly, no changes in the use of this type of medication were observed in approximately 60% of the adults and 50% of the children at 12 months and in approximately 50% of the adults and 40% of the children at 24 months after baseline. In most other patients, the use of this type of medication became less frequent over time. In in a few cases, a patient who had never used this type of medication at baseline used it frequently at 12 months (3 patients) and/or at 24 months (1 patient) (T 13.2-4.7.2).

Table 9-68: Changes in concomitant use of inhaled beta-2 agonists (overview) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	17	(14.7)	74	(63.8)	4	(3.4)	21	(18.1)	**
24 mo. *vs.* baseline	19	(16.4)	54	(46.6)	2	(1.7)	42	(36.2)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	35	(34.0)	50	(48.5)	7	(6.8)	11	(10.7)	***
24 mo. *vs.* baseline	34	(33.0)	39	(37.9)	4	(3.9)	26	(25.2)	***

Source: T 13.2-4.7.1
*** McNemar test (improved *vs.* worsened): p < 0.001.
** McNemar test (improved *vs.* worsened): p < 0.01.

Table 9-69: Changes in concomitant use of inhaled beta-2 agonists (FAS)

	Change of …. grades	**Adults** N = 116		**Children** N = 103	
		N	**(%)**	**N**	**(%)**
12 months after baseline	-3	8	(6.9)	5	(4.9)
	-2	5	(4.3)	15	(14.6)
	-1	4	(3.4)	15	(14.6)
	0	74	(63.8)	50	(48.5)
	1	2	(1.7)	5	(4.9)
	2	1	(0.9)	-	-
	3	1	(0.9)	2	(1.9)
	Missing	21	(18.1)	11	(10.7)
	Median change	0.0	**	0.0	***
24 months after baseline	-3	6	(5.2)	3	(2.9)
	-2	6	(5.2)	11	(10.7)
	-1	6	(5.2)	20	(19.4)
	0	54	(46.6)	39	(37.9)
	1	1	(0.9)	4	(3.9)
	2	-	-	-	-
	3	1	(0.9)	-	-
	Missing	42	(36.2)	26	(25.2)
	Median change	0.0	***	0.0	***

Source: T 13.2-4.7.1
*** Wilcoxon signed rank test: p < 0.001.
** Wilcoxon signed rank test: p < 0.01.
Negative "change scores" indicate that this type of medication was used less frequently by the patient.

For both adults and children, the analysis of LOCF data showed similar improvement rates in month 12 and month 24 (Table 9-70). The same applied to deterioration rates. For further details, see T 13.2-4.7.1 - addB.

Table 9-70: Changes in concomitant use of inhaled beta-2 agonists (overview) (FAS; LOCF)

	Adults N = 116								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	17	(14.7)	74	(63.8)	4	(3.4)	21	(18.1)	**
24 mo. *vs.* baseline	21	(18.1)	72	(62.1)	3	(2.6)	21	(18.1)	***

	Children N = 103								
	Improved		No change		Worsened		Missing data		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	35	(34.0)	50	(48.5)	7	(6.8)	11	(10.7)	***
24 mo. *vs.* baseline	41	(39.8)	47	(45.6)	4	(3.9)	11	(10.7)	***

Source: T 13.2-4.7.1 – addB
*** McNemar test (improved *vs.* worsened): $p < 0.001$.
** McNemar test (improved *vs.* worsened): $p < 0.01$.

9.1.4.4.8 Sum score of concomitant anti-allergic medications

Table 9-71 and Table 9-72 show the changes in the sum score of concomitant anti-allergic medications. For further details, see T 13.2-4.8.

An improvement (reduction) of the sum score was observed in approximately 50% of the adults and 60% of the children at both assessments.

On average, the sum score decreased, i.e., improved, by 2 – 3 points over the observation period from 5 – 6 points at baseline to 2 – 3 points at 12 and 24 months.

An improvement of the sum score in the interval between 12 months and 24 months after the baseline documentation was observed in approximately 30% of the adults and children; worsening was observed in < 20% of the adults and children.

Table 9-71: Sum score of concomitant anti-allergic medications: Changes over time (frequency table) (FAS)

	Adults N = 116								
	Improved		No change		Worsened		Missing		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	61	(52.6)	25	(21.6)	9	(7.8)	21	(18.1)	***
24 mo. *vs.* baseline	54	(46.6)	16	(13.8)	5	(4.3)	41	(35.3)	***
24 mo. *vs.* 12 mo.	31	(26.7)	31	(26.7)	13	(11.2)	41	(35.3)	**

	Children N = 103								
	Improved		No change		Worsened		Missing		
Change …	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**p**
12 mo. *vs.* baseline	63	(61.2)	14	(13.6)	15	(14.6)	11	(10.7)	***
24 mo. *vs.* baseline	61	(59.2)	9	(8.7)	7	(6.8)	26	(25.2)	***
24 mo. *vs.* 12 mo.	34	(33.0)	24	(23.3)	18	(17.5)	27	(26.2)	*

Source: T 13.2-4.8

*** McNemar test (improved *vs.* worsened): $p < 0.001$.
** McNemar test (improved *vs.* worsened): $p < 0.01$.
* McNemar test (improved *vs.* worsened): $p < 0.05$.

Table 9-72: Sum score of concomitant anti-allergic medications: Changes over time (descriptive statistics) (FAS)

		Adults N = 116	Children N = 103
Baseline	Mean ± SD	5.1 ± 4.4	5.5 ± 4.4
	Median (range)	4.0 (0 – 18)	5.0 (0 – 19)
	Missing	3	2
Change 12 months *vs.* baseline	Mean ± SD	-2.8 ± 4.2	-2.6 ± 3.5
	Median (range)	-2.0 *** (-15 – 10)	-2.0 *** (-13 – 3)
	Missing	21	11
Change 24 months *vs.* baseline	Mean ± SD	3.3 ± 4.0	-3.3 ± 3.5
	Median (range)	-3.0 *** (-15 – 7)	-3.0 *** (-16 – 3)
	Missing	41	26
Change 24 months *vs.* 12 months	Mean ± SD	-0.5 ± 2.3	-0.7 ± 2.8
	Median (range)	0.0 * (-7 – 7)	0.0 * (-7 – 8)
	Missing	41	27

Source: T 13.2-4.8

*** Wilcoxon signed rank test: $p < 0.001$
* Wilcoxon signed rank test: $p < 0.05$
Sum scores of concomitant anti-allergic medications could range from *0 = no medications* to *21 = all seven types of medication used frequently*. Negative "change scores" indicate an improvement of the symptom.

