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Klinik mit zertifiziertem Qualitätsmanagementsystem nach DIN EN ISO 9001:2008

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Clinical Trial Report

Synopsis according to ICH E3 guideline

Version 1.1 / date: 30.11.2020
Resubmission of Version 1.0 (date: 29.04.2014)

Immunological response of a single dose of 100,000 I.U. of cholecalciferol (vitamin D3)

Investigational medicinal product (IMP):	**D3-Vicotrat®**
Eudra-CT number:	**2012-003217-33**
Protocol-code:	**ViDImmun**
Indication studied:	**Immune system processes**
Study design:	**placebo-controlled, parallel, double-blind randomized**
Development phase:	**therapeutic exploratory (Phase II)**
Trial dates	**start (first subject enrolled): 5 Feb 2013** **end (last subject completed): 15 May 2013**

Sponsor

Charité - Universitätsmedizin Berlin | Charitéplatz 1 | 10117 Berlin

Authorized representative of sponsor and principal investigator

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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 No unpublished information contained herein will be published or disclosed without prior approval by the sponsor.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.

Authorized representative of sponsor/ principal investigator
Prof. Margitta Worm

Signature: _____ Date: 26 Nov 2020

Project coordinator
Dr. Sabine Dölle-Bierke

Signature: _____ Date: 26/NOV/2020

Table of contents

Table of contents 3
1 Synopsis 4
List of Abbreviations and Definitions of Terms 9
2 Study population 10
3 Efficacy evaluation 10
3.1 Measurement of treatment compliance 10
3.2 Efficacy Results and Tabulations of Individual Subject Data 10
3.2.1 Analysis of efficacy 10
3.2.1.1 Primary efficacy parameter 10
3.2.1.2 Secondary efficacy parameters 11
4 Safety evaluation 12
4.1 Adverse Events 12
4.2 Death, other serious or other significant adverse events (SAE) 12
4.3 Clinical laboratory Evaluation 12
4.4 Vital signs, physical findings, and other observations related to safety 13
4.5 Evaluation of tolerability 13
5 Appendix 14

1 Synopsis

Name of Sponsor: Charité - Universitätsmedizin Berlin **Authorized representative:** Prof. M. Worm	
Name of finished product: D3-Vicotrat®	
Name of active ingredient: Cholecalciferol	

Title of study	Immunological response of a single dose of 100,000 I.U. of cholecalciferol (vitamin D3).
Investigators	Principal investigator Prof. Dr. med. Margitta Worm Charité – Universitätsmedizin Berlin Department of Dermatology, Venereology and Allergology Charitéplatz 1, 10117 Berlin, Germany Phone: +49 (0)30-450 518 105 Fax: +49 (0)30-450 518 931 E-mail: margitta.worm@charite.de Investigator PD Dr. med. Guido Heine Charité – Universitätsmedizin Berlin Department of Dermatology, Venereology and Allergology Charitéplatz 1, 10117 Berlin, Germany (since 09-2019: Universitätsklinikum Schleswig-Holstein, Campus Kiel Department of Dermatology and Allergology Arnold-Heller-Straße 3, 24105 Kiel, Germany)
Study centers	Mono-center Study center Charité – Universitätsmedizin Berlin Department of Dermatology, Venereology and Allergology Charitéplatz 1, 10117 Berlin, Germany Visitor address: 2nd floor, room 14 Luisenstr. 2, 10117 Berlin, Germany
Publication (reference)	The results of the study are partially published in the following reference: Pharmacokinetic Evaluation of a Single Intramuscular High Dose versus an Oral Long-Term Supplementation of Cholecalciferol. Wylon K, Drozdenko G, Krannich A, Heine G, Dölle S, Worm M. PLoS One. 2017 Jan 23;12(1):e0169620. doi: 10.1371/journal.pone.0169620.
Phase of development	Therapeutic exploratory (phase II)
Study period	3.5 months Date of first subject enrolled: 5 February 2013 Date of last subject completed: 15 May 2013

Name of Sponsor: Charité - Universitätsmedizin Berlin **Authorized representative:** Prof. M. Worm	
Name of finished product: D3-Vicotrat®	
Name of active ingredient: Cholecalciferol	

Main objective	The main objective of the trial was to assess the impact of vitamin D3 on immune cells (frequency of $CD38^+$ B cells) in subjects with relative vitamin D3 deficiency after one injection of 100,000 I.U. either intramuscular (i.m.) or subcutaneous (s.c.).
Secondary objectives	Frequency of vitamin D3-responsive T cells. Immunological parameters (T cell phenotype, activation of monocytes, specific immunoglobulins) Pharmacokinetic Safety Tolerability
Methology **- study design**	Placebo-controlled, parallel, double-blind, randomized
- Primary endpoint	Assessment of the frequency of $CD38^+$ B-cells before as well as 7, 28 and (84) days after study drug application. Measurement by flow cytometry. Analysis as pre-post comparison after vitamin D3 injection (i.m. or s.c.).
- Secondary endpoints	- Assessment of the frequency of vitamin D3-responsive T cells carrying vitamin D3-sensitive surface markers before as well as 7, 28 and (84) days after study drug application. Measurement by flow cytometry. Analysis as pre-post comparison after vitamin D3 injection (i.m. or s.c.). - Assessment of immunological parameters (activation of monocytes, specific immunoglobulins) by flow cytometry and ELISA. - Pharmacokinetic: Measurement of vitamin D3 metabolites (25-hydroxyvitamin D3) before and after injection. - Safety assessment happened at every visit and the safety lab was performed at screening, visit 8, visit 12 and visit 13. - Tolerability assessment was done at 2, 6, 24, 48 and 72 h after study drug application by the subject themselves.
Investigational product, dose and mode of administration, batch number	Trade name: D3-Vicotrat Active substance: Cholecalciferol 1 vial with 1 ml Solution for injection contains 2.5 mg Cholecalciferol (equal to 100.000 I.U. vitamin D3) Manufacturer: HEYL Chem.-pharm. Fabrik GmbH & Co. KG, Kurfürstendamm 178-179, 10707 Berlin, Germany; approval number: 6813051.00.00 Other ingredients: Sodiumhydrogenphosphate dihydrate, sodium hydroxide, sorbitol solution 70 % (crystallizing), polysorbat 80, middle chain triglyceride, water for injection Single dose intramuscular (i.m.) or subcutaneous (s.c.) use Batch numbers are listed in appendix-table 1.

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Name of finished product: D3-Vicotrat®	
Name of active ingredient: Cholecalciferol	

Comparator	Placebo Isotonic sodium chloride solution 0.9% Active substance: none Other ingredients: sodium chloride 0.9 g in 100 ml solution, water for injection Manufacturer: B. Braun Melsungen AG, Carl-Braun-Straße 1, 34212 Melsungen, Germany; approval number: 6697366.00.00 Single dose intramuscular (i.m.) or subcutaneous (s.c.) use Batch numbers are listed in appendix-table 1.
Duration of treatment	Intervention phase: 12 weeks
Study population	Planned: 40 Included: 40 (Drop-outs: 1, Excluded due to protocol deviation: 1) Analyzed: 38 (12 vitamin D3 i.m., 13 vitamin D3 s.c., 6 placebo i.m., 7 placebo s.c.) Demographic and other baseline characteristics (see chapter 2)
Diagnosis and main inclusion criteria	• man and woman aged between 18 - 60 years • vitamin D3 deficiency defined as 25-hydroxyvitamin D3 (25-OH-VD) serum level ≤50 nmol/l • written informed consent according to AMG §40 (1) 3b
Criteria for evaluation Efficacy Safety	• frequency of CD38+ B-cells • Frequency of vitamin D3-responsive T-cells carrying vitamin D3-sensitive surface markers. • Immunological parameters (activation of monocytes, specific immunoglobulins) • Pharmacokinetic (25-OH-VD serum level) Safety was assessed by the following: - case history - physical examination - recording of adverse events (AE) by the investigator - safety laboratory including the important parameters to assess vitamin D3-related parameters (calcium, phosphate and creatinine) - pregnancy test - tolerability after 2, 6, 24, 48 an d72 h after study drug injection, assessed by the subjects and investigator on the following scale (1 – very good, 2 – good, 3 – moderate, 4 – poor, 5- very poor)
Statistical methods	All data obtained in this clinical trial and documented in the case report form (CRF)s were analyzed with descriptive group statistics. All randomized sub-

