SYNOPSIS

Name of Sponsor/Manufacturer: LEO Pharma A/S

Name of Investigational Product/Finished Product, if available: DAIVOBET/DOVOBET gel (LEO 80185), DAIVOBET/DOVOBET/TACLONEX ointment

Name of Active Substance: Calcipotriol plus betamethasone dipropionate

Title of study/Protocol Code Number: Calcipotriene plus betamethasone dipropionate gel compared to the gel vehicle in scalp psoriasis, in patients receiving calcipotriene plus betamethasone dipropionate ointment for psoriasis vulgaris of trunk/limbs. MBL 0502 US.

Centre details: 18 centres in the US.

Publication references: To be decided.

Study period details: First patient enrolled on 27-Dec-2005, last patient visit on 02-Jul-2007

Phase of development: III

Objectives/hypothesis, if applicable:
To compare the efficacy and safety of 8 weeks treatment with DAIVOBET/DOVOBET gel with that of gel vehicle in scalp psoriasis, to evaluate the efficacy and safety of 4 weeks treatment with DAIVOBET/DOVOBET ointment in psoriasis vulgaris of trunk/limbs, and to evaluate the safety of 52 weeks treatment with DAIVOBET/DOVOBET gel in scalp psoriasis and with DAIVOBET/DOVOBET ointment in psoriasis of trunk/limbs.

Study methodology:
Patients were randomised on a double-blind basis in a 3:1 ratio to 8 weeks of once daily treatment of scalp psoriasis with either DAIVOBET/DOVOBET gel or gel vehicle. After this all patients received DAIVOBET/DOVOBET gel for a further 44 weeks to use once daily when required. In addition, all patients received DAIVOBET/DOVOBET ointment as once daily treatment when required for psoriasis of trunk/limbs for 52 weeks. Patients were assessed every 2 weeks in the double-blind phase, every 4 weeks after this.
Investigator assessments: global assessment of severity of scalp psoriasis and of psoriasis of trunk/limbs, clinical signs and extent of scalp psoriasis, adverse events.

Patient assessments: global assessment of severity of scalp psoriasis and of psoriasis of trunk/limbs, itching on the scalp.

Other assessments: blood pressure at all visits and laboratory assessments at weeks 0, 2, 4, 12, 24, 40, 52.

An Adjudication Panel identified adverse events of concern associated with long-term topical corticosteroid use with a possible relation to study medication.

Number of patients enrolled:
A total of 178 patients were enrolled, of whom 177 were randomised, 135 to DAIVOBET/DOVOBET gel and 42 to gel vehicle.

Diagnosis and main criteria for patient selection:
Inclusion criteria: scalp psoriasis and psoriasis of trunk/limbs, both of at least a moderate severity; age of at least 18 years; Hispanic/Latino ethnicity or Black/African American race.

Exclusion criteria: other anti-psoriatic therapy; erythrodermic, exfoliative or pustular psoriasis; other inflammatory skin diseases.

Investigational product, dose, method of administration, lot numbers:
DAIVOBET/DOVOBET gel applied topically once daily for 8 weeks, thereafter once daily when required, lot numbers 051756101, 051746101, 062956101. DAIVOBET/DOVOBET ointment applied topically once daily when required, lot numbers 0520761, 0520762, 0622961.

Reference product, dose, method of administration, lot numbers:
Gel vehicle applied topically once daily for 8 weeks, lot number 051736101.

Duration of treatment:
52 weeks

Criteria for evaluation
Efficacy:
Primary response criterion is patients with “Controlled disease” (clear or minimal) by the investigator’s global assessment of severity of scalp psoriasis at week 8.
Secondary response criteria are: patients with “Success” by the investigator’s assessment of clinical signs of scalp psoriasis at week 8 (in total [score ≤1] and for each sign [absent] – redness, thickness and scaliness); patients with “Controlled disease” (clear or very mild) by the patient’s global assessment of severity of scalp psoriasis at week 8.

Tertiary response criteria include percentage of visits per patient with a satisfactory response (clear, minimal or mild) by the investigator’s global assessment of scalp psoriasis and of psoriasis of trunk/limbs during the study and percentage of patients with “Controlled disease” (clear or minimal) at week 4 by the investigator’s global assessment of psoriasis of trunk/limbs.

Safety:
Secondary response criteria are patients with adverse drug reactions (ADRs) to the study gel and study ointment during the first 8 weeks/4 weeks, respectively, and during the complete study period, and events identified by the Adjudication Panel. Tertiary response criteria include adverse events, withdrawals, and changes in laboratory parameters.

Statistical methodology
For the primary response criterion, the proportion of patients with “Controlled disease” was compared between the groups using the Cochran-Mantel-Haenszel (CMH) test adjusting for the effect of centre and ethnicity. The study was planned to have 99% power to detect a difference in proportions (0.83 versus 0.25) between the two groups at the 5% two-sided significance level.