For both adults and children, the analysis of LOCF data showed similar improvement rates in month 12 and month 24 (Table 9-73). The same applied to deterioration rates. The degrees of change were also similar, on average, at both assessments (T 13.2-4.8 – addB).

Table 9-73: Sum score of concomitant anti-allergic medications: Changes over time (frequency table) (FAS; LOCF)

	Adults N = 116				
	Improved	No change	Worsened	Missing	
Change …	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**p**
12 mo. *vs.* baseline	61 (52.6)	25 (21.6)	9 (7.8)	21 (18.1)	***
24 mo. *vs.* baseline	65 (56.0)	25 (21.6)	6 (5.2)	20 (17.2)	***

	Children N = 103				
	Improved	No change	Worsened	Missing	
Change …	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**p**
12 mo. *vs.* baseline	63 (61.2)	14 (13.6)	15 (14.6)	11 (10.7)	***
24 mo. *vs.* baseline	70 (68.0)	14 (13.6)	9 (8.7)	10 (9.7)	***

Source: T 13.2-4.8 – addB

*** McNemar test (improved *vs.* worsened): $p < 0.001$.

9.1.4.5 Sum scores by study completion status

9.1.4.5.1 Sum score of main symptoms

Stratification of the data by study completion status (only baseline completed, i.e., therapy terminated before month 12, *vs.* only 12 months completed, i.e. therapy terminated after month 12 but before month 24 *vs.* 24 months completed) showed that the baseline sum scores of main symptoms were, on average, largely similar in patients who completed 24 months and in both subgroups of prematurely discontinued patients (Table 9-74). The same applied to the change 12 months *vs.* baseline.

Table 9-74: Sum score of main symptoms by study completion status: Changes over time (descriptive statistics) (FAS)

		Adults N = 116		
		Only baseline # N = 22	**Only 12 months completed** N = 19	**24 months completed** N = 75
Baseline	Mean ± SD	4.3 ± 1.9	4.6 ± 1.9	4.8 ± 1.7
	Median (range)	4.0 (0 – 8)	4.0 (2 – 9)	5.0 (1 – 9)
	Missing	0	0	0
Change 12 months *vs.* baseline	Mean ± SD	-2.5 ± 1.6	-2.3 ± 2.6	-2.2 ± 2.0
	Median (range)	-2.5 + (-5 – 0)	-2.0 *** (-9 – 1)	-2.0 *** (-9 – 1)
	Missing	16	0	2

		Children N = 103		
		Only baseline # N = 13	**Only 12 months completed** N = 13	**24 months completed** N = 77
Baseline	Mean ± SD	3.4 ± 1.7	4.6 ± 1.6	4.1 ± 1.7
	Median (range)	3.0 (1 – 8)	5.0 (2 – 7)	4.0 (0 – 9)
	Missing	0	1	0
Change 12 months *vs.* baseline	Mean ± SD	-2.8 ± 1.9	-2.8 ± 1.9	-1.9 ± 1.8
	Median (range)	-2.0 + (-6 – -1)	-2.0 ** (-7 – 0)	-2.0 *** (-7 – 1)
	Missing	8	1	1

Source: T 13.2-1.4 - addA
*** Wilcoxon signed rank test: $p < 0.001$
** Wilcoxon signed rank test: $p < 0.01$
+ Wilcoxon signed rank test: $p \geq 0.05$
# This subgroup included a few patients for whom 12 months data were documented although their therapy was discontinued before month 12.
Sum scores of main symptoms could range from *0 = no main symptoms* to *9 = all three main symptoms severe*. Negative "change scores" indicate an improvement of the symptom.

9.1.4.5.2 Sum score of specific asthma symptoms

Stratification of the data by study completion status showed that the baseline sum scores of specific asthma symptoms were, on average, roughly similar in patients who completed 24 months and prematurely discontinued patients (Table 9-75). The same applied to the change 12 months *vs.* baseline.

Table 9-75: Sum score of specific asthma symptoms by study completion status: Changes over time (descriptive statistics) (FAS)

		Adults N = 116		
		Only baseline N = 22	**Only 12 months completed** N = 19	**24 months completed** N = 75
Baseline	Mean ± SD	2.3 ± 3.3	3.2 ± 2.8	2.9 ± 2.6
	Median (range)	1.0 (0 – 11)	4.0 (0 – 8)	2.0 (0 – 10)
	Missing	0	2	0
Change 12 months *vs.* baseline	Mean ± SD	-0.8 ± 0.8	-1.8 ± 1.9	-2.0 ± 2.5
	Median (range)	-1.0 $^{+}$ (-2 – 0)	-1.0 *** (-6 – 0)	-1.0 *** (-10 – 3)
	Missing	17	2	2

		Children N = 103		
		Only baseline N = 13	**Only 12 months completed** N = 13	**24 months completed** N = 77
Baseline	Mean ± SD	1.3 ± 2.0	2.9 ± 3.2	3.5 ± 3.3
	Median (range)	1.0 (0 – 7)	1.0 (0 – 8)	3.0 (0 – 11)
	Missing	0	1	0
Change 12 months *vs.* baseline	Mean ± SD	-1.4 ± 1.9	-2.2 ± 2.8	-2.2 ± 2.9
	Median (range)	0.0 $^{+}$ (-4 – 0)	-1.0 * (-7 – 1)	-1.0 *** (-10 – 2)
	Missing	8	1	1

Source: T 13.2-2.5 - addA
*** Wilcoxon signed rank test: $p < 0.001$
* Wilcoxon signed rank test: $p < 0.05$
$^{+}$ Wilcoxon signed rank test: $p \geq 0.05$
Sum scores of specific asthma symptoms could range from *0 = no symptom* to *12 = all symptoms severe*. Negative "change scores" indicate an improvement of the symptom.

9.1.4.5.3 Sum score of concomitant ant-allergic medication

Stratification of the data by study completion status showed that the baseline sum scores of concomitant anti-allergic medications were, on average, roughly similar in patients who completed 24 months and in patients who discontinued prematurely (Table 9-76). The same applied to the change 12 months *vs.* baseline.

