Report Synopsis of Study EVITA

EudraCT-Nr.: 2014-002363-15

Vorlage-Nr.: 4040258

1) **Name of Sponsor/Company:** University Medical Center of the Johannes Gutenberg-University Mainz represented by the executive board of the University represented by the scientific member of the executive board Univ.-Prof. Dr. med. U. Förstermann delegated to the Director of III. Medizinische Klinik und Poliklinik Univ.-Prof. Dr. med. Matthias Theobald Langenbeckstrasse 1 D-55131 Mainz, Germany	4) **Individual Study Table Referring to Part of the Dossier:** na[1] Volume: na Page: n.a.	*(For National Authority Use only)*
2) **Name of Finished Product:** Dekristol 1000 I.E. Dekristol 20.000 I.E Placebo		
3) **Name of Active Substance:** Colecalciferol = Vitamin D_3		

5) **Title of Study[2]:**

EVITA Trial: Effect of Vitamin D as add-on Therapy for vitamin D insufficient patients with severe Asthma: a randomized, double-blind, placebo-controlled trial

German title:

EVITA-Studie: Effekt einer zusätzlichen Vitamin-D-Therapie bei Patienten mit Vitamin-D-Mangel und schwerem Asthma: eine randomisierte, doppel-blinde, Placebo-kontrollierte Studie

Protocol versions:

Protocol version 1.1 dated 21.01.2015

Amendment 1 resulting in protocol version 2.0 dated 09.04.2015

- Change of study drug from Vigantoletten 1000 I.E. to Dekristol 1000 I.E. (The reason was changed formulation of Vigantoletten tablets by producer Merck. The changed tablet size was not applicable for blinding anymore.)
- Additions in chapter special precautions & warnings
- Redactional changes

Amendment 2 resulting in protocol final version V3.0 dated 25.09.2015

- Inclusion of Re-Screening after exacerbations/infections/institutional or personal reasons
- Measurement of urinary calcium level as a 24h-collection sample at visit 4 and 8 in patients where the serum calcium value is above the upper reference limit or in case of a suspected vitamin D overdosing
- Addition of information that for activation of supplemented Vitamin D patients should be advised to go into natural light on a daily basis.
- Addition of information for reversibility test (patients cannot withhold it´s bronchodilitators for reversibility testing, patient can remain in study, reversibility should be performed)

[1] This information is only required in connection with filing of a dossier for marketing authorization.

[2] The latest protocol version must be clearly stated, this means including all amendments – the amendments are to be declared and identified.

- specification that eNO test should be performed before spirometry or bodyplethysmography
- Redactional change: questionnaire from BDI (Baseline Dyspnea Index) into TDI (Transitional Dyspnea Index) after baseline
- Redactional change: wording ACQ-5 decrease instead of ACQ-5-increase

6) **Principal Investigator(s):** Coordinating investigator (LKP, according to German Medicinal Product Act): Priv.-Doz. Dr. Stephanie Korn

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8) **Publication (reference):** n.a.

9) **Studied period (years)**[3]:	10) **Phase of development:** IV
Date of first enrolment: 26.06.2015 Date of last completed: 09.03.2017 On 30.09.2016 the sponsor notified the temporary halt of the trial. On 03.04.2017 the sponsor notified the early termination of the trial.	

11) **Objectives:**

The primary objective was to compare the effects of vitamin D therapy with placebo on reducing the need for inhaled or oral corticosteroids in patients with severe asthma and vitamin D insufficiency.

Secondary objectives were to compare the efficacy, safety, and tolerability of vitamin D compared with placebo in patients with severe asthma and vitamin D insufficiency on markers of asthma control and risk including, asthma control, pulmonary function, exacerbation rate, quality of life, and vitamin D level.

12) **Methodology:**

Multicenter, randomized, double-blind, placebo-controlled study

The treatment allocation ratio is 1:1 (balanced design), stratified by type of corticosteroid treatment (ICS or ICS and OCS*).

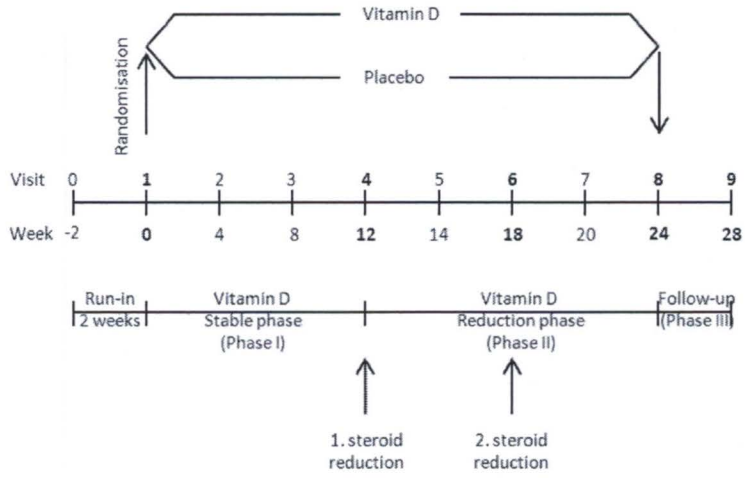
The study consists of a 2-week run-in period, a 24 week double-blind treatment, followed by a follow-up visit 4 weeks after last study medication intake.

The active treatment arm in this study will be standard of care plus vitamin D (loading dose of 100 000 IU upon study entry, to be followed by 4000 IU/day for the rest of the study period) while the comparator arm will be standard of care plus placebo.

Asthma maintenance treatment will remain stable during the first 12 weeks of the trial (Phase I), to be followed by a 12 week

[3] Here also study suspensions and premature terminations of a trial/premature conclusion of a trial should be listed, including the reasons for that.

corticosteroid reduction phase (Phase II) according to a predefined reduction protocol (section 6.1). At study end there will be a 4 week follow-up period (Phase III).



13) **Number of patients (planned and analyzed):**

Planned: n=160 patients, 80 patients per treatment group

This trail was prematurely terminated due to recruiting problems. Patients get recommendations from their attending physicians to take vitamin D or were treated with new asthma drugs (i.e. mepolizumab), so that these patients could not recruited into this trail.

