Clinical trial results:
Explorative Untersuchung zum Einfluss der Vitamin D-vermitteltenr Modulation der initialen subkutanen Gräserpollen-spezifischen Immuntherapie bei Allergikern mit Gräserpollen-induzierter Rhinokonjunktivitis mit/ohne allergischem Asthma

Summary

EudraCT number	2010-021775-80
Trial protocol	DE
Global end of trial date	13 January 2015

Results information

Result version number	v1 (current)
This version publication date	16 September 2021
First version publication date	16 September 2021
Summary attachment (see zip file)	Final_report_ProGIT_2010-021775-80 (CTR_ProGIT_1.1 signed.pdf)

Trial information

Trial identification

Sponsor protocol code	ProGIT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01466465
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Margitta Worm, Charité - Universitätsmedizin Berlin Dpt. of Dermatology Division of Allergy and Immunology, margitta.worm@charite.de
Scientific contact	Margitta Worm, Charité - Universitätsmedizin Berlin Dpt. of Dermatology Division of Allergy and Immunology, margitta.worm@charite.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 January 2015
Global end of trial reached?	Yes
Global end of trial date	13 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is 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.

Protection of trial subjects:

All clinical tests (blood draw, skin prick test, intracutaneous test, conjunctival provocation tests) and therapeutic interventions (immunotherapy injection) were performed according to defined SOPs and clinical standards.
An patient insurance in accordance with the Medicines Act, Section 40, Paragraph 3) was provided for the probands for travel to the study center and for potential therapeutic side effects.
As no specific e.g. painful procedures were performed, no specific procedures were required.

Background therapy:

All participants were grass pollen-allergic and all patients were treated with a regular grass pollen-specific immunotherapy according to the manufacturer's instructions.

Evidence for comparator:

Vitamin D receptors control the IgE class switch in B lymphocytes. Activated immune cells can synthesize the active metabolite of vitamin D, calcitriol, from its precursor. In mice, adjacent vitamin D to specific immunotherapy enhance the immunoregulation and beneficial impact on experimental murine allergic airway inflammation. Also in human, vitamin D supplementation can target immune cells, including B lymphocytes. In summary, supplementation of vitamin D to otherwise deficient individuals should enhance the immunomodulatory effect of specific immunotherapy.

Actual start date of recruitment	18 October 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	36
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment via the in-house outpatients clinics of grass pollen-allergic individuals with hay fever +/- allergic asthma, who planned a specific immunotherapy

Pre-assignment

Screening details:

Grass pollen allergy
No sun/UV-exposure planned during the treatment period (November-April)
No contraindication against immunotherapy (e.g. uncontroled asthma, planned pregnancy)

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The participants were randomly assigned to the vitamin D or placebo group by the Charité pharmacology Dept. 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, calci-um, phosphate) were checked by unblinded study personel to exclude a bias by the blinded physician who were in direct contact within direct contact with the study participants

Arms

Are arms mutually exclusive?	Yes
Arm title	Vitamin D

Arm description:

active drug

Arm type	Experimental
Investigational medicinal product name	Vigantol Öl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, liquid
Routes of administration	Oral use

Dosage and administration details:

vitamin D (5,333 I.U./day) was orally applied by 8 drops daily (2013/2014 10 drops due to a new packaging device and drop size).
It was applied daily between visit 1 and 10 in 3 consecutive treatment years (total 3x 4.5 months).

Arm title	Placebo

Arm description:

Migliol® (neutral carrier oil)

Arm type	Placebo
Investigational medicinal product name	Migliol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

The comparator was orally applied by 8 drops daily (2013/2014 10 drops due to a new packaging device and drop size).
It was applied daily between visit 1 and 10 in 3 consecutive treatment years (total 3x 4.5 months).