Table 9-76: Sum score of concomitant anti-allergic medications by study completion status: Changes over time (descriptive statistics) (FAS)

		Adults N = 116		
		Only baseline N = 22	**Only 12 months completed** N = 19	**24 months completed** N = 75
Baseline	Mean ± SD	5.1 ± 3.6	4.4 ± 4.3	5.2 ± 4.7
	Median (range)	3.5 (0 – 11)	3.5 (0 – 13)	4.0 (0 – 18)
	Missing	0	1	2
Change 12 months *vs.* baseline	Mean ± SD	-3.2 ± 3.3	-3.0 ± 4.5	-2.7 ± 4.3
	Median (range)	-2.5 $^{+}$ (-8 – 0)	-0.5 ** (-13 – 1)	-2.0 *** (-15 – 10)
	Missing	16	1	4

		Children N = 103		
		Only baseline N = 13	**Only 12 months completed** N = 13	**24 months completed** N = 77
Baseline	Mean ± SD	3.1 ± 4.4	4.8 ± 5.5	6.0 ± 4.2
	Median (range)	1.0 (0 – 15)	4.0 (0 – 15)	5.0 (0 – 19)
	Missing	0	2	0
Change 12 months *vs.* baseline	Mean ± SD	-2.2 ± 3.5	-2.8 ± 4.6	-2.6 ± 3.3
	Median (range)	0.0 $^{+}$ (-8 – 0)	-1.0 $^{+}$ (-13 – 1)	-2.0 *** (-13 – 3)
	Missing	8	2	1

Source: T 13.2-4.8 - addA

*** Wilcoxon signed rank test: $p < 0.001$

** Wilcoxon signed rank test: $p < 0.01$

$^{+}$ Wilcoxon signed rank test: $p \geq 0.05$

Sum scores of concomitant anti-allergic medications could range from *0 = no medication* to *21 = all medications taken frequently*. Negative "change scores" indicate an improvement of the symptom.

9.1.4.6 Assessment of effectiveness

In the majority of cases, the physician assessed the effectiveness of treatment with Depigoid® *D. pteronyssinus* or Depigoid® Milben-Mix as *good* or *very good* (Table 9-77). Equally positive assessments were obtained from the patients themselves (Table 9-78).

Table 9-77: Physician's assessment of effectiveness (FAS)

		Adults N = 116	Children N = 103
12 months	1 very good	46 (39.7)	47 (45.6)
	2 good	45 (38.8)	45 (43.7)
	3 moderate	5 (4.3)	2 (1.9)
	4 poor	0	0
	Missing	20 (17.2)	9 (8.7)
24 months	1 very good	43 (37.1)	38 (36.9)
	2 good	28 (24.1)	35 (34.0)
	3 moderate	4 (3.4)	4 (3.9)
	4 poor	0	0
	Missing	41 (35.3)	26 (25.2)

Source: T 13.2-5.1

Table 9-78: Patient's assessment of effectiveness (FAS)

		Adults N = 116		Children N = 103	
		N	**(%)**	**N**	**(%)**
12 months	1 very good	46	(39.7)	43	(41.7)
	2 good	46	(39.7)	47	(45.6)
	3 moderate	7	(6.0)	3	(2.9)
	4 poor	0		1	(1.0)
	Missing	17	(14.7)	9	(8.7)
24 months	1 very good	39	(33.6)	38	(36.9)
	2 good	31	(26.7)	34	(33.0)
	3 moderate	7	(6.0)	5	(4.9)
	4 poor	0		0	
	Missing	39	(33.6)	26	(25.2)

Source: T 13.2-5.1

9.1.4.7 Assessment of tolerability

In the majority of cases, the physician assessed the tolerability of treatment with Depigoid® *D. pteronyssinus* or Depigoid® Milben-Mix as *good* or *very good* (Table 9-79). Equally positive assessments were obtained from the patients themselves (Table 9-80).

Table 9-79: Physician's assessment of tolerability (FAS)

		Adults N = 116		Children N = 103	
		N	**(%)**	**N**	**(%)**
4 weeks	1 very good	72	(62.1)	77	(74.8)
	2 good	38	(32.8)	18	(17.5)
	3 moderate	2	(1.7)	2	(1.9)
	4 poor	0		0	
	Missing	4	(3.4)	6	(5.8)
12 months	1 very good	51	(44.0)	72	(69.9)
	2 good	44	(37.9)	22	(21.4)
	3 moderate	2	(1.7)	0	
	4 poor	0		0	
	Missing	19	(16.4)	9	(8.7)
24 months	1 very good	48	(41.4)	60	(58.3)
	2 good	27	(23.3)	16	(15.5)
	3 moderate	1	(0.9)	1	(1.0)
	4 poor	0		0	
	Missing	40	(34.5)	26	(25.2)

Source: T 13.2-5.2

Table 9-80: Patient's assessment of tolerability (FAS)

		Adults N = 116		Children N = 103	
		N	**(%)**	**N**	**(%)**
4 weeks	1 very good	63	(54.3)	70	(68.0)
	2 good	47	(40.5)	25	(24.3)
	3 moderate	2	(1.7)	2	(1.9)
	4 poor	0		0	
	Missing	4	(3.4)	6	(5.8)
12 months	1 very good	55	(47.4)	56	(54.4)
	2 good	42	(36.2)	38	(36.9)
	3 moderate	3	(2.6)	0	
	4 poor	0		0	
	Missing	16	(13.8)	9	(8.7)
24 months	1 very good	46	(39.7)	50	(48.5)
	2 good	31	(26.7)	27	(26.2)
	3 moderate	2	(1.7)	0	
	4 poor	0		0	
	Missing	37	(31.9)	26	(25.2)

Source: T 13.2-5.2

9.1.4.8 Assessment of patient's acceptance of treatment

In the majority of cases, acceptance of the duration of the build-up phase, the number of injections with Depigoid® *D. pteronyssinus* or Depigoid® Milben-Mix, the frequency of visits to the doctor's, and the total expenditure of time during the build-up phase was *good* or *very good* (Table 9-81). *Poor* acceptance of these features of the SIT treatment regimen was rare, particularly in adults.

Table 9-81: Acceptance of treatment (FAS)

		Adults N = 116		Children N = 103	
		N	**(%)**	**N**	**(%)**
Duration of buildup phase	1 very good	70	(60.3)	67	(65.0)
	2 good	42	(36.2)	24	(23.3)
	3 neutral	0	-	6	(5.8)
	4 poor	0	-	1	(1.0)
	Missing	4	(3.4)	5	(4.9)
Number of injections	1 very good	68	(58.6)	60	(58.3)
	2 good	40	(34.5)	31	(30.1)
	3 neutral	4	(3.4)	6	(5.8)
	4 poor	0	-	1	(1.0)
	Missing	4	(3.4)	5	(4.9)
Frequency of visits to the doctor's	1 very good	61	(52.6)	54	(52.4)
	2 good	43	(37.1)	29	(28.2)
	3 neutral	8	(6.9)	12	(11.7)
	4 poor	0	-	3	(2.9)
	Missing	4	(3.4)	5	(4.9)
Total expenditure of time	1 very good	59	(50.9)	39	(37.9)
	2 good	41	(35.3)	43	(41.7)
	3 neutral	10	(8.6)	14	(13.6)
	4 poor	2	(1.7)	2	(1.9)
	Missing	4	(3.4)	5	(4.9)

Source: T 13.2-5.3

9.1.4.9 Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)

Changes in the patients' health-related quality of life were measured by means of the RQLQ (age appropriate versions) (Juniper and Guyatt, 1991; Juniper *et al.*, 1994; Juniper *et al.*, 1996; Juniper *et al.*, 1998).

