Clinical Study Report

TITLE PAGE

Title	Prospective, multi-centre, non-interventional safety trial to collect real-world data on the safety of immunotherapy with Depigoid® Katze in patients with allergic rhinitis/rhinoconjunctivitis with or without controlled asthma due to feline epithelia.
Study code	LETI **MIAU-KAT** 2022 (**M**ultizentrische Beobachtungsstudie zur Erfassung von Sicherheit und Wirkung einer **I**mmuntherapie bei Patienten mit Katzenallergie mit oder ohne kontrolliertem **A**sthma: **U**ntersuchung unter realen Praxisbedingungen mit Depigoid® **KAT**ze)
Version identifier of the final study report	Not applicable
Date of last version of the final study report	08 MAY 2025
EU PAS register number	EUPAS46091
Active substance	Depigmented allergen extract from feline epithelia polymerised with glutaraldehyde adsorbed on aluminium hydroxide in the form of a suspension given as a subcutaneous injection Pharmacotherapeutic group: Allergen extracts animals ATC code: V01AA11 Animals
Medicinal product	Depigoid Cat (Depigoid® Katze); 100 DPP/ml; sterile suspension for injection
Product reference	Not applicable

Procedure number	Not applicable
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Joint PASS	No
Research question and objectives	The objective of the present study was to collect and evaluate safety data collected during daily clinical practice in patients receiving Depigoid® Katze subcutaneous immunotherapy (SCIT) for moderate to severe allergic rhinitis and/or rhinoconjunctivitis with or without controlled asthma.
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1 Abstract

1.1 Title

Prospective, multi-centre, non-interventional safety study to collect real-world data on the safety of immunotherapy with the SIT medicinal product Depigoid® Katze in patients with allergic rhinitis/rhinoconjunctivitis with or without controlled asthma due to feline epithelia.

1.2 Keywords

NIS-PASS, multi-centre, immunotherapy, allergic rhinoconjunctivitis, cat allergy

1.3 Rationale and background

For decades, only native allergen extracts with a high incidence of side effects were available for subcutaneous immunotherapy (SCIT) to treat allergy to feline epithelia. Modified allergen extracts are a promising alternative to reduce the number of side effects. The purpose of this study was to collect data on the safety of Depigoid® Katze under everyday conditions in routine use.

1.4 Research question and objectives

The objective of the present study was to collect and evaluate safety data collected during daily clinical practice in patients receiving a SCIT with Depigoid® Katze at a concentration of 100 DPP/mL for treatment of moderate to severe allergic rhinitis (AR) and/or rhinoconjunctivitis (ARC) with or without controlled asthma. The focus was on the occurrence of adverse events (AEs) upon injections and the influence of the therapy on quality of life (QoL).

1.5 Study design

The current study was designed as a voluntary non-interventional post authorization safety study (NIS-PASS): observational, prospective, non-randomized, unblinded, and uncontrolled study.

1.6 Setting

The study was conducted in 22 (out of 38) investigational study sites in Germany, specialised in allergology in patients with allergic symptoms to cats observed during a

SCIT with Depigoid® Katze. Patients aged ≥ 12 years suffering from AR and/or ARC with or without controlled asthma caused by sensitisation to cats were eligible for participation. Treatment with Depigoid® Katze was to be administered according one of two different up-dosing schemes (quick or conventional up-dosing scheme).

1.7 Subjects and study size, including dropouts

Assuming the proportion of local and systemic reactions is 16% and the margin of error is 4% a total of 404 patients were calculated for a 95% confidence interval. The expected drop-out rate was 20%. Enrolment of adolescents and adults in a ratio of 1:3 (adolescents: adults) was originally planned.

1.8 Variables and data sources

The primary endpoints of the study were number, severity grade, and time of onset (immediate or late phase) of systemic reactions (SR) and local reactions (LR).

Secondary endpoints were:

- comparison of conventional versus quick up-dosing regimen with regard to the primary endpoint (number, severity, grade and time of onset of SR and LR)
- comparison of conventional versus quick up-dosing regimen in relation to the percentage of patients reaching the maintenance treatment phase
- comparison of the conventional versus quick up-dosing regimen in relation to the percentage of patients with local or systemic reactions
- development of QoL via SF-12 questionnaire.

An electronic data capture system (EDC system) was used for data collection. Patients had to document all symptoms occurring within 2 days after each SCIT injection in an electronic patient diary (eDiary). Documented symptoms and adverse events (AEs) were discussed by the investigator with the patients and reported via paper-based AE forms (Nebenwirkungserfassungsbogen). All study relevant data (including e.g. patient information and declaration of consent, anamnesis, demographic data, and concomitant diseases and medications) were to be documented in the Electronic Case Report Form (eCRF), and the information of Adverse Event (AE) paper-reports to be transferred to the eCRF.

1.9 Results

The declaration of consent for data use was signed by 101 participants and/or their caregivers. Of these individuals, 97 patients were treated with at least one injection. However, data of 6 patients were not usable since documentation by investigators was missing. 91 patients were treated with the study medication, including 59 men and 32 women. 3 patients prematurely discontinued the study, they were dropped-out after V1 (1 patient), during V2 (1 patient) and after V4 (1 patient). 4 patients were screening failures before receiving the treatment. 88 patients completed the entire treatment course.

Underage patients were also included in the study, so that nine adolescents between the ages of 13 and 16 took part in the study, together with 82 adult patients. Their ages ranged from 18 to 67 years. The mean age in both groups was 34 years. Patients had the option of being treated with one of two treatment regimens according to the SmPC. 56 of the patients selected the conventional regimen and 35 the quick regimen. Approximately three quarters of the patients stated that they kept a cat as pet, with a maximum of four per household. These figures changed only marginally over the course of the study. Around one in three of the patients suffered from asthma in addition to allergic rhinitis or conjunctivitis. The majority of patients were polysensitised, two-thirds of them to seasonal allergens, and perennial allergies were diagnosed in about one in four patients. A bit more than half of the patients reported adverse events during the course of the study, with similar percentages for adolescents and adults (56% and 54%). Nevertheless, all but one patients reached the full maintenance dose and 88 out of 91 treated patients terminated the study regularly. This is in clear contrast to other studies (Jutel, 2024) reporting drop-out rates of 20% or more. The a.m. ratio of equal distribution (adolescents/adults) also corresponded to treatment-related adverse events, with no significant differences in occurrence between adults and adolescents. The incidence of side effects also did not differ significantly between the two up-dosing regimens, although a clear tendency with more reactions is seen for the quick regimen. The local reactions were predominantly delayed and in majority they were mild. Also, in total 41 systemic reactions were reported during the study – adolescents/adults 1/40 - with predominantly grade 2 for both immediate and delayed reactions. The majority of systemic reactions were delayed but did not lead to the use of adrenaline or emergency medical intervention. The QoL data collected during the study, did not

reveal significant changes for the observation period of 12 weeks in none of the domains of the SF-12. Most AEs were application site reactions. Other adverse events occurred only sporadically and did not show any persistent impairment of the patients.

1.10 Discussion

This NIS was designed within the regulatory framework of a voluntary PASS. It followed the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology and thus met high methodological standards. The study was started immediately after the market launch of the product Depigoid® Katze in Germany and encountered a difficult medical-economic environment in which the reimbursement of the therapy in patients with cat ownership in particular was questioned. It is therefore not surprising that the recruitment period had to be extended and only around a quarter of the originally planned 400 patients were included. The study protocol was amended accordingly. This raises the question of the generalisability of the findings made here. This applies in particular to the age group of adolescents, in which a total of nine were observed as part of the study. As this study is based on an epidemiological approach, the study participants were not exposed to any unusual health risk by participating in this safety study. The decision for AIT had already been made with the investigator and has been carried out exclusively according to medical routine. During data collection, the principles of the current Declaration of the World Medical Association of Helsinki, the ICH-GCP principles as well as the General Data Protection Regulation (GDPR) applied. The protection of person-related data during the study has been guaranteed at all times.

The effort for the patients in connection with the study participation was low: completion of SF-12 questionnaire twice (approx. 2 min per questionnaire) and keeping the electronic diary after the injections (approx. 5 min per injection). Their participation in the study contributed to improvement of the quality of safety data for Depigoid Katze. The format of a non-interventional study was particularly suitable in this context to collect "real world data" that could not be detected in a defined and limited setting of a clinical trial according to Section 4 (23) sentence 1 AMG. Participation in this non-interventional safety study was justifiable from a medical and patient point of view.

Regardless of the age group, around 50% of patients mainly reported delayed local side effects. Nevertheless, all but one patients reached the full maintenance dose and 88 out of 91 treated patients concluded the study. This is in clear contrast to other studies (Jutel, 2024) reporting drop-out rates of 20% or more.

The number of systemic side effects documented – limited to grades 1 and 2 only - is comparatively low, mainly affected adults and in majority were delayed supporting the safety profile of Depigoid® Katze.

In this study, in almost 100 patients no emergency hospitalisation or use of adrenaline were reported and confirms a significantly better safety profile than with native allergens for subcutaneous application (Lilja, 1989).

QoL did not improve significantly in the overall collective during the relatively short observation period of up to three months. However, in the group of adolescents treated with the quick up-dosing scheme, a clear improvement in mental health was observed. In view of the small number of patients, this finding cannot be statistically confirmed.

To summarise, Depigoid® Katze – a chemically modified allergoid – provides a well-tolerated and safe immunotherapy option for patients with cat allergies in Germany.

The observations made here largely correspond to those found in a recently published real world study in Spain (de La Torrea, 2024).

Sponsor

LETI Pharma GmbH

Names and affiliations of principal investigators

The list can be found in Annex 1.

2 List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AIT	Allergen-specific immunotherapy
AMG	Medicinal Products Act
AR	Allergic rhinitis
ARC	Allergic rhinoconjunctivitis
CRO	Clinical Research Organisation
CUS	Conventional up-dosing scheme
DBPC	Double-blinded, placebo-controlled
DPP	Depigmented and glutaraldehyde Polymerized allergen extract
DRKS	German Clinical Trials Register
EAACI	European Association of Allergy and Clinical Immunology
EC	Ethics Committee
DMP	Data Management Plan
eCRF	Electronic Case Report Form
eDiary	Electronic Patient Diary
EDC system	Electronic data capture system
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS Register	European Union electronic Register of Post-Authorisation Studies
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HDM	House Dust Mite
ICON	Patient Information and Informed Consent
IgE	Immunoglobulin E
ILIT	Intralymphatic immunotherapy
LPLV	Last Patient Last Visit
LR	Local reaction
NIS	Non-interventional study
PASS	Post-authorisation safety study
QoL	Quality of life
QUS	Quick up-dosing scheme
RAST	Radioallergosorbent test
SAP	Statistical Analysis Plan

SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
SmPC	Summary of Product Characteristics
SAE	Serious adverse event
SR	Systemic reaction
V	Visit
WAO	World Allergy Organisation

3 Investigators

Contact details of actively participating investigators can be found in Annex 1.

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5 Milestones

The most relevant milestones of the current non-interventional study are listed in

Table 1.

Table 1: Milestones reached in the LETI MIAU-KAT 2022 study.

Milestone	Planned date	Actual date	Comments
Registration in the EU PAS Register	Before starting data collection	04 March 2022	-
Registration DRKS	Before starting data collection	14 March 2022	Registration number: DRKS00028182
Start of data collection	February 2022	04 May 2022 (FPFV)	-
End of data collection	August 2023	2 April 2024 (LPLV)	Due to slow recruitment, the initially planned end of recruitment was prolonged from August to April 2024
Final report of study results	August 2024	March 2025	-

6 Rationale and Background

Pets are the most common cause of indoor allergies, along with house dust mites (HDM) (Sheehan & Phipatanakul, 2016). Sensitisation to pets is a risk factor for the development of rhinitis and asthma (Simpson & Custovic, 2005), with feline epithelial allergy being one of the most common allergic diseases (Heinzerling, et al., 2009). About 90 % of feline allergy sufferers have an IgE-mediated reaction to Fel d1, a protein produced by cats and one of the most common feline allergens (van Ree, van Leeuwen, Bulder, Bond , & Aalberse, 1999). Fel d1 is mainly produced by sebaceous gland cells and stored on the surface of the epidermis and fur (Charpin, et al., 1991). In addition, Fel d1 is found in saliva, which is transferred to the cat's hair during grooming. Cat hair, containing protein Fel d1, is then distributed in the environment as tiny airborne particles (Charpin, et al., 1991).

In general, three forms of therapy are used with IgE-mediated allergic reactions: 1) allergen avoidance; 2) symptomatic treatment (antihistamines, steroids and bronchodilators); and 3) Allergen-specific ImmunoTherapy (AIT) (Satyaraj, Sun, &

Sherrill, 2021). Immunotherapies available so far are based on the use of native allergen extracts administered subcutaneously or sublingually. Clinical studies have demonstrated the efficacy of using allergen extracts from cats for treatment of feline epithelial allergies (Alvarez-Cuesta, et al., 2007), with clinical efficacy related to the proportion of Fel d1 (Orengo, et al., 2018). Despite the proven clinical success with native extracts, there are reports of a high incidence of adverse allergic reactions (Borchers, Keen, & Gershwin, 2004).

Modified allergen extracts are promising alternatives to reduce these side effects of immunotherapy with native allergen extracts. During the production of LETI Depigoid® Katze, a highly purified and concentrated allergen is produced from the native extract during depigmentation (Morales, et al., 2017), which is subsequently polymerised by glutaraldehyde. These chemical modifications reduce allergenicity while maintaining immunogenic effect, thereby increasing the safety of immunotherapy (Ibarrola, et al., 2004). The unit for the dose/concentration of allergoid in LETI's allergoid products is DPP.

In 2019 Mösges et al. conducted a meta-analysis evaluating the efficacy of SCIT with depigmented-polymerized allergen extracts. Data from patients with pollen- or HDM-induced ARC were analysed. Six DBPC pollen trials and two HDM trials were analysed. For patients with more severe symptoms of ARC, immunotherapy was more efficient than for patients with less severe symptoms of ARC. Moreover, therapy with depigmented-polymerized allergen-extracts did not result in a significantly higher risk for local (OR: 1.55, 95% CI: 0.86-2.79) or systemic reactions (OR: 1.94, 95% CI: 0.98-3.84) compared to placebo.

In summary, subcutaneous immunotherapy with depigmented-polymerized allergen extracts has shown to be effective for patients with ARC with or without allergic asthma (Mösges, et al., 2019).

In 2018 Dhami and Agarwal published a review evaluating the efficacy and safety of cat allergen immunotherapy based on published studies. They focused on the systematic reviews of The European Association of Allergy and Clinical Immunology (EAACI) as evidence including solely randomized double-blind placebo-controlled trials. Efficacy and safety of SCIT, were evaluated for 11 studies. Six studies showed mixed results between treated and placebo group based for the bronchial provocation

test. The number of studies reporting AEs were equal to those reporting no AEs. In one study an AE was reported for the placebo group. Sublingual immunotherapy (SLIT), was just used in two of the trials; one presenting advantage of active treatment in comparison with placebo, in the second study no difference was found. No serious adverse events (SAEs) were reported there. Dhami and Agarwal reported a third possible therapeutic way, the intralymphatic immunotherapy (ILIT). The study using this method revealed a positive response and a good safety profile. No evidence regarding cost-effectiveness of cat AIT could be demonstrated.

In summary, it seems that some patients may benefit from this form of therapy, especially with moderate or severe symptoms. The authors summarized that further evidence is needed, especially large, high-quality placebo-controlled and head-to-head trials of SCIT, SLIT and ILIT plus health economic evaluations of cat AIT (Dhami & Agarwal, 2018).

In the LETI-MIAU-KAT-2022 study, allergoids are used. Carnes et al. reported that nowadays allergoids are an outstanding product for allergy treatment due to the new chemical modification of the agents during production (Carnes, Gallego, Moya, & Iraola, 2018).

7 Research Question and Objectives

Depigoid® Katze was launched in Germany in early 2022 and is used for therapy of IgE-mediated allergy triggered by allergenic substances from feline epithelia. The objective of the present study – performed as voluntary NIS-PASS - was to evaluate safety data collected during daily clinical practice in patients receiving Depigoid® Katze SCIT to treat moderate to severe AR and/or ARC with or without controlled asthma.

8 Amendments and Updates

Two non-substantial amendments resulted in the final version 1.2 (V1.2) of the observational study plan (see Table 2).

Table 2: List and description of non-substantial amendments of the observational study plan of the LETI MIAU-KAT 2022 study.

