**Materials and Methods**

*Data Source*

Data for subgroup analyses were obtained from a randomized, double-blind, multicenter, active and vehicle-controlled study (EudraCT No. 2013-002861-20). The study was performed with the objective to demonstrate that Calcipotriol-Betamethasone Sandoz ointment (test product) has equivalent efficacy, safety and tolerability as Daivobet (reference product) in patients with chronic stable plaque psoriasis.

In total, 444 patients with mild to moderate chronic plaque psoriasis were randomized to receive either test, reference or vehicle product in a 4:4:1 ratio (test product: n = 194, reference product: n = 201, vehicle: n = 49). Patients applied a thin layer of the study medication once daily in the evening for 4 weeks. The primary end point was the mean percentage change from baseline in the modified Psoriasis Area and Severity Index (mPASI) at the end of the 4-week treatment. mPASI in the range of 0–64.8 was used to assess the extent and severity of psoriasis, as the scalp and the face were not included in the treatment with the study medication and psoriasis assessment.

The methodology, study design and results of therapeutic equivalence study have been reported previously [13].

*Study Population*

The efficacy of calcipotriol-betamethasone ointment was assessed in the following subpopulations: baseline demographic characteristics (gender, age, body weight, BMI, blood pressure), habits (smoking, alcohol consumption), baseline disease characteristics (baseline mPASI, age at disease onset, disease duration) and concomitant diseases (obesity, hypertension, hyperlipidemia, diabetes, other cardiovascular diseases).

For the purpose of this study, the BMI was used as a categorical ordinal variable, with values grouped into 4 ordered categories, as follows: <20, 20–24.9, 25–29.9 and ≥30. Patients were classified as being obese if their BMI was ≥30 at baseline. Patients were classified as having hypertension if it was reported as a concomitant disease. Further, patients classified as having hyperlipidemia had either hypercholesterolemia, hyperlipidemia or dyslipidemia reported at baseline, and they were classified as having diabetes if diabetes type I or II, hyperglycemia or any kind of impaired glucose tolerance was reported as a concomitant disease. The “other cardiovascular disease” category includes patients with arrhythmia, myocardial infarction/ischemia, angina, atrial fibrillation and coronary artery disease/bypass.

*Efficacy Assessments*

The mean percentage change in the mPASI from baseline to the end of the 4-week treatment was used for efficacy analyses in the subgroups of patients. This was also the primary efficacy end point in the therapeutic equivalence study. Moreover, PASI75 was analyzed, which includes patients with a reduction in mPASI of at least 75% after the 4-week treatment.

*Statistical Analysis*

Post hoc subgroup analyses were conducted on active treatment arms data. As the test and reference products are therapeutically equivalent [13], data from all patients receiving active treatments were combined to improve the statistical power of analyses. The superiority of test product over vehicle was shown in the therapeutic equivalence study, and due to the small number of patients receiving the vehicle, it was not tested in all subgroups of patients.

Efficacy data were assessed for the full analysis set, and missing data were imputed using the last-observation-carried-forward principle. All analyses were 2-sided and conducted at a significance level of 0.05. Descriptive statistics is provided for the efficacy parameter mPASI across different subgroups.

The strength of the linear relationship between two continuous variables was determined by the Pearson product-moment correlation coefficient, whereas the monotonic relationship between continuous and categorical ordinal variables was determined by Spearman’s rank correlation coefficient (with only the *p* values from the associated *t* test reported). For potential associations among a pair of categorical nominal variables, either the χ2 test or Fisher’s exact test was performed.

Regression and decision trees (data not shown here) were developed with the aim of identifying possible baseline characteristics and comorbidity variables related to percentage reduction in mPASI and PASI75, respectively.

Univariate and multivariate regression analyses for percentage reduction in mPASI were performed with continuous and categorical variables as predictors. For the multivariate analysis, a final model was based on backward selection approach. An analysis of covariance multivariate regression model was fitted to estimate the effect of selected comorbidities on the mean percentage change in mPASI, after the adjustment for baseline mPASI, age and gender.

Likewise, univariate and multivariate logistic regression analyses for PASI75 were performed with continuous and categorical variables as predictors. The final multivariate logistic regression model was selected using the backward technique. Additionally, the selected model was found to have the highest values for the Akaike information criterion and Bayesian information criterion as compared with the other candidate models.

Odds ratios (and the corresponding 95% confidence intervals) for achieving PASI75 were calculated to evaluate the effect of selected comorbidities on mPASI reduction.

All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).