Juniper and Styles describe the RQLQ as follows (Juniper and Styles, no year):

> *The **Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)** was developed to measure the functional problems (physical, emotional, social and occupational) that are most troublesome to adults (17-70 years) with either seasonal or perennial rhinoconjunctivitis of either allergic or non-allergic origin.... The RQLQ has 28 questions in 7 domains (activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems and emotional function). There are 3 'patient-specific' questions in the activity domain which allow patients to select 3 activities in which they are most limited by their rhinoconjunctivitis. Patients recall how bothered they have been by their rhinoconjunctivitis during the previous week and to respond to each question on a 7-point scale (0 = not impaired at all - 6 = severely impaired). The overall RQLQ score is the mean of all 28 responses and the individual domain scores are the means of the items in those domains.*

In contrast to the RQLQ version for adults, the RQLQ version developed to measure the most troublesome functional problems in adolescent children (12-17 years) with rhinoconjunctivitis (hay fever) has only 25 questions in 6 domains (nose symptoms, eye symptoms, practical problems, activity limitation, non-hay-fever symptoms and emotional function).[24] The RQLQ version for younger children with rhinoconjunctivitis has 23 questions in 5 domains (nose symptoms, eye symptoms, practical problems, activity limitation and other symptoms).[25]

The data collected in the present study indicate that, on average, the health-related quality of life improved during the course of the study. In adults and older children, the RQLQ total score as well as all RQLQ domain scores were improved (decreased) by more than 0.5 points, on average, at 12 months after baseline (Table 9-82, Table 9-83). According to Juniper *et al.* (Juniper *et al.*, 1996), mean changes of > 0.5 can be considered as clinically relevant. At 24 months, the mean scores showed an even greater improvement. However, these data have to be interpreted with reservation due to the high number of missing data. The average improvement of RQLQ total and domain scores was less pronounced in smaller children (6 – 12 years). It has to be taken into consideration, however, that the mean baseline values were also lower in this subgroup.

[24] Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (AdolRQLQ) (http://www.qoltech.co.uk/adollrqlq.html).
[25] Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) (http://www.qoltech.co.uk/prqlq.html).

Table 9-82: RQLQ total score (FAS)

		Adults # N = 109	Children 12-17 years # N = 35	Children 6-12 years # N = 57
Baseline	Mean ± SD	2.5 ± 1.2	2.4 ± 1.2	1.6 ± 1.1
	Median (range)	2.6 (0.0 – 5.4)	2.5 (0.0 – 5.4)	1.4 (0.1 – 4.6)
	Missing	1	5	2
Change 12 months *vs.* baseline	Mean ± SD	-0.7 ± 1.1	-0.8 ± 0.9	-0.5 ± 0.8
	Median (range)	-0.6 *** (-4.7 – 2.8)	-0.6 *** (-2.8 – 0.8)	-0.3 *** (-3.6 – 0.6)
	Missing	12	10	10
Change 24 months *vs.* baseline	Mean ± SD	-1.4 ± 1.2	-1.3 ±1.3	-0.8 ± 1.2
	Median (range)	-1.4 *** (-4.6 – 1.3)	-1.5 *** (-3.3 – 1.3)	-0.6 *** (-4.5 – 1.0)
	Missing	31	19	13

Source: T 13.2-6.1
*** Wilcoxon signed rank test: $p < 0.001$
RQLQ total scores could range from 0 to 6 with 6 indicating a lower quality of life.
Classification according to type of questionnaire completed by the patient. Patients whose age deviated by more than 1 year from the intended age range of the questionnaire were excluded from analysis.

Table 9-83: RQLQ domain scores (FAS)

	Adults N = 109			Children 12-17 years of age N = 35			Children 6-12 years of age N = 57		
	Mean	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
Activity limitation									
Baseline	3.4	1.6	105	3.0	1.7	30	1.5	1.3	55
12 mo. *vs.* baseline	-0.9	1.6	92	-0.9	1.5	25	-0.7	1.1	47
24 mo. *vs.* baseline	-1.8	1.8	75	-1.8	1.6	15	-0.9	1.3	44
Sleep problem									
Baseline	2.5	1.5	108	N/A-	-	-	N/A-	-	-
12 mo. *vs.* baseline	-0.8	1.5	97	N/A-	-	-	N/A-	-	-
24 mo. *vs.* baseline	-1.6	1.5	79	N/A-	-	-	N/A-	-	-
Nose symptoms									
Baseline	2.9	1.5	108	3.2	1.3	29	2.2	1.4	55
12 mo. *vs.* baseline	-0.9	1.5	97	-1.1	1.4	24	-0.5	1.3	47
24 mo. *vs.* baseline	-1.6	1.6	78	-2.3	1.9	15	-0.8	1.6	44
Eye symptoms									
Baseline	2.1	1.5	107	2.0	1.6	30	1.0	1.3	55
12 mo. *vs.* baseline	-0.6	1.3	97	-0.6	1.1	25	-0.4	1.1	47
24 mo. *vs.* baseline	-1.2	1.5	78	-1.1	1.9	16	-0.7	1.4	44
Non-nose/eye symptoms									
Baseline	2.3	1.3	108	1.9	1.2	29	1.3	1.2	55
12 mo. *vs.* baseline	-0.6	1.1	97	-0.8	1.1	24	-0.4	0.9	47
24 mo. *vs.* baseline	-1.1	1.3	79	-1.0	1.4	15	-0.6	1.4	44
Practical problems									
Baseline	3.1	1.5	108	2.5	1.5	30	2.0	1.4	55
12 mo. *vs.* baseline	-0.9	1.5	97	-0.7	1.2	25	-0.7	1.2	47
24 mo. *vs.* baseline	-1.6	1.4	78	-1.1	1.3	16	-0.8	1.5	44
Emotional function									
Baseline	2.1	1.4	107	1.9	1.5	30	N/A-	-	-
12 mo. *vs.* baseline	-0.6	1.3	97	-0.8	1.1	25	N/A-	-	-
24 mo. *vs.* baseline	-1.2	1.3	78	-1.0	1.2	16	N/A-	-	-

Source: T 13.2-6.2 through T 13.2-6.8
In all domains and age classes, Wilcoxon signed rank test p-values were < 0.05 for changes 12 months *vs.* baseline and 24 months *vs.* baseline; see T 13.2-6.2 through T 13.2-6.8.
N/A not applicable.