Enrolled: n=54, n=27 per treatment group; n_{ICS}=45 , $n_{ICS+OCS}$=9

Analyzed: n=54 , n=27 vitamin D group, n=27 placebo group, n_{ICS}=45 , $n_{ICS+OCS}$=9

Reasons for drop outs: Revocation of informed consent n=3, Poor compliance n=1, Other reason n=6

14) **Diagnosis and main criteria for inclusion:**

Patients with severe asthma and vitamin D insufficiency

Main inclusion criteria:

Subjects meeting all of the following criteria will be considered for enrolment into the trial:

- Male or female, age ≥ 18 years with a pulmonary specialist diagnosis of severe asthma according to the Global Initiative for Asthma (GINA 2014, www.ginasthma.org) and the German Asthma Net (GAN, www. German-asthma-net.de)
- Treatment with long-acting β2-agonists (LABA) and inhaled corticosteroids (ICS) at a dose of at least 1000 µg beclomethasone (or equivalent) per day, chronic oral corticosteroid (OCS) use is allowed
- Asthma Control Questionnaire (ACQ-5) score ≥ 1.5
- Vitamin D insufficiency as defined by a serum vitamin D concentration of <30 ng/ml but ≥ 10 ng/ml at screening

Main exclusion criteria:

Subjects presenting one of the following criteria will not be enrolled in the trial:

- Patients on vitamin D substitution
- Impaired renal function (GFR < 30 ml/min) and history of physician-diagnosed nephrolithiasis
- Within the past 4 weeks respiratory tract infection or asthma exacerbation requiring systemic corticosteroids or increase in systemic corticosteroids
- Chronic respiratory diseases (other than asthma)
- Current smokers or ex-smokers with a smoking history of more than 10 pack-years

15) **Test product, dose and mode of administration, batch number:**

During the 24 week trial period patients received a loading dose of 100.000 IU vitamin D (Dekristol®) followed by vitamin D 4000 IU per day (Dekristol®) per os or an identical placebo.

Colecalciferol (Dekristol®) Batch No: 20.000 IU (140725, 141135, 150523)
Colecalciferol (Dekristol®) Batch No: 1.000 IU (150307, 141216, 150308, 151132)
Placebo (P-Tabletten Lichtenstein) Batch No: 142636

16) **Duration of treatment:**

Single loading dose of 100 000 IU vitamin D or an identical placebo per os

Daily administration of 4000 IU vitamin D or an identical placebo per os for 24 weeks

17) **Reference therapy, dose and mode of administration, batch number:**

Placebo capsules for oral administration once daily for 24 weeks after single administration of loading dose

18) **Criteria for evaluation[4]:**

Efficacy:

The primary endpoint is the relative dose reduction of ICS or OCS at the end of phase II (week 24, visit 8), defined as [initial dose at week 0 – dose at end of phase II (week 24)] / initial dose at week 0. If the dose at the end of phase II has been reduced compared to week 0, but was followed by an exacerbation within 4 weeks after reduction, the dose before that reduction will be used for the calculation of relative dose reduction.

The secondary objectives of the trial are to evaluate further efficacy of vitamin D as assessed by the following:

- Exacerbations (rate of and time to first and subsequent exacerbations) at the end of the study at week 24 (visit 8) and at the end of the follow-up period (visit 9).

  A moderate asthma exacerbation is defined by a worsening of asthma requiring:

  - The use of systemic corticosteroids (or a temporary increase in a stable oral corticosteroid background dose) for at least 3 days
  - An emergency room visit due to asthma that required systemic corticosteroids (per above)

  A severe asthma exacerbation is defined by a worsening of asthma requiring:

  - An inpatient hospitalization due to asthma
- Asthma Control Questionnaire at every visit
- Asthma Quality of Life at Baseline and Transition Dyspnea Indexes at weeks 12, 18, 24, and 28
- Pulmonary function test results, as measured by forced vital capacity, forced expiratory volume, residual volume, total lung capacity, airway resistance, and inspiratory capacity, CO diffusion capacity at every visit
- Serum concentrations of vitamin D, parathormone, calcium, interleukins (IL) 10 and 17, as well as TNF-alpha at weeks 12, 18, 24, and 28
- Proportion of patients that achieved vitamin D sufficiency (vitamin D responder: 25-hydroxyvitamin D level ≥ 30 ng/mL) at week 24

Safety:

Assessment of safety and tolerability by documentation of adverse events (AEs), serious adverse events (SAEs), vital signs, physical examination and laboratory parameters (laboratory test abnormalities/test value changes over time) at pre-specified visits as outlined in the time and events table.

In this trial, the period of observation for collection of adverse events extends from first intake of study medication up to the end of the 4-week follow-up period.

19) **Statistical methods:**

Efficacy: Relative dose reduction of inhaled or oral corticosteroids

Description of the primary efficacy analysis and population:

The relative dose reduction at the end of study phase II (week 24) will be compared between treatment groups by a two-sided stratified Mann-Whitney-U test (van Elteren test) stratified for the type of corticosteroid treatment (ICS or ICS and OCS) at study enrolment with a significance level of 0.05. A nonparametric test will be applied as data are expected to be tied at 0%, 25% and 50% due to the study design.

Safety:

AEs will be described by MedDRA classification. Incidence and severity of SAEs will be analyzed descriptively per organ system. Frequencies between active and placebo group will be compared.

[4] This section should also contain information about the chosen risk management approach, as outlined by ICH E3, section 9.6 (only if the study was approved after June 14th, 2017).

Secondary endpoints:

Secondary endpoints will be evaluated according to their distribution. The risk of exacerbations will be compared between treatment groups by time to event modeling, all other secondary endpoints by analysis of covariance with treatment as factor and the corresponding baseline assessment as a covariate.

Due to the premature termination of the study and the resulting reduced sample size, some analyses are omitted or changed. The primary and explorative analyses will be unstratified, and not stratified by type of corticosteroids. The originally planned primary analysis will be conducted as a sensitivity analysis instead. The analysis of subgroups and the analysis of time to subsequent exacerbations will be omitted as the number of patients in the originally planned subgroups is very small and there were only a few patients with more than one exacerbation. The outcome "death" did not occur in the study and is consequently also not addressed in the primary and secondary analyses. FEV1/FVC Percentage of target is not meaningful and will be omitted in the analysis. After excluding patients with significant protocol violations, the sample size is very small. Consequently, the per protocol (PP) analysis will be reduced. The PP population will be described based on the baseline values and only the primary and the main secondary analysis will be performed on the PP population.

20) **Summary – Conclusions**[5]**:**

The study was prematurely terminated due to failure to recruit a sufficient number of subjects in the planned study period. It was planned to include 160 subjects in this trial.

On 30.09.2016 the sponsor notified the temporary halt of the trial because the recruitment has clearly decreased in the EVITA study; partially no more patients could be recruited for a longer period. For this reason it was not possible to reach the aimed patient's number in an adequate period. 10 Patients still received study medication at time of the halt. After the last patient completed the trial the sponsor notified the early termination of the trial on 03.04.2017.