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Name of active ingredient: Cholecalciferol	

	jects who got the single injection of study drug either i.m. or s.c. represent the intent-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. <u>Sample Size</u> Although the clinical trial had an exploratory character a sample size calculation was performed as demanded by the IEC. The In total, 36 subjects were randomized into four arms: • Vitamin D3 i.m. (n=12) • Vitamin D3 s.c. (n=12) • Placebo i.m. (n=6) • Placebo s.c. (n=6) A drop-out rate of 10% was assumed. Thus, 40 subjects were randomized. As there were no immunological changes expected in the placebo group, the i.m. and s.c. group were taken together: Group 1: Vitamin D3 i.m. (n=13) Group 2: Vitamin D3 s.c. (n=13) Group 3: Placebo i.m. and Placebo s.c. (n=14) The primary endpoint was the frequency of $CD38^+$ B cells in comparison before and after study drug injection. The groups mean values (in %) were assumed to be: Group 1: $\mu_{\Delta 1} = 1.4$ Group 2: $\mu_{\Delta 2} = 1.4$ Group 3: $\mu_{\Delta 3} = 0$ The vitamin D3 groups are not taken together as those groups may be different and may be detect in the exploratory analyses.
Changes in the conduct of the clinical study	The clinical trial was conducted according to the protocol version 1.4 dated 28th January 2013 with the subject information version 1.5 from 5th Feburary 2013 and the informed consent version 1.2 from 15th January 2013. During the clinical study no additional documents were sent to the IEC for reviewing (no protocol amendments). No study discontinuation occurred.
Efficacy conclusion	After vitamin D3 supplementation a significant increase of $CD38^+$ plasma but not naive or memory cells was observed. The data indicates that CD38 is a candidate surrogate marker in the context of vitamin D3 supplementation but does not correlate with 25-OH-VD serum levels.

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	The vitamin D3 injection either i.m. or s.c. lead to an increase of 25-OH-VD and peaked after 28 days. The 25-OH-VD serum level at the peak was below the maximal levels that can be reached by any vitamin D3 supplementation but reached levels to compensate vitamin D3 deficiency. There was no significant difference between the serum levels between the different routes of application of vitamin D3. Detailed description depicted below chapter 3.
Safety conclusion	The safety of the investigational drug was assessed by the safety laboratory measures especially of calcium and phosphate. All safety parameters were clinically correlated and no (serious) adverse events due to lab values were noted. The tolerability of the application and side effects were assessed by the subjects and the physician using a subject tolerability score ranging from one (very good) to six (poor). The injections of vitamin D3 and placebo were well tolerated. No side effects or AEs events related to the investigational drug were noted throughout the clinical study. The evaluation of tolerability by the subjects was excellent. Detailed description depicted below chapter 4.
Discussion and overall conclusion	Vitamin D3 supplementation was successful and peaked after 28 days. There was no significant difference between the 25-OH-VD serum levels of the vitamin D3-treated groups, which could be important for future drug certification. After vitamin D3 supplementation CD38 expression was only significantly induced in a sub-population of B cells (plasma but not naive or memory cells). The increase of CD38 expression after vitamin D3 supplementation on plasma cells did not correlate with the 25-OH-VD serum levels. Other immunological changes were not determined before and after supplementation. The safety and tolerability was very good, no drug-related AE or SAE were observed. The pharmacokinetic analysis shows that after vitamin D3 supplementation the 25-OH-VD serum levels increase to sufficient values compensating the vitamin D3 deficiency. No toxic or insufficient levels were reached. Most interestingly, the pharmacokinetics indicates no differences of the 25-OH-VD serum levels between the different routes of application (i.m. versus s.c.) and an equivalent tolerability suggesting that both routes are suitable to be used in clinical practice.

List of Abbreviations and Definitions of Terms

AE	adverse event
AMG	Arzneimittelgesetz (German drug law)
ALT	alanine aminotransferase
CRF	case report form
CD	cluster of differentiation
GCP	good clinical practice
GGT	gamma glutamyltransferase
HLA-DR	human leucocyte antigen with the gene locus DR
ICH	international conference of harmonization
IEC	independent ethics committee
IMP	investigational medicinal product
i.m.	intramuscular
ITT	intention-to-treat
PP	per-protocol
SAE	severe adverse event
s.c.	subcutaneous
SD	source date
SOP	standard operating procedures
25-OH-VD	25-hydroxyvitamin D3

2 Study population

Demographic and other baseline characteristics

An overview over the subjects is provided in the CONSORT flow diagram (appendix figure 1). The baseline characteristics are summarized in Table 1. The individual subject data for baseline characteristics is listed in (appendix table 2).

Table 1: Baseline characteristics.

Variable	Group 1 (Vitamin D3 i.m.)	Group 2 (Vitamin D3 s.c.)	Group 3 (Placebo)
Number (n)	12	13	13
Sex (f/m)	8 / 4	9 / 4	9 / 4
Age (Years)	34,9 ± 9,1	31,4 ± 9,4	36 ± 13
Height (cm)	172,9 ± 8,0	170,7 ± 8,3	172,1± 6,8
Weight (kg)	66,4 ± 9,6	65,7 ± 11,6	66,4 ± 12,7
Body Mass Index (BMI)	22,2 ± 3,2	22,4 ± 2,5	22,3 ± 3,6

3 Efficacy evaluation

3.1 Measurement of treatment compliance

The application of the study drug was conducted by an unblinded study nurse on day 1 of the clinical study. Thus, 100% compliance was given.

3.2 Efficacy Results and Tabulations of Individual Subject Data

3.2.1 Analysis of efficacy

3.2.1.1 Primary efficacy parameter

The primary efficacy parameter was the determination of the proportion of vitamin D3-responsive cells ($CD38^+$ B cells) circulating in peripheral blood before and after cholecalciferol injection (i.m. or s.c.) in vitamin D3 deficient individuals. The picture of $CD38^+$ B cells is represented by the specific subsets: $CD38^+$ naive, memory or plasma B cells.
There were no significant differences concerning the blood circulating $CD38^+$ B cell subsets in comparison between i.m. and s.c. injection detectable.
In detail, $CD38^+$ plasma B cells increased significantly ($p < 0.01$) one month after vitamin D3 injection. However, this did not correlate with the 25-OH-VD serum level.
The $CD38^+$ naive B cell and $CD38^+$ memory B cell frequencies did not change from baseline (visit 1) to day 28 (visit 8) within all groups.
An additional measurement for $CD38^+$ B cells was performed on day 84 (3 months after injection, visit 13). As this visit was dated in the beginning/mid of May 2013, the 25-OH-VD serum levels were elevated for all subjects due to the natural sun exposure. Thus, the data for $CD38^+$ may be biased and therefore are not shown in Fig. 1. All individual values throughout the clinical study are listed in the individual data listing of $CD38^+$ B cells (appendix table 3).