Observational study plan version number	Differences between versions	Date of version
V1.0	-	1 December 2021
V1.1	Non-substantial change of the documentation of AEs and SAEs: instead of using two separate documents, both AEs/SAEs and adverse drug reactions (ADR) are to be documented via ADR report (Nebenwirkungserfassungsbogen) Further, an additional question referring to the number of cats living in the household of the patient has been added.	25 February 2022
V1.2	Non-substantial change of a wrongly cited paragraph of the German Medicinal Products Act (§ 4 paragraph 23 sentence 3 corrected to § 4 paragraph 23 sentence 2) in chapter 6.	23 May 2022

9 Research Methods

9.1 Study Design

The current study was a voluntarily initiated, NIS-PASS performed with product Depigoid® Katze, launched in Germany in February 2022.

Collection of the safety data related to application to the investigated medicinal product took place during everyday medical practice. The decision for the therapy had to be made prior to inclusion of a patient into this safety study.

During treatment period, participating patients had to document in an electronic patient diary occurrence or absence of AEs the day of an injection and during the following two days. Before start and at the end of the study, patients documented their QoL via SF-12 questionnaire. Information of AEs were transferred by the investigators into the eCRFs, following a discussion with the patient, where necessary.

Primary Endpoints of the study are listed below:

- Number and severity of systemic reactions (SR) (WAO criteria)
- Number and severity of local reactions (LR) (classified as immediate/delayed reaction and intensity as mild, moderate or severe)
- Onset of SR and/or LR (immediate or late phase)

Secondary endpoints of the study are listed below:

- Comparison of two up-dosing regimens (Conventional up-dosing versus Quick up-dosing) regarding the primary variables
- Comparison of Conventional up-dosing and Quick up-dosing in terms of the proportion of patients reaching the maintenance treatment phase
- Comparison of Conventional up-dosing and Quick up-dosing regarding the proportion of patients with LRs or SRs and the level of intensity
- Determination of the QoL progression determined using the SF-12 questionnaire (assessment period: 1 week)

9.2 Setting

This NIS PASS was conducted in accordance with § 4 paragraph 23 of the German Medicinal Law (AMG) and sponsored by LETI. It was performed as multicentre study in Germany, in sites specialised in allergology. Patients with allergic symptoms to cats were observed during SCIT with Depigoid® Katze.

After each injection, immediately occurring ADRs were documented by the treating physicians, whereas late phase ADRs experienced between 30 minutes and 48 hours after injection were first documented by patients in their electronic patient diaries and later transferred to the eCRF by the investigators.

Initially it was planned to conduct the study in up to approx. 80 investigational sites in Germany. However, finally patients were recruited only in 22 active study centres.

The total duration of the study was planned to be about 1.5 years. Due to slow recruitment, the study period was prolonged, thereby lasting from May 2022 until April 2024.

9.3 Subjects

Patients aged ≥ 12 years suffering from persistent moderate to severe AR and/or ARC with or without controlled asthma caused by clinically relevant sensitisation to cats, confirmed by a positive skin prick test (wheal diameter ≥ 3 mm) for Felix domesticus animal epithelia, were eligible for the participation in the study. Concomitant asthma had to be controlled and stable with no exacerbations within 3 months prior to inclusion in the study.

Treatment with Depigoid® Katze IT is administered as perennial therapy. Patients recruited for the study had an indication for SCIT, based on their symptoms and anamnesis and, together with their doctor, treatment with Depigoid® Katze was chosen in accordance with standard clinical practice.

Prior to enrolment to the study patients were informed about the study project and signed the Informed Consent document to confirm their agreement and the use of their (anonymized) health data for this study project.

Patients had the right to discontinue participation in the study at any time without giving a reason and without any disadvantage to further medical treatment.

9.4 Variables

9.4.1 Study Flow

Therapy of the patients could either be started with conventional or quick up-dosing regimen in accordance with the SmPC. Depending on the dosing regimen, 3 visits (quick dose regimen) or 5 visits (conventional dose regimen) of the immunotherapy course were documented and the overall duration of study participation per patient lasted 2 or 3 months (Figure 1: Visit Schedule for the Conventional and Quick up-dosing regimen). Study flow charts for both dose regimens are shown in

Table 3 and

Table 4.

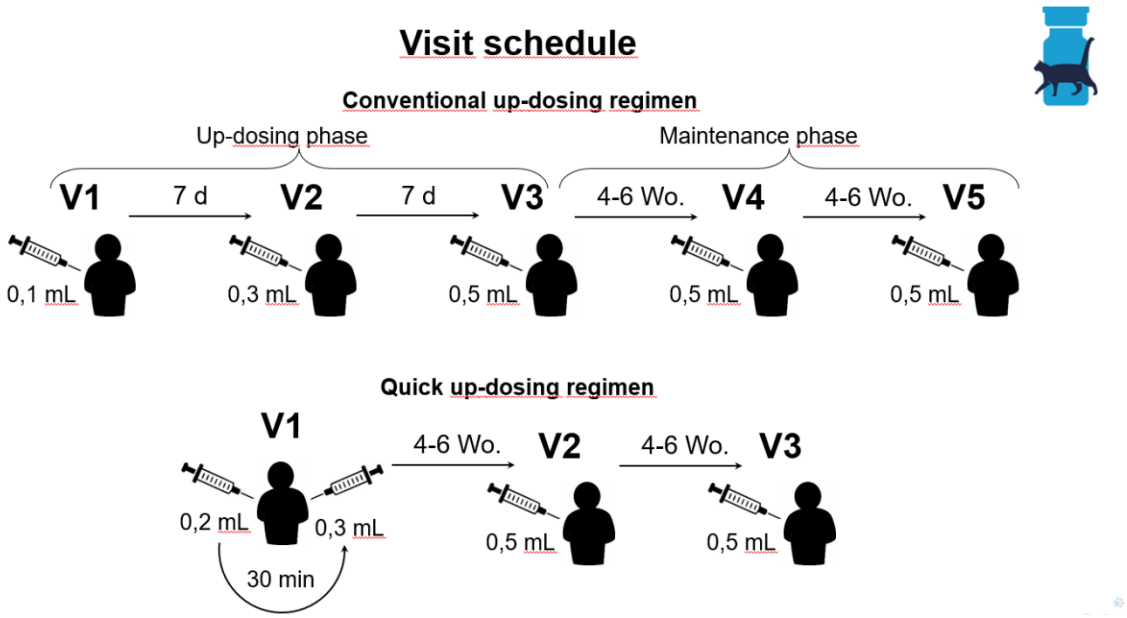


Figure 1: Visit Schedule for the Conventional and Quick up-dosing regimen

Both the quick and conventional dose regimen consist of an initial up-dosing phase, finished upon reaching the maximal injection dose of 0,5 mL, followed by the maintenance phase with applications of the maximum dose of 0,5 mL (see Figure 1). Investigators were asked to adhere to the time schedules, however, medically justified adaptations in line with the SmPC were acceptable. After the third (quick) or fifth (conventional) visit with administration of Depigoid® Katze, patients' participation in the study terminated. Thereafter immunotherapies were continued in accordance with the normal clinical practice.

Table 3: Study flow chart: Conventional up-dosing regimen.

Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**
	Day 1	7 days after V1	7 days after V2	4 weeks after V3	4 weeks after V4
Injection volume (mL) Depigoid® Katze (according to SmPC) without consideration of dose adjustments	0.1	0.3	0.5	0.5	0.5
Declaration of consent	X				
Demography (age, gender)	X				
Number of cats in the household	X				X
Allergological anamnesis (clinical manifestation of rhinitis, conjunctivitis, asthma)	X				
Documentation of allergy diagnostics based on existing findings (prick test, IgE)	X				
Documentation of concomitant diseases and concomitant medication	X				
Change in concomitant medication, if applicable		X	X	X	X
Completion of the SF-12 questionnaire (patients ≥ 14 years)	X				X
Establishment of access to the electronic patient diary	X				
Documentation of adverse events during the visit by the physician	X	X	X	X	X
Patient documentation of any adverse drug reaction that may occur on the evening of the day of the injection and on two subsequent days	X	X	X	X	X
Discussion and documentation of any adverse event that may have occurred after the visit incl. events reported by the patient in the diary		X	X	X	X

Table 4: Study Flow Chart: Quick up-dosing regimen.

Visit (V)	**V1**	**V2**	**V3**
	Day 1	4 weeks after V1	4 weeks after V2
Injection volume (mL) Depigoid® Katze (according to product information) without consideration of dose adjustments	0.2 mL (arm 1) and 30 min later 0.3 mL (arm 2)	0.5	0.5
Declaration of consent	X		
Demography (age, gender)	X		
Number of cats in the household	X		X
Allergological anamnesis (clinical manifestation of rhinitis, conjunctivitis, asthma)	X		
Documentation of allergy diagnostics based on existing findings (prick test, IgE)	X		
Documentation of concomitant diseases and concomitant medication	X		
Change in concomitant medication, if applicable		X	X
Completion of the SF-12 questionnaire (patients ≥ 14 years)	X		X
Establishment of access to the electronic patient diary	X		
Documentation of adverse events during the visit by the physician	X	X	X
Patient documentation of any adverse drug reaction that may occur on the evening of the day of the injection and on two subsequent days	X	X	X
Discussion and documentation of any adverse event that may have occurred after the visit incl. events reported by the patient in the diary		X	X

9.4.2 Patient Information and Declaration of Consent (ICON)

Following the decision for treatment with Depigoid® Katze, patients were informed about the study and respective collection of their data by their physician and the ICON form.

The following ICON forms were used during the current study:

- for adults
- for adolescents aged ≥12 years (to be signed by the adolescent)
- for legal guardians of adolescents ≥12 years (to be signed by both parents/legal guardians, if applicable)

Patients – and if applicable parents/guardians - had sufficient time to read, understand and ask questions before signing the ICON. After signature by the investigators, patients were enrolled into the safety study.

In addition, patients aged ≥14 years had to be informed about contact details of the data protection officer (a request of the leading EC from Cologne). This information had to be documented on the respective ICON of adolescents (e.g. by handwritten note).

Where requested by local ECs, specific ICON forms were created.

9.4.3 Demographic Data

The following demographic parameters were documented:

- Age
- Gender (male, female, diverse)

9.4.4 Documentation of Cats in the Household

The number of cats living in the household.

9.4.5 (Allergological) Medical History

During the first visit (V1), an allergological anamnesis was documented including the presence/absence and date of diagnosis of the following indications:

- allergic rhinitis
- allergic conjunctivitis
- asthma (no inclusion for uncontrolled asthma)

9.4.6 Documentation of Cat Allergy

Evidence of feline epithelial allergy was documented via results:

- Skin prick test (SPT) with Felix domesticus animal epithelia (wheal diameter [mm])
- Feline epithelial-specific/ Fel d1-specific IgE (RAST class)

9.4.7 Concomitant diseases and concomitant medication

Concomitant diseases and concomitant medication including changes – if applicable - during the study were checked and documented during the entire study period.

9.4.8 Documentation of adverse events (AEs)

9.4.8.1 AE Documentation by Investigators

Investigators were obliged to document all AEs occurring during the study. ARs within 30 minutes after injection were documented as immediate reactions and reactions later than >30 minutes after injection were documented as late phase reaction.

AEs were graded into LRs and SRs. LRs (wheal and redness) were scored as immediate or delayed reactions and classified as mild, moderate or severe according to the following scoring scheme (see Table 5). If only itching or pain at the injection site were observed as LR (without wheal and/or redness), this was judged as mild LR.

Table 5: Evaluation of severity of local reactions

Severity of local reaction	**Diameter of wheal/redness**
Mild	>0 to ≤5 cm
Moderate	>5 to ≤10 cm
Severe	>10 cm

SRs were evaluated as grade 1 to 5 according to WAO criteria (2010) (Cox, Larenas-Linnemann, Lockey, & Passalacqua, 2010).

A study specific ADR report-form (paper and via eCRF) had to be completed by the investigators.

9.4.8.2 AE Documentation by Patients

The presence or absence of AEs were to be recorded in the patient eDiary on day 1 (day of 1st injection), day 2 and day 3 (quick up-dosing) or on days 1 to 5 (conventional up-dosing) respectively, after each injection using the following questionnaires:

- No adverse events (AEs)
- Local AEs at the injection site:
  - Swelling at the injection site > 0 ≤ 10 cm
  - Swelling at the injection site >10 ≤ 15 cm
  - Swelling at the injection site > 15 cm
  - Redness at the injection site > 0 ≤ 10 cm
  - Redness at the injection site >10 ≤ 15 cm
  - Redness at the injection site > 15 cm
  - Itching at the injection site
- Other: _____
- Other AEs :
  - Unusually loud breathing noise
  - Cough
  - Wheezing
  - Shortness of breath
  - Difficulty breathing (dyspnoea)
  - Itchy throat
  - Strong clearing of the throat (itchy palate)
  - Swelling in the area of the larynx
  - Voice disorder
  - Sneezing
  - Runny nose
  - Blocked nose
  - Redness of the eyes
  - Tearing of the eyes
  - Tingling of the lips
  - Metallic taste in the mouth
  - Swollen tongue
  - Extensive, burning wheals on the skin (urticaria)
  - Itching off the injection site. If yes, body region: _____
  - Water retention in the skin. If yes, body region: _____
  - Feeling of warmth. If yes, body region: _____
  - Uterus cramps
  - Abdominal cramps

- Diarrhoea
- Nausea
- Vomiting
- Headache
- Low blood pressure
- Fainting
- Other: _____

For each AE, start and end (date, time) had to be recorded by patients.

9.4.9 SF-12 Questionnaire

The SF-12 questionnaire is a validated instrument to measure health-related QoL in adults and adolescents aged 14 years and older (Huo, Guo, Shenkman, & Muller, 2018). On the basis of 12 items, 8 aspects/dimensions are assessed: general health state/perception of health, physical capability, physical pain, physical ability to act, social capability, emotional ability to act, psychological well-being, and vitality. The questions are to be answered by patients in accordance with given rating scales.

During V1 and during the last study visit (V3 or V5, depending on the dosing scheme) Patients aged ≥14 years completed a paper-based SF-12 health-related QoL questionnaire during an interview with the investigator. Thereafter data entered to the SF-12 questionnaire partly were transferred by the investigator to the eCRF (for details regarding eCRF, see chapter 9.5).

Adolescents aged 12-13 years did not complete a questionnaire.

9.4.10 Depigoid® Katze Medicinal Product

1 ml Depigoid® Katze contains 100 DPP cat epithelium and the excipients sodium chloride, Phenol (0,5% in physiological saline solution), hydrated aluminium hydroxide (3 mg/ml) and water for injections.

Depigoid® Katze is administered via subcutaneous injection. Different dosing schemes (conventional or quick) are described in the SmPC. Treatment starts with a phase of up-dosing, followed by a phase of maintenance treatment.

In this current study, patients were observed for 2-3 months (see Figure 1).

In general, the Guidelines recommend an overall duration for effective immunotherapies of 3 up to-5 years.

9.5 Data sources and measurement

During the current study, an EDC system was used for data collection. Data were entered into the eCRF by the physicians or their study team.
The user concept of the secuTrial® software ensured that data access was only permitted for trained and authorised persons. The study-specific database stored in secuTrial® is cloud-based and stored in Germany on the servers of noris network AG hosted by the company iAS. This company is certified according to ISO/IEC 20000 and ISO-27001.
The CRO was responsible for processing the pseudonymised study data for scientific purposes. With the publication of results in the form of scientific presentations or publications, the confidentiality of person-related patient data remains guaranteed. During the course of the study and evaluation of the results data were processed by the CRO, stored on servers hosted by the CRO and operated by the company Arwanet GmbH in Germany.

9.5.1 Electronic Case Report Forms

Study data was documented electronically using a study-specific eCRF programmed with the software secuTrial® (iAS, Berlin).

9.5.2 Electronic Patient Diaries

Patients documented AEs (see 9.4.8.2) in an electronic patient diary. During V1, participating patients were instructed and trained for the usage of the eDiary. A hand-out with the respective login data was provided. Only in justifiable exceptions (e.g. absence of internet), patients were allowed to document their symptoms in paper diaries.

9.5.3 Patient Identification Numbers

Data in this study were collected in a pseudonomized way. Thus, participating patients received a unique patient identification number (Pat-ID), consisting of 3 digits characterising the centre plus 2 digits assigned to the patients/site in ascending order: I__I__I__I- I__I__I (Example centre 001: 001-01, 001-02, 001-03 etc.).

9.6 Bias

No bias reducing measures (such as blinding or a control group) were implemented for this open label observational study. No limitations for the number of patients enrolled per study site were given. Patients were enrolled as they arrived for routine medicinal care of their allergy.