Efficacy results:

The primary analysis will be conducted using the intention to treat analysis set (ITT). In total, 54 patients were randomized (placebo: n=27, vitamin D n=27).

Demographics and baseline characteristics

Mean age was 56.4 (±12.5) years in the Vitamin D group and 58.4 (±11.6) in the placebo group. More patients were female in the vitamin D group than in the placebo group (Table 1).

Table 1: Patient characteristics

		Placebo	Vitamin D	All	Fisher's Exact Test p-value (2-tail)
ASTHMA	J45.0 (vorwiegend allergisches)	12 (44.4%)	7 (25.9%)	19 (35.2%)	0.21
	J45.1 (nicht allergisches)	8 (29.6%)	6 (22.2%)	14 (25.9%)	.
	J45.8 (Mischformen)	7 (25.9%)	13 (48.1%)	20 (37.0%)	.
	J45.9 (nicht näher bezeichnet)	0 (0.0%)	1 (3.7%)	1 (1.9%)	.
ETHNIC	Kaukasisch	25 (92.6%)	25 (92.6%)	50 (92.6%)	0.49
	Asiatisch	0 (0.0%)	1 (3.7%)	1 (1.9%)	.
	Afrikanisch	0 (0.0%)	1 (3.7%)	1 (1.9%)	.
	Andere	2 (7.4%)	0 (0.0%)	2 (3.7%)	.
GENDER	F	12 (44.4%)	20 (74.1%)	32 (59.3%)	0.05
	M	15 (55.6%)	7 (25.9%)	22 (40.7%)	.

	Placebo							Vitamin D							
	N	Mean	Std Dev	Media n	Lower	Upper	Min	Max	N	Mean	Std Dev	Media n	Lower	Upper	Min	Max	t-test p-value
Age (yrs)	27	58.44	11.59	59.00	52.00	67.00	79.00	27	56.04	12.51	53.00	43.00	67.00	79.00	**0.4666**
BMI	27	29.12	4.16	27.78	26.03	31.96	37.89	27	29.55	5.88	28.71	25.08	34.38	41.77	**0.7569**

[5] Results should also summarize important deviations from the predefined quality tolerance limits and remedial actions taken (only if the study was approved after June 14th, 2017).

WEIGHT	27	86.41	14.11	86.00	73.00	95.00	123.00	27	82.89	19.24	82.00	70.00	91.00	130.00	**0.4470**
Height (cm)	27	172.19	7.64	174.00	167.00	178.00	185.00	27	167.15	7.83	168.00	160.00	173.00	183.00	**0.0204**
PB Sys	27	130.48	14.12	127.00	120.00	141.00	160.00	27	127.22	16.25	130.00	111.00	136.00	158.00	**0.4350**
PB Dia	27	84.07	10.64	84.00	78.00	90.00	106.00	27	82.15	12.39	83.00	74.00	93.00	103.00	**0.5426**
Pulse	27	76.41	10.53	75.00	67.00	85.00	94.00	27	73.89	11.32	75.00	65.00	81.00	90.00	**0.4011**

There was no significant difference in ICS dose regarding the treatment groups. Only 1 patient in the vitamin D group was treated with OCS in comparison with 7 patients in the placebo group.

There was no significant difference in ACQ-5, Mini-AQLQ and BDI scores at visit 1 (table 2).

Table 2: ACQ-5, Mini-AQLQ and BDI scores

	Placebo							Vitamin D							
	Mean	Std Dev	Median	Lower Quartile	Upper Quartile	Min	Max	Mean	Std Dev	Median	Lower Quartile	Upper Quartile	Min	Max	t-test p-value (2-tail)
ACQ-5 sum Visit 1	2.66	0.94	2.20	2.00	3.60	1.60	5.00	2.60	0.91	2.60	2.10	2.70	0.60	4.80	**0.8098**
	5							4							
Mini-AQLQ Symptoms Visit 1	4.05	1.23	3.80	3.40	4.80	2.00	6.80	4.13	1.18	4.10	3.40	4.70	2.20	7.00	**0.8240**
	5							4							
Impairment Visit 1	4.25	1.31	4.00	3.30	5.30	2.00	6.80	4.03	1.12	4.30	3.15	4.80	2.00	6.30	**0.5176**
	5							4							
Emotional life Visit 1	4.62	1.56	5.00	3.30	6.00	1.30	7.00	4.50	1.56	4.70	4.00	5.50	1.00	7.00	**0.7892**
	5							4							
Environmental Visit 1	3.72	1.47	3.70	2.70	4.30	1.70	7.00	3.39	1.52	3.15	2.00	4.85	1.00	6.00	**0.4457**
	5							4							
BDI	7.67	2.33	8.00	6.00	9.00	2.00	12.00	7.71	1.99	8.00	6.00	9.00	3.00	12.00	**0.9472**
	4							4							
Functional	2.76	1.05	3.00	2.00	3.00	0.00	4.00	2.79	0.93	3.00	2.50	3.00	0.00	4.00	**0.9118**
	5							4							
Capacity	2.63	0.77	3.00	2.00	3.00	1.00	4.00	2.71	0.81	3.00	2.00	3.00	1.00	4.00	**0.7159**
	4							4							
Effort size	2.29	0.86	2.00	2.00	3.00	1.00	4.00	2.21	0.83	2.00	2.00	3.00	1.00	4.00	**0.7345**
	4							4							

Lung function parameters and airway inflammation were similar in both groups (table 3).