9.1.5 Other analyses

9.1.5.1 Allergen exposure during the study

T 13.2-7 gives an overview of the allergen exposure at baseline and at 12 and 24 months after the baseline documentation. Worth mentioning might be that the number of patients for whom remedial measures – in particular regarding the bedclothes and the mattress – were taken increased slightly during the course of the study.

However, these data have to be interpreted with reservation due to the high number of missing values at the later assessments.

9.1.5.2 Adverse events and adverse reactions

Summary tables for AE data (safety population) are provided in T 13.3.1-1 to T 13.3.1-3.3; individual AE data are listed in L 13.3.2-1 (non-serious AEs; nsAEs) and L 13.3.2-2 (SAEs).[26]

Adverse events were documented slightly more often for children than for adult patients (7% *vs.* 3%) (Table 9-84). SAEs were rare in both groups: 3 adults (3%) and 1 child (1%) experienced one or more SAEs, some of which were classified as unrelated to the study treatment. All nsAEs, on the other hand were classified as related to the study treatment (non-serious adverse drug reactions; nsADRs).

No deaths were reported.

Table 9-84: Summary of adverse events (safety population)

	Adults N = 117		Children N = 103	
	$N_{patients}$	(%)	$N_{patients}$	(%)
AE, total	4	(3.4)	7	(6.8)
nsAE	1	(0.9)	5	(4.9)
nsADR	1	(0.9)	5	(4.9)
nsAEnr	-	-	-	-
SAE	3	(2.6)	1	(1.0)
SADR	2	(1.7)	-	-
SAEnr	2	(1.7)	1	(1.0)
Seriousness missing #	-	-	1	(1.0)
Deaths	-	-	-	-

Source: T 13.3.1-1
ns: non serious; nr: not related; AE: adverse event; ADR: adverse drug reaction; SAE: serious adverse event; SADR: serious adverse drug reaction.
AE without information on seriousness: Mild pruritus lasting for one day, resolved, no action taken, related. The AE was classified as nsAE for the analysis of AEs.

[26] "L 13…" refers to listing no. … in Appendix Volume 1.

All nsADRs reported, e.g. erythema, swelling and pain, were injection site conditions (Table 9-85).

Two adult patients experienced serious adverse drug reactions (Table 9-86 and listing T 13.3.2-2):

- A 33 year-old male patient (012/01) experienced an anaphylactic reaction after administration of the first dose of Depigoid® Milben-Mix (2 DPP). The reaction was successfully treated with oral antihistamines and the patient was withdrawn from the study.[27] The investigator classified this AE as *definitely* related to the study treatment. Since the patient was not hospitalized and only treated with oral antihistamines the case can be considered as a grade 2 reaction following EAACI criteria.
- A 48 year-old male patient (170/01) with a medical history of COPD experienced two 4-day episodes of exacerbation of an infection. The first episode began 3 days before administration of a (maintenance) dose of 50 DPP of Depigoid® Milben-Mix, and was classified as *not related* to the study treatment. The second episode started 6 days later, i.e., 3 days after administration of Depigoid® Milben-Mix 50 DPP, and was classified as *possibly related.* The patient was admitted to hospital. Both events were resolved without sequelae. Since both infections are considered COPD related the case rather qualifies for an SAE instead of a serious adverse drug reaction.

Further *non-related* SAEs were experienced by two other patients (Table 9-87):

- pneumonia in a 55 year-old female patient (199/01) and
- sarcoidosis in an 11 year-old boy (243/02).

Table 9-85: Incidence of non-serious adverse drug reactions (safety population)

MedDRA preferred term*	Adults N = 117		Children N = 103	
	$N_{patients}$	(%)	$N_{patients}$	(%)
Total	1	(0.9)	5	(4.9)
Injection site erythema	1	(0.9)	-	-
Injection site swelling	1	(0.9)	1	(1.0)
Local swelling	-	-	3	(2.9)
Pain in extremity	-	-	1	(1.0)
Erythema	-	-	3	(2.9)
Pruritus	-	-	3	(2.9)

Source: T 13.3.1-2.2
* MedDRA: Medical Dictionary for Regulatory Activities

[27] No data other than the details of this AE were documented for this patient. Therefore, the patient was not included in the FAS.

Table 9-86: Incidence of serious adverse drug reactions (safety population)

MedDRA preferred term	Adults N = 117		Children N = 103	
	$N_{patients}$	(%)	$N_{patients}$	(%)
Total	2	(1.7)	-	-
Anaphylactic reaction	1	(0.9)	-	-
Infection	1	(0.9)	-	-

Source: T 13.3.1-3.2
* MedDRA: Medical Dictionary for Regulatory Activities

Table 9-87: Incidence of serious adverse events, not related (safety population)

MedDRA preferred term	Adults N = 117		Children N = 103	
	$N_{patients}$	(%)	$N_{patients}$	(%)
Total	2	(1.7)	1	(1.0)
Sarcoidosis	-	-	1	(1.0)
Infection	1	(0.9)	-	-
Pneumonia	1	(0.9)	-	-

Source: T 13.3.1-3.3
* MedDRA: Medical Dictionary for Regulatory Activities

9.2 Epidemiological survey

At the beginning of the study, a 3-month epidemiological survey was conducted to gather information about the treatment of domestic mite allergies in general.

9.2.1 Participants

The participants of the epidemiological survey (EPI) were documented at 7 study centers in total. Two centers documented adults and 7 centers documented children. On average, 46.3 ± 49.0 patients were documented per center (T 13.1-1.2).

The EPI included 324 patients in total (124 adults and 200 children). Most of these patients did not receive any treatment with Depigoid® Milben-Mix or Depigoid® *D. pteronyssinus* (Table 9-88).

Table 9-88: Study population (EPI)

	Adults	Children #	Total
Total number of patients	124	200	324
No treatment ##	120	183	302
Depigoid® Milben-Mix	4	17	21
Depigoid® *D. pteronyssinus*	0	0	0

Source: T 13.1-2.1
11 patients with missing age were assumed to be children, as all were documented at centers where only children or only one adult was included.
this category includes patients for whom no information on Depigoid® therapy was provided.

9.2.2 Descriptive data (EPI; no study medication)

In the following subsection, only the data of patients without Depigoid® *D. pteronyssinus* or Depigoid® Milben Mix therapy are presented, since most of the few other patients were also included in the 2-year observation part of the study (T 13.2-8.1 and T 13.2-8.2).