9.7 Study Size

The sample size calculation was based on an estimation of SRs and LRs described by (Lwanga & Lemeshow, 1991) using the formula shown below:

$$n = \frac{{z_{\propto/2}}^2 * (\hat{p} * (1-\hat{p}))}{\varepsilon^2}$$

Variable	Description
z	z-Score
ε	Margin of error
α	Type 1 required error
n	Sample size
p̂	Share of the population

Based on the assumption that the proportion of LRs or SRs is 16% and the margin of error is 4%, a sample size of 404 patients was calculated, considering a 95% confidence interval and an expected drop-out rate of 20%. It was aimed to enrol adolescents and adults in a ratio of 1:3 (adolescents: adults).

9.8 Data Transformation

No data transformation was performed.

Data processing in accordance with ICH-GCP was presented in a data management plan (DMP).

A protected export file was transmitted to the biostatistician via a file-sharing service.

9.9 Statistical Methods

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 or older (Armonk, NY: IBM Corp.) or other validated statistical software. The endpoints of the study were analysed with descriptive and exploratory statistics. Subgroups were analysed exploratively (e.g. subgroups in terms of gender, age, etc.).

The statistical analysis plan (SAP) can be provided upon request.

9.9.1 Main Summary Methods

Continuous data were analysed by statistical ratios (mean, standard deviation, median, minimum and maximum values). Categorical data were analysed by absolute frequencies and the percentage of valid cases.

9.9.2 Main Statistical Methods

Confidence intervals were calculated using Clopper-Pearson equation. Student t-test or Mann Whitney U-tests were used for continuous variables and Chi-square test or Fisher's exact test for categorical variables in group comparisons for exploratory purposes. The P-value was set at 0.05.

9.9.3 Missing Values

Missing values were not replaced, and therefore no imputation rules were applied.

9.9.4 Sensitivity Analyses

Not applicable.

9.9.5 Amendments to the Statistical Analysis Plan

Not applicable.

9.10 Quality Control

The CRO performing the current study is certified in accordance to ISO 9001.

9.10.1 EDC System

SecuTrial® as a web-based programme for capturing patient data for clinical studies was audited in January 2021, reviewing the practices, procedures and documentation used with the software and the alignment with regulatory requirements including

21 CFR Part 11. Installation Qualification and Operational Qualification were provided by the manufacturer iAS. All versions of the study-specific eCRF were verified and validated by ClinCompetence Cologne GmbH in cooperation with the sponsor (Performance Qualification) prior to release.

During the study, updates of the productive version of the eCRF were necessary, resulting in the following released versions:

Table 6: Different versions of the EDC system

Version number	Differences between versions	Date of version
1.0	Initial version	24 March 2023
2.0	• Separation of eDiary entry forms for V4 and V5 into two individual pages • Resolution of the time limit (formerly 3 days after the visit) for eDiary entries	31 March 2023
3.0	• Introduction of additional form for fixed-combination medications • implementation of query system	30 May 2023

9.10.2 Monitoring

Up to five on-site visits per centre were planned for this non-interventional safety study: one site initiation visit, up to 3 regular monitor visits and the close/out visit. During the initiation visit, study procedures and tasks were explained and eCRF use was trained. During the regular monitor visits, correctness and completeness of the declaration of consent forms as well as the transfer of relevant data (especially AE) from the patient file to the eCRF were checked. Continuous remote monitoring of the data in the eCRFs, focussed on completeness and plausibility was performed. Documentation of AEs in the eCRF were crosschecked with AE report forms (source data).

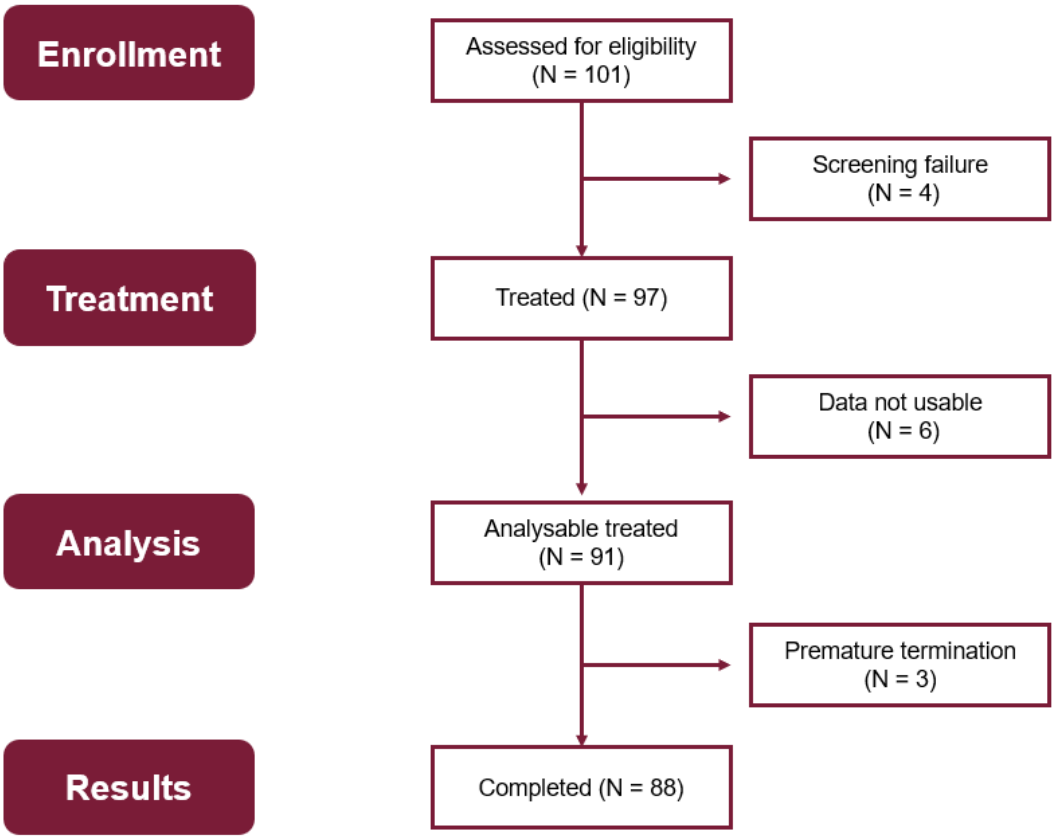
9.10.3 Remote Monitoring

Completed eDiaries were continuously checked by the CRO. If applicable, investigators were asked to re-train patients to improve quality of the entries.

10 Results

10.1 Participants

Initially, 400 patients (300 adults, 100 adolescents) were planned to be recruited for the study; however, due to slow recruitment, 101 patients only could be included by the end of the recruitment phase.



10.2 Descriptive Data

In total 91 analysed patients received SIT with Depigoid® Katze, 59 male and 32 female patients. 9 adolescent patients aged 13-16 years and 82 adult patients aged 18-67 years were treated.

The conventional up-dosing scheme (CUS) was used in 56 patients aged 13-67 years, and in 35 patients aged 14-64 years, the Quick up-dosing scheme (QUS) was applied.

For details pls. refer to Table 7 (Analysis table 1).

In the CUS-group 71.4% of the patients at least had one cat living in their household, and 77.1% of patients in the QUS-group. Only few changes with regard to cat ownership took place during the course of the study (Table 8: Analysis table 2).
Number of cats in the household in the adolescent group ranged from 0 to 3 (CUS-group) and 2 (QUS-group) with a median of 1, while in the adult group this range was 0 to 4 for both groups (CUS and QUS). At the last study visit the only group with a difference of -1 cat was the adult CUS-group, in all other groups the number stayed the same. (Table 9: Analysis table 3).

In the total study population, 94.6% CUS- / 94.3% QUS-patients were suffering from allergic rhinitis, 78.6% (CUS) / 74.3% (QUS) suffering from allergic conjunctivitis and 30.4% (CUS) / 34.3% (QUS) suffering from allergic asthma (Table 10: Analysis table 4).

Major part of the study population was co-sensitized/allergic to the following 2 main types of co-allergies:

- Seasonal co-allergies were most frequent in both age groups: adolescents (CUS: 66.7% / QUS: 85.7%) and adults (CUS: 61.2% / QUS: 64.6%), with grass allergy being the most reported one (Table 11: Analysis table 6A).
- Perennial allergies: in adolescents a co-allergy to animals (CUS: 11.1% / QUS: 14.3%) was most frequent, in all patients caused by horses. Surprisingly no dog co-allergy was reported, but the population analysed is quite small (n=9). (Table 11: Analysis table 6A).
  For adults however, a co-allergy to mites was most prevalent in the CUS-group (25.9%) while for the QUS-group this were also animals (15.2%) (Table 11: Analysis table 6A).

The remaining cases of co-allergies were individual cases.

The distribution of concomitant diseases reported as medical history of the study population was:

- For adolescents: 4 diseases, with first 2 of them at a prevalence of more than 10%: asthma (CUS: 50% / QUS: 25%), atopic dermatitis (QUS: 25%), hypothyroidism (QUS: 25%) and migraine (CUS: 50% / QUS: 25%).

- For adults: the most frequent diseases reported were asthma (CUS: 22.2% / QUS: 13.3%) and hypertension (CUS: 14.8% / QUS: 20.0%) (Table 12: Analysis table 6B).

The following means calculated for the results of the health-related QoL assessment (SF-12) for ‘mental health’ at V1 in adolescents were 42.76 (CUS) and 39.9 (QUS), whereas for adults the mean was 43.07 (CUS) and 44.93 (QUS). For ‘physical health’ adolescents showed slightly higher mean values with 42.9 (CUS) and 44.4 (QUS) compared to adults with 41.95 (CUS) and 41.82 (QUS). (Table 13: Analysis table 7).

Analyses of the SF-12 for ‘mental health’ at the last study visit showed for adolescents means of 43.35 (CUS) and 48.50 (QUS), while in adults the means were 43.19 (CUS) and 45.25 (QUS). For ‘physical health’ adolescents had means of 42.79 (CUS) and 41.04 (QUS) while adult means were 41.71 (CUS) and 42.10 (QUS) (Table 14: Analysis table 8).

The results of prick tests to cat allergy performed for the study participants at V1 resulted in wheal diameters of 3 to 50 mm. Mean diameters documented for adolescents were 9.5mm in the CUS-group and 10 mm in the QUS group. For adults the diameters were smaller with 6.97 mm in the CUS-group and 6.96 mm in the QUS-group. Maximum diameters were 15 mm in the adolescent group, and 50 mm in the adult group.

The RAST-classes analysed for adolescents were minimum class 3 and maximum class 4, resulting in a mean of 3.5 (CUS group). The distribution for adults ranged from class 0 to class 6 with a mean of 2.87 in the CUS-group and 3.55 in the QUS-group (Table 15: Analysis table 5).

10.3 Outcome Data

The primary variables of the study were number, severity grade, and time points (immediate or late phase) of SRs and LRs.

In total 139 AEs were reported and 132 events thereof were related AEs (ADRs). Moreover, of these 139 events 105 occurred with CUS and 34 with QUS. All AEs reported in the QUS-group were treatment related AEs.

For adolescents in total 14 AEs were reported, 11 thereof in the CUS-group. 9 events were classified related (ADRs).

For adults in total 125 AEs were reported, 94 thereof in the CUS-group and 31 in the QUS-group. 89 events in the CUS-group and 31 in the QUS-group were classified related (ADRs) (Table 16: Analysis table 10).

Also of 139 AEs reported in total, 119 events were LRs – immediate or delayed - occurring after administration of subcutaneous AIT (see Table 17). The intensity of LRs was categorized as mild, moderate or severe.

In the CUS adolescent group no immediate LR was reported, whereas 9 delayed LRs occurred, thereof 6 were mild and 3 moderate. In the QUS adolescent group 1 mild immediate LR and 2 delayed LRs – one mild, one severe – were seen.

In the CUS adult group 19 immediate LRs occurred, the majority (94.7%) were mild and 1 moderate LR (5.3%). Most of the delayed LRs reported in adults were mild (90.9%). In the CUS-group from the total of 61 LRs, 55 (90.2%) were mild, 4 (6.6%) were moderate, and only 2 (3.3%) were severe. Proportionally, more mild LRs were reported in the QUS-group (15 = 93.8% of all 16 LRs reported) than in the CUS-group. One moderate delayed LR (6.3%) and no severe LR occurred.

Overall, immediate local reactions in both age groups were mostly mild, with a few moderate and only 1 severe event in adults. Delayed reactions were predominantly mild for both adolescents and adults, with moderate and severe events being also less common, especially in adolescents. Adults seemed to have a slightly higher rate of severe events than adolescents, especially for delayed reactions (Table 17: Analysis table 11).

A total number of 41 SRs occurred, 40 in adults and 1 in an adolescent. This SR in the adolescent patient was described as delayed grade 2. The majority of delayed SRs in adults were reported with CUS (23 out of 29 in adults). In total, more delayed SRs (30) were observed than immediate SRs (11). The 7 immediate SRs which occurred with QUS, were categorized as grade 2 (Table 18: Analysis table 12).

A systemic reaction in a 47-year-old female patient was categorised as grade 2 by the investigator but was documented as serious (SAR). The reaction occurred during the administration of the first injection with a dose of 0.1 ml (CUS) and led to severe

asthma, coughing and tingling of the palate after 15 minutes. The patient was administered a salbutamol metered dose inhaler and given a 10 mg cetirizine tablet orally resulting in a complete recovery from the reactions within 30 minutes. The patient was discharged symptom-free and AIT-treatment according to the observation plan was continued (CUS). In both QUS-groups of adolescents and adults no non-related AEs were documented. In total, the majority of AEs were related and occurred mostly in the CUS-group (Table 19: Analysis table 13).

Summarized, 49 related AEs were reported, 5 in adolescents and 44 in adults, thereof 33 in the CUS-group and 16 in the QUS-group. For adolescents, mostly 3 related AEs were reported per patient (75% in CUS, 100% in QUS), with no adult patient having 4 or 5 AEs.

Out of the 91 analysed patients in this study, 49 (54%) reported at least one AE. Under therapy with CUS, the majority (59%) experienced at least one AE, in 57% adults and in 80% adolescents. In contrast, the majority of QUS patients (54%) did not experience an AE, 75% of the adolescents and 52% of the adults experienced no AE. For 1 adult patient an SAE was reported.

Both p-values using the Chi-Square and Fisher`s exact test comparing the number of related AEs (ADRs) for adolescents (p=0.206) and adults (p=0.455) respectively were not statistically significant including also the comparison between adolescents and adults (p=0.914) (Table 20: Analysis table 14A).

For the adolescent patients, 3 out of 5 under CUS and 1 out of 4 under QUS experienced at least one AE. The difference is not statistically significant (p = 0.294).

In the adult population, 24 out of 51 patients under CUS and 15 out of 31 under QUS experienced at least one AE. The difference is not statistically significant (p = 0.907) as well.

4 out of 9 adolescent patients experienced at least one ADR, compared to 39 out of 82 adult patients. Also, this difference is not statistically significant (p = 0.859) (Table 21: Analysis table 14B).

In adolescents no statistically significant difference was seen between CUS and QUS treatment groups in terms of number of AEs and related AEs (p=0.180, p=0.180). This situation is similar in adults (p=0.098, p=0.098) and for the total study population

(p=0.059, p=0.059) as well. Also, no statistically significant difference was seen between adult and adolescent population in terms of number of AE (p=0.894) (Table 22: Analysis table 14C).

10.4 Main results

The primary endpoints of this non-interventional study describe the safety (SRs) and the tolerability (LRs) of the cat-specific allergen-immunotherapy. As secondary endpoints of the study, comparisons between conventional versus quick up-dosing regimen regarding the primary endpoints were performed.

The first comparison was the question of the proportion of patients reaching the maintenance phase. Except from one adult patient in the CUS-group (1 out of 51 adult CUS patients, presenting 2%), all participants reached the maintenance phase (See table 15). Also, all 9 participating adolescent patients reached the maintenance phase (Table 23: Analysis table 15).

Furthermore, no statistically significant difference was seen between the therapy regimen groups regarding the proportion of patients entering the maintenance treatment phase (p-value: p=1.0). In numbers, this means that 35 out of 35 patients treated with QUS reached the maintenance treatment phase (100%) and 55 out of 56 with CUS (98.2%). Concerning the difference between age groups, there is no statistically significant difference (p-value of 1.0) (Table 24: Analysis table 18).