Table 3: Lung function parameters and airway inflammation

	Placebo							Vitamin D							
	Mean	Std Dev	Median	Lower Quartile	Upper Quartile	Min	Max	Mean	Std Dev	Median	Lower Quartile	Upper Quartile	Min	Max	t-test p-value (2-tail)
FEV1 absolute	1.95	0.69	1.90	1.42	2.53	0.73	3.22	1.94	0.47	1.92	1.52	2.19	1.02	2.91	**0.9449**
	7							7							
FEV1 % of target	65.71	21.82	62.00	47.56	81.30	21.00	103.75	71.98	14.71	69.20	58.42	84.00	38.34	94.00	**0.2213**
	7							7							
FVC absolute	3.23	0.90	2.97	2.61	3.88	1.93	5.29	3.02	0.75	3.08	2.43	3.28	1.75	5.29	**0.3455**
	7							7							
FVC % of target	88.24	19.42	90.50	70.84	101.90	56.00	133.09	91.57	11.14	90.20	82.68	100.70	74.90	112.00	**0.4451**
	6							7							
FEV1/FVC absolute	0.60	0.14	0.61	0.53	0.69	0.30	0.84	0.65	0.11	0.65	0.57	0.72	0.40	0.85	**0.1378**
	7							7							
Airway resistance absolute	0.51	0.25	0.44	0.33	0.74	0.21	1.20	0.43	0.18	0.38	0.30	0.55	0.15	1.00	**0.1672**
	7							7							
Airway resistance % of target	161.18	87.08	144.10	86.67	239.50	0.30	399.00	143.90	59.80	132.60	99.30	183.33	51.00	333.33	**0.3995**
	7							7							
Specific airway resistance Absolute	2.41	1.88	1.72	1.16	3.70	0.39	9.13	1.79	1.06	1.59	1.16	2.20	0.51	5.88	**0.1449**
	7							7							
Specific airway resistance % of target	213.39	162.51	158.47	98.31	306.00	1.18	776.00	176.45	104.62	160.60	112.71	228.30	0.96	498.31	**0.3388**
	7							5							
Inspiratory capacity Absolute	2.82	0.78	2.69	2.28	3.45	1.08	4.74	2.63	0.61	2.62	2.27	3.03	1.50	4.10	**0.3881**
	7							7							
Inspiratory capacity % of target	102.16	22.74	100.69	87.00	121.75	67.00	161.08	104.62	21.20	99.58	88.60	116.27	65.04	149.00	**0.6995**
	4							4							
ITGV absolute	4.12	1.60	4.05	3.04	4.73	1.97	9.69	3.60	0.88	3.45	2.87	4.07	2.19	5.68	**0.1455**
	7							7							
ITGV % of target	125.87	38.85	117.76	105.00	136.00	69.86	252.20	122.39	26.40	122.70	103.00	139.46	75.30	168.30	**0.7019**
	7							7							
DLCO absolute	7.08	2.20	7.13	5.65	8.98	2.22	11.95	6.74	1.55	6.67	6.25	7.06	3.29	11.09	**0.5485**
	2							2							
DLCO % of target	77.76	18.91	78.88	66.00	88.30	30.00	110.21	82.80	13.47	84.85	74.00	91.30	50.15	106.20	**0.3148**
	2							2							
Residual volume absolute	3.50	1.58	3.33	2.37	4.17	1.51	8.85	3.00	0.77	3.08	2.37	3.54	1.76	4.39	**0.1425**
	7							7							
Residual volume % of target1	156.86	58.33	144.80	111.60	187.00	79.47	331.70	151.23	36.28	153.50	121.00	169.61	83.80	226.90	**0.6719**
	7							7							
Total lung capacity absolute	6.77	1.74	6.49	5.68	7.65	4.25	12.57	6.01	1.11	5.93	5.13	7.02	4.32	8.20	**0.0628**
	7							7							
Total lung capacity % of target	108.54	17.19	104.84	95.80	119.00	89.00	163.20	109.50	13.38	109.91	97.64	120.00	89.50	137.20	**0.8189**
	7							7							
eNO	33.37	27.91	22.00	15.00	48.00	8.00	128.00	35.20	40.67	18.00	15.00	34.00	5.00	177.00	**0.6999 (log-transformation)**
	7							5							

Primary analysis

The primary endpoint of this study was the relative dose reduction of ICs or OCS at visit 8 (table 4). The two-sided Mann-Whitney-U-test for relative dose reduction at week 24 (visit 8) shows no statistically significantly difference between treatment groups (p-value: 0.8839, table 5).

Table 4: Number of patients who reduced dose at visit 8 by at least 25% and 50% compared to baseline

	Placebo		Vitamin D		All	
	N	%	N	%	N	%
Relative dose reduction at visit 8						
Reduction < 25%	21	77.8	21	77.8	42	77.8
Reduction >= 25%	6	22.2	6	22.2	12	22.2
Relative dose reduction at visit 8	26	96.3	25	92.6	51	94.4

Reduction < 50%						
Reduction >= 50%	1	3.7	2	7.4	3	5.6

Table 5: two-sided Wilcoxon-Mann-Whitney-U-test for relative dose reduction at week 24 (visit 8)

Wilcoxon Two-Sample Test	
Statistic (S)	737.0000
Normal Approximation	
Z	-0.1192
One-Sided Pr < Z	0.4525
Two-Sided Pr > |Z|	0.9051
t Approximation	
One-Sided Pr < Z	0.4528
Two-Sided Pr > |Z|	0.9055
Exact Test	
One-Sided Pr <= S	0.4419
Two-Sided Pr >= |S - Mean|	0.8839
Z includes a continuity correction of 0.5.	

Secondary endpoints

The exacerbations were collected together with the other adverse events, but labelled as "exacerbation".

There was no significant difference in exacerbation rate or time to first exacerbation (table 6, figure 1 and 2). The analysis of subsequent exacerbation was omitted, because of very few patients experiencing more than one exacerbation.

Table 6: Absolute frequency (relative frequency in brackets) of patients with no exacerbation, at least 1 exacerbation and at least 2 exacerbations at visit 8 and visit 9, respectively

	Placebo						Vitamin D							
	All		ICS		ICS+OCS		All		ICS		ICS+OCS		All	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Number of exacerbations up to Visit 8														
No Exacerbation	20	74.1	16	80.0	4	57.1	19	70.4	18	72.0	1	50.0	39	72.2
One Exacerbation	7	25.9	4	20.0	3	42.9	7	25.9	6	24.0	1	50.0	14	25.9
Two or More Exacerbations	.	.	.	.	.	.	1	3.7	1	4.0	.	.	1	1.9
Number of exacerbations up to Visit 9														
No Exacerbation	19	70.4	15	75.0	4	57.1	18	66.7	17	68.0	1	50.0	37	68.5
One Exacerbation	6	22.2	4	20.0	2	28.6	7	25.9	7	28.0	.	.	13	24.1
Two or More Exacerbations	2	7.4	1	5.0	1	14.3	2	7.4	1	4.0	1	50.0	4	7.4

The following table 7 displays the exacerbations by severity (mild, moderate, severe). The number of exacerbation was similar in both treatment groups. There were no severe exacerbation.

