1 TITLE PAGE

STUDY TITLE:	A phase IV, randomised, double-blinded, placebo-controlled, parallel study to estimate the influence of vitamin D (D-CURE®) supplementation on the 25-hydroxyvitamin D serum concentration in patients aged over 50 years.
EudraCT NUMBER:	2010-023510-32
STUDY DRUG:	SMB D-CURE®
STUDY INDICATION:	25-hydroxyvitamin D serum concentration
DESIGN:	Phase IV, interventional, randomised, parallel, double-blinded, placebo-controlled study.
SPONSOR:	Laboratoires SMB S.A. Rue de la Pastorale 26-28 1080 Brussels, Belgium
PROTOCOL CODE:	D-CURE-IV-10-1 (HCR: 1741/LSMB)
PHASE:	Phase IV
INITIATION:	23 January 2011, screening of first patient included in the study
COMPLETION:	22 July 2011, final examination of the last patient
COORDINATING INVESTIGATOR:	Dr. Werner Faché
GCP STATEMENT:	This study was performed in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments) and local legal and regulatory requirements.
ARCHIVING:	The study documents will be archived according to ICH GCP regulations.
DATE OF REPORT:	31 January 2012
EARLIER REPORTS:	None.

SYNOPSIS

Name of Sponsor/company: Laboratoires SMB S.A	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: D-CURE®	Volume:	
Name of Active Ingredient(s): Vitamin D	Page:	

Title of the study:
A phase IV, randomised, double-blinded, placebo-controlled, parallel study to estimate the influence of vitamin D (D-CURE®) supplementation on the 25-hydroxyvitamin D serum concentration in patients aged over 50 years

Coordinating Investigator:
Dr. Werner Faché, Zuidstationstraat 3B bus 1, B-9000 Gent, Belgium

Study centre(s):
40 centres in Belgium were initiated and 32 were active.

Publication:
Not applicable

Study period:	**Phase of Development:** IV
23 January 2011 (first enrolment) 22 July 2011 (last completed)	

Objectives:

- To determine the most adapted supplementation in vitamin D (D-CURE®) in regard to the baseline serum concentrations in 25-hydroxyvitamin D of the patients.
- To assess the safety of the test product versus placebo.

Methodology:

This was a phase IV randomised, parallel, double-blinded, placebo-controlled study. The patients were screened within 14 days prior to starting the study. Patients who met all inclusion and none of the exclusion criteria were randomized to one of the four strata based on their baseline 25-OH vitamin D serum concentration. The patients took the study medication under the supervision of the study personnel at Visit 2 (week 0), Visit 3 (week 2), Visit 4 (week 4) and Visit 5 (week 8). The total duration of the study was 12 weeks. Blood samples for measurement of 25-OH Vitamin D concentration, calcium, phosphorus and albumin were collected at each visit. Blood and urine samples for safety laboratory tests were collected at screening and week 12.

Number of patients:
Planned: 200 total, 160 in the D-CURE ® groups and 40 in the placebo group
Analysed: 175 total, 140 in the D-CURE ® groups and 35 in the placebo group

Main criteria for inclusion:

1) Male and female over 50 years old (50 years inclusive);
2) Caucasian (defined as European and North African);
3) Body mass Index between 18 and 35 kg/m² inclusive;
4) Able to comply with all study procedures;
5) Written, informed consent to participate in the study, indicated by a personal signature and date on the patient consent form;
6) If the patient was female and of childbearing potential, she had to use an efficient means of birth control, as determined by the investigator and provide a negative blood pregnancy test at the screening visit.

Exclusion criteria:

Name of Sponsor/company: Laboratoires SMB S.A Name of Finished Product: D-CURE® Name of Active Ingredient(s): Vitamin D	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)

