Charité | Universitätsmedizin Berlin

**KLINIK FÜR DERMATOLOGIE,
VENEROLOGIE UND ALLERGOLOGIE**

Klinik mit zertifiziertem Qualitätsmanagementsystem nach
DIN EN ISO 9001:2000

ALLERGIE-CENTRUM-CHARITÉ
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European Centre for Allergy Research Foundation

Pilot trial to determine the impact of the vitamin D-mediated modulation of the initial subcutaneous grass pollen-specific immunotherapy in patients with grass pollen-induced rhinoconjunctivitis with/without allergic asthma

Explorative Untersuchung zum Einfluss der Vitamin D-vermittelten Modulation der initialen subkutanen Gräserpollen-spezifischen Immuntherapie bei Allergikern mit Gräserpollen-induzierter Rhinokonjunktivitis mit/ohne allergischem Asthma

Investigational medicinal products (IMP):	**Vigantol Öl** **Allergovit Gräser**
Eudra-CT number:	**2010-021775-80**
Protocol-code:	**ProGIT**
Indication studied:	**rhinoconjunctivitis, allergic asthma**
Study design:	**double-blind, placebo controled**
Development phase:	**therapeutic exploratory (phase IIa)**
Trial dates	**- start (first subject enrolled): 18.10.2011** **- end (last subject completed): 13.01.2015**

Clinical Trial Report

Version 1.0 / date: 12.01.2016

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Signature Page

- Confidentiality -

This document is a confidential communication of the sponsor Prof. Dr. med. Margitta Worm. No unpublished information contained herein will be published or disclosed without prior approval by the sponsor. However, this document can be disclosed to authorize representatives of national or international regulatory authorities under the condition that they respect its confidential nature.

This trial was performed in compliance with Good Clinical Practices (GCP) and Standard Operating Procedures (SOP) of the study unit of Prof. Worm for all processes involved, including the archiving of essential documents.

All the following persons have read this clinical trial report and confirm that to the best of their knowledge it accurately describes the conduct and results of the clinical trial.

Sponsor/principal investigator/signatory
Prof. Dr. med. Margitta Worm

Signature: _____ Date: 12/16

Investigator/fellow signatory
PD Dr. med. Guido Heine

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Study coordinator/fellow signatory
Dr. rer. Med. Sabine Dölle

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2 Synopsis

Title	Pilot trial to determine the impact of the vitamin D-mediated modulation of the initial subcutaneous grass pollen-specific immunotherapy in patients with grass pollen-induced rhinoconjunctivitis with/without allergic asthma
Investigatonal medical product (IMP)	Vigantol Öl® Allergovit-Gräser®
Active ingredient	Cholecalciferol (also termed vitamin D) Grass pollen
Phase of development	Therapeutic exploratory (phase IIa)
Sponsor / Principle investigator	Charité – Universitätsmedizin Berlin Prof. Dr. med. Margitta Worm Allergie-Centrum-Charité (ACC) Klinik für Dermatologie, Venerologie und Allergologie Charitéplatz 1, 10117 Berlin Tel.: 030-450 518 105 Fax: 030-450 518 931 margitta.worm@charite.de
Study centers	Mono-center
Publication (reference)	Manuscript in preparation
Study period	18 Oct 2011 13 Jan 2015
Main objective	To determine whether concomitant vitamin D supplementation promotes that the allergen specific immunotherapy-induced action onset regarding the intracutaneous test reaction to 500 SBU grass pollen.
Secondary objectives	Modulation of the grass pollen-specific humoral and cellular immune response
Methodology **- study design** **- primary endpoint** **- secondary endpoint**	 Prospective randomized placebo-controlled, parallel, double-blind, randomized two-armed explorative pilot trial wheal diameter after intracutaneous test (ICT) of 500 SBU grass pollen on visit 11, 2-11 and 3-11 compared between vitamin D (verum) and placebo group after the 1st, 2nd and 3rd treatment year in comparison between verum / placebo: area under the curve of titrated ICT; titrated conjucntival provocation test (CPT); skin prick test; humoral immune parameters (increased ration from grass pollen.specific Ig; cellular parameters: activation and cytokine production of peripheral lymphocytes; retrospective symptome score and general symptome assessment of the rhinoconjunctivitis compared to the season 2011; symptom-medication-score (SMS) during the grass pollen-season 2012, 2013, 2014 compared between verum / placebo

Investigational product	Medication 1 (Cholecalciferol): trade name Vigantol Öl® , active substance cholecalciferol, 5.333 I.U. (133 µg = 8 drops) daily between visit 1 and 10 in 3 consecutive treatment years (total 3x 4.5 months) Medication 2 (Gräser pollen-immunotherapy): trade name Allergovit® Gräser, active substance grass pollen (100%). Applied according to the manufacturers' instructions concomitantly with the vitamin D intake as described above.
Comparator	Neutral oil (middle chained triglycerides), 8 drops daily as described for cholecalciferol above.
Intervention phase	4.5 months each in 3 consecutive years; all over 3.5 yrs
Study population	Planned: 36 Included: 36 (2 recruited during in 2nd treatment year) Drop-outs (overall within 3 yrs): 13 Excluded due to protocol deviation: 0 Patients analyzed: yr1 = 33, yr2 = 27, yr3 = 22
Main inclusion criteria	• Written informed consent according AMG §40 (1) 3b • Men or women between 18 - 55 years • Serum 25-hydroxyvitamin D ≤50 nM, NTF3: 80 nM • Clinically relevant grass pollen allergy ≥2 years, retrospective symptom score ≥12 points • Positive skin prick test and intracutaneous test to grass pollen, specific IgE ≥2 CAP class 2 in the serum • Lung function: FEV_1 >70%
Efficacy conclusion	Vitamin D supplementation was efficient and restored physiological concentrations of its storage metabolite 25-hydroxyvitamin D in the serum. Grass pollen specific immunotherapy efficiently improved the ICT, ECT and pricktest values in most of the participants. There was no significant impact of cholecalciferol on these parameters.
Safety conclusion	No side effects or adverse events were observed related to the investigational product 1 (cholecalciferol) were noted throughout the clinical study. Related to the investigational product 2 (grass pollen-specific immunotherapy), minor local side effects and 2 systemic reactions (allergic rhinoconjunctivitis) occurred in both treatment groups in comparables frequencies.

Table of contents

3 List of Abbreviations and Definitions of Terms

(≙Point 4, ICH E3)

25OHD	25-hydroxyvitamin D_3; inactive storage metabolite; determines vitamin D status, large physiologic range, deficiency < 50 nmol/L, toxicity > 350 nmol/L
AE	adverse event
AMG	Arzneimittelgesetz (German drug law)
Calcitriol	1alpha,25-dihydroxyvitamin D_3, active vitamin D receptor agonist mediates vitamin D functions, small therapeutic range
cholecalciferol	vitamin D; unhydroxylated seco-steroid, supplementation form, enzymatically metabolized to the storage metabolite 25OHD
CRF	case report form
GCP	good clinical practice
ICH	international conference of harmonization
IEC	independent ethics committee
IMP	investigational medicinal product
ITT	intention-to-treat
PP	per-protocol
SAE	severe adverse event
SD	source date
SIT	allergen-specific immunotherapy
SmPC	summary of product characteristics
SOP	standard operating procedures
TMF	trial master file

4 Ethics

4.1 Independent Ethics Committee (IEC)

The protocol of the clinical trial as well as the subject information and informed consent was approved by the local Independent Ethics Committee (IEC) of Berlin. The principal investigator (here also sponsor: Prof. Dr. med. M. Worm) was responsible for submitting the documents to the IEC of Berlin. During the trial 3 amendments were sent to the IEC for reviewing (No.1 from 18.07.2011: issue that Vigantol was off-market in 2010-Summer 2011, minor protocol changes; No.2 from 14.04.2012: introduction of a questionaire to assess the symptom-medication-score during pollen season; No.3 from 11.07.2012: prolongation for 2 more study years). At the end of the clinical trial, the sponsor/principal investigator notified the IEC of Berlin about the trial completion. The synopsis of the final report will be provided to the IEC within approximately 30 days after signing of the final report.
The address and chairmen of the IECs are given in section 5.

4.2 Ethical conduct of the clinical trial

The clinical trial was conducted in accordance with applicable regulations governing the protection of human patients, such as national drug laws (German Drug Law: AMG [1], ICH-GCP guidelines [2,3] and the Declaration of Helsinki [4].

According to the AMG, the sponsor/principal investigator covered insurance for all subjects who gave informed consent to this clinical trial.

4.3 Subject information and informed consent

IEC approval of the written subject information and informed consent was obtained prior to their use. The informed consent contains a phrase by which consent was given for the access to the non-personalized data by the sponsor, national and regulatory authorities. In addition, it states that the subject was free to withdraw from the clinical trial at any time without any negative consequences. The subject information gives a complete and comprehensive explanation of the significance, nature, extent and possible risks of the clinical trial. Additionally to the written subject information, oral informing was done by the investigator. It complied with all applicable regulations governing the protection of human subjects, such as national drug laws [1], ICH-GCP guidelines [2,3] and the Declaration of Helsinki [4].

5 Investigators and Trial Administrative Structure

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Agency of the ethic committee of Berlin
Chairman: PD Dr. Hans-Herbert Fülle, FA Innere Medizin (commission No. 2)
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For the chairmen and member of the responsible committee of the local IEC participating in the clinical trial, please refer to appendix 15.1.3.

The curricula vitae of the investigators and other important participants of the clinical trial are provided in appendix 15.1.4.

6 Introduction

The only causal treatment of type I-allergies is allergen-specific immunotherapy [5]. Although improved during the past 20 years, limitations are the late onset of action, onset of non-responders and transient remission. By experimental and preclinical data, we and other research groups identified vitamin D as putative immunomodulatory adjuvant [6-9]. Vitamin D deficiency is common in Berlin during the UV-deprived winter months, as shown by a representatitve cohort and confirmed by own data [10,11].
In this double-blind placebo controlled pilot trial, we sought to determine a potential therapeutical function of vitamin D on specific immunotherapy.

7 Study objectives

To determine whether concomittant vitamin D supplementation with pre-seasonal allergen-specific immunotherapy improves the onset of action and remission time in patients with relative vitamin D deficiency.

8 Investigational plan

8.1 Overall study design and plan: description

In this monocentric, prospective 2-armed randomized double-blind placebo controlled clinical pilot trial, grass pollen allergic patients (18-55 yrs) with allergic rhinoconjunctivitis with or without allergic asthma for ≥ 2 years were screened during winter (no UV-vitamin D biosynthesis[12,13]). Vitamin D deficient (serum 25-hydroxyvitamin D (25OHD) < 50 nmol/L) individuals

were randomized to receive cholecalciferol (oral form of vitamin D) or placebo (neutral carrier oil) in a 1:1 ratio.
All participants received a pre-seasonal grass pollen-specific immunotherapy (Allergovit Gräser®). It was started between November-January according to the manufacturer's instructions (s.c. 7 updosing injections in weekly intervals, then 3 maintenance doses in monthly intervals). During immunotherapy, 5000 I.U. cholecalciferol (Vigantol Öl®) or placebo (Migliol®, neutral oil) was applied orally. This regimen was repeated 3 times for 3 consecutive years.
The grass pollen-specific immune reaction to a titrated intracutaneous test, conjuctival provocation test, skin prick test, measurement of specific immune cells and serologic analysis was assessed before and after the immunotherapy courses and complemented by analysis of circulating immune cells and specific antibodies during immunotherapy and a questionnaire-based seasonal symptom-medication-score.

8.2 Discussion of study design, including the choice of control group

All patients reported grass pollen-induced allergic rhinoconjunctivitis and with or without allergic asthma for ≥ 2 years, which was complemented by positive skin prick test, specific IgE values ≥ CAP class 2 and positive intracutaneous test (500 SBU) to ensure grass pollen allergy. Only adult individuals were screened (18-55 years). The age was limited to that range to reduce the impact of confounding comorbidities. Adequate lung function determined by FEV1 ≥ 70% and the use oral contraception during childbearing age required to exclude immunotherapy and vitamin D contraindication, respectively. Treatment with vitamin A derivatives, immunosuppressants/-modulators, glucocorticosteroids, or other medication contraindicated for immunotherapy or vitamin D supplementation were excluded for safety reasons or to reduce confounding factors..

Only vitamin D-deficient participants were included into the study. Vitamin D deficiency was determined according to the serum 25OHD concentrations [14]. Values below 50 nmol/L are considered as deficient [13]. Current data suggest that vitamin D sufficiency is observed in concentrations above 70-80 nmol/L regarding iPTH concentrations [15], calcium absorption [16], bone mineralization [17] and circulating vitamin D-responsive immune cells [18]. Planned UV-exposure, ongoing vitamin D therapy or contraindication of vitamin D supplementation were exclusion criteria. Serum 25OHD, calcium and phosphate levels were monitored as safety parameters.

The participants of this prospective two-armed study were randomly assigned to the vitamin D or placebo group by the Charité pharmacologist Dr. Cornelia Eberhardt. The cholecalciferol or placebo control drug (neutral oil, Migliol® carrier substance of Vigantol®) was packaged identically to maintain the double-blind character. The safety laboratory (serum 25OHD, calcium, phosphate) were checked by unblinded study personel to exclude a bias by the blinded physician who were in direct contact with the study participants.

8.3 Selection of study population

8.3.1 Inclusion criteria

- Written informed consent according to AMG §40 (1) 3b
- Men or women between 18 - 55 years
- 25-hydroxyvitamin D (25OHD) serum concentration ≤ 50 nM
- Clinically relevant grass pollen allergy ≥ 2 years
- Positive grass pollen-specific skin prick test (wheal ≥3 mm, negativ reaction to NaCl)
- Wheal diameter of ≥ 10 mm using 500 SBU/ml grass pollen intracutaneously
- Grass pollen-specific IgE in the serum ≥ CAP-class 2
- Lung function: FEV1 >70%
- Retrospective symptom score (rSS) ≥12 points
- Women in childbearing age: effective contraception

8.3.2 Main exclusion criteria

- Serum 25OHD >50 nmol/L[1], planned UV-exposure (tanning, traveling to a place with UV-index/day >5)
- Incompatibility against ingredients of Vigantol® Öl or Allergovit® Gräser
- Contraindication agains specific immunotherapy, started, current or complete grass-SIT within the past 2 years, vaccination 7 days before SIT
- Abnormal serum calcium, phosphate or kreatinin values or clinically relevant abnormal blood counts
- Treatment with vitamin A-derivatives, hypercalciaemia, -uria, kidney stones, sarcoidosis, pseudohyperparathyreoidism
- Pregnancy or lactation

Prohibited concomitant drugs:

- phenytoin, barbiturates, thiazides, glycosides, tricyclic psychopharmacons, neuroleptics (the latter until 2 weeks before screening)
- symptomatic treatment of rhinokonjunctivitis- or asthma except beta-2-agonists or antihistamines
- beta receptor blockers, immunosuppressants or –modulators, incl. corticosteroids

8.3.3 Removal of subjects from treatment or assessment

The criteria for withdrawal of a subject from the clinical trial were the following, the cases occurring during study are attached in brackets:

- Personal desire of the participant (n=6. occupational reasons: moving from Berlin: R02, changes in the working scheduling/times: R04, R12, R26, R34, R35)
- Unmet inclustion/exclusion criteria (n=3. uncontrolled asthma before start of the therapy-R16, banned drugs-R18, pregnancy-R20)
- Non-compliance (n=4. lost-to-follow-up R06, R07, R10, R25)

8.4 Treatments

8.4.1 Treatment administration

The investigational medicinal product (IMP) 1, Vigantol Öl® and the comparator is orally applied by 8 drops daily (2013/2014 10 drops due to a new packaging device and drop size).

The IMP 2, Allergovit-Gräser® was injected subcutaneously according to the manufacturer's instructions.

8.4.2 Identity of the investigational product

IMP 1: Vigantol Öl® by Merck Serono GmbH, Darmstadt (approval number 6154275.00.01) contains 20,000 I.U. cholecalciferol / ml dissolved in neutral oil (middle chain triglycerides, nitrogen, carbondioxide). Neutral oil without vitamin D was used as placebo as comparator in identically labelled flasks. Each flask contained 10 ml.
IMP 2: Allergovit-Gräser® by Allergopharma, Reinbek, Hamburg (approval number of the Paul-Ehrlich-Institute 553a/91a-b). Two flasks are provided: Strenghth A (1.000 TE/ml, 3 ml, 553a/91a) and B (10.000 TE/ml, 3 ml, 553a/91b). Other ingredients: aluminiumhydroxide [Al(OH)3], phenol, sodiumchloride, aqua dest.