Table 7: Absolute frequency (relative frequency in brackets) of patients with at least one exacerbation at visit 9

Number of Patients with...	**Vitamin D (N=27)**	**Events**	**Placebo (N=27)**	**Events**	**Total (N=54)**	**Events**
... at least one exacerbation	9 (33.33%)	11	8 (29.63%)	10	17 (31.48%)	21
... mild exacerbation	1 (3.70%)	1	3 (11.11%)	3	4 (7.41%)	4
... moderate exacerbation	8 (29.63%)	10	5 (18.52%)	7	13 (24.07%)	17
... severe exacerbation	0 (0.00%)	0	0 (0.00%)	0	0 (0.00%)	0

Figure 1: Kaplan-Meier-curve: Time to first exacerbation (p=0.6978), censored at V8

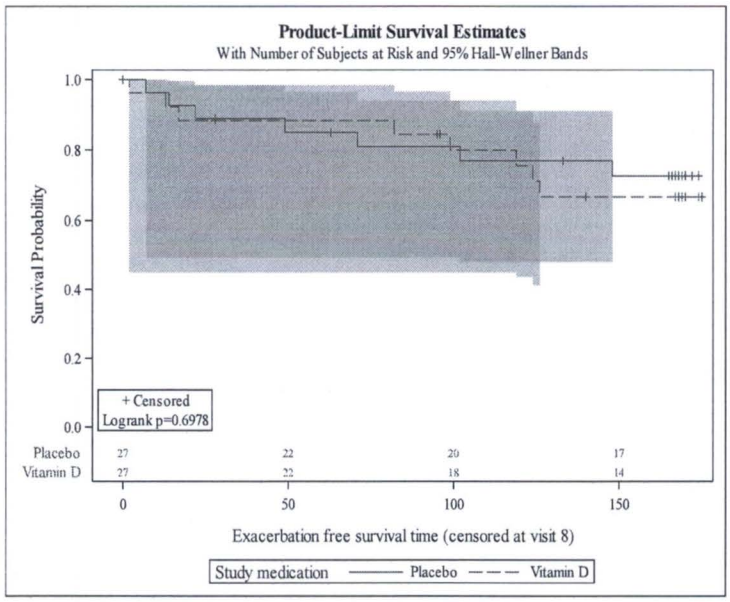
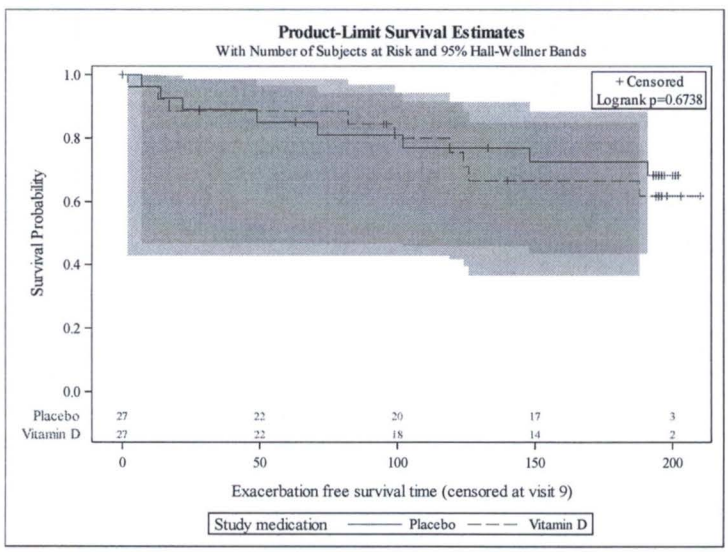


Figure 2: Kaplan-Meier-curve: Time to first exacerbation (p=0.6738), censored at V9



There was no effect of vitamin D substitution on Asthma Control Questionnaire, Asthma Quality of Life, Transition Dyspnea Indexes and pulmonary function throughout the study.

Vitamin D level at baseline was lower in the placebo group than in the vitamin D group (median 11.5 ng/ml vs. 18.9 ng/ml). After 24 weeks vitamin D level was significant higher in the vitamin D group (median 44.7 ng/ml) than in the placebo group (median 9.5 ng/ml, p<0.001).

Despite one patient all patients in the vitamin D group were vitamin D responders at visit 8 (vitamin D level > 30 ng/ml, table 8).

Table8: Responder status

	Placebo		Vitamin D		Fisher's Exact Test
	N	%	N	%	p-value (2-tail)
Responder Visit 8					
no	20	(51.28%)	1	(2.56%)	.
yes	0	(0%)	18	(46.15%)	**0.0000**
Responder Visit 9					
no	20	(46.51%)	8	(18.60%)	.
yes	0	(0%)	15	(34.88%)	**0.0000**

Because of low sample number available, analysis of serum concentrations of parathormone, calcium, interleukins (IL) 10 and 17, as well as TNF-alpha was omitted.

Safety results:

The safety was assessed continuously throughout the clinical study by adverse events, vital signs, laboratory values and physical examination as well as concomitant medication.

Vital signs: Systolic and diastolic blood pressure, pulse and body weight were slightly higher in the placebo treatment group at baseline and also throughout the treatment phase and follow-up. BMI seems to be similar in both treatment groups, although with a higher variance in the Vitamin D treatment group. For body temperature no differences between treatment groups were apparent.

Physical examination was done at every treatment visit. Abnormal changes to the baseline assessment were documented as adverse events. Therefore the physical examination was not analyzed by summary statistics. Other safety parameters are not part of the safety chapters of this report.

Laboratory values: There were no treatment differences apparent.

Previous and concomitant diseases were coded by MedDRA terminology. The following table displays the previous and concomitant diseases by system organ class (SOC) and MedDRA preferred term (PT) within SOC.

	Number (%) of Subjects / Events			
	Placebo (All)		Vitamin D (All)	
System Organ Class/ Preferred Term	**(N=27)**	**(nMH=195)**	**(N=27)**	**(nMH=188)**
Subjects with any previous and concomitant diseases	27 (100.00%)	195 (100.00%)	27 (100.00%)	188 (100.00%)
Respiratory, thoracic and mediastinal disorders	24 (88.89%)	36 (18.46%)	24 (88.89%)	35 (18.62%)
Asthma	23 (85.19%)	23 (11.79%)	23 (85.19%)	28 (14.89%)
Cough	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (0.53%)
Nasal polyps	2 (7.41%)	2 (1.03%)	1 (3.70%)	1 (0.53%)
Nasal septum deviation	1 (3.70%)	1 (0.51%)	0 (0.00%)	0 (0.00%)
Respiratory failure	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (0.53%)
Rhinitis allergic	3 (11.11%)	3 (1.54%)	4 (14.81%)	4 (2.13%)
Rhonchi	1 (3.70%)	1 (0.51%)	0 (0.00%)	0 (0.00%)
Sleep apnoea syndrome	4 (14.81%)	5 (2.56%)	0 (0.00%)	0 (0.00%)
Wheezing	1 (3.70%)	1 (0.51%)	0 (0.00%)	0 (0.00%)
Immune system disorders	13 (48.15%)	24 (12.31%)	11 (40.74%)	29 (15.43%)
Allergy to animal	3 (11.11%)	3 (1.54%)	4 (14.81%)	4 (2.13%)
Allergy to plants	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (0.53%)
Drug hypersensitivity	1 (3.70%)	1 (0.51%)	2 (7.41%)	3 (1.60%)
Dust allergy	1 (3.70%)	1 (0.51%)	3 (11.11%)	3 (1.60%)
Food allergy	1 (3.70%)	1 (0.51%)	1 (3.70%)	1 (0.53%)
Hypersensitivity	2 (7.41%)	2 (1.03%)	0 (0.00%)	0 (0.00%)
Mite allergy	4 (14.81%)	4 (2.05%)	5 (18.52%)	5 (2.66%)
Multiple allergies	3 (11.11%)	3 (1.54%)	3 (11.11%)	3 (1.60%)
Mycotic allergy	1 (3.70%)	1 (0.51%)	0 (0.00%)	0 (0.00%)
Seasonal allergy	5 (18.52%)	8 (4.10%)	7 (25.93%)	9 (4.79%)
Vascular disorders	17 (62.96%)	22 (11.28%)	12 (44.44%)	13 (6.91%)