For analysis of the secondary efficacy response criteria, P-values <0.01 were considered statistically significant to account for multiplicity. The proportions of patients with “Success” or “Controlled disease” were compared between the groups using the CMH test adjusting for the effect of centre and ethnicity.

For the secondary safety response criteria, the proportion of patients with ADRs to the gel was compared between treatment groups using Fisher’s exact test.
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Name of Active Substance: Calcipotriol plus betamethasone dipropionate

Summary – Conclusions

Of the 177 randomised patients, 55.9% were Hispanic/Latino and 44.1% were Black/African American.

Efficacy results:

For the primary response criterion of investigator’s global assessment of scalp psoriasis at week 8, there were 71.9% of patients with “Controlled disease” in the DAIVOBET/DOVOBET gel group compared to 40.5% in the gel vehicle group. The difference between treatments was statistically significant (odds ratio (OR) 3.30; 95% CI 1.62 to 6.72; P<0.001).

For the five secondary response criteria, three (investigator’s assessment of total sign score and of thickness, and patient’s global assessment) showed that DAIVOBET/DOVOBET gel was statistically significantly more effective than gel vehicle, and the other two (investigator’s assessment of redness and scaliness) approached statistical significance in favour of DAIVOBET/DOVOBET gel.

Hence DAIVOBET/DOVOBET is statistically significantly more effective than gel vehicle in the treatment of scalp psoriasis over 8 weeks. During the complete study period patients in the DAIVOBET/DOVOBET gel group had a median of 100% of visits with a satisfactory response by the investigator’s global assessment of scalp psoriasis.

At the end of the first 4 weeks, 22.6% of patients had controlled disease by the investigator’s global assessment of psoriasis of the trunk/limbs. During the complete study period, patients had a median of 85.7% of visits with a satisfactory response by the investigator’s global assessment of psoriasis of trunk/limbs.

Safety results:

During the double-blind phase, there was no significant difference (P=1.0) between the percentage of patients with ADRs to the gel in the DAIVOBET/DOVOBET gel group (7.0%) and the gel vehicle group (7.9%). During the complete study period, 14.3% of patients had ADRs to DAIVOBET/DOVOBET gel. The most common ADRs were headache, paraesthesia and pruritus. The Adjudication Panel identified 5.0% of patients...
with adverse events of concern associated with topical corticosteroid use and possibly related to DAIVOBET/DOVOBET gel, the most common being folliculitis and acne. During the first 4 weeks, 4.2% of patients had ADRs to the DAIVOBET/DOVOBET ointment, and during the complete study period, this figure was 11.4%. The most common ADRs were paraesthesia and pruritus. The Adjudication Panel identified 8.4% of patients with adverse events of concern associated with topical corticosteroid use and possibly related to ointment, the most common being folliculitis and pruritus.

During the complete study period, 71.9% of patients in the DAIVOBET/DOVOBET gel group and 78.9% in the gel vehicle/DAIVOBET gel (8/44 weeks) group had adverse events. Most were unrelated to treatment (90.2% unrelated to gel, 91.0% unrelated to ointment). Eight patients had serious adverse events, one of whom died as a consequence; all were considered unrelated to study medication by the investigator. A total of 36.7% of patients withdrew during the study; in 5 patients this was due to adverse events. In four of these patients, all the events were considered unrelated to study treatment by investigators, and in the other patient the events of hypertension and headache were considered related. Another 16 patients had adverse events relating to hypertension, and all were considered unrelated to study medication.

Five patients had adverse events relating to glucosuria and/or increased blood glucose, all of which were considered unrelated to study medication by the investigator. There were 45.8% patients with a fasting plasma glucose value above normal at baseline. Fasting plasma glucose values went from normal at baseline to above normal at the end of the study in 24.6% patients, and 11.0% patients changed in the opposite direction (high to normal). There were no clinically significant changes in albumin-corrected serum calcium, serum blood urea nitrogen or serum creatinine.

Conclusion:
DAIVOBET/DOVOBET gel was statistically significantly more effective than gel vehicle in the treatment of scalp psoriasis over eight weeks and would appear to be safe and well tolerated over this time. DAIVOBET/ DOVOBET gel is therefore considered safe and

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Effective in the treatment of scalp psoriasis over eight weeks in the ethnic and racial groups enrolled into the study, with a favourable benefit/risk ratio. The results suggest that this efficacy may also be maintained over 52 weeks and it also appears to be safe over this time.

DAIVOBET/DOVOBET ointment would appear to be safe and effective in the treatment of psoriasis on the trunk/limbs over 52 weeks in the ethnic and racial groups enrolled into the study.

The combined use of DAIVOBET/DOVOBET gel and DAIVOBET/DOVOBET ointment to treat psoriasis of both scalp and trunk/limbs would also appear to be safe over 52 weeks.

Report date: 27-Nov-2007