A comparison of the two therapy regimen groups (CUS vs. QUS) shows the following picture (Table 25: Analysis table 16):

1. Regarding immediate LRs
    1.1. Among adults the severity of LRs does not differ significantly between CUS and QUS
    1.2. Among adolescents the severity of LRs does not differ significantly between CUS and QUS
2. Regarding delayed LRs
    2.1. Among adults the severity of LRs does not differ significantly between CUS and QUS
    2.2. Among adolescents the severity of LRs does not differ significantly between CUS and QUS

3. Regarding SRs (Table 26: Analysis table 17)
    3.1. Among adults the severity of SRs does not differ significantly between CUS and QUS
    3.2. Among adolescents the severity of SRs does not differ significantly between CUS and QUS

In the physical component score of the SF-12 regarding the change of the health-related QoL between first and last visit, in the CUS it can be detected that there is practically no difference with a mean in the adolescents of -0.11 and -0.03 in the adults. The QUS presents a slight decline in the physical component score of the adolescent group with a mean of -3.36, whereas the adult group has a slight increase with 0.26. In total no significant difference is seen in the CUS, whereas in the QUS a slight decline (-0.20) is present but with a bigger standard deviation (5.71).

In the mental component score, there is an increase in the adolescent group with a mean of 0.59 for the CUS and 8.59 for the QUS (mean in the QUS: 7.77, showing that the majority of this patient group had an increase in health-related QoL). The adults present slight changes with a mean of -0.08 in the CUS and 0.11 in the QUS. In total it can be concluded that in the adolescent group the therapy with Depigoid® Katze showed a decline in the physical component score (-3.36 and -0.11) but an increase in the mental component score (0.59 and 8.59). In the adult group there were no significant changes neither in the physical nor in the mental component score (Table 27: Analysis table 9A).

Analysis of table 9B for the SF-12 norm-based QoL assessment between first and last visits, reveals that the means for physical health of SF-12 and SF-12b in the CUS (SF-12: 42.02/ SF-12b: 41.79) and the QUS (SF-12: 42.12/ SF-12b: 41.97) are similar. There is no statistically significant difference between adolescents and adults (p-value of 0.933 for CUS and 0.327 for QUS).

For mental health, the mean in the QUS is slightly higher than in the CUS (SF-12: 43.05 CUS vs. 44.34 QUS/ SF-12b: 43.20 CUS vs. 45.66 QUS).

In total, no statistical differences were seen for these analyses (Table 28: Analysis table 9B).

10.5 Other analyses

Not applicable.

10.6 Adverse events/ adverse reactions

The frequency of AEs shows the following distribution among the therapy regimen groups (CUS vs. QUS) and age groups (adults vs. adolescents), displayed in (Table 29: Analysis table 19):

CUS

Adults

1. General disorders / administration site conditions such as injection site swelling, injection site erythema or injection site pain
2. Respiratory disorders such as rhinorrhoea, nasal congestion, cough, throat irritation

Adolescents

1. General disorders / administration site conditions such as injection site swelling, injection site erythema or injection site pain
2. Respiratory disorders such as rhinorrhoea, nasal congestion, cough, throat irritation

QUS

Adults

1. General disorders / administration site conditions such as injection site swelling, injection site erythema or injection site pain
2. Respiratory disorders such as rhinorrhoea, nasal congestion, cough, throat irritation

Adolescents

1. General disorders / administration site conditions such as injection site swelling, injection site erythema or injection site pain
2. Gastrointestinal disorders

11 Discussion

11.1 Key results

The current study was designed and conducted as a voluntary non-interventional post authorization safety study (NIS-PASS).

The objective of the study was to collect and evaluate safety data during daily clinical practice in patients receiving Depigoid® Katze SCIT for the treatment of moderate to severe AR and/or ARC with or without controlled asthma.

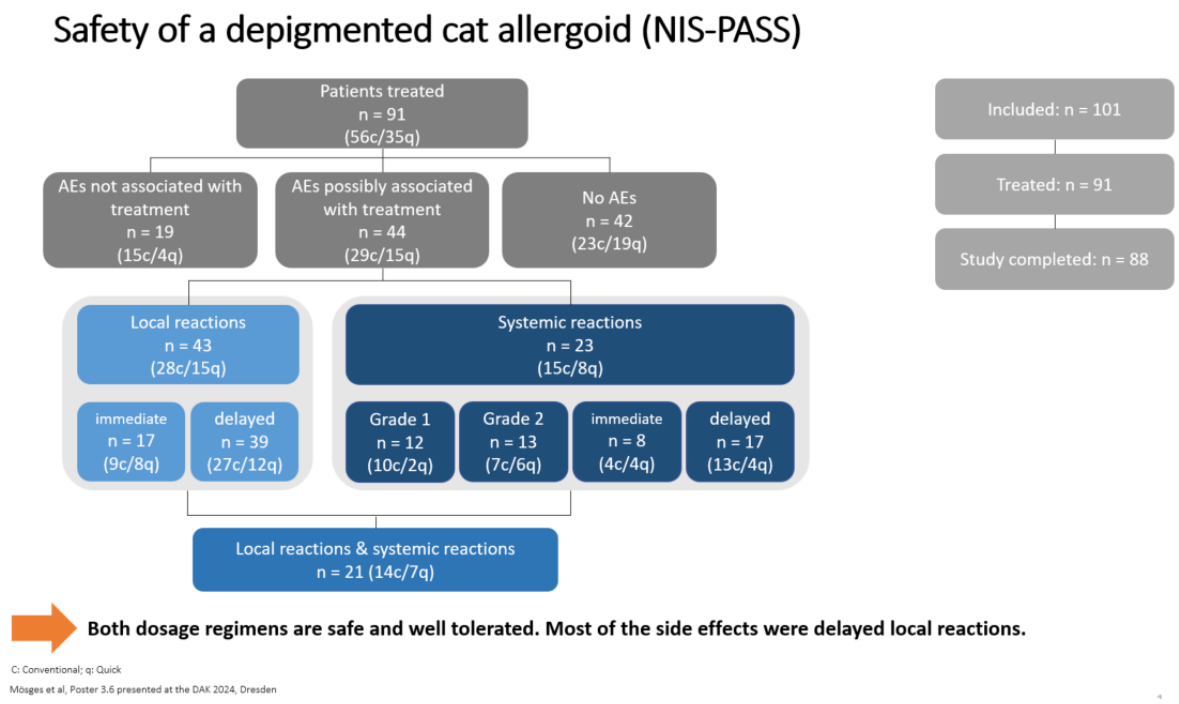


Figure 2: Overview of the conducted study

The primary endpoint of the study was the number, severity, and occurrence of SRs and LRs (both immediate or delayed). The secondary endpoints were

i) comparison of conventional versus quick up-dosing regimen for number, severity and occurrence (immediate/delayed) of SRs and LRs,
ii) the comparison of conventional versus quick up-dosing regimen with regard to the proportion of patients reaching the maintenance phase,
iii) comparison of conventional versus quick up-dosing regimen for proportion of patients with LRs or SRs and
iv) development of QoL under treatment.

The aim to perform a NIS-PASS evaluating safety data collected under routine medicinal practice in patients receiving a SIT with Depigoid® Katze was achieved.

The majority of the AEs occurred with the QUS regimen group (adults and adolescents). Most immediate and delayed LRs were mild. Only for immediate LRs in the QUS adult group a similar frequency for mild and moderate was reported.

In total, slightly more than half of the patients at least reported one AE related (ADR) to the study medication.

All but one adult participant reached the maintenance phase and the distribution of LRs and SRs, did not reveal a difference between CUS-group and QUS-group, nor between adolescents and adults.

QoL of the patients assessed at baseline and end of the study using SF-12 (physical and mental health) seems not to be affected by the IT with Depigoid® Katze, i.e. did not change between the two assessments. However, there was a marked improvement in QoL mental health for the 4 adolescents receiving the quick up-dosing scheme.

11.2 Limitations

For the design of non-interventional studies according to Section 4 (23) sentence 3 of the German Medicines Act (AMG), in contrast to a clinical trial according to Section 4 (23) sentence 1 of the AMG, routine daily clinical practice using guideline-compliant therapeutic concepts need to be considered and data recording and collection is limited to such routine practices.

One limitation of this study is, that the overall number of participants was substantially smaller originally planned in the observation plan. This was mostly due to the limitations imposed on AIT prescriptions by the national guideline, according to which patients only qualify for AIT after avoidance of cat exposure at home (abolition of the pet) and failure of symptomatic treatment. So, the age group of adolescents comprised only 9 participant and therefore was clearly under-represented with regard to the common prevalence in this age group. Both factors affect the generalisability of the results of this post-authorisation-safety-study.

11.3 Interpretation

At least one cat is living in every fourth German household (see Figure 3).

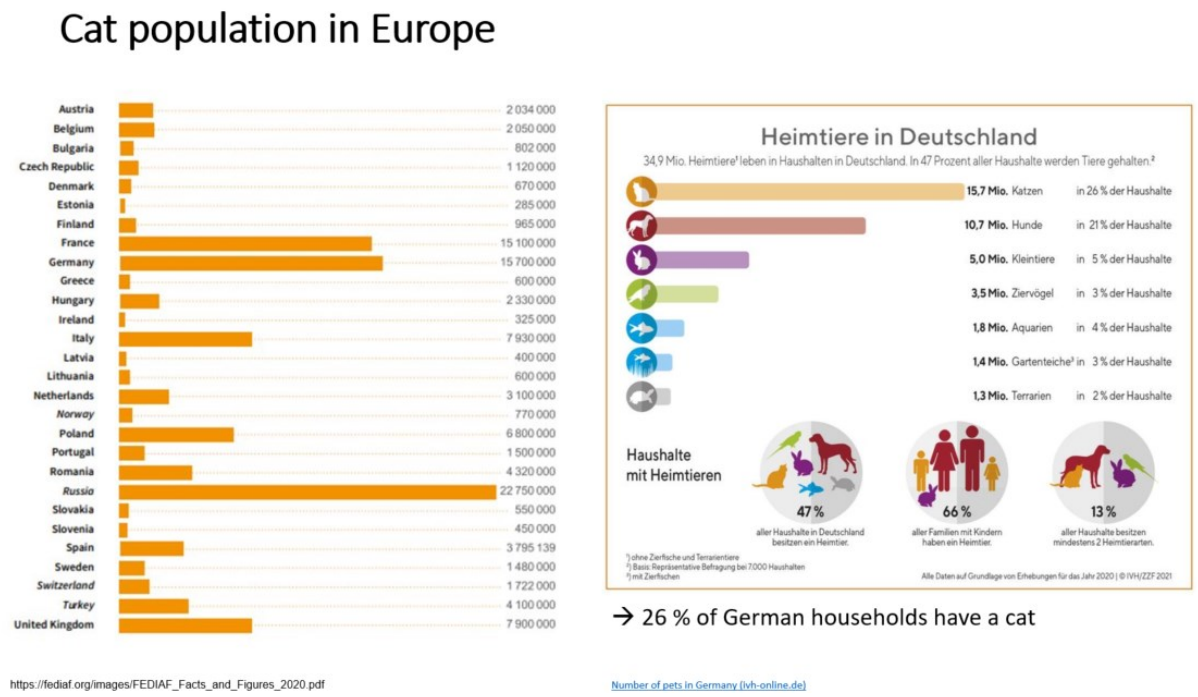


Figure 3: Cat population in Europe

Every third to fourth adult patient in Europe suffering from allergy has a cat allergy (see Figure 4).

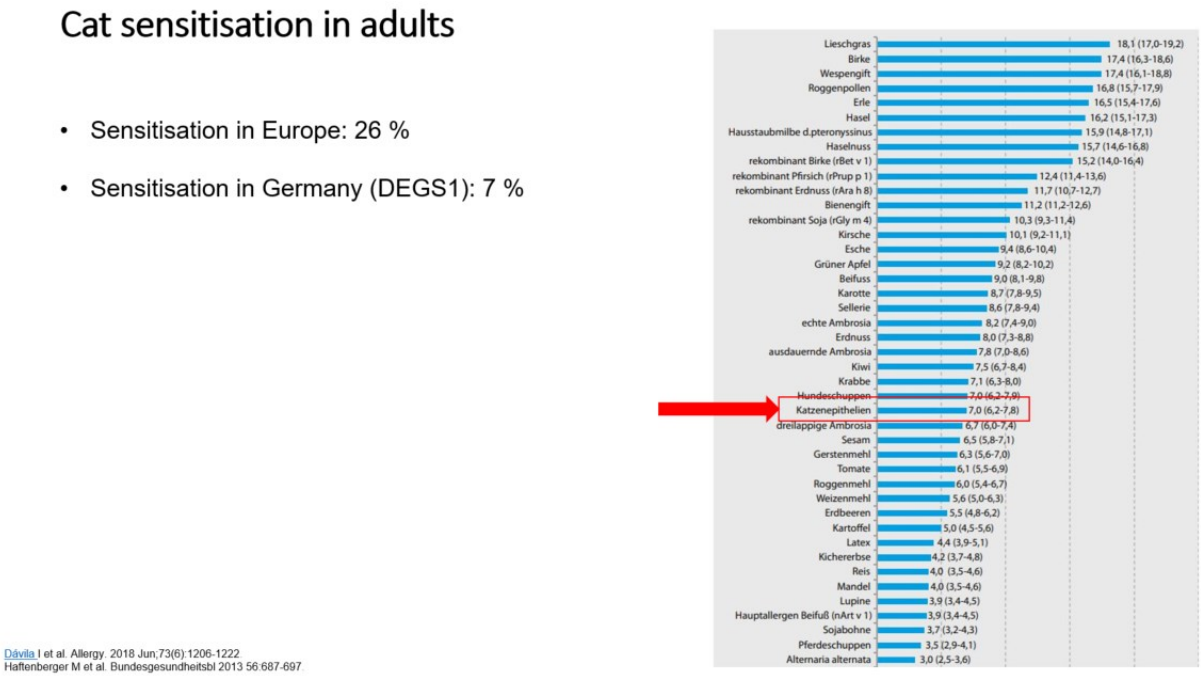


Figure 4: Cat sensitisation in adults

The prevalence of cat allergy in children in Germany is slightly higher than in adults (see Figure 5).

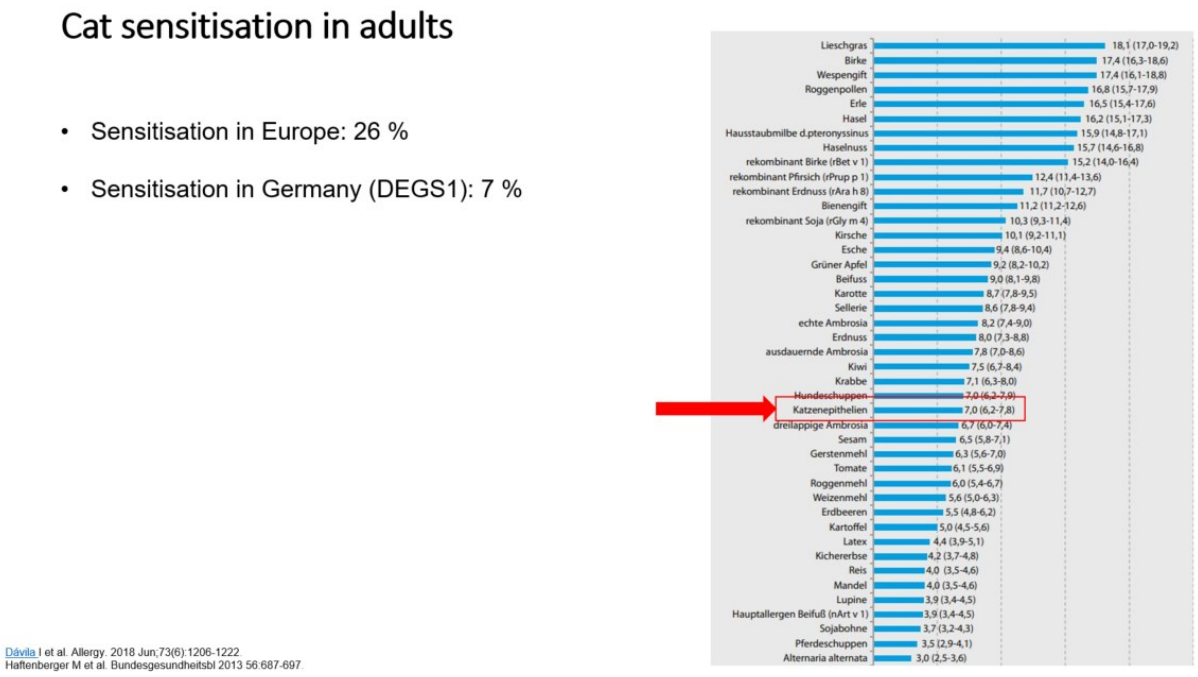


Figure 5: Cat sensitisation in children

Usually the allergies are diagnosed as polysensitisation (see Figure 6).