Number of subjects in period 1	Vitamin D	Placebo
Started	18	18
Completed	12	11
Not completed	6	7
Consent withdrawn by subject	2	4
Adverse event, non-fatal	1	-
Pregnancy	1	-
Lost to follow-up	2	3

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	36	36	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	36	36	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Age			
Units: years			
arithmetic mean	32.5		
standard deviation	± 1.8	-	
Gender categorical			
Gender			
Units: Subjects			
Female	14	14	
Male	22	22	
25OHD			
mean 25-hydroxyvitamin D			
Units: nmol/L			
arithmetic mean	41.1		
standard deviation	± 1.9	-	
Grass-Ig			
determines the concentration of grass pollen-specific IgE in the serum			
Units: kUA/L			
arithmetic mean	30.8		
standard deviation	± 11.1	-	

Subject analysis sets	
Subject analysis set title	Vitamin D Group
Subject analysis set type	Full analysis
Subject analysis set description: all data	
Subject analysis set title	Placebo group

Subject analysis set type	Full analysis

Subject analysis set description:

All data

Reporting group values	Vitamin D Group	Placebo group	
Number of subjects	18	18	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	18	18	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Age			
Units: years			
arithmetic mean	33	32	
standard deviation	± 1.7	± 1.8	
Gender categorical			
Gender			
Units: Subjects			
Female	8	6	
Male	10	12	
25OHD			
mean 25-hydroxyvitamin D			
Units: nmol/L			
arithmetic mean	40.4	41.7	
standard deviation	± 2.9	± 2.6	
Grass-Ig			
determines the concentration of grass pollen-specific IgE in the serum			
Units: kUA/L			
arithmetic mean	27.4	127.6	
standard deviation	± 14.5	± 42.6	

End points

End points reporting groups

Reporting group title	Vitamin D
Reporting group description: active drug	
Reporting group title	Placebo
Reporting group description: Migliol® (neutral carrier oil)	
Subject analysis set title	Vitamin D Group
Subject analysis set type	Full analysis
Subject analysis set description: all data	
Subject analysis set title	Placebo group
Subject analysis set type	Full analysis
Subject analysis set description: All data	

Primary: Intracutaneous 500 SBU

End point title	Intracutaneous 500 SBU

End point description:

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).

End point type	Primary

End point timeframe:

3 years

End point values	Vitamin D Group	Placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: mm				
median (inter-quartile range (Q1-Q3))				
ICT500	17 (12 to 19)	18 (17 to 20)		

Attachments (see zip file)	ICT500/ICT500.png

Statistical analyses

Statistical analysis title	T-Test

Statistical analysis description:

Student's T-Test

Comparison groups	Vitamin D Group v Placebo group
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)

Notes:

[1] - T-Test

Secondary: Area under the curve of the intracutaneous test

End point title	Area under the curve of the intracutaneous test

End point description:

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).

End point type	Secondary

End point timeframe:

3 years

End point values	Vitamin D Group	Placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: AUC				
number (not applicable)				
AUC-ICT	7208	7664		

Attachments (see zip file)	AUC-ICT/AUC-ICT.png

Statistical analyses

Statistical analysis title	AUC-ICT

Statistical analysis description:

comparison of the area under the curve of both groups

Comparison groups	Vitamin D Group v Placebo group
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: Area under the curve - conjuncitval provocation test

End point title	Area under the curve - conjuncitval provocation test

End point description:

The overall AUC of the grass-pollen-specific conjunctival provocation test is increased follow-ing 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, not 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).

End point type	Secondary

End point timeframe:

3 years

End point values	Vitamin D Group	Placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: AUC				
number (not applicable)	110000	310000		

Attachments (see zip file)	AUC-CPT/AUC-CPT.png

Statistical analyses

Statistical analysis title	AUC-CPT
Comparison groups	Vitamin D Group v Placebo group
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: Retrospectiv symptom score (RSS)

End point title	Retrospectiv symptom score (RSS)

End point description:

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 com-parable. Regarding the increased scores at year 2 and 3, a higher pollen count compared to year 1 must be considered (2012=45 particles per m3 (ppm), 2013=110 ppm, 2014=236 ppm).