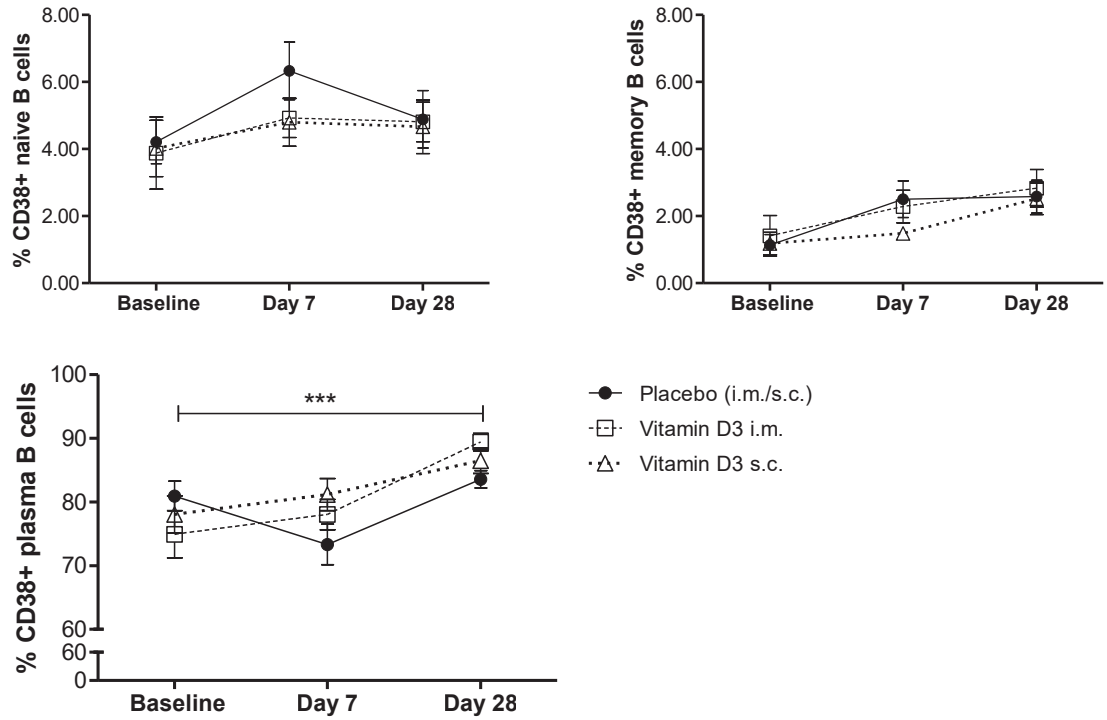

Fig. 1: Primary efficacy parameter CD38⁺ naive B cells, CD38⁺ memory B cells and CD38⁺ plasma B cells; The mean and standard deviation are shown during three consecutive time points (baseline, day 7, day 28). CD38⁺ plasma B cells increased significantly ($p < 0.01$) one month after vitamin D3 injection (i.m. and s.c.). For individual subjects data listing of the CD38⁺ see appendix table 3.

3.2.1.2 Secondary efficacy parameters

The immunological secondary efficacy parameters including changes in CD38⁺ T-cell phenotypes, alteration in monocyte activation and humoral immune response were analyzed and did not reveal any significant changes between before and after treatment. In addition, there were also no differences between the verum and placebo group (data not shown, individual subjects' data listing see appendix table 4 - 6).

The pharmacokinetics, safety and tolerability were assessed as secondary objectives throughout the clinical study.
Concerning the pharmacokinetic analysis the 25-OH-VD serum level increased after vitamin D3 injection by a Δ mean (baseline to day 28) of 40.0 ±20.8 nmol/l in the i.m. group and by 44.2 ±16.9 nmol/l in the s.c. group. As expected there were no changes in the placebo group (Δ baseline to day 28: 0.6 ±9.11 nmol/l) during the UV-deprived winter months. The time course of 25-OH-VD serum levels over 2 month are depicted in Fig..

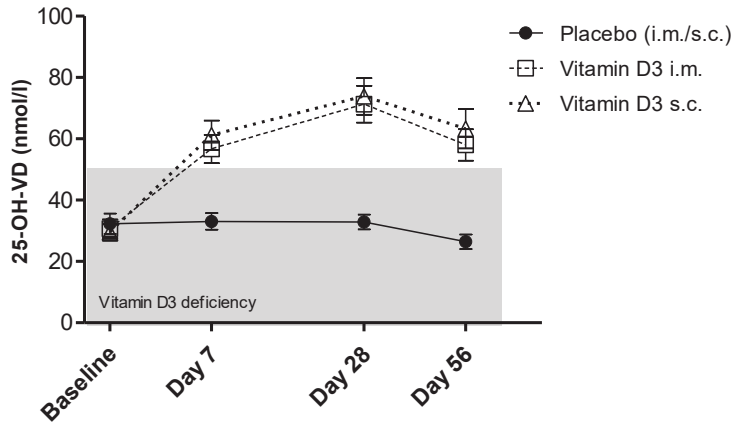

Fig. 2: Serum levels of 25-OH-VD in nmol/l of all individuals over 2 months. The mean and standard deviation is shown in the figure from all three groups. Vitamin D3 deficiency is defined with 25-OH-VD <50 nmol/l (grey shaded area). The last time point of 25-OH-VD measurement is not shown because of natural sun exposure bias. For individual subjects data listing of the $CD38^+$ see appendix table 7.

4 Safety evaluation

4.1 Adverse Events

There were only few AE. An overview is given in Table 2. The majority of AE were connected to the flu season.

Table 2: Overview of AE.

All treatment-emergent AE	**ITT group total 40 subjects**	
System organ class	**F**	**N**
Respiratory, thoracic and mediastinal disorders	11	11
TOTAL	**11**	**11**

Source: appendix table 8
F = number of AE, N = number of subjects with AE

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

No SAE or to death leading events occurred. No other significant AE were reported that shows newly appeared reactions of the study drug.

4.3 Clinical laboratory Evaluation

Serum calcium and phosphate levels were monitored during the clinical study for safety purposes and summarized in Fig. 3. Five individuals showed a clinical not relevant hypophosphatemia which was not related to vitamin D3 supplementation. As those individuals had low non-symptomatic phosphate baseline levels. Three received vitamin D3 and two received placebo.

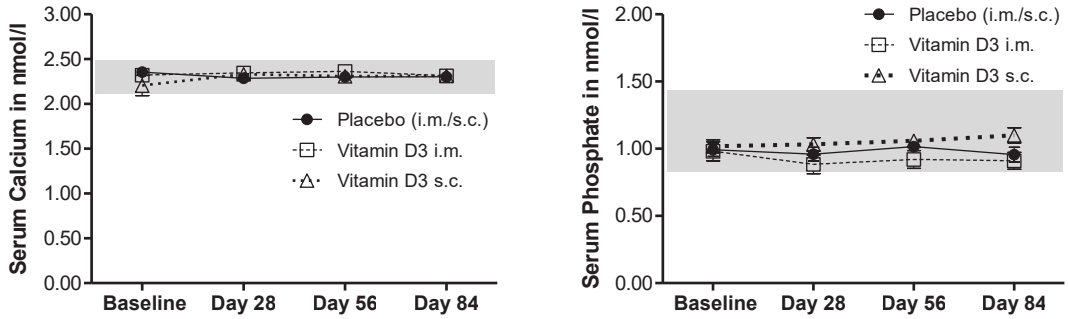

Fig. 3: Serum calcium and phosphate levels of all individuals throughout the clinical study. The mean and standard deviation is shown in the figures from all three groups. Normal ranges of laboratory are grey shaded (serum calcium range 2.15 - 2.5 nmol/l, serum phosphate range 0.87 – 1.45 nmol/l).

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

All subjects were healthy and vital parameters were in physiological range.
No individual listings are enclosed. Evaluation of each vital parameter

4.5 Evaluation of tolerability

The tolerability of the application was assessed by the subject using a 5 point tolerability scale (1 – very good, 2 – good, 3 – moderate, 4 – bad, 5 – very bad). The injections of vitamin D3 and placebo were well tolerated from all 40 subjects with an overall median value of 1 point. The worst score was 3 points in 3 subjects all in the i.m. application of vitamin D3).

Individual subject listing of tolerability see appendix table 9.