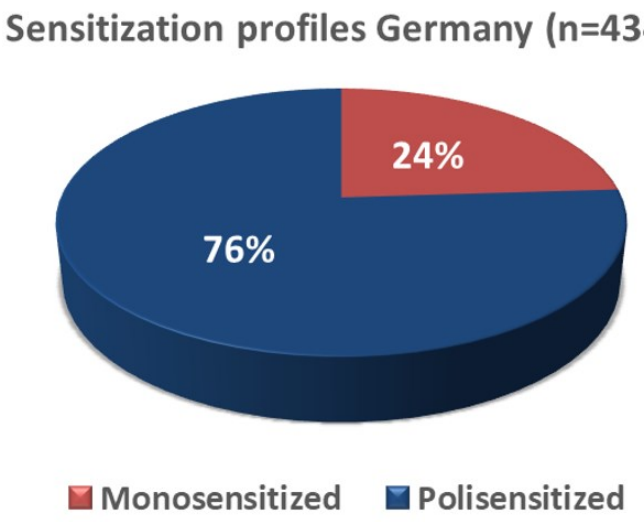


Figure 6: Sensitisation profiles in Germany

Moreover, there is a high risk among patients suffering from cat allergy to develop allergic asthma. Allergen avoidance is not improving the outcome of immunotherapy of cat allergy. and classical native SCIT products caused relevant side effects including frequent anaphylaxis.

While anti-allergic treatment with peptides did not match the expectations, depigmented allergoids are a safe alternative, which is well tolerated and effective. The real-world collected in this study confirms this for the allergoid product Depigoid® Katze used.

11.4 Generalisability

In this study, 91 patients were analysed. This is a small number in comparison to the large DBPC trials conducted in pollen or house dust mite allergies. However, the number of successful published trials in cat-allergy is sparse, and a recent publication from Spain using the same product, as well showed similar results in a smaller number of patients.

12 Other information / justification of the study

As this safety study used a non-interventional setting, study participants were not exposed to any interventional assessment with a possible health risk but only treated and observed according to SmPC. The decision for AIT with Depigoid® Katze was made with the investigator before and was performed exclusively according to medical routine practice. During data collection, the principles of the current Declaration of the World Medical Association of Helsinki, the ICH-GCP principles as well as the GDPR applied. The protection of person-related data during the study has been guaranteed at all times.

The effort for the patients related to the study participation was low with completing the SF-12 questionnaire twice (approx. 2 min per questionnaire) and completion of the electronic diary after the injections (approx. 5 min per injection). By their participation patients contributed to the improvement of the quality of the dataset on safety and tolerability of the medication. The format of a non-interventional study was particularly suitable in this context to collect "real world data" that could not be detected in a defined and limited setting of a clinical trial according to Section 4 (23) sentence 1 AMG.

Participation in this non-interventional safety study was justifiable from a medical and patient point of view.

13 Conclusion

This non-interventional study was designed within the regulatory framework of a voluntary PASS. It followed the ENCePP guidelines and thus met high methodological standards. The study was started immediately after the launch of Depigoid® Katze in the German market and met a difficult medical-economic environment in which the reimbursement of the therapy in patients with cat ownership in particular was questioned by third-party payers. It is therefore not surprising that the recruitment period had to be extended and that only around a quarter of the originally planned 400 participants were included. This raises the question of the generalisability of the findings made here. This applies in particular to the age group adolescent, in which a total of 9 were observed as part of the study. If the groups are further subdivided into those with conventional (CUS) or quick up-dosing (QUS) only a handful of patients remain in 2 groups of adolescents, which of course does not allow statistical conclusions to be drawn. Nevertheless, the main features can be seen. Regardless of the age group, around 50% of patients reported adverse reactions, which mainly occurred locally and delayed.

The number of systemic side effects is comparatively low, affects almost exclusively adults and occurs in the majority of these with a delay. The fact that these side effects are limited to grades 1 and 2 speaks in favour of the high safety level of this innovative therapeutic approach.

In this study, in 91 analysed patients no cases of emergency hospitalisation or use of adrenaline were reported. This shows that the level of safety is significantly better than with native allergens for subcutaneous application. The quick up-dosing regimen is also a particular advantage treated with a low number of applications of the therapeutic allergen.

While the QoL in the admittedly short observation period of up to three months did not improve significantly in the overall collective, there was a clear improvement in mental health in the group of adolescents treated with the quick up-dosing regimen. In view of the small number of patients affected, this finding cannot be statistically confirmed.

In summary, an immunotherapy with Depigoid® Katze, using a depigmented, chemically modified allergoid, is a well-tolerated and safe treatment option for patients with cat allergies in Germany.

The observations of this study largely correspond to those found in a recently published real world study from Spain (de La Torrea, 2024).

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Appendices

Data (analysis) tables

Table 7 (Analysis table 1) Main Characteristics of Study Groups (Gender, Age)

			Adolescents			Adults			Total		
			CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
Gender	female	n	3	4	7	31	21	52	34	25	59
		%	60.0%	100.0%	77.8%	60.8%	67.7%	63.4%	60.7%	71.4%	64.8%
	male	n	2	0	2	20	10	30	22	10	32
		%	40.0%	0.0%	22.2%	39.2%	32.3%	36.6%	39.3%	28.6%	35.2%
	Total	n	5	4	9	51	31	82	56	35	91
		%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Age	Valid N		5	4	9	51	31	82	56	35	91
	Mean		14,40	14,75	14,56	35,43	36,39	35,79	33,55	33,91	33,69
	Standard Deviation		1,14	0,96	1,01	11,80	11,47	11,61	12,78	12,84	12,73
	Minimum		13,00	14,00	13,00	18,00	18,00	18,00	13,00	14,00	13,00
	Percentile 25		14,00	14,00	14,00	25,00	27,00	27,00	24,00	25,00	25,00
	Median		14,00	14,50	14,00	33,00	35,00	33,50	32,50	31,00	32,00
	Percentile 75		15,00	15,50	15,00	44,00	45,00	44,00	41,00	43,00	41,00
	Maximum		16,00	16,00	16,00	67,00	64,00	67,00	67,00	64,00	67,00

CUS: Conventional up-dosing, QUS: Quick up-dosing

Table 8: (Analysis table 2) Number of patients with cats in the household at visit 1 and last visit

		Adolescents						**Adults**						**Total**					
		CUS		QUS		Total		CUS		QUS		Total		CUS		QUS		Total	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Having cats at first visit	No	2	40.0%	2	50.0%	4	44.4%	14	27.5%	6	19.4%	20	24.4%	16	28.6%	8	22.9%	24	26.4%
	Yes	3	60.0%	2	50.0%	5	55.6%	37	72.5%	25	80.6%	62	75.6%	40	71.4%	27	77.1%	67	73.6%
Having cats at last visit	No	2	40.0%	2	50.0%	4	44.4%	13	26.0%	5	17.2%	18	22.8%	15	27.3%	7	21.2%	22	25.0%
	Yes	3	60.0%	2	50.0%	5	55.6%	37	74.0%	24	82.8%	61	77.2%	40	72.7%	26	78.8%	66	75.0%
Change between first and last visits	Decreased	0	0.0%	0	0.0%	0	0.0%	1	2.0%	0	0.0%	1	1.3%	1	1.8%	0	0.0%	1	1.1%
	Not changed	5	100.0%	4	100.0%	9	100.0%	47	94.0%	29	100.0%	76	96.2%	52	94.5%	33	100.0%	85	96.6%
	Increased	0	0.0%	0	0.0%	0	0.0%	2	4.0%	0	0.0%	2	2.5%	2	3.6%	0	0.0%	2	2.3%

CUS: Conventional up-dosing, QUS: Quick up-dosing

Table 9: (Analysis table 3) Number of Cats per Household

		Adolescents			Adults			Total		
		CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
Number of cats per household (First visit)	Valid N	5	4	9	51	31	82	56	35	91
	Minimum	0	0	0	0	0	0	0	0	0
	Median	1	1	1	1	1	1	1	1	1
	Maximum	3	2	3	4	4	4	4	4	4
Number of cats per household	Valid N	5	4	9	50	29	79	55	33	88
	Minimum	0	0	0	0	0	0	0	0	0
	Median	1	1	1	1	1	1	1	1	1
	Maximum	3	2	3	4	4	4	4	4	4
Difference of number of cats last visit-first visit	Valid N	5	4	9	50	29	79	55	33	88
	Minimum	0	0	0	-1	0	-1	-1	0	-1
	Median	0	0	0	0	0	0	0	0	0
	Maximum	0	0	0	2	0	2	2	0	2

CUS: Conventional up-dosing, QUS: Quick up-dosing

Table 10: (Analysis table 4) Clinical Manifestation of Study Groups

			Adolescents			Adults			Total		
			CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
Visit 1 - 5.1.1 Allergic Rhinitis:	Yes	n	5	4	9	48	29	77	53	33	86
		%	100.0%	100.0%	100.0%	94.1%	93.5%	93.9%	94.6%	94.3%	94.5%
	No	n	0	0	0	3	2	5	3	2	5
		%	0.0%	0.0%	0.0%	5.9%	6.5%	6.1%	5.4%	5.7%	5.5%
Visit 1 - 5.2.1 Allergic Conjunctivitis:	Yes	n	3	4	7	41	22	63	44	26	70
		%	60.0%	100.0%	77.8%	80.4%	71.0%	76.8%	78.6%	74.3%	76.9%
	No	n	2	0	2	10	9	19	12	9	21
		%	40.0%	0.0%	22.2%	19.6%	29.0%	23.2%	21.4%	25.7%	23.1%
Visit 1 - 5.3.1 Asthma:	Yes	n	2	2	4	15	10	25	17	12	29
		%	40.0%	50.0%	44.4%	29.4%	32.3%	30.5%	30.4%	34.3%	31.9%
	No	n	3	2	5	36	21	57	39	23	62
		%	60.0%	50.0%	55.6%	70.6%	67.7%	69.5%	69.6%	65.7%	68.1%

CUS: Conventional up-dosing, QUS: Quick up-dosing

Table 11: (Analysis table 6A) Concomitant Allergies Distribution in Study Groups

Allergy term 1	Allergy term 2	**Adolescents**						**Adults**						**Total**					
		CUS		QUS		Total		CUS		QUS		Total		CUS		QUS		Total	
		n	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*
allergy to animals	allergic to dogs	0	0,0%	0	0,0%	0	0,0%	2	2,4%	11	13,9%	13	7,9%	2	2,1%	11	12,8%	13	7,2%
	allergic to horses	1	11,1%	1	14,3%	2	12,5%	2	2,4%	0	0,0%	2	1,2%	3	3,2%	1	1,2%	4	2,2%
	allergy to animals	0	0,0%	0	0,0%	0	0,0%	2	2,4%	1	1,3%	3	1,8%	2	2,1%	1	1,2%	3	1,7%
	Total	1	11,1%	1	14,3%	2	12,5%	6	7,1%	12	15,2%	18	11,0%	7	7,4%	13	15,1%	20	11,1%
allergy to arthropod sting	insect sting allergy	0	0,0%	0	0,0%	0	0,0%	1	1,2%	1	1,3%	2	1,2%	1	1,1%	1	1,2%	2	1,1%
	Total	0	0,0%	0	0,0%	0	0,0%	1	1,2%	1	1,3%	2	1,2%	1	1,1%	1	1,2%	2	1,1%
allergy to metals	Nickel allergy	0	0,0%	0	0,0%	0	0,0%	2	2,4%	0	0,0%	2	1,2%	2	2,1%	0	0,0%	2	1,1%
	Total	0	0,0%	0	0,0%	0	0,0%	2	2,4%	0	0,0%	2	1,2%	2	2,1%	0	0,0%	2	1,1%
allergy to plants	herbal allergy	1	11,1%	0	0,0%	1	6,3%	0	0,0%	0	0,0%	0	0,0%	1	1,1%	0	0,0%	1	0,6%
	Total	1	11,1%	0	0,0%	1	6,3%	0	0,0%	0	0,0%	0	0,0%	1	1,1%	0	0,0%	1	0,6%
citrus allergy	citrus allergy	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	1,3%	1	0,6%	0	0,0%	1	1,2%	1	0,6%

Allergy term 1	Allergy term 2	Adolescents						Adults						Total					
		CUS		QUS		Total		CUS		QUS		Total		CUS		QUS		Total	
		n	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*
	Total	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	1,3%	1	0,6%	0	0,0%	1	1,2%	1	0,6%
dermatitis contact	plaster allergy	0	0,0%	0	0,0%	0	0,0%	1	1,2%	0	0,0%	1	0,6%	1	1,1%	0	0,0%	1	0,6%
	Total	0	0,0%	0	0,0%	0	0,0%	1	1,2%	0	0,0%	1	0,6%	1	1,1%	0	0,0%	1	0,6%
fungal allergy	fungal allergy	0	0,0%	0	0,0%	0	0,0%	0	0,0%	3	3,8%	3	1,8%	0	0,0%	3	3,5%	3	1,7%
	Total	0	0,0%	0	0,0%	0	0,0%	0	0,0%	3	3,8%	3	1,8%	0	0,0%	3	3,5%	3	1,7%
mite allergy	house dust mite allergy	1	11,1%	0	0,0%	1	6,3%	19	22,4%	10	12,7%	29	17,7%	20	21,3%	10	11,6%	30	16,7%
	mite allergy	0	0,0%	0	0,0%	0	0,0%	3	3,5%	1	1,3%	4	2,4%	3	3,2%	1	1,2%	4	2,2%
	Total	1	11,1%	0	0,0%	1	6,3%	22	25,9%	11	13,9%	33	20,1%	23	24,5%	11	12,8%	34	18,9%
perfume sensitivity	fragrance sensitivity	0	0,0%	0	0,0%	0	0,0%	1	1,2%	0	0,0%	1	0,6%	1	1,1%	0	0,0%	1	0,6%
	Total	0	0,0%	0	0,0%	0	0,0%	1	1,2%	0	0,0%	1	0,6%	1	1,1%	0	0,0%	1	0,6%
seasonal allergy	grass allergy	4	44,4%	4	57,1%	8	50,0%	20	23,5%	20	25,3%	40	24,4%	24	25,5%	24	27,9%	48	26,7%
	herbal allergy	0	0,0%	0	0,0%	0	0,0%	2	2,4%	3	3,8%	5	3,0%	2	2,1%	3	3,5%	5	2,8%

Allergy term 1	Allergy term 2	Adolescents						Adults						Total					
		CUS		QUS		Total		CUS		QUS		Total		CUS		QUS		Total	
		n	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*
	pollen allergy grass allergy/ tree allergy	0	0,0%	0	0,0%	0	0,0%	1	1,2%	0	0,0%	1	0,6%	1	1,1%	0	0,0%	1	0,6%
	pollen allergy	1	11,1%	0	0,0%	1	6,3%	5	5,9%	1	1,3%	6	3,7%	6	6,4%	1	1,2%	7	3,9%
	tree allergy grass allergy	0	0,0%	0	0,0%	0	0,0%	1	1,2%	0	0,0%	1	0,6%	1	1,1%	0	0,0%	1	0,6%
	tree allergy	1	11,1%	2	28,6%	3	18,8%	23	27,1%	27	34,2%	50	30,5%	24	25,5%	29	33,7%	53	29,4%
	Total	6	66,7%	6	85,7%	12	75,0%	52	61,2%	51	64,6%	103	62,8%	58	61,7%	57	66,3%	115	63,9%
	Overall total	9	100,0%	7	100,0%	16	100,0%	85	100,0%	79	100,0%	164	100,0%	94	100,0%	86	100,0%	180	100,0%

CUS: Conventional up-dosing, QUS: Quick up-dosing

Table 12: (Analysis table 6B) Medical history diseases distribution in study groups

	Adolescents						**Adults**						**Total**					
	CUS		QUS		Total		CUS		QUS		Total		CUS		QUS		Total	
PT	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Asthma	1	50,0%	1	25,0%	2	33,3%	6	22,2%	2	14,3%	8	19,5%	7	24,1%	3	16,7%	10	21,3%
Autoimmune thyroiditis	0	0,0%	0	0,0%	0	0,0%	1	3,7%	1	7,1%	2	4,9%	1	3,4%	1	5,6%	2	4,3%
Colitis ulcerosa	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	7,1%	1	2,4%	0	0,0%	1	5,6%	1	2,1%
Covid-19	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	7,1%	1	2,4%	0	0,0%	1	5,6%	1	2,1%
Depression	0	0,0%	0	0,0%	0	0,0%	2	7,4%	0	0,0%	2	4,9%	2	6,9%	0	0,0%	2	4,3%
Dermatitis atopic	0	0,0%	1	25,0%	1	16,7%	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	5,6%	1	2,1%
Disturbance in attention	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	7,1%	1	2,4%	0	0,0%	1	5,6%	1	2,1%
Furuncle	0	0,0%	0	0,0%	0	0,0%	1	3,7%	0	0,0%	1	2,4%	1	3,4%	0	0,0%	1	2,1%
Gastroesophageal reflux disease	0	0,0%	0	0,0%	0	0,0%	1	3,7%	0	0,0%	1	2,4%	1	3,4%	0	0,0%	1	2,1%
Herpes zoster	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	7,1%	1	2,4%	0	0,0%	1	5,6%	1	2,1%
Hidradenitis	0	0,0%	0	0,0%	0	0,0%	1	3,7%	0	0,0%	1	2,4%	1	3,4%	0	0,0%	1	2,1%
Hypercholesterolaemia	0	0,0%	0	0,0%	0	0,0%	1	3,7%	1	7,1%	2	4,9%	1	3,4%	1	5,6%	2	4,3%
Hypertension	0	0,0%	0	0,0%	0	0,0%	4	14,8%	3	21,4%	7	17,1%	4	13,8%	3	16,7%	7	14,9%
Hypertriglyceridemia	0	0,0%	0	0,0%	0	0,0%	1	3,7%	0	0,0%	1	2,4%	1	3,4%	0	0,0%	1	2,1%
Hypothyroidism	0	0,0%	1	25,0%	1	16,7%	2	7,4%	1	7,1%	3	7,3%	2	6,9%	2	11,1%	4	8,5%
Migraine	1	50,0%	1	25,0%	2	33,3%	1	3,7%	0	0,0%	1	2,4%	2	6,9%	1	5,6%	3	6,4%