Surgical and medical procedures	5 (18.52%)	10 (5.13%)	9 (33.33%)	16 (8.51%)
Eye disorders	12 (44.44%)	14 (7.18%)	5 (18.52%)	5 (2.66%)
Nervous system disorders	11 (40.74%)	14 (7.18%)	7 (25.93%)	9 (4.79%)
Musculoskeletal and connective tissue disorders	8 (29.63%)	9 (4.62%)	10 (37.04%)	14 (7.45%)
Metabolism and nutrition disorders	11 (40.74%)	13 (6.67%)	9 (33.33%)	11 (5.85%)
Infections and infestations	10 (37.04%)	12 (6.15%)	11 (40.74%)	13 (6.91%)
Gastrointestinal disorders	8 (29.63%)	10 (5.13%)	6 (22.22%)	7 (3.72%)
Endocrine disorders	2 (7.41%)	2 (1.03%)	8 (29.63%)	9 (4.79%)
Skin and subcutaneous tissue disorders	6 (22.22%)	7 (3.59%)	0 (0.00%)	0 (0.00%)
Blood and lymphatic system disorders	0 (0.00%)	0 (0.00%)	4 (14.81%)	5 (2.66%)
Psychiatric disorders	0 (0.00%)	0 (0.00%)	4 (14.81%)	5 (2.66%)
Cardiac disorders	3 (11.11%)	4 (2.05%)	2 (7.41%)	3 (1.60%)
Injury, poisoning and procedural complications	3 (11.11%)	4 (2.05%)	3 (11.11%)	3 (1.60%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (14.81%)	4 (2.05%)	1 (3.70%)	1 (0.53%)

Source Table: Appendix for Tables, Table 7.05

As expected every patient suffered from at least one previous or concomitant disease. The most frequent previous or concomitant diseases were Respiratory, thoracic and mediastinal disorders (48/54 pts, 89%) followed by Vascular disorders (29/54 pts, 54%) and Immune system disorders (24/54 pts, 44%).

Concomitant medication: The following table displays the concomitant medication by ATC level 2 (therapeutic group) and indication related ATC level 4 (chemical/therapeutic/pharmacological subgroup) within therapeutic group.

	Number (%) of Subjects / Events			
	Placebo (All)		**Vitamin D (All)**	
ATC-Class 2/ATC-Class 4	**(N=27)**	**(nCM=275)**	**(N=27)**	**(nCM=326)**
Subjects with any previous and concomitant medication	27 (100.00%)	275 (100.00%)	27 (100.00%)	326 (100.00%)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	27 (100.00%)	109 (39.64%)	27 (100.00%)	134 (41.10%)
Adrenergics and other drugs for obstructive airway diseases	18 (66.67%)	31 (11.27%)	20 (74.07%)	50 (15.34%)
Adrenergics in combination with anticholinergics	2 (7.41%)	2 (0.73%)	1 (3.70%)	1 (0.31%)
Anticholinergics	10 (37.04%)	12 (4.36%)	11 (40.74%)	11 (3.37%)
Glucocorticoids	12 (44.44%)	14 (5.09%)	11 (40.74%)	17 (5.21%)
Leukotriene receptor antagonists	7 (25.93%)	7 (2.55%)	5 (18.52%)	5 (1.53%)
Other systemic drugs for obstructive airway diseases	4 (14.81%)	4 (1.45%)	7 (25.93%)	7 (2.15%)
Selective beta-2-adrenoreceptor agonists	23 (85.19%)	36 (13.09%)	22 (81.48%)	34 (10.43%)
Xanthines	3 (11.11%)	3 (1.09%)	6 (22.22%)	9 (2.76%)
CORTICOSTEROIDS FOR SYSTEMIC USE	13 (48.15%)	42 (15.27%)	10 (37.04%)	30 (9.20%)
Glucocorticoids	13 (48.15%)	42 (15.27%)	10 (37.04%)	30 (9.20%)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	11 (40.74%)	16 (5.82%)	7 (25.93%)	26 (7.98%)
ANTIBACTERIALS FOR SYSTEMIC USE	7 (25.93%)	7 (2.55%)	9 (33.33%)	23 (7.06%)
ANALGESICS	9 (33.33%)	16 (5.82%)	8 (29.63%)	13 (3.99%)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	10 (37.04%)	10 (3.64%)	8 (29.63%)	11 (3.37%)
DRUGS FOR ACID RELATED DISORDERS	10 (37.04%)	10 (3.64%)	8 (29.63%)	9 (2.76%)