1) Evidence of any unstable or untreated clinically significant immunological, neoplastic, endocrine, haematological, hepatic, renal, gastrointestinal, neurological or psychiatric abnormalities or medical disease;
2) Patients with thyroid gland dysfunction;
3) UV light solarium use 2 weeks before the screening visit;
4) Use of drugs which may interfere with vitamin D metabolism e.g. phenobarbital, phenytoin, glucocorticoids;
5) Past or current history of granulomatosis (Besnier-Boek-Schaumann disease), sarcoidosis, urinary lithiasis, renal insufficiency, cardiac disease, cancer, osteomalacia;
6) Patients with a vitamin D concentration > 60 ng/ml at screening;
7) Patients with serum creatinine > 150 µmol/L at screening;
8) Patients with albumin corrected serum calcium > 2.65 mmol/L (corresponding to 10.6 mg/dl) at screening;
9) Use of any of the prohibited medication as detailed in the concomitant medication section;
10) Participation in any other clinical trial within 2 months of the screening visit;
11) Travelling outside European countries during the study participation;
12) Presence of any other condition or illness, which, in the opinion of the investigator, would interfere with optimal participation in the study;
13) Patients with any sensitivity or allergy to any of the products used within this clinical trial;
14) History of drug and/or alcohol abuse;
15) Patient known to have, or at risk of contracting, human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C or patients with positive virology laboratory tests (HBsAg, HCV Ab, HIV 1+2 Ab).

Test product, dose and mode of administration, batch number:
SMB D-CURE® 1ml ampoule for oral use containing 25000 IU/ml of vitamin D taken according to the following scheme:

- Stratum 1: Patients with baseline serum concentrations of 25 OH-vitamin D ≤ 10ng/ml. Intake: 3 ampoules taken at week 0 and 2 followed by 2 ampoules at week 4 and 8. (Subgroup 1)
- Stratum 2: Patients with baseline serum concentrations of 25 OH-vitamin D >10ng/ml and ≤20 ng/ml. Intake: 3 ampoules taken at week 0 followed by 2 ampoules at week 2 and 1 ampoule at week 4 and 8. (Subgroup 2)
- Stratum 3: Patients with baseline serum concentrations of 25 OH-vitamin D >20ng/ml and ≤30 ng/ml. Intake:2 ampoules taken at week 0 followed by 1 ampoule at week 2, 4 and 8. (Subgroup 3)
- Stratum 4: Patients with baseline serum concentrations of 25 OH-vitamin D >30ng/ml and ≤60 ng/ml. Intake:1 ampoule taken at week 0, 2, 4 and 8. (Subgroup 4)

Batch Number: 10J26

Duration of treatment:
After being screened for the study, the patients were randomised in the study during which they received either the test treatment or a placebo (ratio 4:1) for a period of 12 weeks.

Name of Sponsor/company: Laboratoires SMB S.A	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: D-CURE®	Volume:	
Name of Active Ingredient(s): Vitamin D	Page:	

Reference therapy, dose and mode of administration, batch number:
Placebo 1ml ampoule, oral administration taken according to the following scheme:

- Stratum 1: Patients with baseline serum concentrations of 25 OH-vitamin D ≤10ng/ml. Intake: 3 ampoules taken at week 0 and 2 followed by 2 ampoules at week 4 and 8. (Subgroup 5)
- Stratum 2: Patients with baseline serum concentrations of 25 OH-vitamin D >10ng/ml and ≤20 ng/ml. Intake: 3 ampoules taken at week 0 followed by 2 ampoules at week 2 and 1 ampoule at week 4 and 8. (Subgroup 6)
- Stratum 3: Patients with baseline serum concentrations of 25 OH-vitamin D >20ng/ml and ≤30 ng/ml. Intake: 2 ampoules taken at week 0 followed by 1 ampoule at week 2, 4 and 8. (Subgroup 7)
- Stratum 4: Patients with baseline serum concentrations of 25 OH-vitamin D > 30ng/ml and ≤60 ng/ml. Intake: 1 ampoule taken at week 0, 2, 4 and 8. (Subgroup 8)

Batch Number: R567

Criteria for evaluation:
Efficacy:
Primary endpoint:

- Mean change from baseline to week 12 in the 25-hydroxyvitamin D serum concentration.

Other efficacy parameters:

- Percentage of patients reaching 25-hydroxyvitamin D serum concentrations ≥30ng/ml at the end of the study
- Time to raise the 25- hydroxyvitamin D serum concentration up to 30 ng/ml
- Mean change from baseline to week 12 in the phosphorus plasma concentration
- Mean change from baseline to week 12 in the calcium plasma concentration

Safety:

- Adverse events
- Physical examination
- Vital signs
- Laboratory data
- Withdrawals or drop-out rate