Multiple sclerosis	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	7,1%	1	2,4%	0	0,0%	1	5,6%	1	2,1%
Nasal polyps	0	0,0%	0	0,0%	0	0,0%	1	3,7%	0	0,0%	1	2,4%	1	3,4%	0	0,0%	1	2,1%
Post-traumatic stress disorder	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	7,1%	1	2,4%	0	0,0%	1	5,6%	1	2,1%
Psoriasis	0	0,0%	0	0,0%	0	0,0%	1	3,7%	0	0,0%	1	2,4%	1	3,4%	0	0,0%	1	2,1%
Sensation of foreign body	0	0,0%	0	0,0%	0	0,0%	1	3,7%	0	0,0%	1	2,4%	1	3,4%	0	0,0%	1	2,1%
Snoring	0	0,0%	0	0,0%	0	0,0%	1	3,7%	0	0,0%	1	2,4%	1	3,4%	0	0,0%	1	2,1%
Tremor	0	0,0%	0	0,0%	0	0,0%	1	3,7%	0	0,0%	1	2,4%	1	3,4%	0	0,0%	1	2,1%
Vitiligo	0	0,0%	0	0,0%	0	0,0%	1	3,7%	0	0,0%	1	2,4%	1	3,4%	0	0,0%	1	2,1%
Total	2	100,0%	4	100,0%	6	100,0%	27	100,0%	14	100,0%	41	100,0%	29	100,0%	18	100,0%	47	100,0%

CUS: Conventional up-dosing, QUS: Quick up-dosing

Table 13: (Analysis table 7) Health related quality of life assessment (SF-12) at 1st visit

		Adolescents			**Adults**			**Total**		
		CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
1. Wie würden Sie Ihren Gesundheitszustand im Allgemeinen beschreiben?	Valid N	4	4	8	51	30	81	55	34	89
	Percentile 25	1,50	2,00	1,50	2,00	2,00	2,00	2,00	2,00	2,00
	Median	2,00	3,00	2,50	3,00	2,50	3,00	3,00	3,00	3,00
	Percentile 75	2,50	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00
2. Durch Gesundheitszustand eingeschränkt bei ... mittelschwere Tätigkeiten, z.B. einen Tisch verschieben, staubsaugen, kegeln, Golf spielen?	Valid N	4	4	8	51	30	81	55	34	89
	Percentile 25	3,00	3,00	3,00	2,00	3,00	3,00	3,00	3,00	3,00
	Median	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00
	Percentile 75	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00
3. Durch Gesundheitszustand eingeschränkt ... mehrere Treppenabsätze steigen?	Valid N	4	4	8	51	30	81	55	34	89
	Percentile 25	3,00	2,50	3,00	2,00	2,00	2,00	2,00	2,00	2,00
	Median	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00
	Percentile 75	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00
4. Bei Arbeit/ anderen alltäglichen Tätigkeiten: In der vergangenen Woche, haben Sie weniger geschafft als Sie wollten wegen Ihrer körperlichen Gesundheit?	Valid N	4	4	8	51	30	81	55	34	89
	Percentile 25	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Median	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Percentile 75	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Valid N	4	4	8	51	30	81	55	34	89

		Adolescents			Adults			Total		
		CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
5. Bei Arbeit/ anderen alltäglichen Tätigkeiten: In der vergangenen Woche, konnten Sie nur bestimmte Dinge tun wegen Ihrer körperlichen Gesundheit?	Percentile 25	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Median	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Percentile 75	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
6. Bei Arbeit/ anderen alltäglichen Tätigkeiten: In der vergangenen Woche, haben Sie weniger geschafft als Sie wollten wegen seelischer Probleme, z.B. weil Sie sich niedergeschlagen oder ängstlich fühlten?	Valid N	4	4	8	51	30	81	55	34	89
	Percentile 25	2,00	1,50	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Median	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Percentile 75	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
7. Bei Arbeit/ anderen alltäglichen Tätigkeiten: In der vergangenen Woche, konnten Sie nicht so sorgfältig wie üblich arbeiten wegen seelischer Probleme, z. B. weil Sie sich niedergeschlagen oder ängstlich fühlten?	Valid N	4	4	8	51	30	81	55	34	89
	Percentile 25	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Median	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Percentile 75	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
8. Inwieweit haben die Schmerzen Sie in der vergangenen Woche bei der Ausübung Ihrer Alltagstätigkeiten zu Hause und im Beruf behindert?	Valid N	4	4	8	51	30	81	55	34	89
	Percentile 25	1,00	1,00	1,00	1,00	1,00	1,00	1,00	1,00	1,00
	Median	1,00	1,50	1,00	1,00	2,00	1,00	1,00	2,00	1,00
	Percentile 75	1,00	2,50	1,50	2,00	2,00	2,00	2,00	2,00	2,00

		Adolescents			Adults			Total		
		CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
9. Wie oft waren sie in der vergangenen Woche ruhig und gelassen?	Valid N	4	4	8	51	30	81	55	34	89
	Percentile 25	1,50	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Median	2,00	2,00	2,00	3,00	2,00	3,00	3,00	2,00	2,00
	Percentile 75	2,50	2,50	2,50	4,00	3,00	3,00	4,00	3,00	3,00
10. Wie oft waren sie in der vergangenen Woche voller Energie?	Valid N	4	4	8	51	30	81	55	34	89
	Percentile 25	2,50	4,00	4,00	2,00	2,00	2,00	2,00	2,00	2,00
	Median	4,00	4,00	4,00	4,00	3,00	3,00	4,00	3,00	3,00
	Percentile 75	4,00	4,00	4,00	4,00	4,00	4,00	4,00	4,00	4,00
11. Wie oft waren sie in der vergangenen Woche entmutigt und traurig?	Valid N	4	4	8	51	30	81	55	34	89
	Percentile 25	5,00	4,50	5,00	4,00	4,00	4,00	5,00	4,00	5,00
	Median	5,50	5,50	5,50	5,00	5,00	5,00	5,00	5,00	5,00
	Percentile 75	6,00	6,00	6,00	6,00	6,00	6,00	6,00	6,00	6,00
12. Wie häufig haben Ihre körperliche Gesundheit oder seelischen Probleme in der vergangenen Woche Ihre Kontakte zu anderen Menschen (Besuche bei Freunden, Verwandten usw.) beeinträchtigt?	Valid N	4	4	8	51	30	81	55	34	89
	Percentile 25	5,50	6,00	6,00	5,00	6,00	5,00	5,00	6,00	5,00
	Median	6,00	6,00	6,00	6,00	6,00	6,00	6,00	6,00	6,00
	Percentile 75	6,00	6,00	6,00	6,00	6,00	6,00	6,00	6,00	6,00
	Valid N	4	4	8	51	30	81	55	34	89

		Adolescents			Adults			Total		
		CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
SF-12 norm-based standardization physical health	Percentile 25	41,78	43,17	42,01	39,81	40,98	40,19	40,19	41,33	40,57
	Median	43,05	44,96	44,02	41,85	42,53	42,01	42,01	42,84	42,34
	Percentile 75	44,02	45,63	44,96	44,12	44,94	44,50	44,12	45,26	44,51
SF-12 norm based standardization mental health	Valid N	4	4	8	51	30	81	55	34	89
	Percentile 25	39,47	38,70	39,47	41,11	42,74	41,51	41,11	40,17	41,03
	Median	41,05	40,47	40,47	43,99	45,49	44,62	43,59	44,40	43,99
	Percentile 75	46,05	41,10	41,71	46,96	48,50	47,25	46,96	48,39	47,07

CUS: Conventional up-dosing, QUS: Quick up-dosing

Table 14: (Analysis table 8) Health related quality of life assessment (SF-12) at last visit

		Adolescents			Adults			Total		
		CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
1. Wie würden Sie Ihren Gesundheitszustand im Allgemeinen beschreiben?	Valid N	4	4	8	50	29	79	54	33	87
	Percentile 25	1,50	1,50	1,50	2,00	2,00	2,00	2,00	2,00	2,00
	Median	2,50	2,50	2,50	2,00	2,00	2,00	2,00	2,00	2,00
	Percentile 75	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00
2. Durch Gesundheitszustand eingeschränkt bei ... mittelschwere Tätigkeiten, z.B. einen Tisch verschieben, staubsaugen, kegeln, Golf spielen?	Valid N	4	4	8	50	29	79	54	33	87
	Percentile 25	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00
	Median	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00
	Percentile 75	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00
3. Durch Gesundheitszustand eingeschränkt ... mehrere Treppenabsätze steigen?	Valid N	4	4	8	50	29	79	54	33	87
	Percentile 25	3,00	2,00	2,50	2,00	3,00	3,00	3,00	3,00	3,00
	Median	3,00	2,50	3,00	3,00	3,00	3,00	3,00	3,00	3,00
	Percentile 75	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00
4. Bei Arbeit/ anderen alltäglichen Tätigkeiten: In der vergangenen Woche, haben Sie weniger geschafft als Sie wollten wegen Ihrer körperlichen Gesundheit?	Valid N	4	4	8	50	29	79	54	33	87
	Percentile 25	2,00	2,00	2,00	1,00	2,00	2,00	2,00	2,00	2,00
	Median	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Percentile 75	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Valid N	4	4	8	50	29	79	54	33	87

		Adolescents			Adults			Total		
		CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
5. Bei Arbeit/ anderen alltäglichen Tätigkeiten: In der vergangenen Woche, konnten Sie nur bestimmte Dinge tun wegen Ihrer körperlichen Gesundheit?	Percentile 25	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Median	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Percentile 75	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
6. Bei Arbeit/ anderen alltäglichen Tätigkeiten: In der vergangenen Woche, haben Sie weniger geschafft als Sie wollten wegen seelischer Probleme, z.B. weil Sie sich niedergeschlagen oder ängstlich fühlten?	Valid N	4	4	8	50	29	79	54	33	87
	Percentile 25	1,50	2,00	2,00	1,00	2,00	2,00	1,00	2,00	2,00
	Median	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Percentile 75	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
7. Bei Arbeit/ anderen alltäglichen Tätigkeiten: In der vergangenen Woche, konnten Sie nicht so sorgfältig wie üblich arbeiten wegen seelischer Probleme, z. B. weil Sie sich niedergeschlagen oder ängstlich fühlten?	Valid N	4	4	8	50	29	79	54	33	87
	Percentile 25	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Median	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Percentile 75	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
8. Inwieweit haben die Schmerzen Sie in der vergangenen Woche bei der Ausübung Ihrer	Valid N	4	4	8	50	29	79	54	33	87
	Percentile 25	1,00	1,00	1,00	1,00	1,00	1,00	1,00	1,00	1,00
	Median	1,00	1,00	1,00	1,00	1,00	1,00	1,00	1,00	1,00

		Adolescents			Adults			Total		
		CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
Alltagstätigkeiten zu Hause und im Beruf behindert?	Percentile 75	1,00	1,00	1,00	2,00	2,00	2,00	2,00	2,00	2,00
9. Wie oft waren sie in der vergangenen Woche ruhig und gelassen?	Valid N	4	4	8	50	29	79	54	33	87
	Percentile 25	2,00	2,50	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Median	2,50	3,50	3,00	2,50	2,00	2,00	2,50	2,00	2,00
	Percentile 75	3,00	4,00	3,50	4,00	3,00	3,00	4,00	3,00	3,00
10. Wie oft waren sie in der vergangenen Woche voller Energie?	Valid N	4	4	8	50	29	79	54	33	87
	Percentile 25	2,50	2,00	2,00	2,00	2,00	2,00	2,00	2,00	2,00
	Median	3,00	2,50	3,00	3,00	3,00	3,00	3,00	3,00	3,00
	Percentile 75	3,50	3,50	3,50	4,00	3,00	4,00	4,00	3,00	4,00
11. Wie oft waren sie in der vergangenen Woche entmutigt und traurig?	Valid N	4	4	8	50	28	78	54	32	86
	Percentile 25	4,50	4,00	4,00	4,00	5,00	4,00	4,00	5,00	4,00
	Median	5,00	4,00	4,50	5,00	5,00	5,00	5,00	5,00	5,00
	Percentile 75	5,50	4,50	5,00	6,00	6,00	6,00	6,00	6,00	6,00
12. Wie häufig haben Ihre körperliche Gesundheit oder seelischen Probleme in der vergangenen Woche Ihre Kontakte zu anderen Menschen (Besuche bei	Valid N	4	4	8	50	29	79	54	33	87
	Percentile 25	6,00	6,00	6,00	5,00	6,00	5,00	5,00	6,00	5,00
	Median	6,00	6,00	6,00	6,00	6,00	6,00	6,00	6,00	6,00
	Percentile 75	6,00	6,00	6,00	6,00	6,00	6,00	6,00	6,00	6,00

		Adolescents			Adults			Total		
		CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
Freunden, Verwandten usw.) beeinträchtigt?										
SF-12_b norm-based standardization physical health	Valid N	4	4	8	50	28	78	54	32	86
	Percentile 25	41,66	39,39	40,80	40,19	40,49	40,41	40,57	40,49	40,57
	Median	42,74	41,21	42,06	42,34	42,39	42,34	42,34	41,94	42,33
	Percentile 75	43,92	42,68	43,36	44,29	44,63	44,32	44,29	44,11	44,29
SF-12_b norm based standardization mental health	Valid N	4	4	8	50	28	78	54	32	86
	Percentile 25	39,41	45,56	44,49	38,57	43,65	42,11	38,57	44,00	42,15
	Median	45,15	48,31	46,22	44,67	45,81	45,06	44,67	45,91	45,20
	Percentile 75	47,29	51,43	49,38	47,35	47,26	47,35	47,35	47,66	47,35

CUS: Conventional up-dosing QUS: Quick up-dosing

Table 15: (Analysis table 5) Diagnosis Characteristics of Study Groups

		Adolescents			Adults			Total		
		CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
Visit 1 - Wheal diameter	Valid N	4	4	8	48	30	78	52	34	86
	Mean	9,50	10,00	9,75	6,75	6,97	6,83	6,96	7,32	7,10
	Standard Deviation	5,92	0,00	3,88	6,91	3,35	5,78	6,83	3,29	5,67
	Minimum	3,00	10,00	3,00	3,00	3,00	3,00	3,00	3,00	3,00
	Percentile 25	4,50	10,00	8,00	4,00	4,00	4,00	4,00	5,00	4,00
	Median	10,00	10,00	10,00	5,00	6,00	5,00	5,00	6,00	5,00
	Percentile 75	14,50	10,00	12,00	7,00	10,00	8,00	7,50	10,00	9,00
	Maximum	15,00	10,00	15,00	50,00	15,00	50,00	50,00	15,00	50,00
Visit 1 - RAST-Class	Valid N	2	0	2	30	11	41	32	11	43
	Mean	3,50	.	3,50	2,87	3,55	3,05	2,91	3,55	3,07
	Standard Deviation	0,71	.	0,71	1,63	1,37	1,58	1,59	1,37	1,55
	Minimum	3,00	.	3,00	0,00	1,00	0,00	0,00	1,00	0,00
	Percentile 25	3,00	.	3,00	2,00	3,00	2,00	2,00	3,00	2,00
	Median	3,50	.	3,50	3,00	4,00	3,00	3,00	4,00	3,00
	Percentile 75	4,00	.	4,00	4,00	4,00	4,00	4,00	4,00	4,00
	Maximum	4,00	.	4,00	6,00	6,00	6,00	6,00	6,00	6,00