5 Appendix

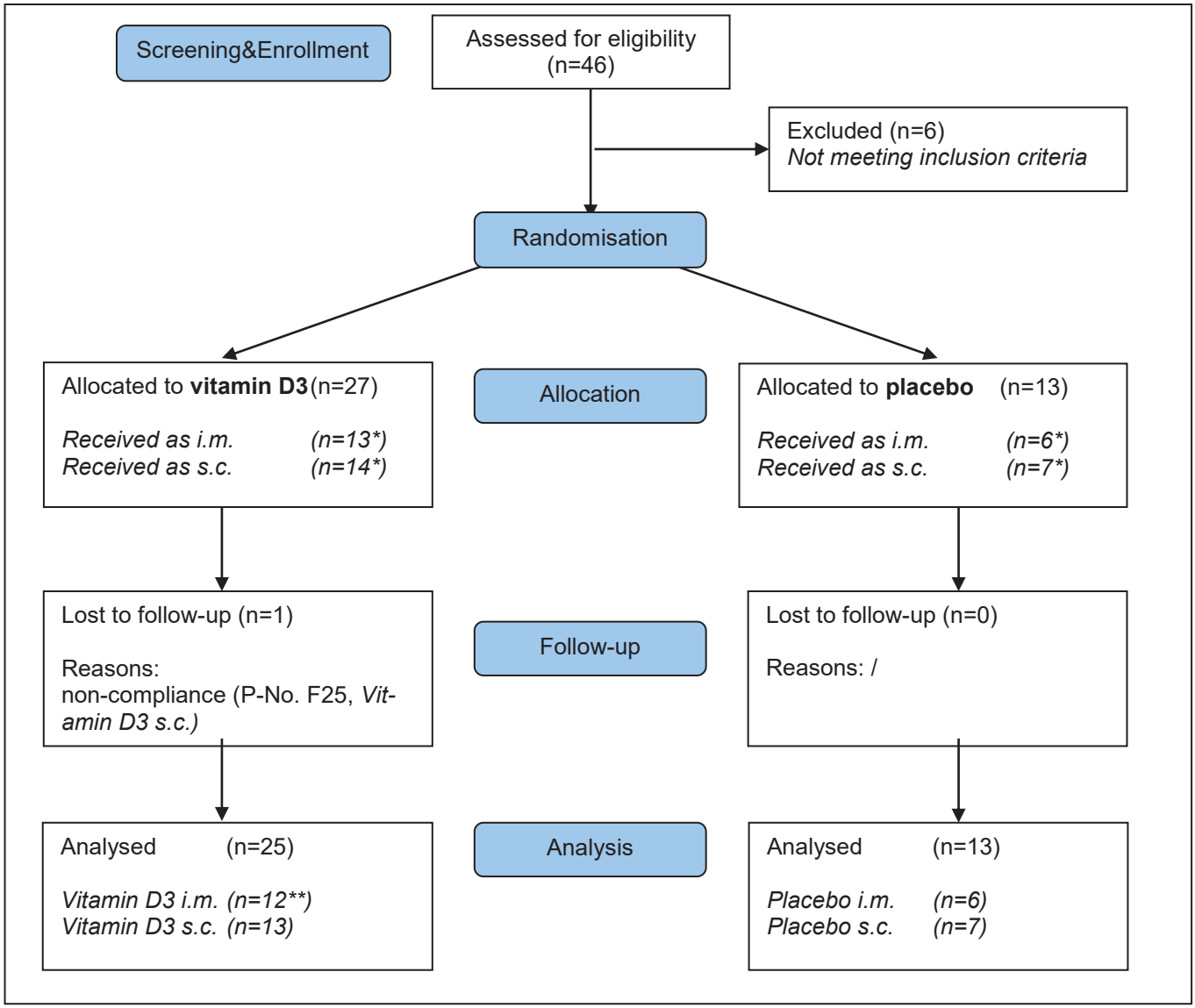

Figure 1: CONSORT Flow Diagram. According to Schulz et al. 2010 [7]. *deviation to the protocol due to randomization schedule (Appendix); **protocol deviation by subject F15.

Appendix-Table 1: Randomization scheme, assignment and batch numbers

R.-No.	Assignment (treatment)	Assigend (yes/no)	Batch-number
F01	Verum s.c.	yes	B111061
F02	Verum i.m.	yes	B111061
F03	Verum i.m.	yes	B111061
F04	Placebo i.m.	yes	12454013
F05	Placebo s.c.	yes	12454013
F06	Verum s.c.	yes	B111061
F07	Verum s.c.	yes	B111061
F08	Placebo i.m.	yes	12454013

R.-No.	Assignment (treatment)	Assigend (yes/no)	Batch-number
01	Verum s.c.	yes	B111061
02	Verum i.m.	yes	B111061
03	Verum i.m.	yes	B111061
04	Placebo i.m.	yes	12454013
05	Verum s.c.	yes	B111061
06	Placebo s.c.	yes	12454013
07	Verum i.m.	yes	B111061
08	Placebo s.c.	yes	12454013

R.-No.	Assignment (treatment)	Assigend (yes/no)	Batch-number
F09	Verum s.c.	yes	B111061
F10	Placebo s.c.	yes	12454013
F11	Verum i.m.	yes	B111061
F12	Verum i.m.	yes	B111061
F13	Verum i.m.	yes	B111061
F14	Verum s.c.	yes	B111061
F15	Placebo i.m.	yes	B111061*
F16	Placebo s.c.	yes	12454013
F17	Verum i.m.	yes	B111061
F18	Verum s.c.	yes	B111061
F19	Verum i.m.	yes	B111061
F20	Verum s.c.	yes	B111061
F21	Placebo i.m.	yes	12454013
F22	Verum s.c.	yes	B111061
F23	Placebo s.c.	yes	12454013
F24	Verum i.m.	yes	B111061
F25	Verum s.c.	yes	B111061
F26	Placebo i.m.	yes	12454013
F27	Placebo s.c.	yes	12454013
F28	Verum s.c.	yes	B111061
F29	Verum i.m.	no	
F30	Verum i.m.	no	
F31	Placebo s.c.	no	
F32	Verum i.m.	no	
F33	Verum i.m.	no	
F34	Verum s.c.	no	
F35	Verum s.c.	no	
F36	Placebo i.m.	no	

R.-No.	Assignment (treatment)	Assigend (yes/no)	Batch-number
09	Verum s.c.	yes	B111061
10	Verum s.c.	yes	B111061
11	Verum i.m.	yes	B111061
12	Placebo i.m.	yes	12454013
13	Verum i.m.	no	
14	Verum i.m.	no	
15	Placebo s.c.	no	
16	Verum s.c.	no	
17	Verum s.c.	no	
18	Placebo i.m.	no	
19	Verum i.m.	no	
20	Placebo i.m.	no	
21	Verum s.c.	no	
22	Placebo s.c.	no	
23	Verum i.m.	no	
24	Verum s.c.	no	
25	Verum i.m.	no	
26	Verum i.m.	no	
27	Placebo i.m.	no	
28	Verum s.c.	no	
29	Placebo s.c.	no	
30	Verum s.c.	no	
31	Verum i.m.	no	
32	Verum i.m.	no	
33	Placebo i.m.	no	
34	Placebo s.c.	no	
35	Verum s.c.	no	
36	Verum s.c.	no	

* assigned wrong -> protocol deviation

Appendix-Table 2: Individual subject date listing of demographic information

S-No.	R-No.	Age (years)	Sex	Height (cm)	Weight (kg)	Ethnic group
1	F03	27	female	156	73	caucasian
2	F11	28	female	178	60	caucasian
3	F06	28	female	162	50	caucasian
4	F07	26	female	163	50	caucasian
5	F04	29	female	171	62	caucasian
6	03	33	male	176	72	caucasian
7	F5	30	female	170	60	caucasian
8	01	20	male	170	75	caucasian
9	04	36	male	183	75	caucasian
10	F02	29	female	176	69	indian

S-No.	R-No.	Age (years)	Sex	Height (cm)	Weight (kg)	Ethnic group
11	F09	45	female	165	62	caucasian
13	F12	30	female	165	60	caucasian
14	F13	29	female	165	50	caucasian
15	09	25	male	192	86	caucasian
18	F08	58	female	157	53	caucasian
19	F10	42	female	165	62	caucasian
20	F14	30	female	173	69	caucasian
21	02	38	male	178	69	caucasian
22	F15	26	female	164	62	caucasian
23	F16	55	female	170	86	caucasian
24	F17	55	female	168	64	caucasian
25	08	21	male	176	73	caucasian
27	F18	36	female	173	68	caucasian
28	F19	29	female	172	55	caucasian
29	F20	26	female	168	56	caucasian
30	F21	28	female	167	53	caucasian
31	F01	48	female	164	65	caucasian
32	07	30	male	182	69	caucasian
33	F22	44	female	163	58	caucasian
34	F23	29	female	173	68	caucasian
35	F24	47	female	176	69	caucasian
36	06	27	male	172	58	caucasian
38	05	26	male	175	75	caucasian
39	F25	26	female	160	48	caucasian
41	F26	24	female	183	60	caucasian
43	10	20	male	173	58	caucasian
44	11	44	male	183	87	caucasian
45	12	61	male	179	97	caucasian
46	F27	34	female	171	56	caucasian
47	F28	34	female	178	83	caucasian