Statistical methods:
A statistical analysis plan was written after completion of the Case report Form. Data from the Marvin database was exported and downloaded from the Marvin Web interface via a secured socket-layer (SSL) connection from the host server to the HCR file server. The raw data was in CDISC ODM XML Version 1.2 compliant format. This ODM XML file was imported into SAS via the SAS procedure 'proc CDISC'. Appropriate SAS programs were prepared and validated according to HCR SOPs. Raw data listings, summary tables, graphs and statistical tests were generated by means of the program SAS Version 9.1 or higher. All statistical tests were performed two-sided. A p-value less than 5% was considered as statistically significant.
The main statistical null hypothesis was that there are no differences between active

Name of Sponsor/company: Laboratoires SMB S.A	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: D-CURE®	Volume:	
Name of Active Ingredient(s): Vitamin D	Page:	

treatment and placebo. The alternative hypothesis of interest was to show that there is a difference between active treatment and placebo.

Primary efficacy parameters

A 2-factorial ANOVA with factors centre and treatment was used for the analysis of the primary endpoint. Applying the closed-testing procedure (Marcus,et al, 1976) further testing within the subgroups was applied if the overall test concerning a difference between active treatment and placebo was shown, i.e. Scheffé's simultaneous 95% confidence intervals (Scheffé et al, 1953) was applied. A similar analysis was performed with the mean change from baseline at week 2, 4 and 8.

Secondary efficacy parameters

Calcium and phosphorus plasma concentrations

The mean change from baseline to week 12 in the calcium and phosphorus plasma concentrations were analysed with the same statistical models as for the primary parameter. As the secondary efficacy parameters were of exploratory nature only, the closed-testing procedure was not applied. The mean change from baseline at weeks 2, 4 and 8 was also analysed. A 2-factorial ANOVA with factors centre and treatment was used for the analysis.

Time to raise the 25-hydroxyvitamin D serum concentration up to 30 ng/ml

The "Time to raise the 25- hydroxyvitamin D serum concentration up to 30 ng/ml" was defined as the time period between baseline (Week 0) and the first time point the patient reached a 25-hydroxyvitamin D serum concentration of at least 30 ng/ml. If the patient did not reach this serum concentration level within the study period of 12 weeks, the patient was censored at week 12. For this time-to-event variable the median time (or lower quartile, in case the median could not be estimated) and the respective 95% confidence intervals for each treatment group was estimated. For each of the subgroup combinations 1 and 5, 2 and 6, 3 and 7 and 4 and 8 (strata) a separate Kaplan-Meier analysis was performed.

Percentage of patients reaching 25-hydroxyvitamin D serum concentrations ≥20ng/ml and ≥30ng/ml at the end of the study

The percentages of patients reaching 25-hydroxyvitamin D serum concentrations ≥20ng/ml and ≥ 30 ng/ml at the end of the study were analysed by means of a Chi-square test comparing SMB D-CURE® and placebo**.** Comparisons of the subgroup combination 1 and 5, 2 and 6, 3 and 7 and 4 and 8 were done by Fisher's exact test.

Safety data

All safety data obtained in this study was tabulated with descriptive statistics. Comparisons between treatment groups were based on descriptive statistics.

All clinical safety and tolerability data were listed for each patient and summarized. Laboratory values outside of the normal ranges were listed separately, together with the associated repeat values (if any) and comments regarding their clinical significance.

All AEs reported in this study were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 13.1). All AEs (whether treatment-emergent or not) were listed, only treatment emergent AEs were presented in tabulations. AEs that were reported as "possibly" and "probably" related to the study medication were considered treatment-related; missing classifications concerning study drug relationship were also considered treatment-related.

If onset date of an AE was before the date of the first administration of study treatment, the

Name of Sponsor/company: Laboratoires SMB S.A Name of Finished Product: D-CURE® Name of Active Ingredient(s): Vitamin D	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)

AE is defined as a pre-treatment event. If date of onset of AE was on or after the date of the first administration of study treatment, it was defined as on-treatment adverse event.
Vital signs and physical examination were listed. Concomitant medication was coded with WHO Drug Dictionary Version Q2/ 2011. Concomitant medications taken at any stage during the study was listed.

Sample size calculation

No statistical based sample size calculation was done for this study. It was planned to gain a first insight in possible vitamin D supplementation strategies in patients with vitamin D deficiency. A sample size of 40 patients in each of the four verum treatment groups and 10 patients in each of the four placebo groups (ratio 4:1) was deemed to be sufficient to demonstrate preliminary efficacy and to draw conclusions for further possible treatment regimens.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

The concentration of 25-OH vitamin D in serum was significantly increased after treatment with SMB D-CURE® compared to placebo for the total analysis.