CUS: Conventional up-dosing, QUS: Quick up-dosing

Table 16: (Analysis table 10) Number and Distribution of Adverse Events (per event)

Related AE events	**Adolescents**			**Adults**			**Total**		
	CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
No	2 (18%)	0 (0%)	2 (14%)	5 (5%)	0 (0%)	5 (4%)	7 (7%)	0 (0%)	7 (5%)
Yes	9 (82%)	3 (100%)	12 (86%)	89 (95%)	31 (100%)	120 (96%)	98 (93%)	34 (100%)	132 (95%)
Total	11 (79%)*	3 (21%)*	14 (100%)*	94 (75%)*	31 (25%)*	125 (100%)*	105 (76%)*	34 (24%)*	139 (100%)*

CUS: Conventional up-dosing, QUS: Quick up-dosing,

*Row percent

Table 17: (Analysis table 11) Number and severity of local reactions (per events)

		Adolescents			**Adults**			**Total**		
		CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total number of LR		9	3	12	80	27	107	89	30	119
Severity of immediate LR	Mild	0 (0%)	1 (100%)	1 (100%)	18 (95%)	5 (45%)	23 (77%)	18 (95%)	6 (50%)	24 (77%)
	Moderate	0 (0%)	0 (0%)	0 (0%)	1 (5%)	5 (45%)	6 (20%)	1 (5%)	5 (42%)	6 (19%)
	Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (9%)	1 (3%)	0 (0%)	1 (8%)	1 (3%)
	Total	0 (0%)*	1 (100%)*	1 (100%)*	19 (63%)*	11 (37%)*	30 (100%)*	19 (61%)*	12 (39%)*	31 (100%)*
Severity of delayed LR	Mild	6 (67%)	1 (50%)	7 (64%)	55 (90%)	15 (94%)	70 (91%)	61 (87%)	16 (89%)	77 (88%)
	Moderate	3 (33%)	0 (0%)	3 (27%)	4 (7%)	1 (6%)	5 (6%)	7 (10%)	1 (6%)	8 (9%)
	Severe	0 (0%)	1 (50%)	1 (9%)	2 (3%)	0 (0%)	2 (3%)	2 (3%)	1 (6%)	3 (3%)
	Total	9 (82%)*	2 (18%)*	11 (100%)*	61 (79%)*	16 (21%)*	77 (100%)*	70 (80%)*	18 (20%)*	88 (100%)*

CUS: Conventional up-dosing, QUS: Quick up-dosing,

*Row percent

Table 18: (Analysis table 12) Number and severity of systemic reactions (per event)

		Adolescents			**Adults**			**Total**		
		CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total number of SR		1	0	1	27	13	40	28	13	41
Grade of immediate SR	Grade 1	0 (0%)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	1 (9%)	1 (25%)	0 (0%)	1 (9%)
	Grade 2	0 (0%)	0 (0%)	0 (0%)	3 (75%)	7 (100%)	10 (91%)	3 (75%)	7 (100%)	10 (91%)
	Total	0 (0%)*	0 (0%)*	0 (0%)*	4 (36%)*	7 (64%)*	11 (100%)*	4 (36%)*	7 (64%)*	11 (100%)*
Grade of delayed SR	Grade 1	0 (0%)	0 (0%)	0 (0%)	12 (52%)	2 (33%)	14 (48%)	12 (50%)	2 (33%)	14 (47%)
	Grade 2	1 (100%)	0 (0%)	1 (100%)	11 (48%)	4 (67%)	15 (52%)	12 (50%)	4 (67%)	16 (53%)
	Total	1 (100%)*	0 (0%)*	1 (100%)*	23 (79%)*	6 (21%)*	29 (100%)*	24 (80%)*	6 (20%)*	30 (100%)*

CUS: Conventional up-dosing, QUS: Quick up-dosing,

*Row percent

Table 19: (Analysis table 13) Comparison of number and distribution of adverse events (per patient)

				Adolescents			Adults			Total		
				CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
				n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Related AE events	No	Number of AE by case	1	0 (0%)	0 (0%)	0 (0%)	3 (60%)	0 (0%)	3 (60%)	3 (50%)	0 (0%)	3 (50%)
			2	1 (100%)	0 (0%)	1 (100%)	2 (40%)	0 (0%)	2 (40%)	3 (50%)	0 (0%)	3 (50%)
			Total	1 (100%)*	0 (0%)*	1 (100%)*	5 (100%)*	0 (0%)*	5 (100%)*	6 (100%)*	0 (0%)*	6 (100%)*
	Yes	Number of AE by case	1	0 (0%)	0 (0%)	0 (0%)	2 (8%)	6 (40%)	8 (21%)	2 (7%)	6 (38%)	8 (19%)
			2	0 (0%)	0 (0%)	0 (0%)	3 (13%)	2 (13%)	5 (13%)	3 (11%)	2 (13%)	5 (12%)
			3	3 (100%)	1 (100%)	4 (100%)	6 (25%)	7 (47%)	13 (33%)	9 (33%)	8 (50%)	17 (40%)
			4	0 (0%)	0 (0%)	0 (0%)	4 (17%)	0 (0%)	4 (10%)	4 (15%)	0 (0%)	4 (9%)
			5	0 (0%)	0 (0%)	0 (0%)	9 (38%)	0 (0%)	9 (23%)	9 (33%)	0 (0%)	9 (21%)
			Total	3 (75%)*	1 (25%)*	4 (100%)*	24 (62%)*	15 (38%)*	39 (100%)*	27 (63%)*	16 (37%)*	43 (100%)*
	Total	Number of AE by case	1	0 (0%)	0 (0%)	0 (0%)	5 (17%)	6 (40%)	11 (25%)	5 (15%)	6 (38%)	11 (22%)
			2	1 (25%)	0 (0%)	1 (20%)	5 (17%)	2 (13%)	7 (16%)	6 (18%)	2 (13%)	8 (16%)
			3	3 (75%)	1 (100%)	4 (80%)	6 (21%)	7 (47%)	13 (30%)	9 (27%)	8 (50%)	17 (35%)
			4	0 (0%)	0 (0%)	0 (0%)	4 (14%)	0 (0%)	4 (9%)	4 (12%)	0 (0%)	4 (8%)
			5	0 (0%)	0 (0%)	0 (0%)	9 (31%)	0 (0%)	9 (20%)	9 (27%)	0 (0%)	9 (18%)
			Total	4 (80%)*	1 (20%)*	5 (100%)*	29 (66%)*	15 (34%)*	44 (100%)*	33 (67%)*	16 (33%)*	49 (100%)*

CUS: Conventional up-dosing, QUS: Quick up-dosing,

*Row percent

Table 20: (Analysis table 14A) Patients having at least one adverse event (per patient)

		Adolescents			**Adults**			**Total**		
		CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Having at least one AE	No	1 (20%)	3 (75%)	4 (44%)	22 (43%)	16 (52%)	38 (46%)	23 (41%)	19 (54%)	42 (46%)
	Yes	4 (80%)	1 (25%)	5 (56%)	29 (57%)	15 (48%)	44 (54%)	33 (59%)	16 (46%)	49 (54%)
	Total	5 (56%)*	4 (44%)*	9 (100%)*	51 (62%)*	31 (38%)*	82 (100%)*	56 (62%)*	35 (38%)*	91 (100%)*
p1		0.206**			0.455***			0.219***		
p2		0.914***								
Having at least one SAE	No	4 (80%)	4 (100%)	8 (89%)	51 (100%)	31 (100%)	82 (100%)	55 (98%)	35 (100%)	90 (99%)
	Yes	1 (20%)	0 (0%)	1 (11%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (1%)
	Total	5 (56%)*	4 (44%)*	9 (100%)*	51 (62%)*	31 (38%)*	82 (100%)*	56 (62%)*	35 (38%)*	91 (100%)*
p1		1.000**			NA			NA		
p2		NA								

CUS: Conventional up-dosing, QUS: Quick up-dosing,

* Row percent **Fisher’s exact test ***Chi-Square test

p1: CUS vs QUS p2: Adolescents vs adults in total group

Table 21: (Analysis table 14B) Proportion of patients who have at least one adverse event related to study medication (per patient)

		Adolescents			**Adults**			**Total**		
		CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Having at least one related AE	No	2 (40%)	3 (75%)	5 (56%)	27 (53%)	16 (52%)	43 (52%)	29 (52%)	19 (54%)	48 (53%)
	Yes	3 (60%)	1 (25%)	4 (44%)	24 (47%)	15 (48%)	39 (48%)	27 (48%)	16 (46%)	43 (47%)
	Total	5 (56%)*	4 (44%)*	9 (100%)*	51 (62%)*	31 (38%)*	82 (100%)*	56 (62%)*	35 (38%)*	91 (100%)*
p1		0.524**			0.907***			0.816***		
p2		0.859***								
Having at least one related SAE	No	4 (80%)	4 (100%)	8 (89%)	51 (100%)	31 (100%)	82 (100%)	55 (98%)	35 (100%)	90 (99%)
	Yes	1 (20%)	0 (0%)	1 (11%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (1%)
	Total	5 (56%)*	4 (44%)*	9 (100%)*	51 (62%)*	31 (38%)*	82 (100%)*	56 (62%)*	35 (38%)*	91 (100%)*
p1		1.000**			NA			NA		
p2		NA								

CUS: Conventional up-dosing, QUS: Quick up-dosing,

*Row percent **Fisher's exact test ***Chi-Square test

p1: CUS vs QUS p2: Adolescents vs adults in total group

Table 22: (Analysis table 14C) Comparison of number and distribution of adverse events and related adverse events (per patient)

		Adolescents						**Adults**						**Total**					
		CUS		QUS		Total		CUS		QUS		Total		CUS		QUS		Total	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Number of AE by case	0	1	20.0%	3	75.0%	4	44.4%	22	43.1%	16	51.6%	38	46.3%	23	41.1%	19	54.3%	42	46.2%
	1	0	0.0%	0	0.0%	0	0.0%	5	9.8%	6	19.4%	11	13.4%	5	8.9%	6	17.1%	11	12.1%
	2	1	20.0%	0	0.0%	1	11.1%	5	9.8%	2	6.5%	7	8.5%	6	10.7%	2	5.7%	8	8.8%
	3	3	60.0%	1	25.0%	4	44.4%	6	11.8%	7	22.6%	13	15.9%	9	16.1%	8	22.9%	17	18.7%
	4	0	0.0%	0	0.0%	0	0.0%	4	7.8%	0	0.0%	4	4.9%	4	7.1%	0	0.0%	4	4.4%
	5	0	0.0%	0	0.0%	0	0.0%	9	17.6%	0	0.0%	9	11.0%	9	16.1%	0	0.0%	9	9.9%
	Total	5	100.0%	4	100.0%	9	100.0%	51	100.0%	31	100.0%	82	100.0%	56	100.0%	35	100.0%	91	100.0%
p1		0.180*						0.098*						0.059*					
p2		0.894																	
Number of SAE by case	0	4	0,8	4	1	8	0,89	51	1	31	1	82	1	55	0,98	35	1	90	0,99
	1	1	0,2	0	0	1	0,11	0	0	0	0	0	0	1	0,02	0	0	1	0,01
	Total	5	100.0%	4	100.0%	9	100.0%	51	100.0%	31	100.0%	82	100.0%	56	100.0%	35	100.0%	91	100.0%
p1		1.000						NA						NA					
p2		NA																	
Number of related	0	2	40.0%	3	75.0%	5	55.6%	27	52.9%	16	51.6%	43	52.4%	29	51.8%	19	54.3%	48	52.7%
	1	0	0.0%	0	0.0%	0	0.0%	2	3.9%	6	19.4%	8	9.8%	2	3.6%	6	17.1%	8	8.8%

AE by case	2	0	0.0%	0	0.0%	0	0.0%	3	5.9%	2	6.5%	5	6.1%	3	5.4%	2	5.7%	5	5.5%
	3	3	60.0%	1	25.0%	4	44.4%	6	11.8%	7	22.6%	13	15.9%	9	16.1%	8	22.9%	17	18.7%
	4	0	0.0%	0	0.0%	0	0.0%	4	7.8%	0	0.0%	4	4.9%	4	7.1%	0	0.0%	4	4.4%
	5	0	0.0%	0	0.0%	0	0.0%	9	17.6%	0	0.0%	9	11.0%	9	16.1%	0	0.0%	9	9.9%
	Total	5	100.0%	4	100.0%	9	100.0%	51	100.0%	31	100.0%	82	100.0%	56	100.0%	35	100.0%	91	100.0%
p1		0.617*						0.091*						0.072*					
p2		0.581*																	
Number of related SAE by case	0	4	0,8	4	1	8	0,89	51	1	31	1	82	1	55	0,98	35	1	90	0,99
	1	1	0,2	0	0	1	0,11	0	0	0	0	0	0	1	0,02	0	0	1	0,01
	Total	5	100.0%	4	100.0%	9	100.0%	51	100.0%	31	100.0%	82	100.0%	56	100.0%	35	100.0%	91	100.0%
p1		1.000						NA						NA					
p2		NA																	

CUS: Conventional up-dosing, QUS: Quick up-dosing,

*Mann Whitney U test

p1: CUS vs QUS p2: Adolescents vs adults in total group

Table 23: (Analysis table 15) Proportion of patients entering the maintenance treatment phase (per patient)

		Age_set																	
		Adolescents						Adults						Total					
		CUS		QUS		Total		CUS		QUS		Total		CUS		QUS		Total	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Maintenance	No	0	0.0%	0	0.0%	0	0.0%	1	2.0%	0	0.0%	1	1.2%	1	1.8%	0	0.0%	1	1.1%
	Yes	5	100.0%	4	100.0%	9	100.0%	50	98.0%	31	100.0%	81	98.8%	55	98.2%	35	100.0%	90	98.9%
	Total	5	100.0%	4	100.0%	9	100.0%	51	100.0%	31	100.0%	82	100.0%	56	100.0%	35	100.0%	91	100.0%

CUS: Conventional up-dosing, QUS: Quick up-dosing

Table 24: (Analysis table 18) Comparison of proportion of patients entering the maintenance treatment phase

		Age_set																	
		Adolescents						Adults						Total					
		Treatment						Treatment						Treatment					
		CUS		QUS		Total		CUS		QUS		Total		CUS		QUS		Total	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Maintenance	No	0	0.0%	0	0.0%	0	0.0%	1	2.0%	0	0.0%	1	1.2%	1	1.8%	0	0.0%	1	1.1%
	Yes	5	100.0%	4	100.0%	9	100.0%	50	98.0%	31	100.0%	81	98.8%	55	98.2%	35	100.0%	90	98.9%
	Total	5	100.0%	4	100.0%	9	100.0%	51	100.0%	31	100.0%	82	100.0%	56	100.0%	35	100.0%	91	100.0%
p*		NA						1.000						1.000					
p2*		1.000																	

p1: Comparison between treatment groups, p2: Comparison between age groups in all patients *Fisher’s exact test

Table 25: (Analysis table 16) Comparison of number and severity of local reactions between groups (per patient)

		Adolescents			**Adults**			**Total**		
Variable	Value	CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
Severity of immediate LR per patient	Mild	0 (0%)	1 (100%)	1 (100%)	8 (67%)	3 (38%)	11 (55%)	8 (67%)	4 (44%)	12 (57%)
	Moderate	0 (0%)	0 (0%)	0 (0%)	4 (33%)	4 (50%)	8 (40%)	4 (33%)	4 (44%)	8 (38%)
	Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)	1 (5%)	0 (0%)	1 (11%)	1 (5%)
	Total	0 (0%)*	1 (100%)*	1 (100%)*	12 (60%)*	8 (40%)*	20 (100%)*	12 (57%)*	9 (43%)*	21 (100%)*
p1**		NA			0.160**			0.254**		
p2**		0.394**								
Severity of delayed LR per patient	Mild	2 (67%)	0 (0%)	2 (50%)	17 (71%)	11 (92%)	28 (78%)	19 (70%)	11 (85%)	30 (75%)
	Moderate	1 (33%)	0 (0%)	1 (25%)	5 (21%)	1 (8%)	6 (17%)	6 (22%)	1 (8%)	7 (18%)
	Severe	0 (0%)	1 (100%)	1 (25%)	2 (8%)	0 (0%)	2 (6%)	2 (7%)	1 (8%)	3 (8%)
	Total	3 (75%)*	1 (25%)*	4 (100%)*	24 (67%)*	12 (33%)*	36 (100%)*	27 (68%)*	13 (33%)*	40 (100%)*
p1**		0.157**			0.151**			0.380**		
p2**		0.190**								

CUS: Conventional up-dosing, QUS: Quick up-dosing

* Row percent **Mann Whitney U test

p1: CUS vs QUS p2: Adolescents vs adults in total group

Table 26: (Analysis table 17) Comparison of number and grade of systemic reactions (per patient)