An overview of the demographic characteristics is given in Table 9-89 and Table 9-90. The male to female ratio was roughly 1:1 among the adults and roughly 2:1 among the children. The adult patients were 44 years old, on average, the children 10 years.

Table 9-89: Demographic characteristics (1) (EPI; no study medication)

		Adults N = 120		Children N = 183	
		N	(%)	N	(%)
Sex	Male	54	(45.8)	125	(69.8)
	Female	64	(54.2)	54	(30.2)
	Missing	2	-	4	-

Source: T 13.2-8.1, T 13.2-8.2

Table 9-90: Demographic characteristics (2) (EPI; no study medication)

		Adults N = 120	Children N = 183
Age [years]	Mean ± SD	44.0 ± 16.7	10.6 ± 2.9
	Median (range)	44.0 (18 – 82)	10.0 (5 – 17)
	Missing	0	11

Source: T 13.2-8.1, T 13.2-8.2

The majority of adult patients were diagnosed as having IgE mediated allergy + domestic mite allergy (94%); the majority of children, were diagnosed with domestic mite allergy alone (74%) (Table 9-91). Prick tests were used in more than 90% of the patients (adults and children) to confirm the diagnosis. Additional antibody analysis was used in the majority of adult patients (86%), but in only 19% of the children.

Treatment regimens including SIT were documented more often for children than for adults (approx. 50% *vs.* approx. 20%). The same applied to remedial measures (approx. 90% *vs.* 40%). Symptomatic treatment was documented for almost all patients (adults and children).

The interval between the first diagnosis of domestic mite allergy and the first visit of the first patient of the EPI population (FPFV) varied between 0 and 13 or 14 years in adults and children, respectively. The mean length of this interval was approximately 4 years in adults and 3 years in children (Table 9-92).

Table 9-91: Diagnosis and therapy decision (EPI; no study medication)

		Adults N = 120		**Children** N = 183	
		N	**(%)**	**N**	**(%)**
Diagnosis	IgE mediated allergy	0		3	(1.7)
	Domestic mite allergy	7	(6.2)	130	(73.9)
	IgE mediated allergy + domestic mite allergy	106	(93.8)	43	(24.4)
	Missing	7		7	
Confirmation of diagnosis	Symptomatic	117	(97.5)	135	(73.8)
	Prick test	118	(98.3)	168	(91.8)
	Antibody analysis (RAST)	103	(85.8)	35	(19.1)
Therapy decision	Symptomatic	119	(99.2)	163	(89.1)
	SIT	26	(21.7)	98	(53.6)
	Remedial measures	51	(42.5)	172	(94.0)

Source: T 13.2-8.1, T 13.2-8.2

Table 9-92: Interval between diagnosis and FPFV (EPI; no study medication)

		Adults N = 120	**Children** N = 183
Interval between diagnosis and FPFV [years]	Mean ± SD	3.8 ± 3.5	3.1 ± 2.9
	Median (range)	3.0 (-0.2 – 13)	2.7 (0.0 – 14)
	Missing	43	4

Source: T 13.2-8.1, T 13.2-8.2

(Note: For comparability, + / - signs are reversed in the above table.)
FPFV = first patient first visit in this study

10 Discussion

10.1 Key results

10.1.1 2-year observation of treatment with Depigoid® *D. pteronyssinus* or Depigoid® MilbenMix

At 70 study centers in total, 219 patients (116 adults; 103 children) were enrolled, received Depigoid® *D. pteronyssinus* or Depigoid® MilbenMix, and had at least one follow-up examination documented (FAS). Approximately 90% of the patients were documented 12 months after the start of therapy and approximately 75% after 24 months – indicating that treatment adherence was relatively good (*cf.* Kiel *et al.*, 2013; Claes *et al*., 2009). None of the patients was reported to have discontinued therapy due to an adverse drug reaction. Further, none of the analyses using data stratified by study completion status revealed any indication that the severity of baseline symptoms or the changes in symptom severity in patients who prematurely discontinued therapy were substantially different from those of patients who completed the full 24 months of therapy.

The overall exposure to domestic mites was judged to be *moderate* in approximately 50% of the patients (physician's assessment based on information about the patient's living situation and remedial measures taken). *High* exposure was relatively rare (13% of the adults and 16% of the children). The adult patients were, on average, 38 years old at study entry, the children 11 years. Approximately 50% of the adults and 60% of the children were male. The median interval between 1st diagnosis of domestic mite allergy and start of therapy was 0.6 years in adults and 2.2 years in children. This indicates that, on average, therapy was started earlier in adults than in children.

The analysis of the relationship between time since 1st diagnosis and severity of symptoms at baseline revealed that, in adults, the length of the time period since diagnosis and the severity of symptoms affecting the eyes and the nose were weakly negatively correlated – indicating that more severe symptoms may have prompted patients to seek treatment earlier. These correlations were not found in children. Time since diagnosis and the severity of chest tightness (adults) and productive cough (children), on the other hand, were weakly positively correlated – indicating that the severity of both symptoms might have increased when treatment was postponed. All of these findings might be incidental – an assumption supported by the fact the correlations were rather weak (Spearman correlation coefficients of +/- .17 or +/- .18 and p-values of only <0.1 in most cases). However, from the clinical and exploratory point of view, they are neither implausible nor irrelevant; see Section 10.3.

