2. SYNOPSIS

Name of Sponsor:	PLIVA HRVATSKA d.o.o. (A member of Teva group)	
Name of Finished Product:	Calcipotriol + Betamethasone 50 µg/g + 0.5 mg/g ointment (PLIVA)	
Name of Active Ingredient:	Calcipotriol + Betamethasone	

Title of study:

A Multicentre, Randomised, Double-Blind, Parallel-group Study of the Efficacy and Safety of a PLIVA Ointment (Calcipotriol + Betamethasone 50 µg/g + 0.5 mg/g ointment) versus Vehicle and Dovobet® in the Treatment of Mild to Severe Plaque-type Psoriasis

Investigators / Study Centres:

Investigators at 40 centres in the Czech Republic, the Slovak Republic and Germany. 1 study site did not randomise any patient.

Prof. [redacted], MD, PhD, DSc, MBA, [redacted]
Czech Republic was the coordinating investigator.

Publication (reference):

None.

Study period:	**Phase of development:**
Date of first enrolment: 16 May 2011 Date of last completed: 1 February 2012	phase III.

Objectives:

- To compare the relative efficacy, safety and tolerability of the PLIVA Ointment of calcipotriol + betamethasone to the already marketed Dovobet® ointment (calcipotriol 50 microgram/g, betamethasone 0.5 mg/g, Leo Laboratories Limited, UK) in patients diagnosed with mild to severe plaque psoriasis.
- To compare test product to a vehicle ointment (placebo) testing for superiority.

Methodology:

The trial was a randomised, double-blind, multicentre, both placebo and active

Name of Sponsor:	PLIVA HRVATSKA d.o.o. (A member of Teva group)	
Name of Finished Product:	Calcipotriol + Betamethasone 50 µg/g + 0.5 mg/g ointment (PLIVA)	
Name of Active Ingredient:	Calcipotriol + Betamethasone	

comparator controlled, parallel group comparative study.

The study required 4 or 5 visits: Screening Visit, Baseline (may be identical to Screening Visit), Weeks 3, 5 and 9. The maximum total time that a subject could be in the study is (4 +) 8 weeks: (possible 4 weeks of washout), 4 weeks under study treatment and 4 weeks without study treatment but without breaking the blind to assess relapse and rebound effects.

At the Baseline Visit, the informed consent was obtained (had not been it done at the Screening Visit) and patients were screened for eligibility. Modified PASI score and other efficacy assessments were evaluated and recorded. Eligible patients entered the study and were randomised into 1 of 3 treatment groups in 3:3:1 fashion:

1. PLIVA Ointment
2. Dovobet®
3. Vehicle.

Patients were required to return for Visit 2 (Week 3), Visit 3 (Week 5, the end of treatment), and Visit 4 (follow-up, Week 9). The efficacy was assessed and adverse events collected at these visits.

Number of patients:

Planned: 651 (to be enrolled)

Analysed: 653 randomised subjects

652 analysed for safety

650 ITT subjects

635 per protocol subjects

Diagnosis and main criteria for inclusion:

- Males or females ≥ 18 years of age (<65 years in the Czech Republic);
- Clinical diagnosis of plaque psoriasis;
- Mild to severe psoriasis, as defined by an Investigator's Static Global Assessment (ISGA) score of at least 2 at Baseline greater than or equal to 10% of one body segment (arms, or legs, or trunk) and less than or equal to 30% of total body surface

Name of Sponsor:	PLIVA HRVATSKA d.o.o. (A member of Teva group)	
Name of Finished Product:	Calcipotriol + Betamethasone 50 µg/g + 0.5 mg/g ointment (PLIVA)	
Name of Active Ingredient:	Calcipotriol + Betamethasone	

area (BSA) affected (excluding the face and scalp);

- Target lesion (greater than 2 cm2) on the trunk or extremities (excluding palms/soles) with a score of at least 2 (on a 0 - 5 scale) for each of erythema, scaling and plaque thickness. Whenever possible, psoriasis on knees or elbows should not be used as a target lesion.