[1] Concerning this exclusion criterion Note to File 2 was created to set the criterion to ≤80 nmol/L.

8.4.3 Method of assigning subjects to study drug

Enrolled probands received consecutive “Patient numbers”, which was linked to the assigned study medication 1. All participants received originally packaged, personally asigned study medication 2 (Immunotherapy).

8.4.4 Selection of dose in the clinical trial

The target dose to achieve above 70 nmol/L, which is discussed as threshold for vitamin D sufficiency [15-18], is approx. 5000 IU daily according to published data [13,19,20].

8.4.5 Blinding

The study medication randomization and labeling was performed in the Charité pharmacy. Envelopes containing the information whether verum/placebo was assigned to the medication were stored within the study department.

8.4.6 Prior and concomitant therapy

The following drugs were not allowed within the study:

• Antihistamines within 3 days before screening, V1, V10, V11, V2-1, V2-10, V2-11, V3-1, V3-10- V3-11, follow upvisit.

* topical glucocorticoids at the same time points.

* vaccination 7 days before and 14 days after SIT

* tricyclic antidepressants, neuroleptics within 14 days before until the end of the study period

* systemic glucocorticoids, immunosuppressive drugs, immunomodulators, vitamin A derivatives, phenytoin, barbiturates, thiazides, glycosides, betablocker.

8.4.7 Treatment compliance

The patients documented in a booklet the intake of the study medication 1 on a daily basis. 25-hydroxyvitamin D-serum levels were determined at V1, V5, V10, V2-1, V2-5, V2-10, V3-1, V3-5 and V3-10.

8.5 Efficacy and Safety Variables

8.5.1 Primary Efficacy Variable

Wheal size of the intracutaneous test with 500 SBU grass pollen compared between the verum and placebo group at V11, V2-11 and V3-11.

8.5.2 Secondary Efficacy Variables

- area under the curve of the titrated intracutaneous test after the 1st, 2nd and 3rd treatment year
- titrated conjunctival provocation test after the 1st, 2nd and 3rd treatment year
- humoral specific immunoglobulin profile after the 1st, 2nd and 3rd treatment year
- Cellular parameters (activation and cytokine production of peripheral lymphocytes after the 1st, 2nd and 3rd treatment year).
- Retrospective symptom score rSS from 2011 compared to the grass pollen season after treatment 2012, 2013 and 2014
- General symptom score of the grass pollen season before treatment (2011) to the treatment after (2012, 2013 and follow-up 2014)
- Skin prick test before and after supplementation (2012, 2013 and 2014) and follow-up (2014)
- Symptom-medication-score (SMS) during grass pollen season 2012, 2013 and 2014

8.5.3 Variables for safety and tolerability

We determined the differential blood counts as well as from the serum 25-hydroxyvitamin D, calcium and phosphorus levels. In addition, the intake and subjective tolerability was recorded by patients in a diary over the treatment period.

8.5.4 Flow Chart

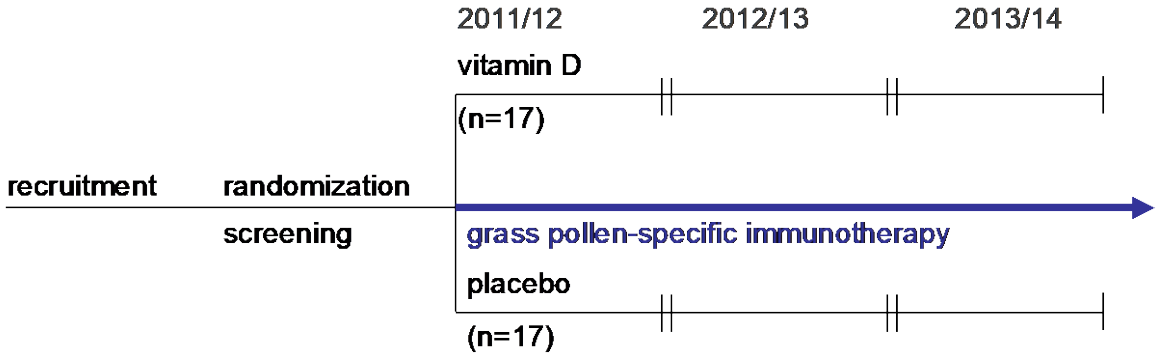


Fig. 8.5 Study chart with all visits and assessments are depicted in Table 13-1.

8.5.5 Appropriateness of Measurements

Intracutaneous, conjunctival provocation and prick test was performed according to international guidelines. The pharmacokinetic parameter 25-OH-VD and all other safety lab parameters were measured by the accredited central lab of Charité – Universitätsmedizin Berlin (since 2011 Labor Berlin – Charité Vivantes GmbH).
Experimental procedures including immune cell monitoring and specific immunoglobulin profiling was performed according to standard operating procedures established in our laboratory based on published protocols.

8.6 Data quality assurance

Data quality control and assurance were performed according to international guidelines (GCP, ICH), standard operating procedures (SOP) or working instructions. The data were documented first in the source data (SD) and afterwards in the case report form (CRF) by the investigator or designed personnel. The data were entered in a database and checked by a trial independent person. Once all data were entered in the data base, a blind data review meeting was assembled. The database was locked and released for reporting and statistical evaluations after all data quality control steps defined in the blind data review meeting were performed. The KKS Charité was involved in the data quality control.

8.6.1 Monitoring (Quality control)

The KKS Charité was delegated to perform the monitoring and one total monitoring report was provided.

8.6.2 Audit (Quality assurance)

External audits were not performed on this clinical trial.

8.7 Statistical Methods Planned in the Protocol and Determination of Sample size

8.7.1 Statistical and Analytical Plans

All data obtained in this clinical trial and documented in the CRFs were analyzed with descriptive group statistics. Details of statistical analyses are found in the statistical analysis plan (appendix 15.1.8).

All randomized subjects who received at least 1 time immunotherapy represent the intention to treat (ITT) population. Safety analysis was performed with the ITT population. In addition, the primary and secondary endpoints are analyzed and compared to the per-protocol set.
The primary and secondary efficacy analyses were performed with the per-protocol (PP) population. This groups include all probands treated for 4.5 months during the first year, reaching the maintenance dose within 2 months, and received at least 5% of all vitamin D/placebo medication. Excluded are individuals according to violation of in-/or exclusion criteria post randomization, incompliant vitamin D/placebo intake and not reaching the immunotherapy maintencance dose within 2 months.
The adverse events are summarized in Table 15.2.10, according to the specific group assignment and categorized by the context without, possible, likely and definite vitamin D/placebo intake, and also by AE/SAE resulting in study premature termination.

8.7.2 Sample Size

Although the clinical trial had an exploratory character a sample size calculation was performed as demanded by the IEC. In total, 36 subjects were randomized into two arms:
· Vitamin D3 (n=18)
· Placebo (n=18)
The sample size calculation based on the primary criterion, changes in the intracutaneous test reaction by immunotherapy in the vitamin D and placebo group. Regarding the potential effect of vitamin D, no data was published until then. Thus, the calculation based on published data on intracutaneous tests during grass pollen immunotherapy with Allergovit-Gräser®. Given a mean wheal diameter of 11 +/- 2.15 mm by 500 SBU grass pollen extract and a decline of 20% more in the vitamin D group compared to placebo, applying a power of 80% and alpha-error of 0.25, calculation using PASS 2008 (www.ncss.com) identified 17 participants per group are sufficient to detect significant differences. As drop-out rate of 5% was assumed during the 1st treatment year (corresponding to 1.7 probands per 34 in total, 2 probands), thus 36 subjects were randomized.

8.8 Changes in the Conduct of the Study or Planned Analyses

The clinical trial was conducted according to the protocol version 2.2 from 18.07.2011, followed by version 3.1 from 3rd September 2012 with the subject information and informed consent version 2.2 from 18.07.2011 and version 3.1 from 11.07.2012. All documents are filed in the trial master file (TMF) and investigator site file (ISF). (appendix 15.1.1)
Eleven notes to file were implemented during the trial (appendix 15.1.1).

9 Study population

9.1 Disposition of subjects

Fifty-three individuals were screened for trial participation. Seventeen subjects were excluded (screening failures, appendix 15.2.1).

Overall, 36 subjects were enrolled to receive immunotherapy and vitamin D/placebo. During the study, in total 13 individuals terminated prematurely n=3 in 1st, n=6 in 2nd, n=4 in 3rd year (dropouts 15.2.2.). Briefly, the reasons for drop out were violating an exclusion criterion (n=3, instable asthma; before 1st immunotherapy application, preganancy, banned drugs), withdrawn consent (n=6 occupational reasons), and compliance (n=4, lost to follow up). The drop out rate was comparable between the groups (Vitamin D: 6 of 18; Placebo 7 of 18)

The first signed informed consent was given on 14th Oct 2011 and the first randomization initiated on 24th Nov 2011. The last patient's follow up was on 13th Jan 2015.

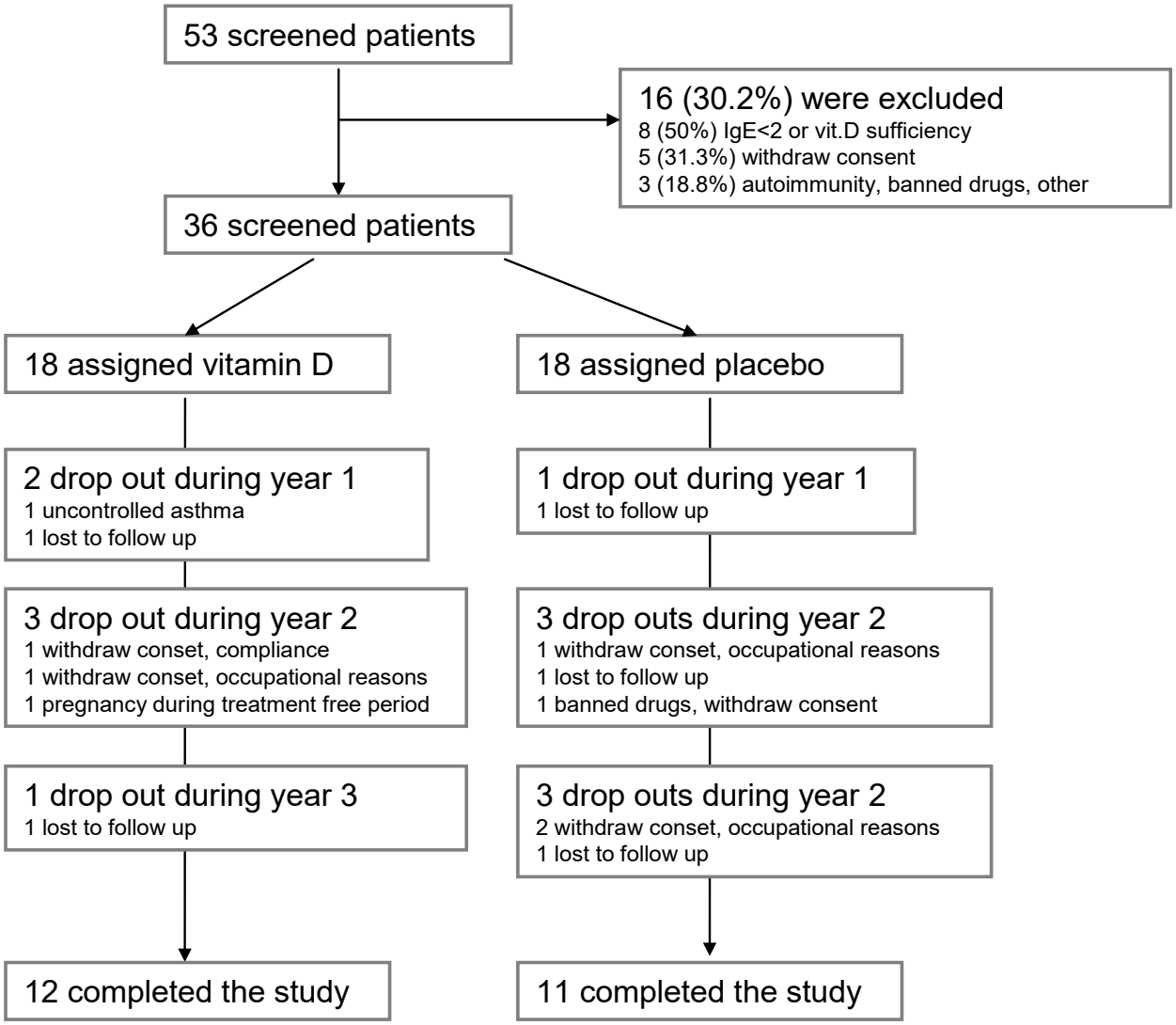


Figure: ProGIT study flow diagram according to CONSORT criteria.

9.2 Protocol deviations

Described above, see 9.1.

9.3 Data sets analysis

All randomized subjects who received at least 1 time immunotherapy represent the intention to treat (ITT) population. Safety analysis was performed with the ITT population. The primary and secondary efficacy analyses were performed with the per-protocol (PP) population, for details see Chapter 8.7.1.

9.4 Demographic and other baseline characteristics

The baseline characteristics are summarized in Table 9-1. The individual subject data for baseline characteristics is listed in appendix table 15.2.9.

Table 9-1: Baseline characteristics. P-value (Mann-Whitney-U-Test, significant p<0.05)

Variable	Vitamin D	PLC	p-value
Number (n)	18	18	
Sex (f/m)	8 / 10	6 / 12	0.73
Age (Years)	33±1.7	32±1.8	0.69
Height (cm)	174±2.2	177±1.78	0.37
Weight (kg)	73±2.8	73±3.0	0.93
Body Mass Index (BMI)	24±0.8	23±0.6	0.65
total IgE (IU/L serum)	195±41.1	288±61.9	0.37
grass-IgE (IU/L serum)	21±4.4	29±5.5	0.47
grass-IgE (CAP class)	3.4±0.2	3.7±0.2	0.44

10 Efficacy evaluation

10.1 Measurement of treatment compliance

Physiologically, vitamin D is derived from UV-biosynthesis or oral intake. As the treatment period of this study is performed during the UV-deficient winter months, increased serum concentrations of the vitamin D storage metabolite termed 25(OH)D reflects the vitamin D intake and serves as compliance parameter (individual data in the appendix 15.2.1).

The data show, that in the vitamin D group the 25(OH)D serum concentrations increase over the treatment period in all participants, as expected. Toxic levels were not observed. During the supplementation free period, the levels decline.

Accordingly, within the placebo group, all 25(OH)D concentrations decrease at the same time, furthermore showing that no vitamin D was acquired by other nutritional source (usually fatty fish or cod liver oil) or hidden UV-exposure (e.g. tanning or travel to UV-rich regions). As expected during the UV-rich summer, the 25(OH)D serum concentration increase in the participants. The 25-hydroxyvitamin D serum concentrations were significantly increased at the end of each supplementation period (p<0.0001).

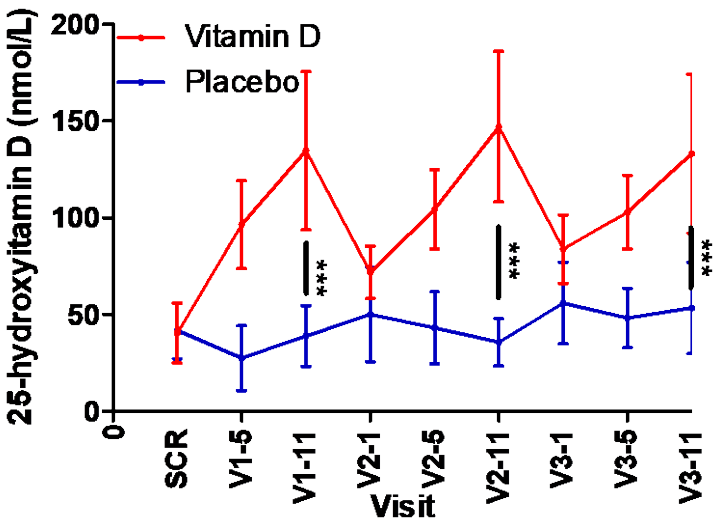


Figure 10.1 The vitamin D status as determined by serum 25-hydroxyvitamin D concentrations over time. Data shown represents the mean concentrations and standard deviations.