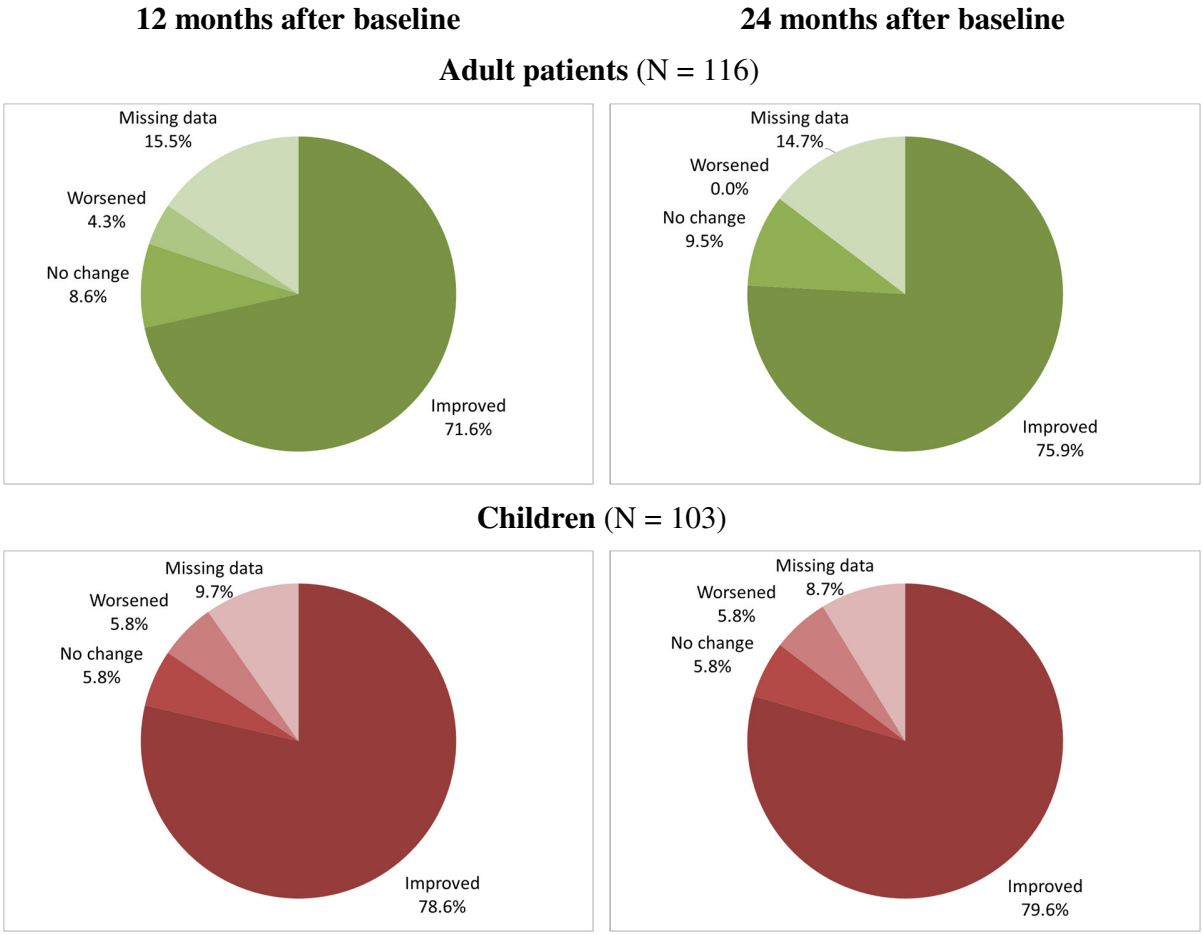
At baseline, most patients suffered from allergy symptoms affecting the nose (99% of the adults, 92% of the children) and often, these symptoms were graded as *severe* (approx. 30% of the patients in both groups). Symptoms affecting the eyes and symptoms affecting the lung were less common (adults: 85% and 63%, respectively; children: 60% and 64% respectively). The mean total sum score of symptoms was 7.5 ± 4.0 in adults and 7.2 ± 4.4 in children at baseline (21-point scale ranging from *0 = no symptoms* to *21 = all main symptoms and all specific asthma symptoms severe*).

Anti-allergic medication was used at baseline by the majority of patients at least on rare occasions. Medications used by more than 50% of the patients in a group were systemic antihistamines, which were used by 53.4% of the adults, and inhaled corticosteroids, which were used by 52.5% of the children. Medications *frequently* used by more than 10% of the adult patients were (in decreasing order) local corticosteroids for the nose, inhaled corticosteroids, and systemic antihistamines. Medications *frequently* used by more than 10% of the children were inhaled corticosteroids, systemic antihistamines, inhaled beta-2 agonists, and local corticosteroids for the nose. In both groups, the median sum score of anti-allergic medications was in the lower range of the 21-point scale (adults: 4.0; children; 5.0).

Almost all patients were treated with Depigoid® Milben-Mix. Only 7 patients (2 adults, 5 children) received Depigoid® *D. pteronyssinus.* The maintenance regimens generally followed the recommendations of the SmPC. Build-up regimens, in contrast, frequently deviated from the recommended scheme. The average mean dose administered to adults was higher than the recommended dose (approx. 30 DPP as compared to approx. 20 DPP) and the average mean interval between administrations was approx. 2 weeks instead of 1 week. The build-up regimens used for children deviated less from the recommended regimen. However, when interpreting the dosing data, it has to be taken into account that the number of injections per phase and the time on therapy varied considerably between patients. In case of early termination of therapy or observation, only one or two injections during the build-up phase might have been documented.

During the course of the study, an improvement of the total sum score of symptoms was observed in the majority of patients (adults and children; both assessments). Worsening of the sum score was rare. On average, the total sum score decreased by 4 – 5 points over the observation period from approximately 7 points at baseline to 3 – 4 points at 12 and 24 months. The median change from month 12 to month 24 was a decrease by 1 point in adults and in children. However, the meaningfulness of this finding is limited by the relatively high number of missing values at month 24.

A phenomenon attributable to the higher number of missing values at 24 months compared to 12 months is that the percentage of patients in whom a specific symptom, a sum score of symptoms, or the use of concomitant anti-allergic medication had improved was lower in month 24 than in month 12. However, a LOCF analysis where missing values at 24 months were substituted by the corresponding 12 months values resulted in similar improvement rates after 12 months of therapy and after 24 months of therapy and did not reveal any signs of a deterioration from 12 to 24 months (Figure 10-1). As the analyses stratified by study completion status revealed no substantial differences at baseline or in changes 12 months *vs.* baseline between patients who discontinued therapy or study and patients who completed the full 24 months of therapy, there is no reason to assume that lack of improvement or, the other way round, exceptionally good improvement were more frequent in patients who discontinued the study than in patients who completed the study.



Source: T 13.2-3 - addB

Figure 10-1: Total sum score of symptoms: Changes during 12 and 24 months of treatment with Depigoid® *D. pteronyssinus* or Depigoid® Milben-Mix (FAS; LOCF)

Both in adults and in children, the use of concomitant anti-allergic medications became less frequent during the observation period. An improvement (reduction) of the sum score of concomitant medications was observed in approximately 50% of the adults and 60% of the children at both assessments.

In the majority of cases, the physician assessed the effectiveness and the tolerability of treatment with Depigoid® *D. pteronyssinus* or Depigoid® Milben-Mix as *good* or *very good*. Similarly positive assessments were obtained from the patients themselves.