For the SMB D-CURE® treatment group the mean serum concentration of 25-OH vitamin D was 18.67 ng/ml at baseline and 31.49 ng/ml at week 12; with a mean change to baseline of 12.9 ng/ml (SD± 10.663). In the placebo group the mean serum concentration of 25-OH vitamin D was 19.09 ng/ml at baseline and 20.74 ng/ml at week 12; the mean change to baseline was 1.66 ng/ml (SD± 6.324).See Table 8 and12.

The mean serum concentration of 25-OH vitamin D observed at week 12 increased for all subgroups compared to baseline in the SMB D-CURE® treatment group in the FA dataset (+19.65, +14.80, +9.53 and +2.45 ng/ml respectively for the subgroups 1, 2, 3 and 4). The increase was inversely dependent on the basal 25-OH vitamin D serum concentration and increased with the dose of SMB D-CURE® administered. Regarding the placebo subgroups, a small increase of the mean serum concentrations of 25-OH vitamin D was observed in the subgroups 5, 6 and 7 (+2.10, +3.50, +4.30 ng/ml) while the mean serum concentration decreased at week 12 in the placebo subgroup 8 (-8.20 ng/ml). The same results were observed in the PP dataset except in subgroup 4 where the mean 25-OH vitamin D serum concentration was slightly decreased at week 12 compared to baseline (-0.87 ng/ml). The negative changes in the subgroup with a baseline >30 ng/ml confirm that even if the target level is reached, a maintenance dose will be required to sustain the serum 25-OH vitamin D around 30 ng/ml.

During the study there was a significant difference between SMB D-CURE® and placebo in the 25-OH vitamin D concentrations at week 2, 4, 8 and 12 ($p < 0.001$ for the global group analysis and in the strata 1 and 2 in PP and FAS datasets. In patients with a baseline 25 OH-vitamin D serum concentration of > 20 ng/ml, there was no significant difference in the mean concentration of 25 OH-vitamin D between SMB D-CURE® and placebo except in strata 3 at week 2.

The maximum serum 25 OH-vitamin D concentration was observed at week 12 with SMB D-CURE® (68 ng/ml) and is far from the toxic limit.

At the end of the study (week 12) 57.1% (n = 80) of patients treated with SMB D-CURE® had a 25 OH-vitamin D serum concentration ≥ 30 ng/ml and 94.3% (n = 132) a concentration

Name of Sponsor/company: Laboratoires SMB S.A	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: D-CURE®	Volume:	
Name of Active Ingredient(s): Vitamin D	Page:	

≥ 20 ng/ml. In the placebo group 20.0% (n = 7) had a 25 OH-vitamin D serum concentration ≥ 30 ng/ml and 54.3% (n = 19) ≥ 20 ng/ml. The highest number of patients to reach 25-hydroxyvitamin D serum concentrations of ≥ 30 ng/ml was seen in patients treated with SMB D-CURE® in strata 3 (77.5%, n = 31/40). There were 17/40 (42.5%) patients in strata 1 treated with SMB D-CURE® and 19/40 (47.5%) patients in strata 2 treated with SMB D-CURE®, who reached serum concentrations of 25 OH-vitamin D ≥ 30 ng/ml at week 12.

Altogether 106 of the 140 patients treated with SMB D-CURE® (75.71%) and 11 of the 35 patients treated with placebo (31.43%) had a serum 25-hydroxyvitamin D concentration of ≥30 ng/ml at one or more time points during the study. The highest number of patients was in subgroup 3; 97.5% of patients achieved a serum 25-hydroxyvitamin D concentration of ≥30 ng/ml but only 77.5% of patients in this group had a serum 25-hydroxyvitamin D concentration of ≥30 ng/ml at the end of the study.

The mean time to reach a serum 25-hydroxyvitamin D concentration ≥30 ng/ml was 42.1 days (SD ± 30.31) for patients treated with SMB D-CURE® and 71.9 days (SD ± 28.99) for patients treated with placebo. The mean shortest time to reach a serum concentration of ≥30 ng/ml was 24.4 days (SD ± 19.73) in patient in strata 3 treated with SMB D-CURE®.