Appendix-Table 3 Individual subject data listings of CD38$^+$ B cell subsets

		% CD38+ cells of total plasma B cells				% CD38+ cells of total naive B cells				% CD38+ cells of total memory B cells			
S-No	R-No	V1	V5	V8	V13	V1	V5	V8	V13	V1	V5	V8	V13
1	F03	59.5	77.9	89.4	87.7	1.41	2.35	8.29	1.22	0.59	1.38	3.59	2.65
2	F11	56.2	58.6	78.6	86.2	1.14	2.73	2.55	1.29	0.02	2.21	1.66	4.45
3	F06	69.9	77.0	83.5	79.1	1.02	1.25	2.29	2.48	0.08	2.03	2.55	7.06
4	F07	83.7	85.6	87.0	88.0	2.01	3.48	3.91	2.38	0.00	1.75	2.31	1.79
5	F04	82.7	85.3	91.4	92.0	1.64	5.78	3.44	2.88	0.11	6.54	2.34	3.04
6	3	60.9	82.2	88.9	90.2	1.40	4.90	6.11	4.64	0.00	1.69	2.61	1.64
7	F05	79.5	n/a	85.4	86.8	2.14	n/a	5.59	5.28	0.09	n/a	2.23	2.47
8	1	60.0	69.2	84.9	91.8	1.73	3.55	2.33	1.98	0.00	1.28	2.60	1.43
9	4	83.3	69.8	78.9	97.0	1.60	2.61	1.93	1.04	0.51	1.84	2.52	1.53
10	F02	56.3	67.9	89.1	80.8	0.37	3.27	1.93	2.27	0.00	1.06	1.35	1.23
11	F09	55.3	60.0	68.0	57.0	1.91	3.33	2.74	1.75	0.01	0.94	1.01	0.73
13	F12	81.6	79.1	85.6	91.8	3.63	8.00	6.75	2.11	0.04	3.43	3.14	4.63
14	F13	83.8	78.8	91.2	84.6	3.18	6.03	5.03	6.00	0.13	1.44	1.54	3.00
15	9	84.8	82.8	92.8	85.0	4.41	3.99	3.23	5.22	1.39	0.76	1.98	2.44
18	F08	82.9	76.5	87.9	91.6	2.77	4.10	2.47	3.01	0.06	3.00	1.78	2.04
19	F10	69.4	62.4	85.6	96.0	2.31	6.95	4.77	1.79	0.02	1.86	0.73	0.58
20	F14	80.1	84.9	85.6	87.3	3.79	4.21	4.84	6.64	2.51	1.56	1.60	3.43
21	2	86.7	73.3	94.2	89.1	2.16	4.14	4.10	7.77	0.00	1.10	1.12	2.00
23	F16	77.6	76.7	77.5	89.1	5.95	5.87	3.04	7.93	1.67	2.02	1.10	1.93
24	F17	79.4	86.0	97.6	98.2	5.80	4.78	4.14	5.84	3.87	2.88	6.85	10.20
25	8	82.9	68.1	84.9	80.4	3.16	8.80	9.44	4.19	0.09	4.46	3.61	2.15
27	F18	86.8	90.0	83.9	74.7	11.60	10.70	9.12	12.10	2.96	2.66	7.31	4.25
28	F19	80.3	88.1	93.2	86.6	6.79	7.07	6.49	5.50	2.01	0.84	1.38	2.46
29	F20	79.1	74.4	82.9	92.5	3.76	4.37	3.70	3.66	0.75	0.75	1.50	2.62
30	F21	87.3	n/a	90.5	94.2	5.65	n/a	4.87	9.22	2.34	n/a	2.18	7.38
31	F01	75.4	89.5	88.8	94.6	1.37	4.50	3.66	3.94	0.31	1.46	1.21	2.14
32	7	83.0	85.6	90.2	88.7	3.43	5.11	4.69	4.23	0.11	7.01	6.41	4.12
33	F22	79.6	79.4	95.1	93.7	4.35	5.01	4.03	5.43	2.84	1.56	1.66	5.61
34	F23	70.3	67.2	78.1	78.4	8.67	9.49	5.92	6.25	2.63	1.44	1.51	8.73
35	F24	80.4	77.6	87.2	77.4	3.13	2.69	1.72	2.62	4.40	2.64	2.71	1.92
36	6	97.6	94.4	85.7	95.9	8.07	10.60	12.70	2.45	0.75	1.34	7.21	7.35

		% CD38+ cells of total plasma B cells				% CD38+ cells of total naive B cells				% CD38+ cells of total memory B cells			
S-No	R-No	V1	V5	V8	V13	V1	V5	V8	V13	V1	V5	V8	V13
38	5	82.5	85.7	83.4	92.3	3.11	9.44	12.20	9.38	0.09	1.09	4.44	2.70
41	F26	66.5	69.7	84.3	83.3	3.67	2.81	2.22	2.99	1.94	1.48	4.32	2.31
43	10	88.9	92.0	95.0	95.0	4.53	5.71	5.60	7.77	2.32	2.02	3.06	6.24
44	11	91.1	81.2	87.7	84.8	14.10	8.00	5.88	7.87	5.80	1.72	1.62	2.27
45	12	83.3	63.2	76.9	71.6	4.23	6.28	4.31	4.71	1.26	1.06	0.70	2.15
46	F27	88.9	n	79.2	95.0	4.85	n	2.82	2.39	3.28	n	3.33	6.23
47	F28	88.5	84.5	93.2	89.4	8.66	2.85	2.99	2.55	2.10	1.47	1.46	2.21

S-No. – Screenning number; R-No. – Random number; n/a – not able to analyse; n – visit not attended
Data is listed for the PP population; missing date F15 and F25

Appendix-Table 4 Individual subject data listings of CD38^{+}CD4^{+} T cell subsets. Visit 8 could not be analysed due to technical reasons.

		% CD38+ cells of total CD4+ naive T cells			% CD38+ cells of total CD4+ effector memory T cells			% CD38+ cells of total CD4+ central memory T cells		
S-No	R-No	V1	V5	V13	V1	V5	V13	V1	V5	V13
1	F03	3.29	11.7	1.49	17.70	0.37	14.60	1.55	1.50	2.61
2	F11	3.55	10.4	6.70	20.40	1.48	20.70	1.89	0.40	1.25
3	F06	11.0	13.7	16.5	26.80	0.32	24.40	3.14	0.70	3.28
4	F07	11.4	13.4	14.0	19.20	0.63	15.30	2.99	0.80	3.59
5	F04	5.12	8.26	7.35	17.90	0.38	16.20	4.08	0.10	2.73
6	3	8.93	11.4	8.45	45.10	1.16	43.50	1.68	0.20	1.19
7	F05	5.97	n/a	11.6	20.80	n/a	23.10	2.38	n/a	0.84
8	1	4.80	13.2	8.53	17.10	1.57	22.40	3.87	0.20	1.94
9	4	12.4	7.01	8.79	36.10	1.16	46.80	3.15	0.30	0.55
10	F02	11.5	20.2	7.63	32.30	0.77	30.20	2.78	0.80	1.68
11	F09	11.3	5.98	9.61	38.10	0.50	43.40	4.41	0.20	1.66
13	F12	6.6	8.98	7.37	27.30	0.69	28.30	4.56	0.80	1.81
14	F13	9.32	8.36	8.03	30.70	0.65	29.30	6.12	0.30	3.26
15	9	4.20	19.1	14.2	28.10	2.81	34.30	0.97	5.40	2.97
18	F08	10.7	8.39	5.13	24.70	1.03	22.60	5.76	0.20	1.54
19	F10	16.8	11.2	12.0	36.10	2.10	36.20	6.21	0.20	0.69
20	F14	1.20	26.4	7.44	17.80	6.46	22.20	0.34	3.80	3.58