The positive assessment of the tolerability of the treatments was supported by adverse event data: Two patients experienced adverse events that were classified as serious adverse drug reactions. A 33 year-old male patient experienced an anaphylactic reaction after administration of the first dose of Depigoid® Milben-Mix (2 DPP). Another patient, a 48 year-old man, experienced two 4-day episodes of exacerbation of an infection. The second episode, which started 6 days after the first episode and 3 days after administration of Depigoid®

Milben-Mix 50 DPP, was classified as *possibly related to treatment.* All other (possibly) treatment related AEs reported were transient, mild to moderate injection site conditions such as erythema, pain and swelling. Such conditions were observed in 1 adult and 6 children. However, the fact that all non-serious AEs reported were injection site conditions might suggest that other types of AEs were under-reported; see Section 10.3.

The RQLQ data collected indicate that, on average, the health-related quality of life improved during the course of the study. In adults and older children, the RQLQ total score as well as all RQLQ domain scores were improved (decreased) by more than 0.5 points, on average, at 12 months after baseline. According to Juniper et al. (Juniper *et al.*, 1996), such a change can be considered as clinically relevant. At 24 months, the mean scores showed an even greater improvement. However, these data have to be interpreted with reservation due to the high number of missing data; see above. The average improvement of RQLQ total and domain scores was less pronounced in smaller children (6 – 12 years). It has to be taken into consideration, however, that the mean baseline values were also lower in this subgroup.

10.1.2 Supplementary epidemiological survey

At the beginning of the study, an epidemiological survey was conducted to gather information about the treatment of domestic mite allergies in general.

Most of the patients included in the epidemiological survey did not receive SIT with Depigoid® *D. pteronyssinus* or Depigoid® Milben-Mix (302 of 324 patients).

The demographic characteristics of the patients included in the epidemiological survey who were not treated with Depigoid® *D. pteronyssinus* or Depigoid® MilbenMix were roughly similar to those of the patients in the 2-year observation part of the study. The male to female ratio was roughly 1:1 among the adults and roughly 2:1 among the children. The adult patients were 44 years old, on average, the children 10 years.

10.2 Limitations

This trial was a non-interventional study with all the advantages and limitations of this type of study. Minimalistic inclusion/exclusion criteria and an assessment plan that followed the clinical routine of the study center rather than a strict, predefined schedule might contribute to a higher external validity of the data collected but they might also limit their internal validity.

Further limitations of the present study result from its non-comparative nature as there was no control group and the fact that no source data verification was performed.

10.3 Interpretation

In summary, the data collected in this study showed that treatment with Depigoid® Milben-Mix and Depigoid® *D. pteronyssinus* was effective, well tolerated, and safe in adults as well as in children. However, the fact that all non-serious AEs reported were injection site conditions might suggest that other types of AEs, particularly AEs that were not serious and

not obviously related to the administration of Depigoid® Milben-Mix or Depigoid® *D. pteronyssinus* were under-reported. Thus, general conclusion regarding the safety of treatment with Depigoid® Milben-Mix or Depigoid® *D. pteronyssinus* may be drawn from the present data only with due reservation.

The median times between diagnosis and start of therapy observed in this study might suggest that, on average, there was less reluctance to start SIT in adults than in children. Further, there might be indications that the severity of some specific asthma symptoms (i.e., chest tightness in adults and productive cough in children) might have increased when treatment was postponed.

10.4 Generalizability

Data from 220 patients in the safety population and 219 patients in the FAS were analyzed in this study. This sample size is considerably smaller than the sample size originally planned (900 patients in 300 centers). The number of patients per study center was within the intended range (mean ± SD: 3.1 ± 1.87 patients). The total number of participating centers, however, was considerably lower than planned (70 *vs.* 300 centers).

It remains to be discussed whether this has an effect on the generalizability of the results. However, there are no indications of an obvious systematic bias regarding the participating study centers.

10.5 Conclusion

The data collected in this study showed that treatment with Depigoid® Milben-Mix and Depigoid® *D. pteronyssinus* was effective, well tolerated, and safe in the patient population studied.

11 References

Bundesinstitut für Arzneimittel und Medizinprodukte & Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel (2010): Empfehlungen des Bundesinstituts für Arzneimittel und Medizinprodukte und des Paul-Ehrlich-Instituts zur Planung, Durchführung und Auswertung von Anwendungsbeobachtungen vom 7. Juli 2010. Available at: http://www.pei.de/SharedDocs/Downloads/pu/klinische-pruefung/100707-awb-kommentierung-fachkreise.pdf. Last acccessed: 24 SEP 2014.

Claes, C.; Mittendorf, T.; Graf von der Schulenburg, J. (2009): Persistence and frequency of prescriptions of subcutaneous allergen-specific immunotherapy (SCIT) prescribed within the German statutory health insurance. Med Klin (Munich) 104(7): 536–542.

Freiwillige Selbstkontrolle für die Arzneimittelindustrie e.V. (FSA) (2008): FSA code of conduct on the collaboration with healthcare professionals. Announced in the Federal Gazette of 7 May 2008. BAnz. No. 68, page 1636.

Juniper, E. F.; Guyatt, G. H. (1991): Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. Clin Exp Allergy 21(1): 77–83.

Juniper, E. F.; Guyatt, G. H.; Dolovich, J. (1994): Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. J Allergy Clin Immunol 93 (2): 413–423.

Juniper, E. F.; Guyatt, G. H.; Griffith, L. E.; Ferrie, P. J. (1996): Interpretation of rhinoconjunctivitis quality of life questionnaire data. J Allergy Clin Immunol 98 (4): 843–845.

Juniper, E. F.; Howland, W. C.; Roberts, N. B.; Thompson, A. K.; King, D. R. (1998): Measuring quality of life in children with rhinoconjunctivitis. J Allergy Clin Immunol 101 (2 Pt 1): 163–170.

Juniper, E. F.; Styles, J. (no year): Measurement of health-related quality of life & asthma control. Available at: http://www.qoltech.co.uk/rqlq.html. Last accessed: 24 SEP 2014.

Kiel, M. A., Roder, E., van Gerth Wijk, R., et al. (2013): Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. J Allergy Clin Immunol 132(2): 353-60.e2.

Verband Forschender Arzneimittelhersteller e.V. (2007a): VFA-Empfehlungen zur Verbesserung der Qualität und Transparenz von nicht-interventionellen Studien (31 JAN 2007). Available at: http://www.vfa.de/download/vfa-empfehlungen-zu-nis.pdf. Last accessed: 24 SEP 2014.

Verband Forschender Arzneimittelhersteller e.V. (2007b): Publizität von Anwendungsbeobachtungen nach strengen Regeln. Pressemitteilung 23 APR 2007. Available at: http://www.vfa.de/de/presse/pressemitteilungen/pm-017-2007-publizitaet-von-anwendungsbeobachtungen-nach-strengen-regeln.html. Last accessed: 24 SEP 2014.

12 Other information

Not applicable.