Test product:

Calcipotriol + Betamethasone 50 µg/g + 0.5 mg/g ointment (PLIVA)
Manufacturer: PLIVA HRVATSKA d.o.o., Croatia
Batch no. 007050
Expiry date: 05.2012

Reference therapy:

Dovobet®
Manufacturer: Leo Laboratories Limited, UK
Batch no. EE1421
Expiry date: 05.2012

Vehicle
Manufacturer: PLIVA HRVATSKA d.o.o., Croatia
Batch no. 001050
Expiry date: 05.2012

Duration of treatment:

4 weeks

Criteria for evaluation – efficacy:

- Modified PASI score and its elements (percentage reduction in Modified PASI score from Baseline to Week 5 was the primary variable)
- Investigator Static Global Assessment (ISGA)
- Relapse or rebound
- Subject Global Assessment

Name of Sponsor:	PLIVA HRVATSKA d.o.o. (A member of Teva group)	
Name of Finished Product:	Calcipotriol + Betamethasone 50 µg/g + 0.5 mg/g ointment (PLIVA)	
Name of Active Ingredient:	Calcipotriol + Betamethasone	

- Pruritus
- Evaluation of target lesion

Criteria for evaluation – safety:

- Adverse events
- Serum calcium level

Statistical methods:

ANOVA: Percentage reduction in Modified PASI Score

Mantel-Haenszel procedure: dichotomous endpoints

EFFICACY RESULTS:

The primary variable was the percentage reduction in Modified PASI score from Baseline to Week 5 (Visit 3).

The mean percentage change in Modified PASI from baseline to the end of treatment (Visit 3) was -65.4% (SD=24.7%) in the PLIVA Ointment group, -67.6% (SD=25.2%) in the Dovobet® group and -25.0% (SD=32.5%) in the vehicle group.

The results of PLIVA Ointment were very similar to the active comparator; the vehicle group was significantly different. The same went for the other visits (i.e. Visit 2 and Visit 4).

The treatment difference of 2.09% (S.E.= 2.12%) in the mean percentage change in Modified PASI from baseline to the end of treatment was not statistically different between PLIVA Ointment and Dovobet at the $\alpha = 0.05$ level of significance. The 95% confidence interval was from -2.08% to 6.26% and fell well within the equivalence margins (-10% to +10%). The treatment difference was of neither statistical significance nor the clinical relevance. This result indicates equivalence of PLIVA Ointment and Dovobet®, i.e. that PLIVA Ointment is equally good as Dovobet®.

The mean difference for PLIVA Ointment minus vehicle was -40.73% (S.E.= 3.03%) with the 95% confidence interval from -46.68% to -34.79%. Not only did the CI exclude zero, but it also fell well to the left of the lower equivalence margin. The treatment difference is of both statistical significance at the $\alpha = 0.05$ level and clinical relevance. This indicates superiority of PLIVA Ointment over placebo, i.e. efficacy of

Name of Sponsor:	PLIVA HRVATSKA d.o.o. (A member of Teva group)	
Name of Finished Product:	Calcipotriol + Betamethasone 50 µg/g + 0.5 mg/g ointment (PLIVA)	
Name of Active Ingredient:	Calcipotriol + Betamethasone	

PLIVA Ointment.

The same goes for the mean difference for Dovobet® minus vehicle, which was -42.82% (S.E.= 3.04%) with the 95% confidence interval from -48.79% to -36.86%. This indicates that the study had assay sensitivity and was able to distinguish effective and ineffective treatments.

Results for the ITT analysis population were similar to those for the PPS and resulted in essentially the same conclusions. Results of the secondary variables analysis supported the primary conclusions drawn.

SAFETY RESULTS:

The incidence of AEs (adverse events) was very limited and similar for all three treatments group. AEs were reported by 37 (13%) patients in the PLIVA Ointment group, by 39 (14%) patients in the Dovobet® group and by 8 (9%) patients in the vehicle group.

There were no patients treated with an active treatment (PLIVA Ointment or Dovobet®) with reported AE considered to be related to the investigational medicinal product (IMP) by the investigator. 3 (3%) patients treated with vehicle had a related AE.

There were 2 SAEs reported by 1 study subjects (Dovobet® group). It was considered to be unrelated to study treatment.

There were no deaths during the study.

CONCLUSION:

PLIVA ointment and Dovobet® are therapeutically equivalent.

Date of the report: 4 APR 2012