		% CD38+ cells of total CD4+ naive T cells			% CD38+ cells of total CD4+ effector memory T cells			% CD38+ cells of total CD4+ central memory T cells		
S-No	R-No	V1	V5	V13	V1	V5	V13	V1	V5	V13
21	2	5.38	16.9	13.2	38.30	2.27	31.00	3.41	0.70	2.37
23	F16	2.97	17.8	9.83	49.60	9.08	49.30	3.14	1.00	3.67
24	F17	3.84	19.8	14.2	29.40	5.11	32.40	1.15	3.40	3.82
25	8	4.48	17.7	5.06	20.10	2.07	16.20	1.20	0.40	1.09
27	F18	5.75	22.8	13.6	21.60	10.80	15.60	4.47	6.10	4.48
28	F19	6.38	30.2	20.7	29.00	5.14	27.80	3.62	7.40	5.19
29	F20	9.54	22.1	14.3	35.70	3.33	32.30	1.15	5.40	4.38
30	F21	2.32	n/a	9.91	20.90	n/a	21.00	0.58	n/a	3.03
31	F01	19.5	4.25	17.9	23.00	0.35	23.50	4.50	0.20	5.34
32	7	16.9	16.8	7.04	38.00	1.99	26.80	3.54	1.40	0.94
33	F22	3.55	17.1	7.08	33.20	6.12	42.60	1.01	4.10	2.52
34	F23	2.50	22.5	6.65	27.40	4.04	26.50	0.65	6.80	3.22
35	F24	3.41	19.9	14.4	16.90	3.89	21.50	0.74	6.50	2.83
36	6	8.34	17.8	10.8	26.50	2.96	39.40	3.53	1.10	1.38
38	5	9.16	28.3	8.1	34.60	2.22	33.80	1.56	0.60	2.23
41	F26	2.27	28.9	3.37	12.50	3.99	12.90	0.28	4.50	1.96
43	10	3.85	24.0	12.3	26.00	8.03	17.90	1.13	9.40	2.63
44	11	6.23	23.6	19.2	28.10	4.69	26.60	1.26	7.50	3.61
45	12	3.39	19.6	14.9	47.70	6.41	29.50	2.61	3.60	2.36
46	F27	2.61	n	4.52	17.70	n	18.50	1.37	n	2.06
47	F28	1.78	9.89	9.14	20.50	4.89	22.00	0.70	2.10	3.22

S-No. – Screenning number; R-No. – Random number; n/a – not able to analyse; n – visit not attended
Data is listed for the PP population; missing date F15 and F25

Appendix-Table 5 Individual subject data listings of monocytes. CD14 is a characteristic marker of monocytes. $CD14^{+}CD16^{+}$ cells are a specific monocyte subset. The activation of this subset may be regulated by vitamin D3. Activation of monocytes is measured by HLA-DR.

		% $CD14^{+}$ monocytes of lymphocytes				% $CD16^{+}HLA\text{-}DR^{+}$ cells of total CD14+ monocytes				% $CD16^{+}HLA\text{-}DR^{-}$ cells of total CD14+ monocytes				% $CD16^{-}HLA\text{-}DR^{+}$ cells of total CD14+ monocytes				% $CD16^{-}HLA\text{-}DR^{-}$ cells of total CD14+ monocytes			
S-No	R-No	V1	V5	V8	V13	V1	V5	V8	V13	V1	V5	V8	V13	V1	V5	V8	V13	V1	V5	V8	V13
1	F03	6.53	8.61	10.9	5.9	2.18	6.79	8.07	2.17	7.07	6.82	8.26	5.36	7.08	6.02	7.91	5.21	83.7	80.4	75.8	87.3
2	F11	14.5	27.2	12.6	21.5	0.37	1.09	1.67	1.77	2.38	5.04	1.36	5.24	1.04	3.97	2.11	2.57	96.2	89.9	94.9	90.4
3	F06	13	14.4	11.7	4.01	1.00	3.00	3.47	2.43	4.60	9.4	8.02	8.44	4.58	3.62	6.37	6.78	89.8	84.0	82.1	82.3
4	F07	6.94	7.75	6.53	5.41	2.41	4.88	4.07	3.71	7.15	11.1	10.7	6.04	8.19	11.6	6.43	7.74	82.2	72.4	78.8	82.5
5	F04	6.77	5.26	9.93	9.5	0.99	4.37	2.48	2.90	14.5	9.89	4.63	6.85	3.46	3.53	3.73	4.33	81.0	82.2	89.2	85.9
6	3	9.51	11.9	2.65	9.66	2.41	4.45	14.5	4.54	20.30	10.2	10.0	6.82	3.44	2.90	8.34	4.93	73.8	82.4	67.1	83.7
7	F05	10.2	n/a	20.4	16.5	2.62	n/a	3.25	6.39	8.16	n/a	6.75	4.72	5.86	n/a	3.95	8.12	83.4	n/a	86.1	80.8
8	1	11.4	11.3	28.6	15.3	0.93	3.22	2.23	4.12	12.0	11.0	4.93	5.39	4.48	5.94	6.28	6.91	82.6	79.9	86.6	83.6
9	4	11.2	12.5	30	17.2	2.22	4.74	3.47	2.72	1.74	2.88	3.36	10.5	5.46	6.08	4.89	3.16	90.6	86.3	88.3	83.6
10	F02	7.44	7.53	12.3	7.6	1.32	2.94	2.02	4.63	9.36	5.46	6.77	8.82	2.88	4.54	2.58	4.33	86.4	86.5	88.6	82.2
11	F09	13.7	20.4	12.8	6.54	2.30	1.51	2.44	3.47	16.9	6.83	2.81	7.37	3.62	3.42	4.17	4.11	77.2	88.2	90.6	85.0
13	F12	8.97	14.7	14.1	11.6	3.85	1.99	2.98	3.56	35.3	7.79	9.84	1.71	3.73	7.19	4.58	6.71	57.1	83.0	82.6	88.0
14	F13	6.24	17.8	9.98	5.26	1.27	2.46	2.40	9.86	16.3	14.2	7.95	11.6	2.65	3.41	2.79	8.12	79.8	79.9	86.9	70.4
15	9	16.8	6.46	12.7	10.8	1.55	2.99	2.81	5.65	3.15	2.14	4.75	1.40	4.76	6.65	2.29	7.14	90.5	88.2	90.2	85.8
18	F08	6.81	11.4	9.49	19.9	1.87	2.93	3.12	2.31	1.81	2.27	2.46	6.70	4.15	5.23	3.91	4.42	92.2	89.6	90.5	86.6
19	F10	9.89	22.1	20.4	12.7	2.76	3.00	2.29	5.96	8.32	4.11	4.33	18.8	5.74	4.49	2.41	5.34	83.2	88.4	91.0	69.9
20	F14	10.2	11.3	14.8	17.5	0.27	4.41	1.90	5.40	2.61	26.3	11.7	12.6	2.75	2.26	2.32	5.13	94.4	67.1	84.1	76.8
21	2	8.64	19.2	19.8	14.1	1.14	1.87	n/a	2.45	7.13	4.13	4.79	4.43	4.19	3.15	5.31	4.74	87.5	90.8	87.6	88.4
23	F16	10.7	26.2	17.7	14.8	1.58	12.4	3.97	4.86	4.50	35.1	47.3	39.2	3.12	3.11	1.20	1.69	90.8	49.4	47.6	54.3
24	F17	9.78	13.4	16.7	13.8	2.58	2.31	1.91	2.72	5.00	2.80	4.92	5.48	5.11	4.57	5.86	3.63	87.3	90.3	87.3	88.2
25	8	11	23.9	14	13.4	1.29	0.84	1.35	1.55	10.40	2.83	5.66	10.5	2.72	3.89	1.89	4.14	85.6	92.4	91.1	83.8
27	F18	30	13	15.3	13.2	1.66	3.45	3.48	5.00	3.53	4.54	3.98	2.36	6.14	3.26	5.12	7.33	88.7	88.7	87.4	85.3
28	F19	9.39	10.3	15.5	9.55	1.80	5.85	4.60	4.32	2.51	13.6	6.95	4.90	4.74	7.07	9.55	11.0	90.9	73.5	78.9	79.8
29	F20	8.74	8.18	14.8	15.5	2.75	4.69	3.27	4.56	9.01	12.3	4.99	11.6	4.09	5.99	7.87	5.59	84.2	77.0	83.9	78.2
30	F21	12.6	n/a	21	16.8	1.16	n/a	3.45	2.42	2.24	n/a	7.37	4.69	3.16	n/a	7.61	4.33	93.4	n/a	81.6	88.6
31	F01	9.5	9.99	13.9	9.97	3.07	3.48	2.11	4.03	8.92	22.3	4.46	3.50	10.6	3.54	5.29	6.03	77.4	70.7	88.1	86.4
32	7	7.67	29.8	17.9	12.6	1.44	2.36	3.97	2.02	24.5	8.94	12.3	8.81	2.17	6.78	5.15	5.58	71.9	81.9	78.5	83.6
33	F22	26.6	24.3	23.3	22.4	0.17	1.90	1.28	1.99	0.95	1.24	2.82	2.06	2.10	3.07	2.09	3.63	96.8	93.8	93.8	92.3
34	F23	11.8	9.52	11.1	6.88	0.17	2.32	1.73	1.70	1.55	2.70	2.88	5.62	3.74	4.93	6.63	4.96	94.5	90.0	88.8	87.7