The estimated median time to reach 30 ng/ml with a 95% CI of [25-35] was 28 days for the total SMB D-CURE® and 88 days (95% CI of [88-]) for placebo (Kaplan-Meier analysis). The shortest estimated median time to reach a serum 25 OH-vitamin D concentration of 30 ng/ml was in patients with baseline concentration of >20 ng/ml & ≤30 ng/ml); the estimated median time for this group was 14 days (95% CI of [14 -17]). In the placebo group the shortest estimated median time to reach a concentration of 30 ng/ml was 28 days (95% CI of [14 -]) seen in patients with a baseline concentration of >30 ng/ml & <= 60 ng/ml.

There were no clinically significant changes to baseline seen in the mean plasma phosphorus and calcium concentrations during the study. The mean change to baseline at week 12 for plasma phosphorus was -0.29 mg/dl (± 1.960) in patients treated with SMB D-CURE® and -0.26 mg/dl (± 0.584) in the placebo group. The mean change to baseline at week 12 for plasma calcium was 0.00 mg/dl ±0.378 in patients treated with SMB D-CURE® and 0.02 mg/dl ±0.259 in the placebo group.

SAFETY RESULTS:

SMB D-CURE® was safe and well tolerated at the doses administered over an observation period of 12 weeks. During the study 15 of the 140 patients (10.7%) treated with SMB D-CURE® and 3 of the 35 patients (8.6%) in the placebo group experienced at least one treatment emergent AE. None of the AEs were considered related to the study medication. The most frequent adverse events reported were infections, mainly nasopharyngitis, rhinitis and sinusitis. Two patients underwent surgical procedures that were classified as SAEs. Neither SAE was related to the study medication.

No clinically relevant trend was observed in the vital signs, the physical findings and in the clinical laboratory results and no clinically significant change was seen in the plasma calcium and phosphorus concentrations.

CONCLUSION:

This was an exploratory study to determine the best dose of vitamin D in older patients with vitamin D deficiency, based on their baseline serum concentration of 25-OH vitamin D. The mean age was 64 years, 62.3% of patients were female and the mean BMI was 26.0 kg/m^2

Name of Sponsor/company: Laboratoires SMB S.A	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: D-CURE®	Volume:	
Name of Active Ingredient(s): Vitamin D	Page:	

±3.99 for SMB D-CURE® treated patients and 26.7±4.01 kg/m^2 for placebo patients.

The concentration of 25-OH vitamin D in serum was significantly increased after treatment with SMB D-CURE® compared to placebo for the total analysis. The increase was inversely dependent on the basal concentration of 25-OH vitamin D and rose with the dose administered. During the 12 weeks of the study, the mean change adjusted from baseline ranged from +2.45 to +19.65 ng/ml with doses from 100 000 UI to 250 000 UI of SMB D-CURE® and from -8.20 to +4.30 with placebo in the FA datasets. The negative change was observed in the subgroup with baseline <30 ng/ml and confirms that even if the target level is reached, a maintenance dose is required to sustain the serum 25-OH vitamin D around 30 ng/ml. Only 42.5% of patients with baseline concentrations of < 10 ng/ml and 47.5% of patients with baseline concentrations of ≤20 ng/ml achieved a 25-OH vitamin D concentration of ≥30 ng/ml at week 12 in the FAS suggesting that the doses of SMB D-CURE® administered in these patients was insufficient to achieve the 30 ng/ml target. In the stratum 3 and 4 there were respectively 77.5% and 65.0% of patients who had concentrations of ≥30 ng/ml at week 12 after treatment with SMB D-CURE®.

The maximum serum 25 OH-vitamin D concentration (68 ng/ml) was observed at week 12 with SMB D-CURE® and is far from the toxic limit.

SMB D-CURE® was well tolerated; there were no drug related AEs reported and no clinically relevant change in safety laboratory parameters and vital signs. No clinically significant change was seen in the plasma calcium and phosphorus concentrations.-

This study explored the change in serum 25 OH-vitamin D concentrations in patients with different baseline concentrations of 25 OH-vitamin D and receiving different doses of SMB D-CURE®. The current doses administered produced a significant change to placebo but serum concentrations of 25 OH-vitamin D ≥ 30 ng/ml were only achieved in 57.1% of patients receiving SMB D-CURE® indicating that the doses of SMB D-CURE® may need to be increased in subsequent studies.

Date of the report: 31 January 2012