OPHTHALMOLOGICALS	5 (18.52%)	8 (2.91%)	1 (3.70%)	1 (0.31%)
Corticosteroids and antiinfectives in combination	1 (3.70%)	1 (0.36%)	0 (0.00%)	0 (0.00%)
Corticosteroids, plain	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (0.31%)
Film-formin Substances	2 (7.41%)	2 (0.73%)	0 (0.00%)	0 (0.00%)
Fluoroquinolones	1 (3.70%)	1 (0.36%)	0 (0.00%)	0 (0.00%)
Other antiallergics	1 (3.70%)	1 (0.36%)	0 (0.00%)	0 (0.00%)
Other ophthalmologicals	2 (7.41%)	2 (0.73%)	0 (0.00%)	0 (0.00%)
Prostaglandin analogues1)	1 (3.70%)	1 (0.36%)	0 (0.00%)	0 (0.00%)
NASAL PREPARATIONS	7 (25.93%)	7 (2.55%)	8 (29.63%)	8 (2.45%)
Corticosteroids	5 (18.52%)	5 (1.82%)	6 (22.22%)	6 (1.84%)
Herbal nasal preparations for systemic application	1 (3.70%)	1 (0.36%)	1 (3.70%)	1 (0.31%)
Sympathomimetics	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (0.31%)
Sympathomimetics, plain	1 (3.70%)	1 (0.36%)	0 (0.00%)	0 (0.00%)
THYROID THERAPY	1 (3.70%)	1 (0.36%)	7 (25.93%)	8 (2.45%)
DRUGS USED IN DIABETES	2 (7.41%)	4 (1.45%)	3 (11.11%)	6 (1.84%)
MINERAL SUPPLEMENTS	0 (0.00%)	0 (0.00%)	3 (11.11%)	6 (1.84%)
CALCIUM CHANNEL BLOCKERS	3 (11.11%)	3 (1.09%)	5 (18.52%)	5 (1.53%)
VACCINES	3 (11.11%)	3 (1.09%)	3 (11.11%)	5 (1.53%)
ANTIEPILEPTICS	3 (11.11%)	4 (1.45%)	0 (0.00%)	0 (0.00%)
ANTIHISTAMINES FOR SYSTEMIC USE	3 (11.11%)	3 (1.09%)	4 (14.81%)	4 (1.23%)
Other antihistamines for systemic use	1 (3.70%)	1 (0.36%)	0 (0.00%)	0 (0.00%)
Piperazine derivatives	2 (7.41%)	2 (0.73%)	4 (14.81%)	4 (1.23%)
COUGH AND COLD PREPARATIONS	3 (11.11%)	3 (1.09%)	4 (14.81%)	4 (1.23%)
Expectorants	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (0.31%)
Herbal expectorants	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (0.31%)
Homeopathic and anthroposophic agents for treatment of common cold	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (0.31%)
Mucolytics	2 (7.41%)	2 (0.73%)	0 (0.00%)	0 (0.00%)
Opium alkaloids and derivatives	1 (3.70%)	1 (0.36%)	1 (3.70%)	1 (0.31%)
LIPID MODIFYING AGENTS	2 (7.41%)	2 (0.73%)	3 (11.11%)	4 (1.23%)
PSYCHOANALEPTICS	3 (11.11%)	3 (1.09%)	3 (11.11%)	4 (1.23%)
ANTITHROMBOTIC AGENTS	3 (11.11%)	3 (1.09%)	2 (7.41%)	2 (0.61%)
DIURETICS	2 (7.41%)	2 (0.73%)	3 (11.11%)	3 (0.92%)
Sulfonamides, plain	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (0.31%)
Thiazides, plain	2 (7.41%)	2 (0.73%)	2 (7.41%)	2 (0.61%)
ANTI-PARKINSON DRUGS	1 (3.70%)	2 (0.73%)	0 (0.00%)	0 (0.00%)
BETA BLOCKING AGENTS	2 (7.41%)	2 (0.73%)	2 (7.41%)	2 (0.61%)
IMMUNE SERA AND IMMUNOGLOBULINS	1 (3.70%)	2 (0.73%)	0 (0.00%)	0 (0.00%)
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	2 (7.41%)	2 (0.73%)	0 (0.00%)	0 (0.00%)
ANESTHETICS	0 (0.00%)	0 (0.00%)	1 (3.70%)	2 (0.61%)
ANTIANEMIC PREPARATIONS	1 (3.70%)	1 (0.36%)	2 (7.41%)	2 (0.61%)
IMMUNOSUPPRESSANTS	0 (0.00%)	0 (0.00%)	2 (7.41%)	2 (0.61%)
MUSCLE RELAXANTS	0 (0.00%)	0 (0.00%)	1 (3.70%)	2 (0.61%)
PSYCHOLEPTICS	0 (0.00%)	0 (0.00%)	1 (3.70%)	2 (0.61%)
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	0 (0.00%)	0 (0.00%)	2 (7.41%)	2 (0.61%)
STOMATOLOGICAL PREPARATIONS	1 (3.70%)	1 (0.36%)	2 (7.41%)	2 (0.61%)
ANTI-ACNE PREPARATIONS	1 (3.70%)	1 (0.36%)	0 (0.00%)	0 (0.00%)

ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	1 (3.70%)	1 (0.36%)	1 (3.70%)	1 (0.31%)
ANTIMYCOTICS FOR SYSTEMIC USE	1 (3.70%)	1 (0.36%)	0 (0.00%)	0 (0.00%)
CHEST EMBROCATIONS AND OTHER INHALANTS	1 (3.70%)	1 (0.36%)	0 (0.00%)	0 (0.00%)
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	1 (3.70%)	1 (0.36%)	0 (0.00%)	0 (0.00%)
PERIPHERAL VASODILATORS	1 (3.70%)	1 (0.36%)	0 (0.00%)	0 (0.00%)
PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS	1 (3.70%)	1 (0.36%)	0 (0.00%)	0 (0.00%)
VITAMINS	1 (3.70%)	1 (0.36%)	1 (3.70%)	1 (0.31%)
Vitamin D and analogues	1 (3.70%)	1 (0.36%)	1 (3.70%)	1 (0.31%)
ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (0.31%)
ENDOCRINE THERAPY	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (0.31%)
NOT CODABLE	1 (3.70%)	1 (0.36%)	0 (0.00%)	0 (0.00%)

Source Table: Appendix for Tables, Table 7.08

All patients had concomitant medication for airways diseases. Overall, the concomitant medication mirrored the previous and concomitant diseases. Remarkably two patients (one in each treatment group) documented Vitamin D as concomitant medication. For one patient (02/003) Vitamin D intake was documented for the day of study end. Another patient (08/002) continued Vitamin D after the end of the treatment phase (V8).

Adverse events: The following three tables summarize the number of adverse events, their causal relationship to study medication as well as their intensity.

Safety table 1: Adverse Events - Overview (Safety Population)

Number of Patients with...	Placebo (All) (N=27)	nAEs	Vitamin D (All) (N=27)	nAEs
...at least one AE	27 (100.00%)	91	24 (88.89%)	99
...at least one AE with causal relationship to initial dose	1 (3.70%)	1	1 (3.70%)	1
...at least one AE with causal relationship to maintenance dose	1 (3.70%)	1	3 (11.11%)	3
...at least one AE with causal relationship to initial or maintenance dose	1 (3.70%)	1	3 (11.11%)	3
...at least one severe AE	3 (11.11%)	4	3 (11.11%)	6
...at least one related (initial or maintenance) severe AE	0 (0.00%)	0	0 (0.00%)	0
...at least one SAE	3 (11.11%)	3	3 (11.11%)	5
...at least one AE leading to death	0 (0.00%)	0	0 (0.00%)	0

Source Table: Appendix for Tables, Table 7.11

All patients in the placebo group and 89% of all patients in the vitamin D group reported at least one AE. A total of 91 AEs (3.4 per patient) in the placebo group and 99 AEs (4.1 per patient) in the vitamin D group were reported.