S-No	R-No	% CD14+ monocytes of lymphocytes				% CD16+HLA-DR+ cells of total CD14+ monocytes				% CD16+HLA-DR- cells of total CD14+ monocytes				% CD16-HLA-DR+ cells of total CD14+ monocytes				% CD16-HLA-DR- cells of total CD14+ monocytes			
		V1	V5	V8	V13	V1	V5	V8	V13	V1	V5	V8	V13	V1	V5	V8	V13	V1	V5	V8	V13
35	F24	11.8	15.6	11	12.5	1.73	4.65	5.11	5.97	8.22	6.97	6.94	15.6	3.32	4.89	4.87	4.99	86.7	83.5	83.1	73.5
36	6	6.08	15.9	12.9	25.5	3.96	2.15	2.17	5.69	14.4	7.50	2.11	35.6	7.75	5.80	7.06	1.60	73.9	81.9	88.7	57.1
38	5	10.7	13.3	11.4	8.98	1.71	1.06	3.37	2.88	11.2	3.76	7.99	7.39	6.81	4.69	7.19	4.97	80.2	90.5	81.4	84.8
41	F26	7.58	7.09	16.6	6.7	1.98	4.65	3.07	4.00	3.22	2.30	6.18	1.79	2.12	3.11	8.33	10.5	92.7	89.9	82.4	83.8
43	10	8.04	16.9	20.1	13.1	3.56	3.92	1.50	4.36	24.8	7.69	4.62	18.1	3.53	5.65	7.07	3.96	68.1	82.7	86.8	73.6
44	11	13.1	14.9	8.58	17.1	1.10	7.11	3.96	2.77	2.27	21.7	3.99	4.56	6.52	5.22	3.59	5.27	90.1	65.9	88.5	87.4
45	12	13.6	10.4	19.3	23.8	1.37	3.89	1.53	2.85	2.06	1.95	1.41	2.35	8.16	10.4	3.99	7.31	88.4	83.7	93.1	87.5
46	F27	5.85	n	23.9	9.67	0.79	n	7.82	2.81	6.17	n	7.50	10.6	1.18	n	14.9	2.99	91.9	n	69.8	83.5
47	F28	21.4	17.7	22.5	17.5	0.63	2.25	0.98	2.95	4.83	5.46	4.65	7.72	2.16	3.77	4.87	5.64	92.4	88.5	89.5	83.7

S-No. – Screenning number; R-No. – Random number; n/a – not able to analyse; n – visit not attended
Data is listed for the PP population; missing date F15 and F25

Appendix-Table 6 Individual subject data listings of humoral immune response. This was only measured at visit 1 and 8.

		CMV (DU/ml)		EBV (in DU)		VSV (in DU)	
S-No	R-No	V1	V8	V1	V8	V1	V8
1	F03	0	56	64.69	65.32	27.94	25.89
2	F11	n/a	n/a	n/a	n/a	n/a	n/a
3	F06	15400	14700	67.54	68.20	23.13	23.40
4	F07	9223	9179	63.29	61.75	21.63	21.54
5	F04	6351	6115	40.10	35.01	7.93	8.57
6	3	0	0	57.61	49.51	23.45	25.00
7	F05	0	158	7.48	5.60	14.56	17.15
8	1	9777	12300	44.75	49.99	19.59	21.51
9	4	0	0	67.98	68.43	31.06	29.69
10	F02	12400	12300	32.52	32.66	17.34	16.68
11	F09	14300	14700	40.58	45.72	17.65	13.07
13	F12	n/a	n/a	n/a	n/a	n/a	n/a
14	F13	460	373	51.09	49.61	17.87	15.21
15	9	1269	2011	13.30	14.48	6.40	7.84
18	F08	14600	408	35.59	5.82	13.21	15.73
19	F10	n/a	n/a	n/a	n/a	n/a	n/a
20	F14	10000	10700	54.50	58.68	17.22	20.30
21	2	13100	13500	61.97	59.82	20.80	20.73
23	F16	0	1958	9.31	9.45	9.67	11.48
24	F17	3	0	33.56	33.24	15.75	10.06
25	8	533	300	38.38	40.44	22.66	21.20
27	F18	11400	12900	67.14	68.43	12.48	15.51
28	F19	9710	10500	61.14	64.85	18.53	19.98
29	F20	11700	12000	52.12	52.28	21.46	20.32
30	F21	1252	1593	22.67	24.23	20.88	21.90
31	F01	14900	15200	34.66	36.81	12.57	13.67
32	7	8310	9991	53.04	48.63	23.47	23.10
33	F22	16200	1027	23.75	44.13	14.28	18.37
34	F23	0	0	65.64	65.48	16.92	15.39
35	F24	15800	15800	23.87	23.19	16.61	15.65
36	6	2308	1081	5.30	6.72	19.68	25.33
38	5	0	1266	5.56	17.71	18.63	20.86
41	F26	1174	0	49.07	49.29	23.17	21.17
43	10	24	71	66.00	66.00	25.88	16.85
44	11	7801	9054	58.60	60.94	13.58	16.49
45	12	9799	9594	26.18	32.78	23.03	22.32
46	F27	0	0	51.13	53.78	14.51	14.92
47	F28	0	135	18.15	19.02	21.98	21.91

Appendix-Table 7 Individual subject data listings of 25-OH-VD values in nmol/l.