10.2 Efficacy Results and Tabulations of Individual Subject Data

10.2.1 Analysis of efficacy

10.2.1.1 Primary efficacy parameter

Wheal sizes of the intracutaneous test with 500 SBU grass pollen were compared between the verum and placebo group at V11, V2-11 and V3-11. Analysis of the ITT population shows a weak, but significant reduction of the wheal diameter of the highest allergen-dose (500 SBU) after 1 and 3 treatment years, but not after 2 years or follow up. However, the reduction was independent of vitamin D or placebo intake (p=0.5-0.3). This results from the high variability and thus limited group size. At the end of the study, a trend towards a reduced wheal diameter in the vitamin D group was observed when compared to the placebo group (p=0.085), see also Table 15.2.5.2.

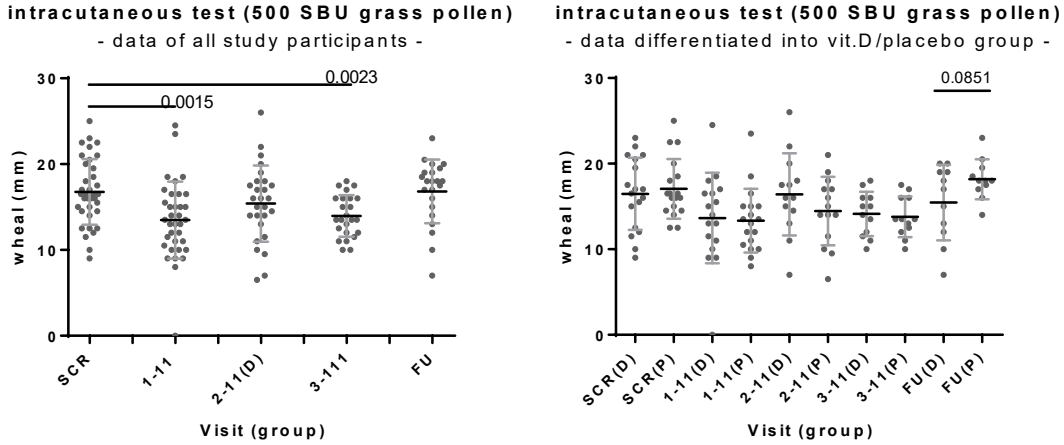


Figure 10.2.1.1: The intracutaneous test at 500 SBU grass pollen-specific before and after immunotherapy is independent of vitamin D-intake. The intention to treat-population (ITT) was analysed before SIT and after 1 year (left) and the per protocol (PP) group after 3 years. Subgroup analysis of the PP-group regarding the vitamin D- and placebo group (D and P) over time (screening; SCR, V1-11, V2-11, V3-11 and follow up, FU).

10.2.1.2 Secondary efficacy parameters

a) **The area under the curve (AUC) of the titrated intracutaneous test** after the 1st, 2nd and 3rd treatment year. The AUC in this setting is mostly dependent on the wheal diameters of the

highest pollen concentrations, which were underlying a significant variation. However, overall the AUC of the grass pollen-intracutaneous reaction is significantly reduced compared to baseline after first year (p=0.003) or third year (p=0.0001), but not to follow-up (p=0.5, not shown), the latter most likely due to a small group size or test allergen-batch variation (left). These data support that higher allergen concentrations are required for mediating a positive test result, as expected. Here, the comparison of the groups show comparable data between vitamin D and placebo at all time points (right), Table 15.2.5.3.

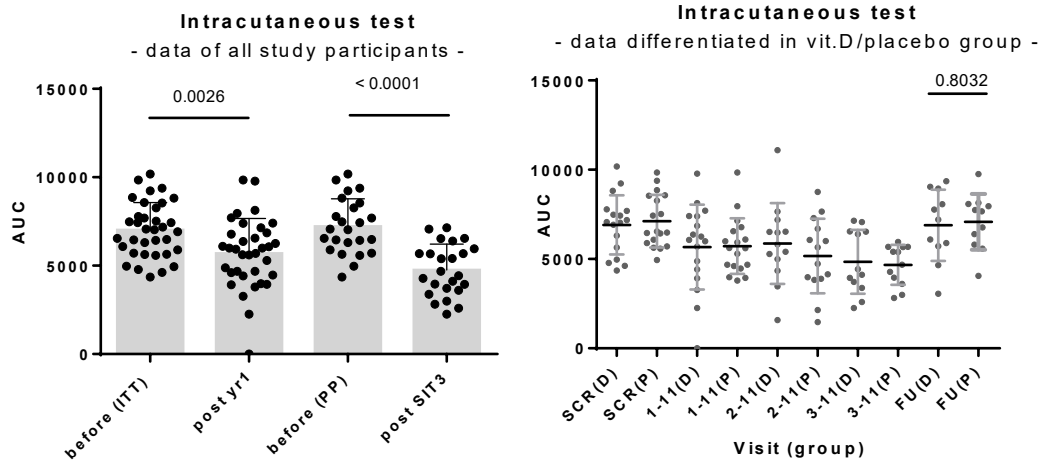


Figure 10.2.1.2: The grass pollen-specific intracutaneous test area under the curve is reduced by immunotherapy, but independent of vitamin D. The intention to treat-population (ITT) was analysed before SIT and after 1 year (left) and the per protocol (PP) group after 3 years. Subgroup analysis of the PP-group regarding the vitamin D- and placebo group (D and P) over time (screening; SCR, V1-11, V2-11, V3-11 and follow up, FU).

b) **The titrated conjunctival provocation test (AUC)** after the 1st, 2nd and 3rd treatment year. The overall AUC of the grass-pollen-specific conjunctival provocation test is increased following immunotherapy, by trend already after the first treatment year failing statistical significance, and more pronounced after all three treatment years (p=0.0010, after FU p=0.0008, nt shown). This effect is expected and reflecting higher allergen concentration thresholds to elicit an allergic reaction. However, intergroup differences were not detectable between the vitamin D or placebo subgroup until FU (0.040, higher in the placebo group).

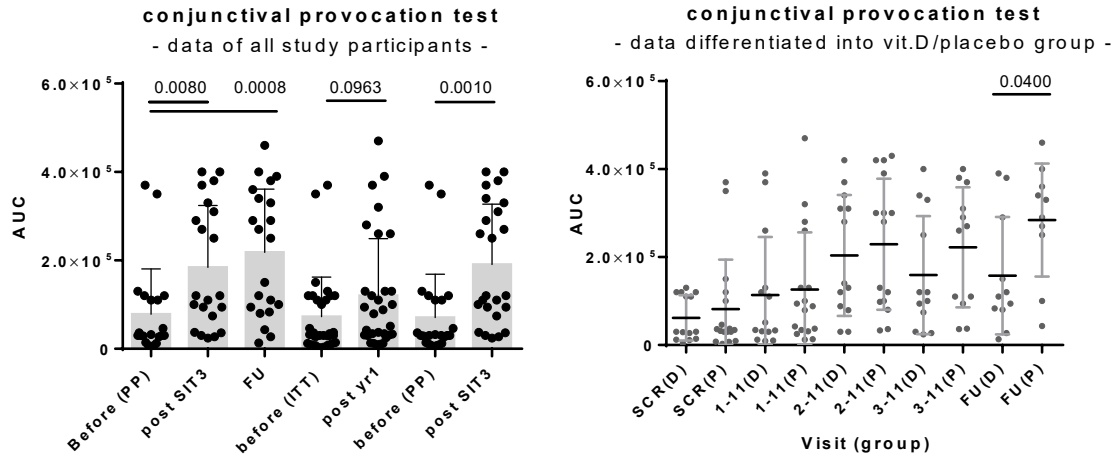


Figure 10.2.1.3: The grass pollen-specific conjunctival provocation test shows a higher area under the curve by immunotherapy, but is largely independent of vitamin D. The intention to treat-population (ITT) was analysed before SIT and after 1 year (left) and the per

protocol (PP) group after 3 years. Subgroup analysis of the PP-group regarding the vitamin D- and placebo group (D and P) over time (screening; SCR, V1-11, V2-11, V3-11 and follow up, FU).

c) humoral specific immunoglobulin profile after the 1st, 2nd and 3rd treatment year and
d) cellular parameters (activation and cytokine production of peripheral lymphocytes after the 1st, 2nd and 3rd treatment year
The data are not available yet due to limitations in resources of this IIT.

e) Retrospective symptom score (rSS) from 2011compared to the grass pollen season after treatment 2012, 2013 and 2014. The retrospective symptom score (RSS) significantly improved in the ITT (after 1-3 treatment years p<0.0001) and also both treatment groups (PP) by immunotherapy ranging from p=0.0001-0.0039 (data not shown). Finally, at the follow-up visit both study groups were comparable. Regarding the increased scores at year 2 and 3, a higher pollen count compared to year 1 must be considered (2012=45 particles per m^3 (ppm), 2013=110 ppm, 2014=236 ppm).

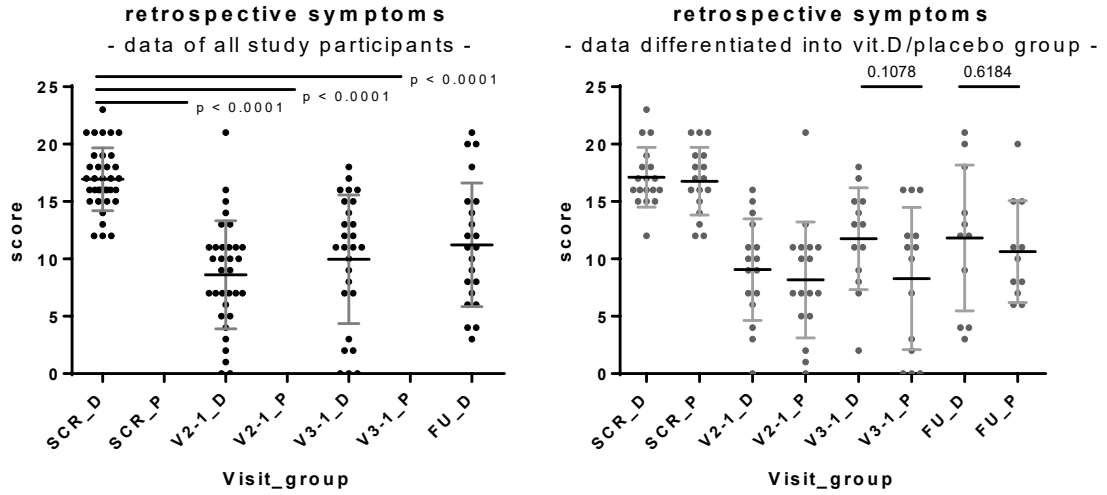


Figure 10.2.1.4: The retrospective symptom score show efficient immunotherapy, but is largely independent of vitamin D. The intention to treat-population (ITT) was analysed before SIT (left) and the per protocol (PP) group over 3 years. Subgroup analysis of the PP-group regarding the vitamin D- and placebo group (D and P) over time (screening; SCR, V1-11, V2-11, V3-11 and follow up, FU).

f) General symptom score of the grass pollen season before treatment (2011) to the treatment after (2012, 2013 and follow-up 2014). The data show that immunotherapy reduces the symptoms regarding eyes, nose and the lung, which is significant after 3 treatment (Fig.10.2.1.5, left). This data is strong, as the maximum and overall pollen counts were increasing (by coincidence, 2012=45, 2013=110, 2014=236). However, subgroup analysis reveal no significant difference between the vitamin D and placebo group (Fig.10.2.1.5, right).

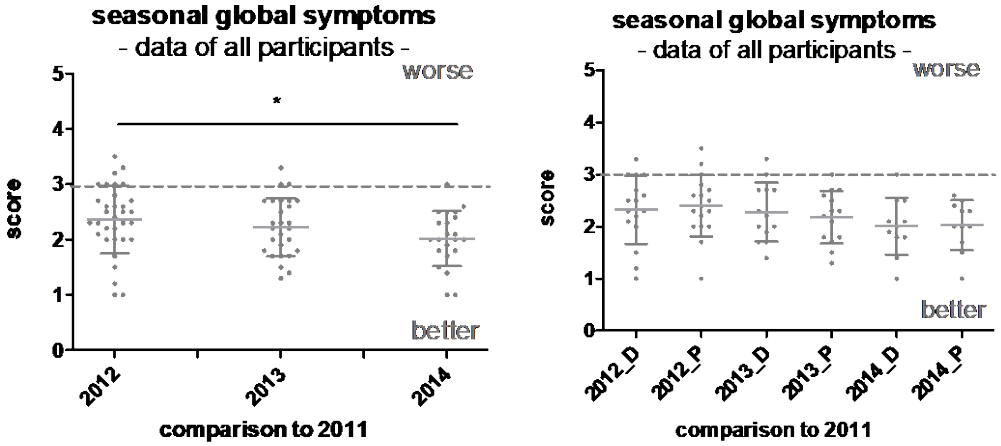


Figure 10.2.1.5: The seasonal global symptom score over time. The probands were regarding their allergic symptoms during the pollen season after each cycle of preseasonal immunotherapy. The intention to treat-population (ITT, left) and subgroup analysis regarding the vitamin D- and placebo group (D and P) of the per protocol (PP, right) group was analyzed over 3 years (V2-1-2012, V3-1-2013, FU-2014). The score reflects the mean subjective evaluation (1=much better, 2=better, 3=same, 4=worse, 5=much worse, dotted line reflects no change to the season before treatment).

g) Skin prick test over time. The data show that a limited but highly significant reduction of the grass pollen-specific skin prick test reaction by specific immunotherapy in % of control (histamine) but also absolute values (mm of the wheal, data not shown). However, comparison between both groups did not identify specific inter-group differences.

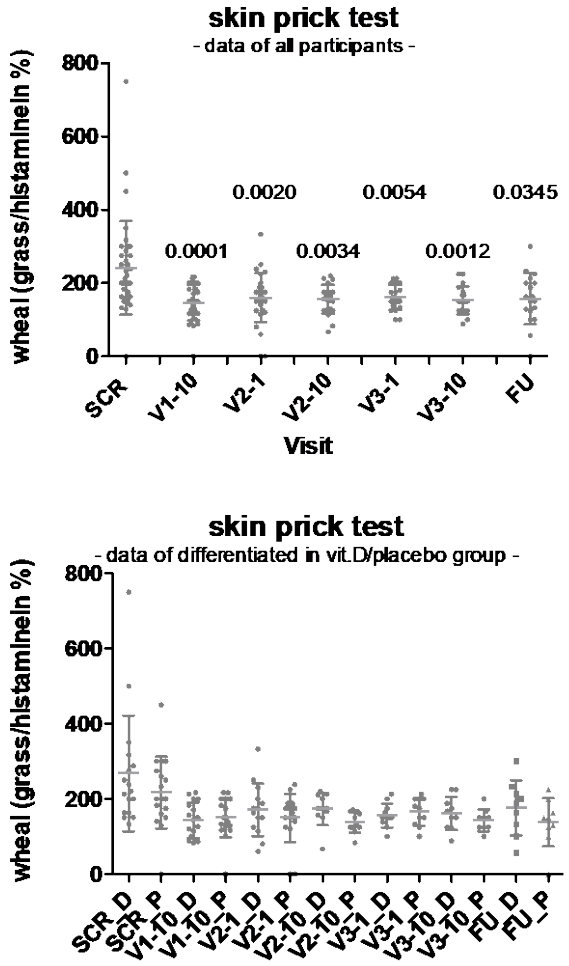


Figure 10.2.1.6: The skin prick during immunotherapy test over time. The intention to treat (ITT, left) and the per protocol (PP, right) group, with subgroup analysis regarding the vitamin D- and placebo group (D and P), were analyzed over time (screening; SCR, V1-11, V2-11, V3-11 and follow up, FU). The wheal induced by grass pollen is expressed in % of histamine (positive control). NaCl served as negative control (all values neg, not shown). P-values are T-Test from normally distributed values (compared to SCR-visit).

h) Symptom-medication-score (SMS) during grass pollen season 2012, 2013 and 2014. For the pollen season 2012 the data shows a pollen-associated increase of the combined symptom-medication-score (SMS) as self-documented from the participants during summer. The data show comparable data between both groups (blue=vitamin D, red dotted=placebo group, both n= 14 returned data sets).

