C O N F I D E N T I A L

CLINICAL STUDY REPORT SYNOPSIS

1. TITLE PAGE

Clinical study Report No.:	Version 1.0	**Protocol No.:**	D-CURE-IV-12-1
		EudraCT No.:	2012-003417-34

Date of Issue:	23/12/2014
Study Title:	A phase IV, two-armed, randomised, cross-over study to compare the compliance of a once-a-month administration of vitamin D3 (D-CURE®) to a daily administration of a fixed-dose combination of vitamin D3 and calcium (STEOVIT FORTE®) during two periods of 6 months.
Acronym	MODACO: MOnthly versus DAily COmpliance
Drug Name:	D-CURE®
Indication:	Compliance study
Methodology:	Interventional, randomised, open, cross-over, comparative study
Drug Development Phase:	Phase IV
Country:	Belgium
Coordinating Investigator:	Prof Jean-Yves Reginster Polyclinique Brull Unité d'exploration du métabolisme osseux 45, quai Godefroid Kurth 4020 Liège, Belgium
First Volunteer First Visit:	15/10/2012
Last Volunteer Last Visit:	17/02/2014
Sponsor:	Laboratoires SMB S.A. Rue de la Pastorale 26-28 1080 Brussels, Belgium

2. SYNOPSIS

Name of Sponsor/Company: Laboratoires SMB S.A.	**Individual Study Table**	**(For National Authority Use only)**
Name of Finished Product: D-CURE®		
Name of Active Ingredient: Cholecalciferol		

Title of Study:
A phase IV, two-armed, randomised, cross-over study to compare the compliance of a once-a-month administration of vitamin D3 (D-CURE®) to a daily administration of a fixed-dose combination of vitamin D_3 and calcium (STEOVIT FORTE®) during two periods of 6 months.

Study Center/Investigator:
One site in Belgium. The principal investigator was professor J-Y Reginster.

Publication (Reference):
Not applicable.

Study Period:	**Phase of Development:**
15 October 2012 (First Volunteer First Visit) 17 February 2014 (Last Volunteer Last Visit)	Phase IV

Objectives:
The aim of the present study was to assess the compliance of a once-a-month administration of vitamin D_3 (D-CURE®) to a daily administration of a fixed-dose combination of vitamin D_3 and calcium (STEOVIT FORTE®) during two periods of 6 months and to see their effect on the level of vitamin D.

Methodology:
Phase IV, two-armed, randomised, open, cross-over study.

Number of volunteers (planned, consented, randomized and analyzed):
Planned: 100 volunteers randomised (50 in each group).
Screened: 100 volunteers screened.
Randomized: 100 volunteers randomized (50 in each group). Nighty-nine volunteers received at least one dose of study treatment.
Completed: 91 volunteers completed the study.
Safety population: 99 volunteers.
ITT population: 93 volunteers.
PP population: 79 volunteers.

Diagnosis and Main Criteria for Inclusion:
Male and female, aged 50 years and older.

Test Product, Dose and Mode of Administration, batch number:
D-CURE® 1 ml ampoule containing 25 000 IU/ml of cholecalciferol taken orally once a month (batch number: GM12-029-12H29/2).

Reference Product, Dose and Mode of Administration, batch number:
STEOVIT FORTE® tablet containing 1000 mg of calcium and 800 IU of cholecalciferol taken orally once a day (batch number: GM12-028/10783682).

Duration of Treatment:
After being screened for the study, volunteers were randomised in the study for two periods of 6 months during which they received each treatment according to the randomisation scheme.

Criteria for Evaluation:

Primary:
- Compliance over 6-month treatment periods

Secondary:
- Mean change from baseline (Month 0) in the 25-OH vitamin D serum concentration at the end of the first 6-month period (Month 6)
- Mean change from Month 6 in the 25-OH vitamin D serum concentration at the end of the second 6-month

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period (Month 12)
- Treatment preference
- Treatment persistence
- Treatment acceptability

❑ **Safety parameters:**
- Adverse events (AEs)

Statistical Methods:

❑ **Demographic data:**

For quantitative variables, comparison between the two groups of treatment (D-CURE® and STEOVIT FORTE®) was assessed by means of a Student t-test for independent populations or a non-parametric Mann-Whitney test if normality was not satisfied. The relationship between qualitative variables and group of treatment was assessed using a Chi² test.

❑ **Compliance data:**

The method used consists of testing a period/sequence effect, then an interaction effect between period and treatment, and finally, and only in case of no significant effect of period and interaction, a treatment effect. All effects are assessed by using a two sample t-test or a non-parametric test of Mann-Whitney. For each sequence of administration of the treatments (D-CURE®/STEOVIT FORTE® and STEOVIT FORTE®/D-CURE®), a Wilcoxon signed-rank test was also computed in order to test the difference between the two treatments

❑ **Vitamin D evolution:**

A Student t-test for independent samples was used in order to test if the mean evolution of vitamin D between T0 and T6, and between T6 and T12, depended on the treatment.

❑ **Preference of the treatment:**

The preference of the treatment was evaluated at the end of the study (T12) and was described in a summary table. The relationship between the main reasons of that preference and the chosen treatment was assessed by a Fisher exact test due to few data.

❑ **Treatment acceptability:**

The acceptability of the treatment was evaluated after 6 and 12 months. For each criteria of acceptability (taste, ease of use, frequency of use, adverse events and overall satisfaction), the categories “not at all satisfied”, “slightly satisfied” and “moderately satisfied” were regrouped due to few data. For the same reason, the categories “very much satisfied” and “extremely satisfied” were also regrouped. For each acceptability criteria, the degree of satisfaction for D-CURE® and STEOVIT FORTE® was compared by means a McNemar test.

The acceptability criteria were also considered as ordinal quantitative variable, coded from 1 (not at all satisfied) to 5 (extremely satisfied). The comparison between the two treatments was in that case assessed by a non-parametric Wilcoxon signed-rank test.

❑ **Treatment persistence:**

The treatment persistence was evaluated at 6 and 12 months and was computed as the difference (in days) between the date of last intake and the date of first intake. The same statistical analysis as for compliance was done.

❑ **Safety analysis:**

The safety analysis was conducted in the safety population subset. The safety profile of both treatments was described over the study.

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Summary - Conclusions:

Efficacy Results:

The study demonstrated a mean compliance >80% in both treatment groups. A higher compliance was observed with D-CURE® (≥100%) for the two periods ($p<0.0001$).

No significant difference was observed between D-CURE® and STEOVIT FORTE® regarding the 25(OH) vitamin D evolution during the study.

The majority of the volunteers (57%) preferred D-CURE® while only 18% had a preference for STEOVIT FORTE® and 25% were without opinion. The main reason of D-CURE® preference was the frequency of use.

The overall satisfaction of treatment was also reported for D-CURE® ($p<0.0001$) with a higher satisfaction concerning the frequency of use and adverse events.

Safety Results:

D-CURE® and STEOVIT FORTE® were well tolerated during the study.

A total of 107 emergent AEs were reported; among them, only 21 were considered as related to the treatment (10 for D-CURE® and 11 for STEOVIT FORTE®). All of them were of mild to moderate intensity and refered to the gastrointestinal system.

7 SAEs were observed while taking d-CURE® and 8 SAEs while taking STEOVIT® but none of them was considered as treatment-related.