End point type	Secondary

End point timeframe: 3 years

End point values	Vitamin D Group	Placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: points				
number (not applicable)				
RSS	12	10		

Attachments (see zip file)	RSS/RSS.png

Statistical analyses

Statistical analysis title	RSS-stats
Statistical analysis description: comparison between both study groups	
Comparison groups	Vitamin D Group v Placebo group
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: Seasonal global symptoms (SGS)

End point title	Seasonal global symptoms (SGS)
End point description: General symptom score of the grass pollen season before treatment (2011) to the treat-ment 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.SGS left). This data is strong, as the maximum and overall pollen counts were in-creasing (by coincidence, 2012=45, 2013=110, 2014=236). However, subgroup analysis re-veal no significant difference between the vitamin D and placebo group (Fig.SGS, right).	
End point type	Secondary
End point timeframe: 3 years	

End point values	Vitamin D Group	Placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: points				
number (not applicable)				
SGS	2	2		

Attachments (see zip file)	SGS/SGS.png

Statistical analyses

Statistical analysis title	SGS-stats
Statistical analysis description: comparison between both study groups	
Comparison groups	Vitamin D Group v Placebo group
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: Skin prick test (SPT)

End point title	Skin prick test (SPT)
End point description: 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.	
End point type	Secondary
End point timeframe: 3 years	

End point values	Vitamin D Group	Placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: wheal/histamin in %				
number (not applicable)				
SPT	188	150		

Attachments (see zip file)	SPT/SPT.png

Statistical analyses

Statistical analysis title	SPT-stats
Statistical analysis description: compare both groups	
Comparison groups	Vitamin D Group v Placebo group
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: Symptom-Medication-Score (SMS)	
End point title	Symptom-Medication-Score (SMS)
End point description: 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).	
End point type	Secondary
End point timeframe: 3 years	

End point values	Vitamin D Group	Placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: points				
number (not applicable)				
SMS	3.3	4.1		

Attachments (see zip file)	SMS-year1/SMS-y1.png

Statistical analyses

Statistical analysis title	SMS-stats
Statistical analysis description: comparing both groups	
Comparison groups	Placebo group v Vitamin D Group

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: Grass-Ig

End point title	Grass-Ig

End point description:

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 thresh-old 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).

End point type	Secondary

End point timeframe:

1 year

End point values	Vitamin D Group	Placebo group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: LU/ml				
Grass-Ig	27	128		

Statistical analyses

Statistical analysis title	Grass-Ig

Statistical analysis description:

to compare vitamin D and placebo group

Comparison groups	Vitamin D Group v Placebo group
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.05
Method	t-test, 2-sided

Notes:

[2] - to compare vitamin D and placebo group

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
3 years	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	all participants

Reporting group description:

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.
1 SAE occurred independent of the treatment.

Serious adverse events	all participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 36 (2.78%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Immune system disorders			
Reactive Arthritis	Additional description: In a treatment-free interval (during the first grass-pollen season), a sexually transmitted uro-genital infection with Ureaplasma induced a reactive arthritis required treatment with methotrexate (banned drug, study exclusion)		
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	all participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 36 (100.00%)		
Nervous system disorders			
Nervous system AEs			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	9		
Eye disorders			

Ophthalmic AEs subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Gastrointestinal disorders Gastrointestinal AEs subjects affected / exposed occurrences (all)	5 / 36 (13.89%) 7		
Respiratory, thoracic and mediastinal disorders Respiratory AEs subjects affected / exposed occurrences (all)	18 / 36 (50.00%) 31		
Skin and subcutaneous tissue disorders Skin disorders subjects affected / exposed occurrences (all)	12 / 36 (33.33%) 17		
Renal and urinary disorders Urogenital AEs subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3		
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorder subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2011	issue that Vigantol was off-market in 2010-Summer 2011
14 April 2012	introduction of a questionaire to assess the symptom-medication-score during pollen season
11 July 2012	prolongation for 2 more study years

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

High drop rate over 3 years (vitD n=18->12, plc n=18->11) due to the extension from originally planned 1 year to a 3 year trial. Most of the drop out probands were reporting changes in the occupation or left Berlin, so they could not further attend.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32750735