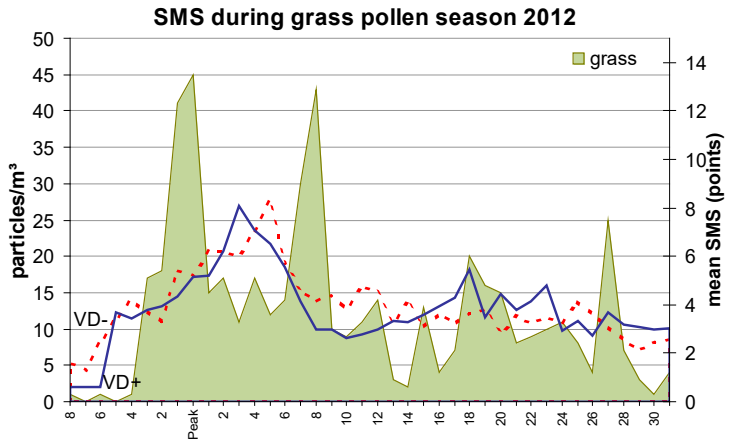


Figure 10.2.1.7: The symptom-medication-score (SMS) during pollen season 2012. Grass pollen count (green), mean SMS per protocol groups with vitamin D intake (blue line) or placebo (red dotted).
During 2013 and 2014 the participants compliance regarding the symptom and medication documentation was low. Due to a strong group bias (vitamin D, 61% and 69% and placebo, 37% and 47% data returned) the data will not be evaluated. Of note, also regarding the global and retrospective symptom scores, which were strongly reduced during immunotherapy, the pollen counts in 2013 and 2014 were overall increased over the season with a higher peak (2012=45 ppm^3, 2013=110 ppm^3, 2014=236 ppm^3).

h) Grass-pollen specific Ig-induction. Before SIT, the data show comparable specific IgE serum concentrations between the groups. Specific IgG4 was low/below the detection threshold in all participants. As expected, SIT strongly induces specific IgE, but interestingly in the vitamin D group this process is almost abolished. In summary, analysis of the grass pollen-specific IgE serum concentrations are statistically significant between both groups (p=0.031). In both groups specific-IgG4 is induced in a comparable amount leading to an increased IgG4/IgE-ratio.

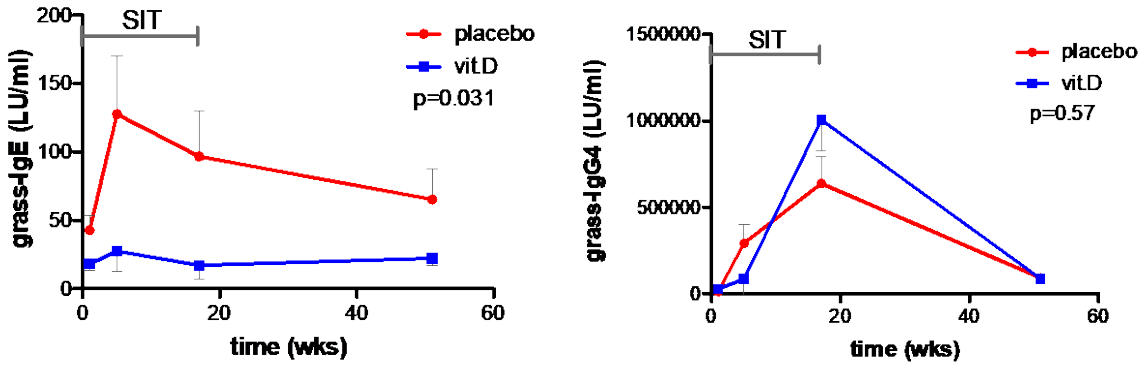


Figure 10.2.1.8: The specific Ig-induction during the first treatment year. Grass pollen-specific Ig serum concentrations were quantified before, during SIT /V1-5) and after SIT (V1-10) and before the 2nd treatment course (V2-1) The data show the mean and SD of the per protocol groups with vitamin D intake (blue line, n=16) or placebo (red dotted,n= 17). Statistical significance was considered p<0.05 (repeated ANOVA-test).

10.2.2 Efficacy conclusion

Grass-pollen specific immunotherapy is effective in patients with grass pollen-induced allergic rhinoconjunctivitis with or without allergic asthma. The treatment is already effective after the first seasonal treatment course, as assessed by the symptom scores, intracutaneous test prick

test and specific IgG4-induction. Maybe due to the effective immunotherapy as such, a significant effect of vitamin D was not observed, regarding the clinical parameters. However, the data clearly show that at the molecular level vitamin D is effective, e.g. by the control of specific IgE and maintained IgG4-induction, leading to an increased IgG4/IgE ratio.

However, whether vitamin D mediates additional beneficial modulatory functions on immunotherapy will be further analyzed by additional analysis including a multifactorial covariate analysis and further exploratory subgroup analysis including correlations of best vitamin D-responders and SIT or best SIT-responders and vitamin D.

11 Safety evaluation

11.1 Adverse Events

Over the three-year study, 77 adverse events occurred in overall 31 different of 36 randomized participants. Most of these were associated to the flu-season during winter (upper respiratory tract infections, headaches), immunotherapy updosing (local skin reactions). All of the AE's recovered during the study period.
All AE's are summarized in Table 11-1.

Table 11-1: Summary of AE's during the study.

All treatment-emergent AE	**ITT group total 36 subjects**	
System organ class	**F**	**N**
Musculoskeletal and connective tissue disorders	6	4
Cardio-vascular disorders	0	0
Skin, mucosa and subcutaneous tissue disorders	17	12
Nervous system disorders	9	5
Ophthalmic disorders	2	2
Endocrinal disorders	0	0
Respiratory, thoracic and mediastinal disorders	31	18
Urogenital disorders	3	3
Gastrointestinal disorders	7	5
TOTAL	**77**	**-**

Source: Appendix Table 15.2.5
F = number of AEs, N = number of subjects with AEs

Compared to our Development Safety Update Report (DSUR) covering to 2012, less AE's occurred suggesting less virulent flu seasons 2012-2014.

In one case, the study was terminated because the participant (P7) withdrew consent after a local reaction > 10 cm to a immunotherapy shot at V2-1. This was the first immunotherapy dose of the second treatment year, after the pollen season and an expected AE. Vitamin D was not taken during summer for 6 months (15.5.-21.11.2012).

11.2 Death, other serious or other significant adverse events (SAE)

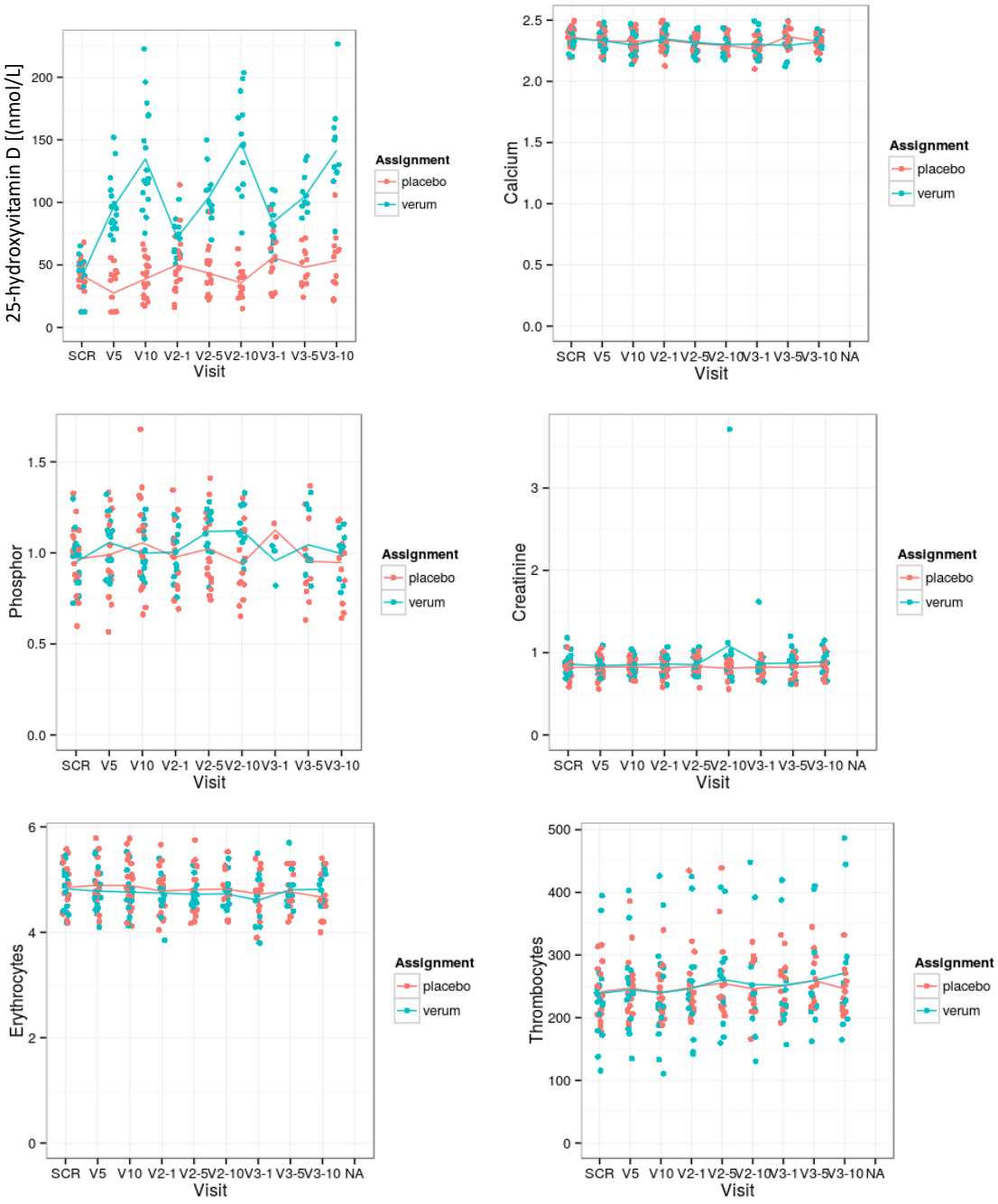
During the entire study period including the follow-up visit, one SAE and no to death leading events occurred. No other significant AE newly appeared was reported until now which was related to the investigated study drugs.
The SAE was not related to the study. During the first pollen season (no study medication administered), a sexually transmitted urogenital infection with Ureaplasma induced a reactive

arthritis. The consecutively initiated treatment included the application of the immunosuppressant methotrexate, thus the patient was excluded from further participation (exclusion criterion banned drugs).

11.3 Clinical laboratory Evaluation

11.3.1 Listing of individual laboratory measurements by subjects

All individual safety parameters were without clinical significance, except for 25-hydroxy-vitamin D deficiency during the treatment period in the placebo group as expected, see Figure 11.3.1. The data and our continued Development Safety Update Report (DSUR) covering until May 2012 prove, that the treatments with specific immunotherapy and vitamin D or placebo was safe. Due to the absence of clinically relevant safety parameters and data shown as single values, we omit an additional table regarding all single values of each individual in addition.



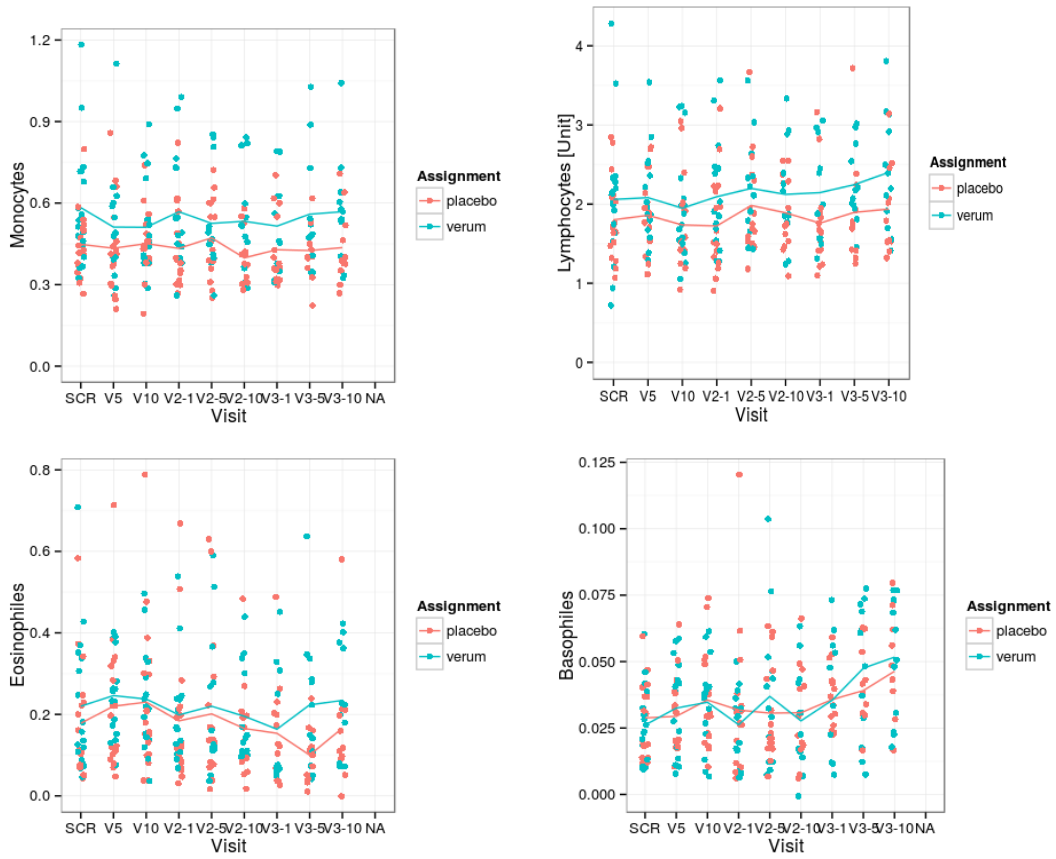


Figure 11.3.1. Laboratory safety parameters. The data show all single values of all participants during the whole study period regarding the vitamin D (green) and placebo (orange) group. The line shows the linked medians. Cells are depicted in cells/nl, calcium and phosphorus in mmol/L, kreatinine in mg/dl, and 25-hydroxyvitamin D in nmol/l.

11.3.2 Evaluation of laboratory parameters

Vitamin D supplementation was efficient in all individuals, reaching values clearly above 80 nmol/L. No toxic concentrations were reached in any individual. Accordingly, the calcium and phosphorus serum concentrations, which can be increased by vitamin D overdosage, were fully normal in all individuals during the entire treatment period and the serum kreatinine concentrations as hallmarks of calcium-kidney stones or impaired renal function was fully normal. As expected, no changes in the differential blood counts were determined in any participant during the study.
The data prove, continued from our Development Safety Update Report (DSUR) covering until May 2012, that the treatment with specific immunotherapy and vitamin D or placebo safe.

11.4 Vital signs, physical findings, and other observations related to safety

All subjects were healthy and vital parameters were in the physiological range. No individual listings are enclosed.

11.5 Evaluation of tolerability

Regarding the vitamin D/placebo intake, tolerabilitiy was reported from all participants in a score ranging from 1-5 (1=very good, 2=good, 3=average, 4=poor, 5=very poor).

All data shows individually constant values between 1-2. The tolerability must be considered as excellent. Thus, no individual listings are enclosed.

Regarding the specific immunotherapy, 28 AEs occurred (24 local, 4 systemic). All systemic reactions were expected. The rhinoconjunctival reaction were treated with 20 mg Cetirizin tablets and resolved within 1 hour.

All were during the updosing phase and must be considered as expected unwanted reactions.

The data show a marginally increased frequency of reactions within the vitamin D group (OR=1.49, p=0.37).

SIT associated AE	Vitamin D	Placebo
Systemic (No)	2	2
Local (No)	14	10
SCIT (No total doses)	462	524

However, as the data were not statistically significant and most reaction occurred during the updosing phase, before vitamin D sufficiency was achieved, the relevance must be evaluated critically. Larger studies are required to validate this finding.

11.6 Safety conclusion

The intake of vitamin D was safe in all individuals. No vitamin D-associated adverse events in context with immunotherapy was observed. Thus, the data suggest that vitamin D in context with immunotherapy should be considered as safe. However, a larger, representative cohort should be investigated to confirm this.

12 Discussion and overall conclusion

In this study, we investigated whether vitamin D intake affects the efficacy of grass-pollen specific immunotherapy in patients with allergic rhinoconjunctivitis with or without allergic asthma and collected data on the clinical and immunological response during immunotherapy. The data of this pilot trial show that specific immunotherapy is efficient as considered by clinical scores, titrated intracutaneous tests and prick tests. The immunologic data suggest a beneficial additional impact of vitamin D on the humoral immune reaction as specific IgE was blocked, but not the specific IgG4 responses. However, a clear superiority or inferiority statement regarding the intake of vitamin D on the efficacy of immunotherapy cannot be made yet, most likely due to the small sample size, but also the methods chosen.

In principle, our data supports the finding in children undergoing house dust mite-specific immunotherapy with or without vitamin D supplementation. In a first pilot trial, vitamin D shows a trend to improve the efficacy [21]. Summarizing 2 pilot trials using the identical protocol revealed a better steroid-sparing effect of vitamin D with immunotherapy, if a serum concentration of 70 nmol/L (30 ng/ml) 25(OH)D was achieved [22].
Own preclinical data prove that 25(OH)D, which is activated in vivo by the immunotherapy-driven immune response to active calcitriol endogenously, enhances the tolerogenic functions of specific immunotherapy in mice resulting in decreased airway inflammation [6]. Supported is our data by the findings of others demonstrating that calcitriol enhance the efficacly for immunotherapy in mice [9 23]. However, calcitriol is pharmacologically limited for use in immunotherapy of patients due to its toxicity, narrow therapeutic range and the half-life of 2 hrs.

We think that the molecular basis is clearly given in our study to determine the vitamin D-mediated modulation of the immunotherapy response as the groups clearly differ in their

25(OH)D status. Vitamin D deficiency is considered below 50 nmol/L [13]. We and others determined concentrations above 70 nmol/L as sufficient to mediate vitamin D-dependent effects [18] [15] [16] . Here, the mean 25(OH)D-serum concentrations in the vitamin D group were with 130 nmol/L (52 ng/ml) at the end of the supplementation period clearly above those from the placebo group (below 50 nmol/L, 20 ng/ml). The data on the blocked grass pollen-specific IgE-induction supports our previous findings that VDR blocks IgE expression [7,24,25] and epidemiologic data [26]. We are looking forward analyzing the data beyond IgE, obtained from the materials obtained during this study.

Regarding the methods used to determine the efficacy of immunotherapy, we applied a combined symptom-medication-score, retrospective global symptom scores, titrated intracutaneous and conjunctival provocation and prick tests. All these methods have their limits, e.g. compliance during the pollen-season, daily data documentation, subjective bias on the global retrospective scores, but also variability in the intracutaneous injection, concomitant factors influencing conjunctival reaction and long-half life on mast cell-bound specific IgE. Now, controlled pollen chambers became available and develop as gold standard to evaluate the pollen-specific reactions [27,28]. Also, intracutaneous test reagents are off-market now as the manufacturers stopped production. Thus, in future trials, analyzing the patients in a pollen chamber would be an attractive option to determine the clinical efficacy of vitamin D in the context of specific immunotherapy.

Figures and tables referred to but not included in the text

Table 13-1: Time schedule for the trial procedure in year 1

	Screen-ing	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**
days, weeks, month	until -W4	D1	D7±1 D	D14±1 D	D21±1 D	D28±1 D	D35±1 D	D42±1 D	W8+3D	W12±3 D	W16±3 D	W17+3D
inform	✓											
consent	✓											
history	✓											
inclusion criteria	✓	✓										
exclusion criteria	✓	✓										
ethnicity	✓											
bdoy height and weight	✓											
vitals[#]	✓										✓	
inspection	✓										✓	
pregnancy test[##]	✓											
lung function (FEV_1)	✓	✓[+]	✓[+]	✓[+]	✓[+]	✓[+]	✓[+]	✓[+]	✓[+]	✓[+]	✓	
skin prick test	✓										✓	
conjunctival provocation		✓									✓	
intracutaneous test	✓											✓
immunoglobulin profile	✓[###]	✓									✓	
safety lab	✓					✓					✓	
25-OH-Vitamin D	✓					✓					✓	
immune cells		✓				✓						✓
genotyping		✓										
provide dairy		✓						✓	✓	✓		
control dairy			✓	✓	✓	✓	✓	✓	✓	✓		
collect dairy								✓	✓	✓	✓	
rSS°	✓											
global symptoms												
provide study medica-tion1*		✓					✓		✓	✓		
provide dairy			✓	✓	✓	✓	✓	✓	✓	✓		
control dairy							✓		✓	✓	✓	
collect dairy		----------5.333 I.E./T----------										
stop supplementation											✓	
compatibility of the study medication			✓°°	✓°°	✓°°	✓°°	✓°°	✓°°	✓°°	✓°°	✓°°	
grass SIT (flask/dose in ml)		✓ A/0,1	✓ A/0,2	✓ A/0,4	✓ A/0,8	✓ B/0,15	✓ B/0,3	✓ B/0,6*	✓ B/0,6	✓ B/0,6	✓ B/0,6	
		----------updosing----------					----------maintenance----------					
adverse event inquiry		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
medication inquiry	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

V – visit, D – day, W – week, M – month, conjunctival provocation test, I.U. – international units
[#] vitals include blood pressure and pulse
[##] in women in childbearing age
[+] FEV is assessed in participants with asthma before SIT injection, if < 70% the SCIT is applied on a following day.
[###] only total IgE and grass-specific IgE is determined
° retrospective symptom score (rSS): at screening visit the participant evaluates the most intensive rhinoconjunctivitis symptoms of 2011
°° compatibility is assessed via a dairy
* first injection of the SCIT-maintenance dose

Table 13-1: Time schedule for the trial procedure in year 2 and 3

	V2-1 V3-1	**V2-2 V3-2**	**V2-3 V3-3**	**V2-4 V3-4**	**V2-5 V3-5**	**V2-6 V3-6**	**V2-7 V3-7**	**V2-8 V3-8**	**V2-9 V3-9**	**V2-10 V3-10**	**V2-11 V3-11**	**FU**
interval to previous visit	mind. 11 M nach V1 bzw. V2-1	T7+1T	T7+1T	T7+1T	T7+1T	T7+1T	T7+1T	W2+3T	W4±3T	W4±3T	W1+3T	mind. 11 M nach V3-1
inform	✓§											
consent	✓§											
vitals#	✓§§									✓		✓
inspection	✓§§									✓		✓
pregnancy test##	✓											
lung function (FEV_1)	✓	✓+	✓+	✓+	✓+	✓+	✓+	✓+	✓+	✓		
skin prick test	✓§§									✓		✓
conjunctival provocation	✓									✓		✓
intracutaneous test	✓§§										✓	✓
immunoglobulin profile	✓§§									✓		
safety lab					✓					✓		
25-OH-Vitamin D	✓§§				✓					✓		✓
immune cells	✓§§				✓						✓	✓
provide dairy	✓						✓	✓	✓		✓§§§	
control dairy		✓	✓	✓	✓	✓	✓	✓	✓			
collect dairy							✓	✓	✓	✓		
rSS°	✓§§											✓
global symptoms	✓§§											✓
provide study medication1*	✓					✓		✓	✓			
provide dairy		✓	✓	✓	✓	✓	✓	✓	✓			
control dairy						✓		✓	✓	✓		
supplementation	----------5.333 I.E./T----------											
rSS°		✓°°	✓°°	✓°°	✓°°	✓°°	✓°°	✓°°	✓°°	✓°°		
grass SIT (flask/dose in ml)	✓ A/0,1	✓ A/0,2	✓ A/0,4	✓ A/0,8	✓ B/0,15	✓ B/0,3	✓ B/0,6*	✓ B/0,6	✓ B/0,6	✓ B/0,6		
	----------updosing----------					----------maintenance----------						
adverse event inquiry	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
medication inquiry	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

V – Visit, D – day, W – week, M – month, conjunctival provocation test, I.U. – international units
vitals include blood pressure and pulse
in women in childbearing age
+ FEV1is assessed in participants with asthma before SIT injection, if < 70% the SCIT is applied on a following day.
only total IgE and grass-specific IgE is determined
° retrospective symptom score (rSS): at screening visit the participant evaluates the most intensive rhinoconjunctivitis symptoms of 2011
°° compatibility is assessed via a dairy
* first injection of the SCIT-maintenance dose
§ inform and consent for the prolongation of the study
§§ these investigations take place, also if the participant is not continuing during year 2 and 3 and prematurely stops the study
§§§ the symptom-medication-log for the grass-pollen season is giben to the participant, which is returned thereafter (Amendment 02)

13 Reference list

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14 Appendix

15.1 Trial information

15.1.1 Protocol of the clinical trial, subjects information and informed consent

The clinical trial was conducted according to the protocol version 2.2 from 18.07.2011, followed by version 3.1 from 3rd September 2012 with the subject information and informed consent version 2.2 from 18.07.2011 and version 3.1 from 11.07.2012. All documents are filed in the trial master file (TMF) and investigator site file (ISF).
11 Note to Files were created during the clinical trial:

Note to File 1 (18.07.2011) „not allowed drugs“:
No antihistamines and topical glucocorticoids before screening, visit 1, visit 10 and follow up are allowed”.
It is changed and also valid for visit 11, regarding topical glucocorticoids not visit 1 but also visit 11. A skin prick tst, conjunctival provocation test and/or intracutaneous test is performed.

Note to File 2 (05.01.2012) „correction definition vitamin D deficiency at inclusion“:
To participate in the study, the inclusion criterium serum 25-hydroxyvitamin D concentrations <50 nmol/L are defined. Current scientific data show a higher threshold for vitamin D function (80-100 nmol/L) and also 5000 IU vitamin D daily is considered safe. Thus, the threshold to exclude vitamin D sufficiency is now 80 nmol/L.

Note to File 3 (31.01.2012) „treatment with Allergovit® Gräser“:
According to the manufacturer’s instruction Allergovit® Gräser is recommended to keep an interval between the first and second maintenance dose (flask B 0,6 ml) of 14 days. Thus, the intervall between V7 and 8 is reduced from 28 days (+3 Tage) to 14 days (+3 days).

Note to File 4 (24.02.2012) „treatment scheme with Allergovit® Gräser“:
Visit 11 should be performed before pollen season. To guarantee this, all patients who will not achieve this according to the protocol to finish visit 10 until 1st May, will receive the doses 3-weekly starting at visit 8, as stated possible according to the manufacturer’s recommendations.

Note to File 5 (03.04.2012) „treatment scheme with Allergovit® Gräser“:
Although Note to File 4 was established, not all patients complete visit 10 until 1st May. Thus, to avoid that visit 10 is during grass pollen season, visit 9 replaces visit 10.

Note to File 6 (08.05.2012) „files notes“:
All Note to Files are valid for later protocol versions after 2.2 from 18.07.2011.

Note to File 7 (27.08.2012) „25-hydroxyvitamin D values by an independent person“:
The 25-hydroxyvitamin D values of the 2. treatment year 2013 are at visit 5 and 10 checked by a person independent of the study, the hard copies are collected.

Note to File 8 (15.11.2013) „Changed drop volume of Vigantol Öl by Fa.Merck “:
In January 2012, the drop volume of Vigantol Öl is changed by Fa.Merck. According to the manufacturer’s instructions (“Fachinformation”), 1 drop contains now 500 IU. In the study protocol is stated that 1 drop contains 667 IU, and 8 drops should be taken by the participants (5336 IU). For this 3rd study year, a new batch was ordered by the pharmacy (Charité Apotheke) and the participants were instructed to take 10 drops (5000 IU). Participants already before 15th November starting the 3rd study year are instructed on the following visit (weekly basis).

Note to File 9 (15.11.2013) „Protocol Chapter 9 Discontinuation and continuation, 9.1 Stop criterion “not-reaching the SIT-maintenance dose within 2 months”.
Grass-SIT is administered according to the manufacturer’s recommendations. The regular up-dosing phase is completed during 6 weeks. As intervals of 1-2 weeks are possible, it can be prolonged up to 12 weeks. Thus the discontinuation criterion is changed into:
“Not-reaching the grass-SCIT maintenance dose within 3 months”.

Note to File 10 (15.11.2013) „Protocol Chapter 2 and treatment scheme 6.2.1 2 Allergovit Gräser”.
Grass-SIT is administered according to the manufacturer’s recommendations. The regular up-dosing intervals can be between 7-14 days. Thus, delays during the study within this time frame need not to be commented.
During maintenance therapy, the intervals from 14-34 days are suggested. Scheduling of the stud visits (originally 28 days+3) within these time frames are not protocol deviations and need not to be commented.

Note to File 11 (30.09.2014) „CRF/SD”.
The following CRF items are to be ignored, as they are not required in the protocol:
- check of the inclusion/exclusion criteria V2-1, V3-1
- check (*) in overall-rSS in V2-1, V3-1
- global symptom assessment line “gesamt”, as mean values are calculated (V2-1, V3-1, FU), Symptom “runny nose” ist to be ignored (FU).
- 25-hydroxyvitamin D is defined “abnormal” > 250 nmol/L
- CRF is the source data entry for the immunology parameters in V2-1 and V3-1
- Conjunctival provocation test is positive ≥ 5 points

Source data documentation
- V1-11 in header of treatment year is to be ignored
- V3-1 is the question immunoglobulin profile normal/abnormal to be ignored
- Safety lab results are until the study termination to be deposited by the unblinded person

Patients’ diary and symptom-medication-scores documentation
- the dairies are seperately stored in files labelled “Tagebücher”
- the symptom-medication-scores (SMS) are assessed during 14.5.-12.8.2012, 13.5.-18.8.2013 and 12.5.-17.8.2014.

15.1.2 Sample Case Report (CRF)

A sample CRF is filed in the TMF section 2.8 with all visit pages.

15.1.3 Chairmen and member of the local IEC

Chairman: PD Dr. Hans-Herbert Fülle, FA Innere Medizin (commission No. 2)
Members: Frau Dr. Inge Gorynia (FÄ für Physiologie), Herr Prof. Dr. Jens Tank (FA Innere Medizin, klinische Pharmakologie, Pathophysiologie), Frau Dr. Stefphanie Roll (Biometrikerin), Herr Christoph M. Stegers (Volljurist, Rachtsanwalt), Herr Dr. Wolfgang Mehnert (Apotheker), Herr Dr. Martin Knechtges (Laie).

15.1.4 List of investigators and other important participants in the clinical trial including curricula vitae

Professor Margitta Worm, MD, is the principle investigator and delegated sponsor of the clinical trial “ProGIT”.

Curriculum vitae Professor Margitta Worm, MD
Date of Birth: 25th October 1964
Present Position: Head of Allergy branch, Clinical study unit; Department of Dermatology and Allergology, Charité – Universitätsmedizin Berlin, Germany
Medical graduation and/or Other Professional Training:
2007 - Specialisation course for study coordination in clinical trials; KKS-Charité
Since 2003 - University professor at Charité, Berlin
2002 - Specialisation in allergy and environmental medicine
Since 2000 - Senior physician at Dpt. of dermatology, Charité, Berlin
1998 - Specialisation in dermatology and venerology
1995-2000 - Assistant doctor at Dpt. of dermatology, Charité, Berlin
1993-1995 - Research fellow at Children's Hospital, HavardMedical school, Bosten/USA
1993 - Medical licence (Approbation)
1991-1993 - Resident and research fellow at Dpt. of dermatology, Charité, Berlin
1991 - Medical Doctor at Freie Universität Berlin
Experience in Controlled Clinical Trials:
Since 1998 principle investigator and investigator in numerous clinical trials (>80) phases II-III in allergology and dermatology, main focus specific immunotherapy with different allergens, immunmodulation of atopic dermatitis, allergic asthma and autoimmune diseases.
Regular ICH-GCP training (internal bi-weekly, training with certificate at least twice a year)

PD Dr. med. Guido Heine, is sub-investigator and project coordinator in the clinical trial "ProGIT".
Curriculum vitae
Date of Birth: 12th May 1975
Present Position: Consulting Dermatologist, Department of Dermatology and Allergology, Charité –Universitätsmedizin Berlin, Germany
Medical Graduation and/or Other Professional Training:
2014 – Habilitation and *venia legendi*
2012 - Specialisation in dermatology
2009 - Basic principles for clinical trials; KKS-Charité including GCP/ICH-training
Since 2003 - Resident at Dpt. of dermatology, Charité, Berlin
2002 - Medical Graduation at Humboldt Universität, Berlin
2000 - Doctoral thesis at Humboldt Universität, Berlin
Experience in Controlled Clinical Trials:
Sub-Investigator in >30 controlled clinical trials phases II-III since 2004, e.g. specific immunotherapy with different allergens, atopic dermatitis, immunmodulation.
Regular ICH-GCP training (internal bi-weekly, training with certificate at least twice a year)

Dr. rer. Med. Sabine Dölle, studied nutrition science and is specialised in allergology. She is study coordinator in the clinical trial "ProGIT".
Curriculum vitae
Date of Birth: 20th October 1980
Present Position: Scientific assistant; Department of Dermatology and Allergology, Charité – Universitätsmedizin Berlin, Germany
Professional Training:
2012 - Graduation in medical science at Charité - Universitätsmedizin Berlin
2011 - Special training for monitoring including GCP/ICH-training, Amandec, Berlin
Since 2007 - Study & project coordinator for IITs (working group Prof. Worm), Charité, Berlin
2006 - Basic & special course for study nurses, KKS-Charité, Berlin
Since 2006 - Scientific research assistant (working group Prof. Worm), Charité, Berlin
Experience in controlled clinical trials:
Study nurse in different controlled clinical trials phases II-III since 2006, e.g. specific

immunotherapy with different allergens, immunmodulation in atopic dermatitis, food allergy; Study coordinator in IITs since 2007; Experienced in audit performance; Regular Regular ICH-GCP training (internal bi-weekly, training with certificate at least twice a year)

Dr. med. Juliane Hiepe, is sub-investigator and representative of Guido Heine in the clinical trial “ProGIT” until April 2012.
Curriculum vitae
Date of Birth: 27th April 1982
Present Position: Assistant Doctor, Department of Dermatology and Allergology, Charité – Universitätsmedizin Berlin, Germany
Medical Graduation and/or Other Professional Training:
06/2009 - Resident in dermatology and allergology at Charité - Universitätsmedizin Berlin
06/2009 - Special training: Investigator in clinical studies - certificate; KKS-Charité
09/2009 - Doctor's degree at Charité - Universitätsmedizin Berlin
12/2008 - Medical graduation at Charité-Universitätsmedizin Berlin (Approbation)
Experience in Controlled Clinical Trials;
Sub-Investigator in different controlled clinical trials since 2009:
Regular ICH-GCP training (internal bi-weekly, training with certificate at least twice a year)

Dr. med. Anna Dinkloh, is sub-investigator and representative of Guido Heine in the clinical trial “ProGIT” , starting from 09th January 2012 until 31th July 2013.
Curriculum vitae
Date of Birth: 23th January 1983
Position at study time: Assistant Doctor, Department of Dermatology and Allergology, Charité – Universitätsmedizin Berlin, Germany; current position Dermatologist, Munich
Medical Graduation and/or Other Professional Training:
06/2009 - Resident in dermatology and allergology at Charité - Universitätsmedizin Berlin
06/2009 - Special training: Investigator in clinical studies - certificate; KKS-Charité
09/2009 - Doctor's degree at Charité - Universitätsmedizin Berlin
12/2008 - Medical graduation at Charité-Universitätsmedizin Berlin (Approbation)
Experience in Controlled Clinical Trials;
Sub-Investigator in different controlled clinical trials since 2009:
Regular ICH-GCP training (internal bi-weekly, training with certificate at least twice a year)

Dr. med. Alexandra Werner-Busse, is sub-investigator and representative of Guido Heine in the clinical trial “ProGIT”, starting from 09. January 2012 until end of the study.
Curriculum vitae
Date of Birth: 17th September 1984
Position at study time: Assistant Doctor, Department of Dermatology and Allergology, Charité – Universitätsmedizin Berlin, Germany; current position Dermatologist, Hamburg
Medical Graduation and/or Other Professional Training:
11/2012 - Doctoral thesis at Heinrich-Heine-Universität, Düsseldorf
2011 - Special training: Investigator in clinical trials; KKS-Charité with certificate Since
2011 - Resident in dermatology and allergology, Charité-Universitätsmedizin Berlin
2011 Medical graduation at Heinrich Heine University, Düsseldorf (Approbation)
Experience in Controlled Clinical Trials:
Started as sub-investigator in October 2011 (atopic dermatitis, autoimmune disease, immunotherapy)
Regular ICH-GCP training (internal bi-weekly, training with certificate at least twice a year)

Dr. med. Katharina Sophie Wylon, is sub-investigator and representative of Guido Heine in the clinical trial "ProGIT" , starting from October 2012 until end of the study.
Curriculum vitae
Date of Birth: 20th July 1984
Present Position: Assistant Doctor, Department of Dermatology and Allergology, Charité – Universitätsmedizin Berlin, Germany
Medical Graduation and/or Other Professional Training:
2015 Doctor's degree, Charité – Universitätsmedizin Berlin
2012 Resident at Dpt. of dermatology, Charité, Berlin
2012 Special training: Investigator in clinical studies; KKS-Charité, Berlin
2010-2012 - Foundation Programme Year I + II, Glasgow, UK
2010 Medical Graduation at Universität of Warsaw, Poland
Experience in Controlled Clinical Trials:
Started as sub-investigator in October 2012
Regular ICH-GCP training (internal bi-weekly, training with certificate at least twice a year)

Dr. med. Dirk Tomsitz, is sub-investigator and representative of Guido Heine in the clinical trial "ProGIT" , starting from February 2012 until September 2014.
Curriculum vitae
Date of Birth: 27th November 1985
Position at study time: Assistant Doctor, Department of Dermatology and Allergology, Charité – Universitätsmedizin Berlin, Germany; current position Dermatologist, Munich
Medical Graduation and/or Other Professional Training
2012-2014 Resident in dermatology and allergology at Charité, Berlin
02/2012 Special training: Investigator in clinical studies with ICH-GCP training; KKS-Charité
11/2011 Medical graduation and licence (Approbation) at Johannes Gutenberg Universität Mainz
Experience in Controlled Clinical Trials
Since 2012 sub-investigator in clinical trials (atopic dermatitis, autoimmune disease, immunotherapy)
Regular ICH-GCP training (internal bi-weekly, training with certificate at least twice a year)

Ariane Lungwitz, study nurse
Curriculum vitae
Date of Birth: 09th November 1978
Present position: Study nurse, Scientific assistant; Department of Dermatology and Allergology, Charité – Universitätsmedizin Berlin, Germany
Professional Training
since 09/2008 Study nurse at study unit Prof. Worm, Charité - Universitätsmedizin Berlin
04/2004 Study nurse seminar GlaxoSmithKline with ICH-GCP training
2004 - 2005 Study nurse & study coordinator at ClinGuard GmbH, with ICH-GCP training
2001 - 2004 Trainee as doctors assistant at medical practice Dr. Thiele, Berlin
Experience in Controlled Clinical Trials:
Experiences in about 40 controlled clinical trials phase II-III since 2004, e.g. asthma, COPD, rhinitis, specific immunotherapy, atopic dermatitis, Lupus erythematodes
Regular ICH-GCP training (internal bi-weekly, training with certificate at least twice a year)

Nora Schumacher, study assistant from start of the study until November 2013.
Curriculum vitae
Date of Birth: 31th January 1989
Present position: Medical Student; Department of Dermatology and Allergology, Charité – Universitätsmedizin Berlin, Germany

Professional Training
2011/12 Assistant for Guido Heine
since 2008 Student of Human Medicine, Charité - Universitätsmedizin Berlin

15.1.5 Sample of labels for the trial medication

ZUR KLINISCHEN PRÜFUNG BESTIMMT
Sponsor: Charité – Universitätsmedizin Berlin Allergie-Centrum Charitéplatz 1 10117 Berlin
LKP: Prof. Dr. M. Worm Tel. 030 450 518105
EudraCT-Nr. 2010-021775-80 Prüfplancode: ProGIT
Random Nr.: 000
PID: _____
Lösung zum Einnehmen Inhalt: 10 ml
1 ml Lösung enthält Colecalciferol (Vitamin D3) 20.000 I.E oder Placebo
Dosierung: nach Anweisung durch den Prüfarzt
Ch.-B: GI-LP/00 Verwendbar bis: 00.00.0000
Flasche dicht verschlossen und vor Licht geschützt aufbewahren. Nicht über 30°C lagern. Für Kinder unzugänglich aufbewahren.
CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN Apotheke I Augustenburger Platz 1 I 13353 Berlin I 030-450 56 11 04

15.1.6 Randomization scheme and codes (subject identification and treatment assigned

R.-No	Assignment	Assigned
1	verum	yes
2	placebo	yes
3	verum	yes
4	placebo	yes
5	placebo	yes
6	placebo	yes
7	verum	yes
8	verum	yes
9	verum	yes
10	placebo	yes
11	placebo	yes
12	verum	yes
13	placebo	yes
14	verum	yes
15	placebo	yes
16	verum	yes
17	verum	yes
18	placebo	yes
19	placebo	yes
20	verum	yes
21	verum	yes
22	verum	yes
23	placebo	yes
24	placebo	yes
25	verum	yes
26	placebo	yes

27	verum	yes
28	placebo	yes
29	placebo	yes
30	verum	yes
31	placebo	yes
32	verum	yes
33	placebo	yes
34	verum	yes
35	placebo	yes
36	verum	yes
37	verum	no
38	verum	no
39	placebo	no
40	placebo	no
41	verum	no
42	placebo	no
43	verum	no

15.1.7 Publications based on the study

A manuscript is in preparation.

15.1.8 Documentation of statistical methods

The statistical analysis plan is enclosed in the TMF section11.2.

15.2 Subject listing

15.2.1 Discontinued subjects

Table 0.1 Listing of subjects who gave informed consent but could not be randomised (screening failure).

S.-No.	R.-No.	Age (years)	Sex	Observation excluded	Date	Reason(s)
S1	No randomisation	26	m	Screening	14.10.2011	EC (withdraw consent)
S10	No randomisation	50	m	Screening	26.10.2011	EC (sIgE<CAP2)
S12	No randomisation	35	f	Screening	27.10.2011	EC (25Vit.D > 80 nmol/L)
S13	No randomisation	48	m	Screening	31.10.2011	EC (withdraw consent)
S16	No randomisation	22	m	Screening	01.11.2011	EC (sIgE<CAP2)
S17	No randomisation	22	w	Screening	01.11.2011	EC (withdraw consent)
S24	No randomisation	22	w	Screening	11.11.2011	EC (withdraw consent)
S25	No randomisation	29	w	Screening	14.11.2011	EC (withdraw consent)
S27	No randomisation	29	m	Screening	16.11.2011	EC (autoimmunity)
S28	No randomisation	49	m	Screening	1611.2011	EC (banned drug intake)
S32	No randomisation	20	w	Screening	17.11.2011	EC (25Vit.D > 80 nmol/L)
S33	No randomisation	34	m	Screening	22.11.2011	IC (treatment benefit unclear)
S36	No randomisation	30	m	Screening	25.11.2011	EC (sIgE<CAP2)
S41	No randomisation	29	w	Screening	06.12.2011	EC (25Vit.D > 80 nmol/L)
S47	No randomisation	52	w	Screening	02.01.2012	EC (sIgE<CAP2)
S50	No randomisation	27	w	Screening	04.01.2011	EC (sIgE<CAP2)

S.-No. = Screening number, R.-No. = Random number, f = female m = male, EC – exclusion criteria, IC – inclusion criteria
S42 was not assigned

15.2.2 Intend-to-treat and Per-Protocol population

Table 15.2.2.1 A Listing of subjects who dropped out after randomisation.

R.-No.	Age (years)	Sex	Date of drop out	Reason(s)
R2	31	m	23.10.2013	withdraw consent (occupational move from Berlin)
R4	19	m	13.12.2013	withdraw consent (occupational; new Job)
R6	22	m	05.03.2013	compliance (lost to follow up)
R7	25	m	29.11.2012	withdraw consent (occupational moving, compliance)
R10	25	f	27.01.2015	compliance (lost to follow up)
R12	39	m	08.12.2012	compliance (lost to follow up)
R16	26	m	13.12.2011	uncontrolled asthma, treatment not started
R18	24	m	29.04.2013	banned drugs, withdraw consent
R20	53	m	13.11.2012	pregnancy
R25	33	m	27.01.2015	compliance (lost to follow up)
R26	27	m	27.01.2015	withdraw consent (occupational move from Berlin)
R34	32	m	10.12.2012	withdraw consent (occupational move from Berlin)
R35	26	f	06.01.2014	withdraw consent (occupational, compliance)

*The study team tried several times to approach the patient via e-mail and telephone, unsuccessfully.

15.2.3 Individual primary efficacy criterion (listing)

Table 0.3 Wheal size upon intracutaneous testwith 500 SBU grass pollen. Data shown in mm. Patients identified by randomization number, missing values were not determined (all due to drop out).

P-No	SCR 500 SBU	V1-11 500 SBU	V2-11 500 SBU	V3-11 500 SBU	FU 500 SBU
1	10.0	15.0	15.0	13.5	12.0
2	12.5	10.0	9.5		
3	21.0	13.0	13.0	12.0	17.0
4	16.0	18.5	14.0		
5	18.5	12.0	17.0	16.0	19.5
6	16.5	13.5			
7	12.0	11.0			
8	20.5	16.5	18.0	18.0	19.0
9	21.0	16.5	14.5	11.5	19.0
10	18.0	13.0	6.5	13.5	
11	20.0	15.0	14.0	11.0	20.5
12	16.0	10.0			
13	25.0	23.5	14.0	12.5	18.5
14	9.0	11.5	7.0	10.0	10.0
15	16.0	8.0	17.0	13.0	17.5
16	15.0				
17	17.5	9.0	11.0	16.0	18.0
18	22.5	13.5			
19	12.5	10.5	16.0	13.5	14.0
20	15.5	17.0			
21	12.5	0.0	16.0	11.0	20.0
22	19.5	13.0	17.5	17.5	13.0
23	16.0	11.0	21.0	10.0	18.0
24	14.5	10.0	10.0	13.5	23.0
25	17.0	15.5	17.5	15.0	
26	14.0	14.0			
27	23.0	18.0	22.0	14.0	15.0
28	22.5	9.0	15.0	17.5	18.0
29	15.0	15.0	18.0	16.0	17.0
30	16.5	14.0	20.0	15.0	7.0
31	16.5	15.0	11.5	17.0	18.0
32	17.0	24.5	26.0	16.0	20.0
33	16.5	16.5	19.0	12.0	16.0
34	11.5	18.5			
35	14.5	12.0			
36	22.0	9.0	16.0		

15.2.4 Individual secondary efficacy criteria (listing)

Table 15.2.4.1 Individual specific intracutaneous test reaction to 500 SBU grass pollen over time. P-No = randomized patient number, Scr=Screening, V=visit, red=vitamin D group, blue=placebo group, missing values were not determined (all due to drop out).

P-No	SCR	V1-11	V2-11	V3-11	FU	
1	10,0	15,0	15,0	13,5	12,0	v
2	12,5	10,0	9,5			p
3	21,0	13,0	13,0	12,0	17,0	v
4	16,0	18,5	14,0			p
5	18,5	12,0	17,0	16,0	19,5	p
6	16,5	13,5				p
7	12,0	11,0				v
8	20,5	16,5	18,0	18,0	19,0	v
9	21,0	16,5	14,5	11,5	19,0	v
10	18,0	13,0	6,5	13,5		p
11	20,0	15,0	14,0	11,0	20,5	p
12	16,0	10,0				v
13	25,0	23,5	14,0	12,5	18,5	p
14	9,0	11,5	7,0	10,0	10,0	v
15	16,0	8,0	17,0	13,0	17,5	p
16	15,0					v
17	17,5	9,0	11,0	16,0	18,0	v
18	22,5	13,5				p
19	12,5	10,5	16,0	13,5	14,0	p
20	15,5	17,0				v
21	12,5	0,0	16,0	11,0	20,0	v
22	19,5	13,0	17,5	17,5	13,0	v
23	16,0	11,0	21,0	10,0	18,0	p
24	14,5	10,0	10,0	13,5	23,0	p
25	17,0	15,5	17,5	15,0		v
26	14,0	14,0				p
27	23,0	18,0	22,0	14,0	15,0	v
28	22,5	9,0	15,0	17,5	18,0	p
29	15,0	15,0	18,0	16,0	17,0	p
30	16,5	14,0	20,0	15,0	7,0	v
31	16,5	15,0	11,5	17,0	18,0	p
32	17,0	24,5	26,0	16,0	20,0	v
33	16,5	16,5	19,0	12,0	16,0	p
34	11,5	18,5				v
35	14,5	12,0				p
36	22,0	9,0	16,0			v

Table 15.2.4.2 Individual specific titrated intracutaneous test reaction (area under the curve) to grass pollen over time. P-No = randomized patient number, Scr=Screening, V=visit, FU=follow up, red=vitamin D group, blue=placebo group, missing values were not determined (all due to drop out).

P-No	SCR	V1-11	V2-1	V2-11	V3-1	V3-11	FU	group
1	5642	6852	7335	6518	7463	6391	5898	v
2	4941	3983	6768	2138				p
3	7479	5994	6210	5276	6323	4433	7208	v
4	7519	7953	9225	6071	7218			p
5	5895	4680	2925	3825	3308	3600	7952	p
6	8568	6775						p
7	4622	4876						v
8	7781	6064	4635	5411	7884	6525	9038	v
9	9235	6262	7020	4995	5310	2588	9357	v
10	5585	6093	4703	1463	3240	5686		p
11	8547	7149	9290	4140	6480	3960	8078	p
12	6917	2250						v
13	9849	9842	8998	3893	5477	2813	6390	p
14	4352	4419	6311	1576	4500	2250	5715	v
15	8263	3941	5974	7290	6498	5400	8146	p
16								v
17	10177	3918	6931	3465	5603	7065	7763	v
18	8859	5933	8550					p
19	5710	4466	7280	6694	5452	5389	6764	p
20	7427	7711						v
21	4966	0	7018	7189	4613	3713	8939	v
22	7699	6368	5625	7650	3861	3938	4658	v
23	6545	5297	10550	8759	4118	2993	4050	p
24	6451	4601	6345	3983	5063	4275	9754	p
25	7074	7398	6199	6536	5108	3375		v
26	5625	5613	9150					p
27	8813	8134	7616	5816	4500	6541	6098	v
28	9383	3795	6919	4736	4523	5670	7738	p
29	7437	5999	8267	7651	4365	5951	5805	p
30	6311	5699	3983	6480	6030	4118	3060	v
31	6485	5603	10373	5657	6030	5681	7664	p
32	7033	9778	8708	11097	8537	7139	8064	v
33	6435	6559	6011	6008	4635	4680	5580	p
34	4785	7405						v
35	6084	4680						p
36	7178	3263	4050	4343	3488			v

Table 15.2.4.3 Individual specific titrated conjunctival test reaction (area under the curve) to grass pollen over time. P-No = randomized patient number, Scr=Screening, V=visit, FU=follow up, red=vitamin D group, blue=placebo group, missing values were not determined (all due to drop out).

Pati-ent-No	SCR	V1-11	V2-11	V3-11	FU	
1	8,4E-05	3,2E-05	8,4E-06	1,1E-05	6,6E-06	v
2	6,6E-06	3,6E-06	3,3E-06			p
3	3,4E-05	9,2E-06	3,3E-05	3,3E-05	8,8E-06	v
4	3,5E-04	9,6E-06	8,5E-06			p
5	2,8E-06	1,1E-05	2,4E-06	3,2E-06	2,7E-06	p
6						p
7						v
8	3,3E-05	3,0E-05	1,1E-05	8,5E-06	1,1E-05	v
9	7,9E-06	3,9E-06	3,3E-06	2,5E-06	2,6E-06	v
10	1,1E-04	2,4E-05	3,4E-06	3,9E-06		p
11	1,3E-04	3,2E-05	2,6E-06	1,1E-05	3,6E-06	p
12						v
13	3,4E-05	2,7E-05	2,3E-06	2,6E-06	3,9E-06	p
14	2,7E-04	1,1E-04	3,6E-06	4,2E-05	1,2E-05	v
15	2,2E-05	2,9E-05	1,0E-05	9,5E-06	2,5E-06	p
16						v
17	8,9E-06	8,1E-06	3,2E-06	3,9E-06	3,4E-06	v
18	2,9E-05	1,3E-05				p
19	3,3E-05	8,2E-05	3,0E-05	2,7E-05	1,0E-05	p
20						v
21	3,6E-05	3,0E-05	2,4E-06	3,7E-05	3,7E-05	v
22	9,0E-06	8,5E-05	2,9E-06	3,0E-06	2,6E-06	v
23	1,3E-04	7,6E-06	1,0E-05	2,8E-05	2,3E-05	p
24	3,2E-05	3,9E-05	1,2E-05	2,5E-06	2,2E-06	p
25	9,2E-05	2,0E-05	7,1E-06	2,9E-06		v
26	2,7E-05	3,9E-06				p
27	8,1E-06	7,9E-06	1,3E-05	1,3E-05	8,1E-06	v
28	2,7E-06	2,1E-06	2,4E-06	3,7E-06	3,5E-06	p
29	2,8E-05	1,1E-05	3,5E-06	2,7E-06	3,0E-06	p
30	3,3E-05	3,3E-05	7,6E-06	8,5E-06	1,2E-05	v
31	3,3E-05	7,7E-05	2,8E-05	9,0E-06		p
32	7,2E-05	9,7E-05	3,3E-05	1,0E-05	7,5E-05	v
33	8,2E-06	3,2E-06	3,3E-06	3,5E-06	2,9E-06	p
34	8,5E-06	2,6E-06				v
35	9,6E-06	7,9E-06	7,9E-06			p
36	8,1E-06	2,7E-06	2,7E-06			v

Table 15.2.4.4 Individual retrospective symptom score over time. P-No = randomized patient number, Scr=Screening, V=visit, FU=follow up, red=vitamin D group, blue=placebo group, missing values were not determined (all due to drop out).

#	mRSS_SCR				
P-No	SCR	V2-1	V3-1	FU	
1	16	10	15	12	v
2	14	1	2		p
3	17	11	7	12	v
4	17	0	0		p
5	14	7	0	6	p
6	21	21			p
7	20	21			v
8	21	4	2	4	v
9	15	3	8	9	v
10	16	2	11		p
11	15	5	3	7	p
12	16				v
13	14	7	9	8	p
14	22	13	12	18	v
15	20	5	17	8	p
16	12				v
17	21	6	16	4	v
18	22	7			p
19	15	11	16	6	p
20	21	9			v
21	22	15	25	21	v
22	16	0	14	14	v
23	21	13	11	15	p
24	16	11	12	10	p
25	25	12	12		v
26	13	11			p
27	12	7	12	3	v
28	14	7	10	11	p
29	23	13	12	15	p
30	21	18	22	20	v
31	19	13	21	20	p
32	19	7	11	13	v
33	19	10	0	11	p
34	13	9			v
35	13				p
36	15	14	9		v

Table 15.2.4.5 Individual season symptom score over time. P-No = randomized patient number, Scr=Screening, V=visit, FU=follow up, red=vitamin D group, blue=placebo group, missing values were not determined (all due to drop out).

P-No	2012	2013	2014	
1	3	3	3	v
2	2	2		p
3	2	2	2	v
4	1	1		p
5	3	2	2	p
6	2			p
7	2			v
8	2	2	1	v
9	3	3	2	v
10	2	2		p
11	3	2	2	p
12				v
13	2	3	2	p
14	2	2	2	v
15	2	2	2	p
16				v
17	1	1	1	v
18	3			p
19	3	3	2	p
20	3			v
21	2	2	3	v
22	1	3	2	v
23	2	2	1	p
24	3	3	2	p
25	3	2		v
26	4			p
27	3	3	2	v
28	3	3	2	p
29	2	2	3	p
30	3	3	3	v
31	3	3	3	p
32	3	2	2	v
33	2	2	2	p
34	3			v
35				p
36	2	2		v

Table 15.2.4.6 Individual grass-skin prick test over time. P-No = randomized patient number, Scr=Screening, V=visit, FU=follow up, red=vitamin D group, blue=placebo group, missing values were not determined (all due to drop out).

	SCR		V1-10		V2-1		V2-10		V3-1		V3-10		FU		
P-No	hist	grass	hist	grass	hist	grass	hist	grass	hist	grass	hist	grass	hist	grass	
1	3,0	7,0	3,0	4,5	4	6,5	4,0	5,0	4	6	4,0	7,5	4	6	v
2	3,5	4,5	3,5	4,5	4	7	4,0	5,0	3	6					p
3	3,0	9,0	3,0	6,0	4	6	3,5	4,5	4	8	4,0	5,0	4	8	v
4	2,0	9,0	3,0	6,0	5	9,5	5,0	7,0	4	5					p
5	4,0	6,0	3,0	6,5	5	7	5,0	8,0	4	8,5	4,0	6,0	4	6,5	p
6	3,0	5,5	3,0	4,5	4	7,5									p
7	4,0	8,0	3,0	3,5	4	9									v
8	5,0	7	3,0	6,5	4	6	4,0	6,0	3	6	3,0	4,5	4	5	v
9	2,0	5,5	4,0	6,0	5	7,5	4,5	7,5	4	7	4,0	5,0	4	9	v
10	2,0	6,0	3,0	4,0	4	7,5	3,5	6,0	4	6	3,0	5,0			p
11	4,0	8,0	3,5	4,5	4	7	4,0	4,5	4	5	4,0	4,0	7	9	p
12	4,0	8,0	4,0	4,0											v
13	4,0	10,0	4,0	7,0	4	7	4,0	6,5	4	12	4,0	6,0	4	6	p
14	4,0	7,0	3,0	3,5	4	5	6,0	5,0	4	4	4,0	6,0	4	4	v
15	5,0	8,0	3,0	6,0	5	6	6,0	10,0	3	4	4,0	8,0	4	6	p
16	5,0	7,5													v
17	3,0	9,0	4,0	5,5	4	9,5	4,0	5,0	5	9	4,0	5,0	4	6	v
18	5,0	13,0	3,0	5,5	6	8									p
19	4,0	9,5	2,5	5,0	4	7,5	5,0	11,0	4	5	4,0	7,0	4	4	p
20	4,0	6,5	3,5	3,0											v
21	4,0	6,5	4,5	6,5	7	8	5,0	7,0	4	7	5,0	5,5	4	7	v
22	2,0	5,0	3,5	3,5	5	3	6,0	4,0	4	6	4,0	7,5	4	6,5	v
23	2,0	7,0	3,0	6,0	4	6	4,0	8,5	4	6	4,5	7,5	7	4	p
24	2,0	5,5	3,5	4,0	5	6	4,0	4,5	3	5	4,0	4,0	4	6	p
25	3,0	15,0	5,0	6,0	4	6	4,0	7,0	4	6	4,0	9,0			v
26	4,0	10,0	4,0	5,0	3	5									p
27	2,0	15,0	5,5	7,0	4	7	7,0	11,0	4	6,5	4,0	6,0	4,5	10,5	v
28	4,0	11,5	3,0	4,5	4	10	4,0	8,5	4,5	6,5	4,0	6,0	4	9	p
29	5,0	10,0	3,0	6,5	4	8	4,0	8,0	4	7	4,0	3,5	4	8,5	p
30	6,0	8,0	3,0	2,5	4	6,5	4,0	7,0	4	8	4,0	9,0	4	8	v
31	6,0	19,0	4,0	8,5	4	7	5,0	10,5	4	4	4,5	5,5	4	7,5	p
32	7,0	10,5	4,0	3,5	5	11,5	4,5	7,5	4	6	4,0	6,0	4	12	v
33	5,0	11,0	3,5	6,0	3	10	4,0	7,0	4	8,5	4,0	5,0	6	8	p
34	5,0	10,0	3,5	5,5	5	4									v
35	4,0	6,0	4,0	3,5											p
36	4,0	8,5	3,0	5,5	4	5	4,0	6,0	4	5,5					v

15.2.5 Individual safety data listings

Table 15.2.5.1 Individual compliance parameters (25(OH)D) over time. P-No = randomized patient number, Scr=Screening, V=visit, red=vitamin D group, blue=placebo group, missing values were not determined (all due to drop out).

P-No.	Scr	V1-5	V1-10	V2-1	V2-5	V2-10	V3-1	V3-5	V3-10	
1	49.6	105.2	170.1	59.8	99.8	189	94.5	120	150	v
2	12.5	12.5	20.6	16	24	15.2	27			p
3	32.2	109.9	169.2	74.7	114	114.6	67.7	97.1		v
4	38.4	12.5	25.9	44.7	36.1	27.8	25.2			p
5	32.5	12.5	22.9	38.4	35.6	26.2	44.5	35.8	35.3	p
6	46.8	12.5	41.9	36.6	26.4					p
7	47.5	83.8	115.5	72.6						v
8	33.1	151.9	222.7	102.6	134.6	198.9	109.4	133.8	226.6	v
9	45.8	79.9	102.3	60.5	87.7	110.7	61.2	92.2	123.6	v
10	37.3	12.5	18.4	31.4	22.2	24.2	47.6	24.2	23	p
11	41.4	12.5	35	47.3	35.7	32.7	80.5	61	71.7	p
12	39	95.1	107.8							v
13	57.7	42.4	48.9	55.5	42.1	39.7	46.6	35	21.4	p
14	12.5	79	117.4	58.2	97.7	169.9	54.3	99.1	124.7	v
15	55.7	53.4	66.7	72.9	62	63	71	54.2	65.4	p
16										v
17	44.5	98.9	125.7	73.3	92.8	145.2	82.7	87.3	130.1	v
18	51.6	39	49.7	114	92.6					p
19	49.3	12.5	32.5	42.2	37.9	30.6	53.2	33.3	36.9	p
20	65.1	139	179.4	80.4						v
21	52.4	83.7	114.9	80.9	93.3	131.6	89.9	105.1	152.1	v
22	58.7	119.6	196.2	86.8	149.8	203.8	110.3	136.9	166.9	v
23	68	43.5	56.8	85.7	64.8	44.6	68.2	59.2	56.6	p
24	52.2	45.7	43.2	60.9	51	50.7	56.8	52.2	106	p
25	41.5	79	93.7	62.2	97	105	81.1	70.1	76.7	v
26	12.5	12.5	16.9	18.3						p
27	43.6	85.6	118.9	71.2	101.1	146.5	98.4	105.6	128.2	v
28	36.3	12.5	35.1	30.1	24.3	32	27.8	40	41.2	p
29	42.2	55.8	44.3	66.7	53.6	39.9	63.4	42.1	60.7	p
30	12.5	89.9	87.9	80.2	109.6	167.7	96.2	108.6	117	v
31	50	41.1	62.2	57	50.5	44.5	77	71.5	62.3	p
32	12.5	73.8	149.2	55.3	110.5	154.7	71.4	100.2	159.6	v
33	37.5	37.7	55.3	55.5	53.1	40.6	94.3	70	60.7	p
34	45.7	96.6	143.7	80.3						v
35	29	24.3	23.5	29	24.3	23.5				p
36	50.9	69.9	75.4	73.3	83	62.2				v

Table 15.2.5.2 Individual safety parameters (serum-calcium) over time. P-No = randomized patient number, V=visit, red=vitamin D group, blue=placebo group, missing values were not determined (all due to drop out). Values in mmol/l.

P-No	V1-1	V1-5	V1-10	V2-1	V2-5	V2-10	V3-1	V3-5	V3-10	
1	2,38	2,3	2,2	2,34	2,33	2,27	2,21	2,12	2,29	v
2	2,2	2,29	2,25	2,25	2,26	2,24	2,17			p
3	2,43	2,48	2,32	2,45	2,4	2,42	2,39	2,34	2,36	v
4	2,42	2,27	2,3	2,22	2,35	2,19	2,26			p
5	2,36	2,26	2,29	2,32	2,31	2,25	2,29	2,4	2,32	p
6	2,35	2,41	2,31	2,38	2,25					p
7	2,38	2,4	2,34	2,32						v
8	2,31	2,28	2,38	2,4	2,34	2,36	2,29	2,27	2,35	v
9	2,29	2,37	2,38	2,35	2,36	2,31	2,41	2,33	2,36	v
10	2,37	2,21	2,34	2,24	2,38	2,39	2,3	2,26	2,32	p
11	2,29	2,28	2,16	2,13	2,17	2,21	2,1	2,27	2,23	p
12	2,45	2,31	2,38							v
13	2,4	2,39	2,46	2,48	2,39	2,43	2,37	2,32	2,4	p
14	2,2	2,24	2,14	2,3	2,24	2,29	2,24	2,29	2,18	v
15	2,27	2,32	2,4	2,26	2,32	2,35	2,3	2,43	2,27	p
16	2,4									v
17	2,33	2,41	2,37	2,37	2,33	2,31	2,34	2,44	2,24	v
18	2,35	2,34	2,46	2,45	2,27					p
19	2,45	2,45	2,42	2,5	2,36	2,42	2,38	2,44	2,41	p
20	2,33	2,33	2,29	2,24						v
21	2,38	2,3	2,26	2,33	2,44	2,3	2,47	2,16	2,33	v
22	2,43	2,35	2,24	2,35	2,35	2,35	2,2	2,31	2,43	v
23	2,49	2,36	2,44	2,36	2,38	2,29	2,17	2,37	2,38	p
24	2,31	2,33	2,35	2,41	2,33	2,27	2,32	2,37	2,3	p
25	2,44	2,44	2,47	2,46	2,43	2,43	2,49	2,49	2,41	v
26	2,45	2,3	2,42	2,44						p
27	2,22	2,39	2,4	2,31	2,29	2,27	2,26	2,36	2,35	v
28	2,34	2,29	2,26	2,33	2,21	2,24	2,26	2,34	2,24	p
29	2,43	2,42	2,29	2,42	2,37	2,29	2,28	2,49	2,39	p
30	n.d.	2,18	2,2	2,28	2,2	2,2	2,17	2,14	2,27	v
31	2,36	2,36	2,18	2,27	2,36	2,25	2,2	2,41	2,27	p
32	n.d.	2,29	2,21	2,29	2,18	2,23	2,29	2,28	2,28	v
33	n.d.	2,47	2,25	2,29	2,26	2,27	2,3	2,3	2,35	p
34	2,32	2,34	2,26	2,35						v
35	2,28	2,2	2,28							p
36	2,29	2,26	2,22	2,43	2,24	2,18	2,18			v

Table 15.2.5.3 Individual safety parameters (serum-phosphorus) over time. P-No = randomized patient number, V=visit, red=vitamin D group, blue=placebo group, missing values were not determined (all due to drop out). Values in mmol/l.