		Adolescents			**Adults**			**Total**		
Variable	Value	CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
Grade of immediate SR per patient	Grade 1	0 (0%)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	1 (13%)	1 (25%)	0 (0%)	1 (13%)
	Grade 2	0 (0%)	0 (0%)	0 (0%)	3 (75%)	4 (100%)	7 (88%)	3 (75%)	4 (100%)	7 (88%)
	Total	0 (0%)*	0 (0%)*	0 (0%)*	4 (50%)*	4 (50%)*	8 (100%)*	4 (50%)*	4 (50%)*	8 (100%)*
p1**		NA			0.248**			0.248**		
p2**		NA								
Grade of delayed SR per patient	Grade 1	0 (0%)	0 (0%)	0 (0%)	7 (58%)	2 (50%)	9 (56%)	7 (54%)	2 (50%)	9 (53%)
	Grade 2	1 (100%)	0 (0%)	1 (100%)	5 (42%)	2 (50%)	7 (44%)	6 (46%)	2 (50%)	8 (47%)
	Total	1 (100%)*	0 (0%)*	1 (100%)*	12 (75%)*	4 (25%)*	16 (100%)*	13 (76%)*	4 (24%)*	17 (100%)*
p1**		NA			0.083**			0.083**		
p2**		0.289**								

CUS: Conventional up-dosing, QUS: Quick up-dosing

*Row percent **Mann Whitney U test

p1: CUS vs QUS p2: Adolescents vs adults in total group *

Table 27: (Analysis table 9A) Change of health-related quality of life assessment (SF-12) between 1st and last visits

		Adolescents			**Adults**			**Total**		
		CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
PCS12_diff	Valid N	4	4	8	50	28	78	54	32	86
	Percentile 25	-1,27	-4,97	-2,65	-2,13	-2,87	-2,57	-1,96	-2,91	-2,57
	Median	-0,41	-2,65	-1,51	0,04	-0,65	0,00	0,00	-0,94	-0,11
	Percentile 75	1,06	-1,75	-0,41	1,70	2,51	2,49	1,70	2,10	1,71
MCS12_diff	Valid N	4	4	8	50	28	78	54	32	86
	Percentile 25	-4,35	4,46	-0,25	-2,68	-3,12	-3,01	-3,09	-2,54	-3,01
	Median	0,29	7,77	5,00	0,14	-0,79	0,00	0,14	-0,05	0,00
	Percentile 75	5,53	12,73	8,31	2,48	2,55	2,48	2,67	4,27	3,23

CUS: Conventional up-dosing, QUS: Quick up-dosing

Table 28: (Analysis table 9B) Comparison of quality of life assessment (SF-12) between 1st and last visits

		Adolescents			**Adults**			**Total**		
		CUS	QUS	Total	CUS	QUS	Total	CUS	QUS	Total
SF-12 norm-based standardization physical health	Valid N	4	4	8	51	30	81	55	34	89
	Percentile 25	41,78	43,17	42,01	39,81	40,98	40,19	40,19	41,33	40,57
	Median	43,05	44,96	44,02	41,85	42,53	42,01	42,01	42,84	42,34
	Percentile 75	44,02	45,63	44,96	44,12	44,94	44,50	44,12	45,26	44,51
SF-12_b norm-based standardization physical health	Valid N	4	4	8	50	28	78	54	32	86
	Percentile 25	41,66	39,39	40,80	40,19	40,49	40,41	40,57	40,49	40,57
	Median	42,74	41,21	42,06	42,34	42,39	42,34	42,34	41,94	42,33
	Percentile 75	43,92	42,68	43,36	44,29	44,63	44,32	44,29	44,11	44,29
p*		0.715	0.068	0,069	0.888	0.683	0,831	0.933	0.327	0,517
SF-12 norm based standardization mental health	Valid N	4	4	8	51	30	81	55	34	89
	Percentile 25	39,47	38,70	39,47	41,11	42,74	41,51	41,11	40,17	41,03
	Median	41,05	40,47	40,47	43,99	45,49	44,62	43,59	44,40	43,99
	Percentile 75	46,05	41,10	41,71	46,96	48,50	47,25	46,96	48,39	47,07
SF-12_b norm based standardization mental health	Valid N	4	4	8	50	28	78	54	32	86
	Percentile 25	39,41	45,56	44,49	38,57	43,65	42,11	38,57	44,00	42,15
	Median	45,15	48,31	46,22	44,67	45,81	45,06	44,67	45,91	45,20
	Percentile 75	47,29	51,43	49,38	47,35	47,26	47,35	47,35	47,66	47,35
p*		0.715	0.068	0,093	0.680	0.792	0,844	0.702	0.456	0,429

CUS: Conventional up-dosing, QUS: Quick up-dosing *Mann Whitney U test

Table 29: (Analysis table 19) General AE symptoms distribution in study groups

		Adolescents						Adults						Total					
		CUS		QUS		Total		CUS		QUS		Total		CUS		QUS		Total	
	PT	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Cardiac disorders	Palpitations	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	0,8%	1	0,3%	0	0,0%	1	0,7%	1	0,2%
	Total	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	0,8%	1	0,3%	0	0,0%	1	0,7%	1	0,2%
Ear and labyrinth disorders	Ear pain	0	0,0%	0	0,0%	0	0,0%	1	0,4%	0	0,0%	1	0,3%	1	0,3%	0	0,0%	1	0,2%
	Total	0	0,0%	0	0,0%	0	0,0%	1	0,4%	0	0,0%	1	0,3%	1	0,3%	0	0,0%	1	0,2%
Eye disorders	Conjunctivitis	0	0,0%	0	0,0%	0	0,0%	1	0,4%	0	0,0%	1	0,3%	1	0,3%	0	0,0%	1	0,2%
	Eye pruritus	1	2,6%	0	0,0%	1	1,9%	1	0,4%	0	0,0%	1	0,3%	2	0,6%	0	0,0%	2	0,4%
	Lacrimation increased	0	0,0%	0	0,0%	0	0,0%	4	1,4%	1	0,8%	5	1,3%	4	1,3%	1	0,7%	5	1,1%
	Ocular hyperaemia	0	0,0%	0	0,0%	0	0,0%	6	2,2%	2	1,6%	8	2,0%	6	1,9%	2	1,5%	8	1,8%
	Total	1	2,6%	0	0,0%	1	1,9%	12	4,3%	3	2,5%	15	3,8%	13	4,1%	3	2,2%	16	3,6%
Gastrointestinal disorders	Abdominal pain	0	0,0%	1	7,1%	1	1,9%	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	0,7%	1	0,2%
	Diarrhoea	1	2,6%	0	0,0%	1	1,9%	0	0,0%	0	0,0%	0	0,0%	1	0,3%	0	0,0%	1	0,2%
	Dysphagia	0	0,0%	0	0,0%	0	0,0%	1	0,4%	0	0,0%	1	0,3%	1	0,3%	0	0,0%	1	0,2%
	Nausea	0	0,0%	1	7,1%	1	1,9%	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	0,7%	1	0,2%
	Oral pruritus	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	0,8%	1	0,3%	0	0,0%	1	0,7%	1	0,2%
	Paraesthesia oral	0	0,0%	0	0,0%	0	0,0%	1	0,4%	1	0,8%	2	0,5%	1	0,3%	1	0,7%	2	0,4%

		Adolescents						Adults						Total					
		CUS		QUS		Total		CUS		QUS		Total		CUS		QUS		Total	
	PT	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Total	1	2,6%	2	14,3%	3	5,8%	2	0,7%	2	1,6%	4	1,0%	3	1,0%	4	2,9%	7	1,6%
General disorders and administration site conditions	Allergic cough	0	0,0%	0	0,0%	0	0,0%	1	0,4%	0	0,0%	1	0,3%	1	0,3%	0	0,0%	1	0,2%
	Chest discomfort	0	0,0%	0	0,0%	0	0,0%	1	0,4%	0	0,0%	1	0,3%	1	0,3%	0	0,0%	1	0,2%
	Chest pain	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	0,8%	1	0,3%	0	0,0%	1	0,7%	1	0,2%
	Discomfort	0	0,0%	0	0,0%	0	0,0%	1	0,4%	0	0,0%	1	0,3%	1	0,3%	0	0,0%	1	0,2%
	Fatigue	0	0,0%	2	14,3%	2	3,8%	4	1,4%	1	0,8%	5	1,3%	4	1,3%	3	2,2%	7	1,6%
	Feeling hot	1	2,6%	0	0,0%	1	1,9%	4	1,4%	0	0,0%	4	1,0%	5	1,6%	0	0,0%	5	1,1%
	Injection site erythema	7	18,4%	1	7,1%	8	15,4%	48	17,4%	20	16,4%	68	17,1%	55	17,5%	21	15,4%	76	16,9%
	Injection site haematoma	0	0,0%	0	0,0%	0	0,0%	2	0,7%	1	0,8%	3	0,8%	2	0,6%	1	0,7%	3	0,7%
	Injection site induration	0	0,0%	0	0,0%	0	0,0%	0	0,0%	2	1,6%	2	0,5%	0	0,0%	2	1,5%	2	0,4%
	Injection site pain	0	0,0%	3	21,4%	3	5,8%	16	5,8%	5	4,1%	21	5,3%	16	5,1%	8	5,9%	24	5,3%
	Injection site pruritus	4	10,5%	2	14,3%	6	11,5%	49	17,8%	19	15,6%	68	17,1%	53	16,9%	21	15,4%	74	16,4%
	Injection site swelling	8	21,1%	2	14,3%	10	19,2%	63	22,8%	19	15,6%	82	20,6%	71	22,6%	21	15,4%	92	20,4%

		Adolescents						Adults						Total					
		CUS		QUS		Total		CUS		QUS		Total		CUS		QUS		Total	
	PT	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Injection site urticaria	0	0,0%	0	0,0%	0	0,0%	1	0,4%	2	1,6%	3	0,8%	1	0,3%	2	1,5%	3	0,7%
	Injection site warmth	0	0,0%	0	0,0%	0	0,0%	1	0,4%	0	0,0%	1	0,3%	1	0,3%	0	0,0%	1	0,2%
	Injection site warmth	1	2,6%	0	0,0%	1	1,9%	12	4,3%	1	0,8%	13	3,3%	13	4,1%	1	0,7%	14	3,1%
	Pyrexia	0	0,0%	0	0,0%	0	0,0%	1	0,4%	0	0,0%	1	0,3%	1	0,3%	0	0,0%	1	0,2%
	Sensation of foreign body	0	0,0%	0	0,0%	0	0,0%	2	0,7%	0	0,0%	2	0,5%	2	0,6%	0	0,0%	2	0,4%
	Total	21	55,3%	10	71,4%	31	59,6%	206	74,6%	71	58,2%	277	69,6%	227	72,3%	81	59,6%	308	68,4%
Infections and infestations	COVID-19	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	0,8%	1	0,3%	0	0,0%	1	0,7%	1	0,2%
	Nasopharyngitis	0	0,0%	0	0,0%	0	0,0%	3	1,1%	0	0,0%	3	0,8%	3	1,0%	0	0,0%	3	0,7%
	Rhinitis	1	2,6%	0	0,0%	1	1,9%	2	0,7%	0	0,0%	2	0,5%	3	1,0%	0	0,0%	3	0,7%
	Total	1	2,6%	0	0,0%	1	1,9%	5	1,8%	1	0,8%	6	1,5%	6	1,9%	1	0,7%	7	1,6%
Investigations	Breath sounds abnormal	1	2,6%	0	0,0%	1	1,9%	0	0,0%	3	2,5%	3	0,8%	1	0,3%	3	2,2%	4	0,9%
	Total	1	2,6%	0	0,0%	1	1,9%	0	0,0%	3	2,5%	3	0,8%	1	0,3%	3	2,2%	4	0,9%
Metabolism and nutrition disorders	Fluid retention	0	0,0%	0	0,0%	0	0,0%	1	0,4%	0	0,0%	1	0,3%	1	0,3%	0	0,0%	1	0,2%
	Food craving	0	0,0%	1	7,1%	1	1,9%	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	0,7%	1	0,2%
	Total	0	0,0%	1	7,1%	1	1,9%	1	0,4%	0	0,0%	1	0,3%	1	0,3%	1	0,7%	2	0,4%

		Adolescents						Adults						Total					
		CUS		QUS		Total		CUS		QUS		Total		CUS		QUS		Total	
	PT	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Nervous system disorders	Dizziness	0	0,0%	0	0,0%	0	0,0%	1	0,4%	0	0,0%	1	0,3%	1	0,3%	0	0,0%	1	0,2%
	Headache	3	7,9%	0	0,0%	3	5,8%	8	2,9%	3	2,5%	11	2,8%	11	3,5%	3	2,2%	14	3,1%
	Total	3	7,9%	0	0,0%	3	5,8%	9	3,3%	3	2,5%	12	3,0%	12	3,8%	3	2,2%	15	3,3%
Psychiatric disorders	Mood swings	0	0,0%	1	7,1%	1	1,9%	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	0,7%	1	0,2%
	Total	0	0,0%	1	7,1%	1	1,9%	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	0,7%	1	0,2%
Respiratory, thoracic and mediastinal disorders	Allergic cough	0	0,0%	0	0,0%	0	0,0%	2	0,7%	1	0,8%	3	0,8%	2	0,6%	1	0,7%	3	0,7%
	Asthma	0	0,0%	0	0,0%	0	0,0%	1	0,4%	1	0,8%	2	0,5%	1	0,3%	1	0,7%	2	0,4%
	Bronchial hyperreactivity	0	0,0%	0	0,0%	0	0,0%	1	0,4%	0	0,0%	1	0,3%	1	0,3%	0	0,0%	1	0,2%
	Cough	2	5,3%	0	0,0%	2	3,8%	6	2,2%	2	1,6%	8	2,0%	8	2,5%	2	1,5%	10	2,2%
	Dysphonia	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	0,8%	1	0,3%	0	0,0%	1	0,7%	1	0,2%
	Dyspnoea	1	2,6%	0	0,0%	1	1,9%	4	1,4%	5	4,1%	9	2,3%	5	1,6%	5	3,7%	10	2,2%
	Nasal congestion	2	5,3%	0	0,0%	2	3,8%	7	2,5%	2	1,6%	9	2,3%	9	2,9%	2	1,5%	11	2,4%
	Nasal obstruction	0	0,0%	0	0,0%	0	0,0%	1	0,4%	1	0,8%	2	0,5%	1	0,3%	1	0,7%	2	0,4%
	Rhinitis allergic	0	0,0%	0	0,0%	0	0,0%	1	0,4%	6	4,9%	7	1,8%	1	0,3%	6	4,4%	7	1,6%
	Rhinorrhoea	2	5,3%	0	0,0%	2	3,8%	2	0,7%	3	2,5%	5	1,3%	4	1,3%	3	2,2%	7	1,6%
	Sneezing	1	2,6%	0	0,0%	1	1,9%	7	2,5%	5	4,1%	12	3,0%	8	2,5%	5	3,7%	13	2,9%

		Adolescents						Adults						Total					
		CUS		QUS		Total		CUS		QUS		Total		CUS		QUS		Total	
	PT	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Throat clearing	0	0,0%	0	0,0%	0	0,0%	0	0,0%	4	3,3%	4	1,0%	0	0,0%	4	2,9%	4	0,9%
	Throat irritation	2	5,3%	0	0,0%	2	3,8%	5	1,8%	7	5,7%	12	3,0%	7	2,2%	7	5,1%	14	3,1%
	Total	10	26,3%	0	0,0%	10	19,2%	37	13,4%	38	31,1%	75	18,8%	47	15,0%	38	27,9%	85	18,9%
Skin and subcutaneous tissue disorders	Pruritus	0	0,0%	0	0,0%	0	0,0%	3	1,1%	0	0,0%	3	0,8%	3	1,0%	0	0,0%	3	0,7%
	Total	0	0,0%	0	0,0%	0	0,0%	3	1,1%	0	0,0%	3	0,8%	3	1,0%	0	0,0%	3	0,7%
Overall total		38	100,0%	14	100,0%	52	100,0%	276	100,0%	122	100,0%	398	100,0%	314	100,0%	136	100,0%	450	100,0%

CUS: Conventional up-dosing, QUS: Quick up-dosing

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	1.1	18-Oct-2024	List of Symptoms
2	1.2	22-Nov-2024	List of participating investigators
3	1.3	30-Oct-2024	List of data tables

Annex 2. Additional information

Number	Document reference number	Date	Title
4	1.4	22-Nov-2024	Federal state specific ICF versions

Signature of sponsor’s responsible Medical Director

I have read the report and confirm, that to the best of my knowledge it accurately describes the conduct and the results of the study

Date / Place

Dr. Angelika Sager