S-No	R-No	Group	Baseline (Scr)	Day 3 (V4)	Day 7 (V5)	Day 14 (V6)	Day 21 (V7)	Day 28 (V8)	Day 42 (V10)	Day 56 (V12)	Day 84** (V13)
1	F03	Verum i.m.	24.4	32.1	40.6	54.7	52.6	54.8	48.9	44.2	57.8
2	F11	Verum i.m.	36.6	47.0	62.0	57.9	n/a	72.0	67.1	55.0	82.9
3	F06	Verum s.c.	27.7	47.9	61.1	45.8	69.9	81.7	67.9	64.2	92.0
4	F07	Verum s.c.	35.0	53.2	62.7	61.0	67.7	77.5	75.6	71.7	87.8
5	F04	Placebo i.m.	45.9	x	51.4	x	x	44.2	x	37.9	55.6
6	03	Verum i.m.	27.3	44.9	57.1	73.1	80.5	92.8	83.1	80.3	67.9
7	F5	Placebo s.c.	25.0	x	31.6	x	x	24.4	x	21.0	32.8
8	01	Verum s.c.	31.5	50.4	63.4	69.0	75.1	82.7	n/a	x	92.9
9	04	Placebo i.m.	38.3	x	37.6	x	x	36.5	x	40.3	52.2
10	F02	Verum i.m.	12.5	26.7	22.7	n/a	36.9	33.3	35.8	28.3	33.0
11	F09	Verum s.c.	47.2	57.2	70.6	59.1	70.6	83.1	81.4	77.7	114.1
13	F12	Verum i.m.	40.9	70.6	64.0	76.5	84.4	100.9	90.7	73.8	102.5
14	F13	Verum i.m.	27.9	65.7	73.7	104.6	75.1	89.1	82.1	65.6	58.4
15	09	Verum s.c.	33.6	61.3	71.2	67.5	74.9	89.5	73.3	n/a	55.5
18	F08	Placebo i.m.	38.1	x	44.4	x	x	43.0	x	41.7	56.5
19	F10	Placebo s.c.	27.6	x	30.0	x	x	34.7	x	26.9	46.9
20	F14	Verum s.c.	21.8	39.7	47.5	n/a	57.4	61.1	55.4	51.4	58.1
21	02	Verum i.m.	32.0	43.6	45.5	62.4	59.4	55.5	n/a	52.9	79.0
22	F15	Verum i.m.	31.5	29.9	35.9	27.9	35.5	28.6	31.0	28.3	43.8
23	F16	Placebo s.c.	14.7	x	22.0	x	x	21.1	x	16.6	34.0
24	F17	Verum i.m.	39.4	59.7	66.2	n/a	n/a	77.1	76.4	69.6	95.6
25	08	Placebo s.c.	17.8	x	21.9	x	x	26.1	x	19.4	33.3
27	F18	Verum s.c.	23.6	n/a	51.8	48.5	46.3	56.9	55.5	50.1	68.7
28	F19	Verum i.m.	49.7	65.6	80.0	x##	81.9	86.7	n/a	n/a	84.1
29	F20	Verum s.c.	24.5	33.0	42.7	42.3	n/a	57.9	58.0	42.0	56.5
30	F21	Placebo i.m.	41.0	x	34.9	x	x	31.3	x	23.8	53.1
31	F01	Verum s.c.	16.0	37.8	38.9	38.1	35.0	43.4	55.1	37.5	57.1
32	07	Verum i.m.	36.5	58.3	69.7	67.8	77.3	80.1	76.4	67.8	104.4
33	F22	Verum s.c.	23.7	45.4	55.8	51.4	51.2	62.7	62.2	62.3	62.3
34	F23	Placebo s.c.	23.8	x	28.0	x	x	20.1	x	18.0	66.1
35	F24	Verum i.m.	17.1	35.6	48.9	47.4	57.0	70.3	65.2	67.9	75.0

S-No	R-No	Group	Baseline (Scr)	Day 3 (V4)	Day 7 (V5)	Day 14 (V6)	Day 21 (V7)	Day 28 (V8)	Day 42 (V10)	Day 56 (V12)	Day 84** (V13)
S-No	R-No	Group	Baseline (V1)	Day 3 (V4)	Day 7 (V5)	Day 14 (V6)	Day 21 (V7)	Day 28 (V8)	Day 42 (V10)	Day 56 (V12)	Day 84** (V13)
36	06	Placebo s.c.	18.9	x	24.5	x	x	34.9	x	23.5	22.6
38	05	Verum s.c.	54.0*	x##	97.8	x##	107.3	110.6	x##	103.4	105.6
39	F25	Verum s.c.	27.4	x#	n/a	x#	n/a	69.9	n/a	n/a	n/a
41	F26	Placebo i.m.	38.8	x	27.2	x	x	26.1	x	21.3	31.9
43	10	Verum s.c.	21.6	63.9	86.3	98.1	103.6	107.7	n/a	92.3	104.3
44	11	Verum i.m.	24.0	44.2	49.6	50.2	53.5	43.1	46.4	32.7	51.3
45	12	Placebo i.m.	55.1*	x	43.4	x	x	41.0	x	30.9	48.8
46	F27	Placebo s.c.	34.4	x	n/a	x	x	43.7	x	22.5	45.4
47	F28	Verum s.c.	25.8	x	45.4	37.1	40.3	45.4	n/a	43.9	54.4

S-No. – Screenning number; R-No. – Random number;
x – Day 3. 14. 21 and 42 were analysed after unblinding only in the verum group. #was not measured because the subject dropped out (F25); ##could not be measured (technical reasons); n/a – not applicable due to missed visit
F15 – excluded due to protocol deviation;

*Note-to-File number 1 is applicable; ** 25-OH-VD values at visit 13 may be elevated due to natural sun exposure

Appendix-Table 8 Individual subject data listing of adverse events (AE)

R-No.	AE-No.	Diagnosis	Date of start	Date of end	Intensity	Drug relation	Other treatment	Outcome
F05	1	Common cold	15.02.2013	18.02.2013	mild	no	no	recovered
F02	1	Commen cold	21.02.2013	27.02.2013	mild	no	no	recovered
F10	1	Commen cold	06.03.3013	15.03.2013	moderate	no	no	recovered
F14	1	Flu	04.03.2013	08.03.2013	severe	no	no	recovered
F16	1	Commen cold	29.02.2013	10.03.2013	mild	no	no	recovered
F17	1	Flu	27.02.2013	04.03.2013	severe	no	Gelomytrol. Ibuprofen	recovered
F18	1	Commen cold	20.02.2013	24.02.2013	mild	no	no	recovered
F19	1	Commen cold	10.03.2013	10.03.2013	moderate	no	no	recovered
07	1	Angina	06.05.2013	09.05.2013	moderate	no	Penicillin	recovered
F27	1	Commen cold	22.02.2013	01.03.2013	mild	no	no	recovered
F27	2	Common cold	28.03.2013	01.04.2013	moderate	no	Aspirin. Paracodeine	recovered

Appendix-Table 9 Individual subject data listing of tolerability assessed by the subject on a 5 point scale (1 – very good. 2 – good. 3 – moderate. 4 – bad. 5 – very bad).

		Hours after injection					Median values (in points)
S-No	R-No	2 hours	6 hours	24 hours	48 hours	72 hours	
1	F03	2	3	3	2	2	2.0
2	F11	1	1	1	1	1	1.0
3	F06	2	2	2	2	2	2.0
4	F07	1	2	2	2	2	2.0
5	F04	1	1	1	1	1	1.0
6	03	1	1	1	1	1	1.0
7	F05	1	2	2	2	2	2.0
8	01	1	1	1	1	1	1.0
9	04	1	1	1	1	1	1.0
10	F02	1	2	2	2	1	2.0
11	F09	1	1	1	1	1	1.0
13	F12	1	1	1	1	1	1.0
14	F13	1	1	1	1	1	1.0
15	09	2	2	2	2	2	2.0
18	F08	1	1	1	1	1	1.0
19	F10	1	1	1	1	1	1.0
20	F14	2	2	2	2	2	2.0
21	02	1	1	1	1	1	1.0
22	F15	2	2	1	1	1	1.0
23	F16	3	2	2	2	2	2.0
24	F17	1	2	3	1	2	2.0
25	08	1	1	1	1	1	1.0
27	F18	2	2	2	2	2	2.0
28	F19	1	1	1	1	1	1.0
29	F20	1	2	2	1	2	2.0
30	F21	2	2	2	1	1	2.0
31	F01	1	2	2	2	2	2.0
32	07	1	1	1	1	1	1.0
33	F22	1	1	1	1	1	1.0
34	F23	1	2	2	2	2	2.0
35	F24	2	2	3	2	1	2.0
36	06	1	1	1	1	1	1.0
38	05	1	1	1	1	1	1.0
39	F25	2	2	1	1	1	1.0
41	F26	2	2	1	1	1	1.0
43	10	1	2	2	1	2	2.0
44	11	1	1	1	1	1	1.0
45	12	1	1	2	2	1	1.0
46	F27	1	1	1	1	1	1.0
47	F28	2	1	1	1	1	1.0