P-No	V1-1	V1-5	V1-10	V2-1	V2-5	V2-10	V3-1	V3-5	V3-10	
1	1,03	1,23	1,21	0,9	1,18	1,12	n.d.	n.d.	0,82	v
2	1,09	1,2	1,32	0,91	1,19	1,19	1,16			p
3	0,75	0,88	0,96	0,83	1,04	1,08	n.d.	0,96	1	v
4	1,05	1,33	1,3	0,98	1,32	n.d.	1,09			p
5	0,72	0,76	0,8	0,75	0,86	0,71	n.d.	0,63	1,05	p
6	1,23	1,24	0,96	0,8	0,97					p
7	1,3	1,17	0,88	1,06						v
8	0,98	0,85	0,86	1	1,21	1,27	1,04	n.d.	1,14	v
9	0,76	1,09	0,88	0,76	0,81	0,91	1,01	0,82	0,78	v
10	1,08	1,11	1,36	0,98	0,8	1,13	n.d.	0,97	1,01	p
11	1,12	0,96	0,81	1,02	0,74	0,65	n.d.	0,83	0,72	p
12	0,89	1,09	0,95							v
13	0,6	0,76	1,68	0,89	1,22	0,83	n.d.	0,86	0,67	p
14	0,88	1,12	1,19	1,19	1,23	0,95	n.d.	1,33	1,16	v
15	1,01	1,11	1,15	1,05	0,95	1,12	n.d.	n.d.	1,18	p
16	0,84									v
17	1,03	1,04	1,12	1,1	1	1,16	n.d.	1,24	1,01	v
18	0,88	1,15	1,09	1,18	1,16					p
19	1,13	0,85	1	1,24	1,41	1,02	n.d.	1,27	0,97	p
20	1,01	1,32	1,24	0,91						v
21	0,99	0,86	1,08	0,87	1,17	1,06	n.d.	0,96	1,08	v
22	1,05	1,11	1,15	1,15	1,24	1,1	n.d.	n.d.	1,03	v
23	0,94	0,98	1,21	1,08	1,13	0,97	n.d.	1,02	1,18	p
24	1,33	0,96	1,14	1,35	1,19	1,3	n.d.	1,37	1,18	p
25	0,99	0,96	0,83	1,07	1,2	1,27	n.d.	0,98	1,04	v
26	1,02	0,89	1,12	1,07						p
27	1,14	0,96	0,92	1,21	1,28	1,33	n.d.	1,27	0,86	v
28	0,73	0,72	0,66	0,74	0,88	0,83	n.d.	0,73	0,64	p
29	0,85	0,9	0,82	1,07	0,92	0,74	n.d.	0,79	0,91	p
30	n.d.	1,1	0,95	1,01	1,11	0,96	n.d.	0,96	1	v
31	0,76	1,04	0,98	0,82	0,84	0,84	n.d.	1,19	1	p
32	n.d.	1,12	0,89	1,06	1,05	1,11	n.d.	0,88	1,03	v
33	n.d.	0,57	0,7	0,69	0,77	0,89	n.d.	0,84	0,85	p
34	0,84	0,83	1,01	0,94						v
35	0,87	1,29	0,89							p
36	0,72	1,23	0,86	n.d.	1,01	1,26	0,82			v

Table 15.2.5.4 Individual safety parameters (serum-creatinine) over time. P-No = randomized patient number, V=visit, red=vitamin D group, blue=placebo group, missing values were not determined (all due to drop out). Values in mg/dl.

P-No	V1-1	V1-5	V1-10	V2-1	V2-5	V2-10	V3-1	V3-5	V3-10	
1	0,9	0,84	0,73	0,83	0,79	0,82	0,83	0,84	0,84	v
2	0,82	0,96	0,78	0,93	0,96	0,92	0,87			p
3	1,04	0,92	0,97	0,99	0,95	0,83	0,78	0,74	0,81	v
4	0,87	0,79	0,75	0,73	0,81	0,76	0,76			p
5	0,91	0,93	0,95	0,89	0,97	0,89	0,92	0,93	0,99	p
6	0,84	0,77	0,76	0,85	0,8					p
7	1,18	0,98	0,9	0,97						v
8	0,812	0,76	0,75	0,78	0,81	0,8	0,69	0,74	0,88	v
9	0,76	0,78	0,83	0,71	0,84	0,85	0,75	0,9	0,88	v
10	0,83	0,73	0,76	0,8	0,77	0,88	0,83	0,83	0,76	p
11	0,78	0,7	0,76	0,72	0,93	0,87	0,81	0,84	1,01	p
12	0,85	0,83	0,88							v
13	0,9	0,78	0,88	0,8	0,79	0,76	0,75	0,75	0,8	p
14	0,74	0,74	0,7	0,74	0,75	0,71	0,65	0,65	0,67	v
15	0,72	0,78	0,8	0,74	0,83	0,73	0,77	0,71	0,77	p
16	0,88									v
17	0,67	0,66	0,67	0,94	0,81	0,66	0,85	1,2	0,76	v
18	0,92	0,81	0,92	0,79	0,75					p
19	0,86	0,89	0,8	0,88	0,82	0,82	0,9	0,85	0,91	p
20	0,76	0,84	0,8	0,61						v
21	1,07	1,09	1,04	1,07	1,02	1,12	1,62	1,08	1,15	v
22	0,91	0,95	0,89	0,84	0,89	0,94	0,86	1,02	1,09	v
23	0,64	0,56	0,66	0,66	0,73	0,56	0,71	0,62	0,68	p
24	0,69	0,74	0,81	0,91	0,78	0,83	0,85	0,85	0,87	p
25	0,77	0,77	0,81	1	1,07	0,96	0,95	0,82	0,94	v
26	0,86	0,8	0,86	0,75						p
27	0,94	0,83	0,95	0,9	0,93	1,02	0,86	0,91	1,01	v
28	0,58	0,64	0,65	0,58	0,57	0,65	0,67	0,66	0,72	p
29	0,8	1	0,97	0,93	1,02	0,87	0,98	0,98	1,05	p
30	0,69	0,69	0,76	0,72	0,71	0,71	0,78	0,62	0,65	v
31	1,06	1,06	0,91	1,01	0,94	0,94	0,91	1,01	0,65	p
32	0,84	0,91	0,94	0,83	0,71	0,98	0,81	0,96	0,98	v
33	0,88	0,97	0,92	0,9	0,84	0,87	0,83	0,84	0,85	p
34	0,96	0,84	1,02	0,93						v
35	0,85	0,87	0,97							p
36	0,73	0,87	0,86	0,95	0,82	3,71	0,86			v

Table 15.2.5.5 Individual safety parameters (blood-leucocytes) over time. P-No = randomized patient number, V=visit, red=vitamin D group, blue=placebo group, missing values were not determined (all due to drop out). Values in cells per nl.

P-No	V1-1	V1-5	V1-10	V2-1	V2-5	V2-10	V3-1	V3-5	V3-10
1	5,16	n.d.	4,45	6,38	4,67	4,16	6,2	5,89	6,13
2	4,14	n.d.	4,04	4,31	7,79	5,85	4,79		
3	5,15	5,69	5,57	5,57	6,18	6,87	n.d.	4,87	5,64
4	3,91	3,99	3,62	2,87	4,48	5,28	3,62		
5	3,74	4,06	4,67	4,58	4,91	4,82	4,7	4,2	5,57
6	6,99	4,74	4,88	4,82	7,06				
7	5,92	6,28	3,24	3,81					
8	7,9	5,63	5,83	8,79	9,2	7,41	8,69	8,01	9
9	7,5	5,35	5,92	5,81	5,39	5	5,98	6,92	5,96
10	8,11	6,25	6,89	7,21	8,34	7,17	4,91	6,57	6,49
11	n.d.	4,99	4,67	5,88	5,84	5,54	6,13	5,35	5,19
12	5,59	5,08	4,71						
13	3,33	3,5	3,55	3,58	6,05	4,61	4,04	4,33	4,1
14	2,4	4,16	4,45	4,56	4,08	4,04	4,41	5,58	4,79
15	4,77	3,65	3,84	3,85	4,37	4,94	4,59	9,3	5,36
16	4,69								
17	8,17	8,29	7,27	7,48	8,09	6,8	6,79	6,66	7,04
18	5,64	7,33	6,48	10,81	9,62				
19	5,47	5,07	6,25	6,31	7,33	5,32	7,16	8,09	5,34
20	5,17	5,29	5,64	10,15					
21	10,26	8,74	7,81	8,48	8,01	7,42	8,41	7,96	8,93
22	4,94	3,7	5,2	4,48	4,73	4,57	4,35	6,06	8,43
23	6	6,85	7,64	8,74	6,36	6,43	6,23	7,67	5,17
24	4,54	4,3	5,18	4,92	5,47	5,61	5,36	5,31	6,31
25	5,62	3,94	3,26	4,06	5,54	3,92	5,16	5,55	5,51
26	5,54	5,22	4,75	4,45					
27	4,99	3,85	5,17	4,89	5,03	4,86	4,77	5,23	6,41
28	6,85	5	5,69	5,92	6,03	5,94	6,25	7,44	5,91
29	4,38	4,44	4,58	6,2	6,61	5,32	9,39	4,87	7,23
30	5,12	6,42	6,49	7,71	6,53	6,72	9,18	7,6	9,86
31	5,56	5,83	10,41	4,85	6,22	5,78	8,81	5,35	9,89
32	6,1	5,35	6,5	6,58	5,99	5,49238	5,53	5,81	4,25
33	6,26	6,56	5,63	4,5	4,23	4,44	4,46	6,55	5,04
34	8	5,68	2,91	5,96					
35	5,83	6,85	5,57						
36	8,11	8,09	5,89	4,96	4,9	7,88	6,01		

15.2.9. Individual demographic and other baseline characteristics

Table 15.2.9.1. Individual demographic characteristics.

P-No	Age (yr)	Sex	Total IgE (kU/L)	sIgE grass (kU/L)	CAP-grass	height (cm)	weight (kg)	BMI	
1	24	female	34	10,0	3	167	60	21,5	v
2	31	male	83	2,1	2	172	61	20,6	p
3	44	male	229	28,4	4	173	72	24,1	v
4	19	male	1636	100,0	6	175	60	19,6	p
5	46	female	103	1,3	2	169	65	22,8	p
6	22	male	97	24,3	4	175	74	24,2	p
7	25	male	393	75,6	5	188	90	25,5	v
8	28	female	63	19,4	4	171	57	19,5	v
9	36	male	531	31,7	4	177	102	32,6	v
10	25	female	39	5,4	3	163	60	22,6	p
11	49	male	177	11,0	3	186	85	24,6	p
12	39	male	16	3,7	3	186	80	23,1	v
13	29	male	71	12,7	3	182	69	20,8	p
14	31	female	36	1,6	2	162	55	21,0	v
15	33	female	291	56,6	5	180	77	23,8	p
16	26	male	530	47,5	4	178	65	20,5	v
17	49	female	435	17,6	4	159	71	28,1	v
18	24	male	146	21,7	4	190	84	23,3	p
19	22	male	650	100,0	6	180	110	34,0	p
20	24	female	82	23,2	4	163	50	18,8	v
21	53	male	413	11,7	3	168	83	29,4	v
22	26	female	59	3,1	2	173	68	22,7	v
23	35	female	74	16,4	3	175	70	22,9	p
24	32	male	100	22,3	4	175	63	20,6	p
25	33	male	86	16,8	3	190	85	23,5	v
26	27	male	54	7,7	3	190	75	20,8	p
27	26	male	101	10,2	3	189	72	20,2	v
28	26	female	429	21,3	4	163	56	21,1	p
29	27	male	668	70,6	5	167	56	20,1	p
30	21	female	23	2,1	2	168	50	17,7	v
31	48	male	151	23,0	4	181	84	25,6	p
32	31	male	611	100,0	6	180	80	24,7	v
33	47	male	130	19,8	4	195	103	27,1	p
34	32	male	53	1,1	2	185	82	24,0	v
35	26	female	nd	3,3	2	168	56	19,8	p
36	34	female	150	4,5	3	160	78	30,5	v

15.2.10. Individual adverse events

Table 15.2.9.1. Individual adverse events.

P-No	AE-no.	Diagnosis	
1	1	Sinusitis	v
1	2	Pharyngitis	v
1	3	Local reaction at SIT-puncture	v
1	4	Respiratory infection	v
1	5	Unspecific abdominal pain	v
1	6	Cystitis	v
1	7	Respiratory infection	v
2	1	Headache	p
2	2	Recurrent Headache	p
2	3	Recurrent Headache	p
2	4	Headache	p
3	1	Worse rhinoconjunctivitis due t	v
3	2	Worse rhinoconjunctivitis due t	v
3	3	Worse rhinoconjunctivitis due t	v
3	4	Respiratory infection	v
4	1	Local reaction at SIT-puncture	p
4	2	Local reaction at SIT-puncture	p
4	3	Respiratory infection	p
5	1	Cold	p
5	2	Cold	p
5	3	Cystitis	p
5	4	Cold	p
5	5	Cold	p
5	6	Cold	p
6	1	Systemic reaction due to SIT	p
7	1	Local reaction at SIT-puncture	v
7	2	Respiratory infection	v
7	3	Cold	v
7	4	Respiratory infect	v
7	5	Gastritis	v
7	6	Local reaction at SIT-puncture	v
8	1	Local reaction at SIT-puncture	v
8	2	Headache	v
8	3	Local reaction at SIT-puncture	v
8	4	Cold	v
8	5	Local reaction at SIT-puncture	v
8	6	Cold	v
10	1	Gastroenteritis	p
11	1	Respiratory infection	p
12	1	Local reaction at SIT-puncture	v
12	2	Hordeolum	v
12	3	Local reaction at SIT-puncture	v
12	4	Headache	v
13	1	Local reaction at SIT-puncture	p
13	2	Local reaction at SIT-puncture	p
14	1	Abdominal pain	v
14	2	Abdominal pain	v
14	3	Abdominal pain	v
14	4	cold	v
14	5	toothache	v
14	6	Cold	v
14	7	pain due to known hernia ingui	v
14	8	pain due to known hernia ingui	v
14	9	toothache	v
14	10	hernia OP (outpatient)	v
15	1	Cold	p
15	2	Respiratory infect	p
15	3	Local respiratory intect	p
15	4	Medial collateral ligament teat	p
15	5	Respiratory infect	p
17	1	Local reaction at SIT-puncture	v
17	2	Systemic reaction due to SIT	v
18	1	Headache	p
18	2	Reactive arthritis knee left	p
19	1	Endoskopy of ankle joint	p
20	1	Local reaction at SIT-puncture	v
20	2	Cold	v
21	1	Respiratory infect	v
21	2	Worse GINA I	v
22	1	Cold	v
22	2	Local reaction at SIT-puncture	v
22	3	Vaginitis	v
22	4	Cold	v
23	1	Local reaction at SIT-puncture	p
23	2	Local reaction at SIT-puncture	p
23	3	local and systemic reaction at	p
24	1	Respiratory infect	p
25	1	Conjunctivitis	v
25	2	Local reaction at SIT-puncture	v
25	3	suspected slipped disk	v
25	4	Cold	v
27	1	Local reaction at SIT-puncture	v
27	2	Respiratory infect	v
27	3	Cold	v
29	1	Local reaction at SIT-puncture	p
29	2	Respiratory infect	p
29	3	Influenzal infection	p
30	1	Systemic reaction due to SIT	v
30	2	Inguinal pain	v
30	3	Cold	v
30	4	Dyspnoea	v
30	5	recurrent headache	v
31	1	Local reaction at SIT-puncture	p
31	2	Respiratory infect	p
31	3	infectionof upper respiratory tra	p
31	4	infectionof upper respiratory tra	p
31	5	Influenzal infection	p
31	6	Cold / Influenzal infection	p
32	1	Local reaction at SIT-puncture	v
32	2	Tonsillitis	v
34	1	Cold	v
34	2	Gastrointestinal infect	v