The overview table does not suggest any treatment differences in adverse events between groups. When looking at the adverse events by system organ class (SOC), the most frequent AEs were respiratory, thoracic and mediastinal disorders in 15 patients (55.6%) from the placebo treatment group (most frequent preferred terms: asthma (37.0%), cough (18.5%)) and in 19 patients (70.4%) from the Vitamin D treatment group (most frequent preferred terms: asthma (55.6%), but no coughs were observed). Frequent were also AEs from the SOC Infections and Infestations (Placebo: 18 pts (66.7%), Vitamin D 15 pts (55.6%)), followed by Musculoskeletal and connective tissue disorders (Placebo: 7 pts (25.9%), Vitamin D 6 pts (22.2%)) and Gastrointestinal disorders (Placebo: 1 pt (3.7%), Vitamin D 6 pts (22.2%)). Apart from Gastrointestinal disorders there were no differences between treatment groups apparent. In the Gastrointestinal disorders SOC 3 patients (11.1%) suffered from diarrhea with Vitamin D treatment and none with placebo treatment.

Safety table 2: Adverse Events - Overview (Safety Population of patients receiving only ICS)

Number of Patients with...	Placebo (ICS) (N=20)	nAEs	Vitamin D (ICS) (N=25)	nAEs
...at least one AE	20 (100.00%)	64	23 (92.00%)	96
...at least one AE with causal relationship to initial dose	1 (5.00%)	1	1 (4.00%)	1
...at least one AE with causal relationship to maintenance dose	1 (5.00%)	1	3 (12.00%)	3

...at least one AE with causal relationship to initial or maintenance dose	1 (5.00%)	1	3 (12.00%)	3
...at least one severe AE	2 (10.00%)	3	3 (12.00%)	6
...at least one related (initial or maintenance) severe AE	0 (0.00%)	0	0 (0.00%)	0
...at least one SAE	2 (10.00%)	2	3 (12.00%)	5
...at least one AE leading to death	0 (0.00%)	0	0 (0.00%)	0

Source Table: Appendix for Tables, Table 7.12

The ICS only subgroup mirrors the results of the entire safety population. All seven gastrointestinal events occurred in the subgroup of patients only receiving ICS.

Safety table 3: Adverse Events - Overview (Safety Population of patients receiving ICS+OCS)

Number of Patients with...	Placebo (ICS+OCS) (N=7)	nAEs	Vitamin D (ICS+OCS) (N=2)	nAEs
...at least one AE	7 (100.00%)	27	1 (50.00%)	3
...at least one AE with causal relationship to initial dose	0 (0.00%)	0	0 (0.00%)	0
...at least one AE with causal relationship to maintenance dose	0 (0.00%)	0	0 (0.00%)	0
...at least one AE with causal relationship to initial or maintenance dose	0 (0.00%)	0	0 (0.00%)	0
...at least one severe AE	1 (14.29%)	1	0 (0.00%)	0
...at least one related (initial or maintenance) severe AE	0 (0.00%)	0	0 (0.00%)	0
...at least one SAE	1 (14.29%)	1	0 (0.00%)	0
...at least one AE leading to death	0 (0.00%)	0	0 (0.00%)	0

Source Table: Appendix for Tables, Table 7.13

In the ICS+OCS subgroup there were too few patients to detect meaningful treatment group differences.

Serious adverse events (SAEs): n=7

In the placebo treatment group 3 patients (11.1%, 06/002, 07/001, 12/001) suffered from serious adverse events. Patient 06/002 receiving only ICS suffered from hypersensitivity (Verbatim: "Allergische Reaktion") with severe intensity. The relationship to initial dose and maintenance dose was assessed as unrelated. The SAE was medicinally treated and was improved after 10 days. Study treatment remained unchanged during treatment. Patient 07/001 receiving only ICS suffered from breast cancer (Verbatim: "Karzinom der Mamma links") with severe intensity. The relationship to initial dose and maintenance dose was assessed as unrelated. The SAE was medicinally treated and recovered after 23 days. The patient was discontinued from the study. Patient 12/001 receiving ICS+OCS experienced a tibia fracture (Verbatim: "Tibiakopffraktur") with severe intensity. The relationship to initial dose and maintenance dose was assessed as unrelated. The SAE needed treatment and improved after 15 days. The patient had to be discontinued from the study.

In the Vitamin D treatment group 3 patients (11.1%, 07/002, 09/001, 09/004) suffered from serious adverse events. Patient 07/002 receiving only ICS experienced twice from pneumonia and once from asthma (Verbatim (1 term was split): "Pneumonie", "Pneumonie (Asthma Exacerbation)") with severe intensity in all cases. The relationship to initial dose and maintenance dose was always assessed as unrelated. The SAEs had to be medicinally treated and recovered after 5, 7 and 7 days. Study treatment was interrupted for the first pneumonia and remained unchanged during treatments. Patient 09/001 receiving only ICS suffered from abdominal adhesions (Verbatim: "abdominal adhesions") with moderate intensity. The relationship to initial dose and maintenance dose was assessed as unrelated. No treatment was undertaken because of the SAE and the patient recovered after 38 days. Study treatment remained unchanged during the SAE. Patient 09/004 receiving only ICS experienced a peritonsillar abscess (Verbatim: "Peritonsillar abscess") with severe intensity. The relationship to initial dose and maintenance dose was assessed as unrelated. The SAE needed treatment and recovered after 6 days. Study treatment remained unchanged during treatment.

Conclusion:

There was no statistical significant difference in the primary endpoint (relative dose reduction of ICS or OCS at visit 8).

In addition, most of the secondary endpoints showed no favourable outcome for vitamin D substitution: The number of exacerbations and time to first exacerbation was similar in both groups. There was no effect of vitamin D substitution on Asthma Control Questionnaire, Asthma Quality of Life, Transition Dyspnea Indexes and pulmonary function throughout the study.

Levels of vitamin D increased to > 30 ng/ml in all but one patient in the vitamin D group.

In summary, the results demonstrate that a sufficient level of vitamin D was not associated with any clinical effect in patients with severe asthma and vitamin D deficiency.

I hereby confirm, that the data in the results report were collected properly and are correct.

21) **Date of the report:** 01.07.2019

Print Name: PD Dr. Stephanie Korn

Signature: