

Final Public Assessment Report

Scientific discussion

Enstilar

**50 µg/g + 0.5 mg/g cutaneous foam
(Calcipotriol monohydrate + betamethasone
dipropionate)**

DK/H/2478/001/DC

Date: 25 April 2017

This module reflects the scientific discussion for the approval of Enstilar. The procedure was finalised on 18 March 2016. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Enstilar 50 µg/g + 0.5 mg/g cutaneous foam, from LEO Pharma A/S.

The product is indicated for topical treatment of psoriasis vulgaris in adults. A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a full, stand-alone application with known active substances.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

Calcipotriol is a synthetic vitamin D3 analogue. Calcipotriol acts by binding to the vitamin D receptor, involved in regulation of various genes. It has been shown that calcipotriol inhibits proliferation and induces differentiation in human keratinocytes. Calcipotriol is also known to exert anti-inflammatory activities.

Betamethasone dipropionate is a synthetic corticosteroid, which acts by binding to and activating the glucocorticoid receptor which subsequently has effects on gene transcription. Corticosteroids have a broad mechanism of action including inhibition of inflammation, proliferation and immunologic response.

The fixed combination of calcipotriol 50 µg/g (as monohydrate) and betamethasone 0.5mg/g (as dipropionate) has been marketed for the topical treatment of psoriasis vulgaris since 2001 in the European Union (EU) and 2006 in the United States (US). These products are marketed in the US under the trade name Taclonex and in Europe under other trade names such as Daivobet, Dovobet, and Xamiol. Daivobet ointment was first approved in Denmark in March 2001 and is today approved in more than 90 countries all over the world. In the US, it was approved in January 2006 under the trade name Taclonex Ointment.

Daivobet gel was first approved for the treatment of psoriasis vulgaris of the scalp in the US (under the trade name Taclonex Topical Suspension) and in the EU in 2008; the indication was extended to include the body in the EU in 2009 and in the US in 2012. Daivobet gel is today approved in more than 70 countries all over the world.

Enstilar has been developed to supplement existing ointment and gel formulations as a potentially more attractive formulation in terms of cosmetic properties and ease of use than Daivobet ointment in order to provide an efficacious product with improved user friendliness (convenience of application and ease of use) for the treatment of psoriasis vulgaris.

The Enstilar formulation consists of drug substances, excipients and the propellants dimethyl ether and butane. The formulation and propellants are filled into an aluminium can and administered through a continuous valve.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is a cutaneous foam intended for topical use. The drug product contains two drug substances calcipotriol 50 µg/g (equivalent to 52.2 µg/g calcipotriol monohydrate) and betamethasone 0.5 mg/g (equivalent to 0.643 mg/g betamethasone dipropionate). The drug product is a white to off-white opalescent liquid in a pressurized aluminium spray can, with a polyamide-imide inner lacquer,

with a continuous valve and actuator. At administration, the propellants immediately evaporates leaving a white to off-white foam on the application site.

The can contains 60 g of foam, not including the amount of propellants.

Pack sizes of 60 g and 2 x 60 g are available. However, not all pack sizes may be marketed.

The excipients are: liquid paraffin; polyoxypropylene stearyl ether; all-*rac*- α -tocopherol; white soft paraffin; butylhydroxytoluene (E321); butane and dimethyl ether.

The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

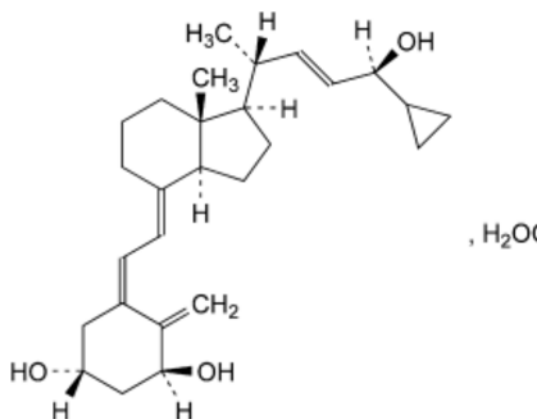
The drug product contains two active substances calcipotriol monohydrate and betamethasone dipropionate.

Calcipotriol monohydrate

The active substance, calcipotriol monohydrate, is described in the European Pharmacopoeia 2284. It is a white or almost white crystalline powder. The monohydrate crystal form is used because it is more stable as raw material than the anhydrous form.

Calcipotriol monohydrate is practically insoluble in water and liquid paraffin and freely soluble in ethanol and propylene glycol.

Chemical structure:



Calcipotriol monohydrate is very sensitive to acids.

The satisfactory compatibility of calcipotriol with the excipients in Enstilar appears from the stability data.

A reversible isomerization to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds.

The documentation on the active substance calcipotriol monohydrate is based on a Certificate of Suitability.

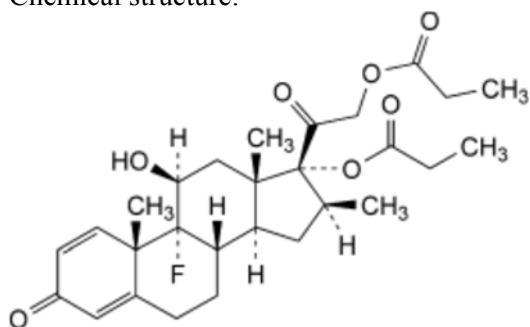
The active substance is controlled according to the Certificate of Suitability. The re-test period is according to the CEP.

Betamethasone dipropionate

The active substance, betamethasone dipropionate, is described in the European Pharmacopoeia, monograph 04/2012:0809. It is a white or almost white, crystalline powder, practically insoluble in water, freely soluble in acetone and in methylene chloride, sparingly soluble in ethanol (96 per cent).

Betamethasone dipropionate and other corticosteroids are sensitive to an alkaline pH environment. At pH 4, an optimum stability of the drug substance is ensured and at higher pH levels hydrolysis of the ester bonds occurs.

Chemical structure:



The satisfactory compatibility of betamethasone dipropionate with the excipients in Enstilar appears from the stability data.

The documentation on the active substance betamethasone dipropionate is based on a Certificate of Suitability.

Betamethasone dipropionate is controlled according to the Ph.Eur. monograph 0809 and CEP for betamethasone dipropionate.

An appropriate re-test period has been set based on presented stability studies.

II.3 Medicinal Product

The finished product is a cutaneous foam intended for topical use. The drug product is manufactured by dissolving an ointment intermediate in two propellants, dimethyl ether and butane.

The ointment intermediate is a fixed combination containing 50 µg/g calcipotriol (as monohydrate) and 0.5 mg/g betamethasone (as dipropionate).

The development of the product has been described, the choice of excipients is justified and their functions explained.

The formulation benefit/risk profile has been challenged due to use of propellants in the formulation. These are classified as “extremely flammable” and the formulation should be handled with caution. The hazard and precaution statements are given in the proposed SmPC, PL and labelling. It is argued that flammable hazard of the Enstilar aerosol product is very low when used under normal conditions.

The proposed formulation exhibits the superior efficacy when compared with the current product Daivobet ointment. Beneficial effect of the propellants on efficacy of the test formulation is related to the supersaturated state of betamethasone dipropionate in the cutaneous foam. It is argued that patients with psoriasis prefer solution and foam vehicles to creams, gels, and ointments for reasons of convenience and cosmetic acceptability.

Elements of a Quality by Design approach are used for the product development. A risk assessment has been performed for the impact of Critical Material Attributes (formulation components) and of Process Parameters (manufacturing process) on the drug product quality.

Delivery rate and delivered amount have been excluded from the finished product specification, as these are not considered critical quality attributes. The homogeneity of the product is controlled by in-process controls of the fill weights.

The manufacturing process is considered to be non-standard due to low content of the active substances in the formulation (less than 2% of the composition). The presented process validation is considered satisfactory. The size of the validation batches is considered representative for commercial scale production.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 4 batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 2 years with the storage condition “Do not store above 30°C” is considered acceptable. The following precautions are included in the SmPC: Extremely flammable aerosol. Pressurised container. May burst if heated. Protect from sunlight. Do not expose to temperatures exceeding 50°C. Do not pierce or burn, even after use. Do not spray on an open flame or other ignition source. Keep away from sparks, open flames and other ignition sources. No smoking.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Enstilar and Daivobet ointment are both topical products, containing the same active substances and excipients, in the same concentrations disregarding the propellants. However, Enstilar has the appearance of a foam, which is different from Daivobet ointment. The Enstilar application is based on the same non-clinical documentation used for Daivobet ointment supplemented with two more recent pharmacological studies, investigating combination effects of calcipotriol and betamethasone dipropionate on differentiation and activity of human Th1/Th17 cells (Study No. REP-PAL-2012-01) and on biomarkers for skin atrophy (Study No. REP-HND-2012-03).

III.2 Pharmacology

The primary pharmacodynamic properties of calcipotriol and betamethasone dipropionate as single substances are considered well-known and sufficiently documented by scientific literature and results derived from previous non-clinical studies performed by the Applicant for Daivobet ointment. In addition, the well-established use of both compounds in the clinic and the regulatory basis for this application supersedes the need for further pharmacodynamics studies.

The combination of calcipotriol and betamethasone dipropionate in cellular systems was shown to have a larger effect on the immune-mediated mechanisms of psoriasis than either of the mono-therapies used alone. Furthermore, the combination increased the inhibitory effect on the Th17 and Th1 cytokines compared to the respective mono-treatments. The pharmacological effects of calcipotriol and betamethasone dipropionate seem to complement each other in their actions against the underlying

parameters of psoriasis vulgaris, including inflammation, keratinocyte hyper proliferation and incomplete differentiation. Furthermore, a recent study suggests that the combination of the two active components may have less skin anthropogenic potential compared to betamethasone dipropionate monotherapy. According to the Applicant, these results are in accordance with clinical experience from use of Daivobet ointment.

No new non-clinical safety pharmacology studies were performed for this application. Reference is given to previous studies investigating effects of single doses of calcipotriol and betamethasone on CNS, cardiovascular and respiratory functions in rats and dogs. The NOEL for calcipotriol was found to be 100-200 µg/kg (rats) and 5 µg/kg (dogs). For both species, the NOEL for betamethasone was 2 mg/kg. The lack of new studies is considered acceptable.

III.3 Pharmacokinetics

Only one pharmacokinetic study has been performed specifically in support of Enstilar, Study No. PMPN1005-282. A written summary of all completed non-clinical pharmacokinetic studies with calcipotriol, betamethasone dipropionate, and the combination in Daivobet ointment was provided for assessment.

The pharmacokinetic properties of calcipotriol and betamethasone dipropionate have been described in sufficient detail previously for Daivobet gel and ointment. One new pharmacokinetics study was performed for the proposed formulation, Enstilar. An approximately 2-fold increased dermal permeation of both calcipotriol and betamethasone dipropionate was observed in this in vitro study with pig skin. The Applicant has provided a discussion on the potential increased risks for patients from a higher systemic absorption of calcipotriol and betamethasone dipropionate based on measuring Enstilar's clinically meaningful effects on calcium metabolism and on adrenal function through HPA axis testing using standard methodology (e.g. Study No. LEO 90100-30). According to the Applicant, there was no clinical evidence of potential increased dermal permeation as measured by PK parameters and effects on HPA axis and calcium metabolism, and the increased in vitro dermal permeation from LEO 90100 did not appear to have any significance with respect to clinical safety.

III.4 Toxicology

The non-clinical toxicology documentation for Enstilar is based on the non-clinical documentation for Daivobet ointment. Apart from an in vitro skin permeation and penetration study, only one non-clinical study (Study No. 72281) has been performed with Enstilar. In this study, once daily dermal treatment of mini pigs for 4 weeks with Enstilar cutaneous foam resulted in very slight, clinically and microscopically visible skin irritation and minimal multifocal epidermal atrophy. Similar treatment with Daivobet ointment caused slight diffuse epidermal atrophy with no signs of skin irritation. Minimal foci with epidermal hyperplasia was observed only in application sites treated with Enstilar cutaneous foam. No skin changes were seen after treatment with the corresponding spray- or ointment vehicles.

It is acknowledged that the pharmacological action of products containing calcipotriol/betamethasone dipropionate yields expected findings such as epidermal hyperplasia, epidermal atrophy and possibly subsequent irritation of the skin. The Applicant states that 'the epidermal hyperplasia is considered to be the result of an irritant effect of long-term treatment with the formulation'.

Previous evaluation of the dermal photo(co)carcinogenesis of calcipotriol (Daivonex) suggested that calcipotriol may enhance the effect of UVR to induce skin tumors. The clinical relevance of the finding is unknown. The UV/VIS spectra obtained of Daivobet ointment and Enstilar before and after evaporation of the propellants were found to be very similar, and according to the Applicant, the propellants do not have any impact on the spectra (Rørbæk, internal LEO report, 2012). Therefore, the phototoxicity data for the Daivobet ointment are considered to be representative for Enstilar as well. Phototoxicity and photoallergy studies have been performed with Daivobet ointment in humans and no

phototoxic or photoallergic reactions were observed. As these studies have been performed in man it was not considered pertinent to test for phototoxicity and photoallergy in animals.

A new degradation product, LEO 123547 (tachysterol of calcipotriol), was detected when a change in analytical procedure for organic impurities of calcipotriol was implemented during stability studies of Enstilar in the current container closure system. The new degradation product is closely related to calcipotriol and pre-calcipotriol used in the synthesis of calcipotriol. It is not known to what degree LEO 123547 has the same pharmacological activities and potency as calcipotriol. It has no structural alerts for genotoxicity (Derek Nexus; Sarah), carcinogenicity or other toxicological end-points, but does possess an equivocal alert for skin sensitization. According to ICH guideline Q3B: ICH Note for Guidance on Impurities in New Drug Products (CPMP/ICH/2738/99), the qualification threshold for a calcipotriol organic impurity is 1.0 %, equivalent to 7.5 µg/day. This is considered a worst case exposure. The Applicant states that a more realistic estimate based on medical experience is that "high-use" patients may use an average of 3.30 g per treatment day distributed over a life-long treatment.

A specification limit of 1.5% was proposed for LEO 123547 based on the levels of LEO 123547 in the available stability data. The Applicant argues that the 'realistic' exposure to LEO123547 in psoriasis patients can be based on a less than lifetime calculation, resulting in an exposure less than the threshold of toxicological concern for genotoxic impurities. This approach is acceptable. The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule-based and statistical) was performed, according to ICH M7.

Propellants DME and butane

Dimethyl ether (DME) and butane are used as propellants in Enstilar.. Toxicology Expert Statement reports were provided for both propellants. The toxicology studies cited in the expert report regarding both acute and chronic inhalational toxicity of DME are considered acceptable. Dimethyl ether has not shown genotoxicity potential in vitro and sub-chronic, chronic and cancerogenicity inhalation studies carried out in rats and hamster exposed to high levels of the compound (up to 47106 mg/m³) have not identified any significant toxic effect.

One of two reproductive and developmental inhalation toxicity studies reported with dimethyl ether has shown no compound related effects at doses up to 52759 mg/m³, whereas the other study has established a no-effect level of 1250 ppm (equivalent to 2355 mg/m³).

The rate of propellant evaporation from Enstilar sprayed in a thin layer onto a piece of paper, was used to mimic the intended administration of the product to skin. It seemed reasonable to conclude that the content of propellants, and hence risk of absorption, is significantly reduced shortly after administration of a thin layer of Enstilar. It was also acknowledged that bioavailability after dermal exposure is considered to be less than after inhalation.

No data were available for dermal or oral exposure of DME or butane in acute or repeat-dose toxicity studies.

III.5 Ecotoxicity/environmental risk assessment (ERA)

For calcipotriol, a PBT screening assessment was triggered by exceeding the log Kow of 4.5, but the applicant provided acceptable data to verify the poor chemical stability for the compound which is in agreement with its chemical structure. Therefore, the compound can be excluded from a PBT screening. Since the Phase I - PEC falls below the trigger value, there are no additional open points for calcipotriol to be considered.

Regarding betamethasone dipropionate it is endorsed to cover the agreed data requirements (LogPow reference; OECD 301 test on Ready Biodegradability followed by a chronic fish full-life cycle study and possibly an OECD 308 test) with a post-authorization measure.

IV. CLINICAL ASPECTS

IV.1 Introduction

The Applicant has submitted data substantiating the efficacy and safety of Enstilar cutaneous foam applied once daily for 4 weeks in patients with psoriasis vulgaris located on the body and scalp. This is based on controlled trials showing superiority of Enstilar cutaneous foam relative to the two active ingredients (calcipotriol and betamethasone dipropionate) in a 3-armed, randomized and double-blind study (Phase-II trial LEO 90100-7), significant superior efficacy of the product relative to Daivobet ointment in a 4-armed, randomized, investigator-blind study (Phase-II trial LEO 90100-35) and finally significant superiority compared to placebo in a randomized, double-blind, 2-armed study (LP0053-1001). In all studies, treatment duration was 4 weeks and the topical products were applied once daily. Long-term safety and efficacy studies of Enstilar cutaneous foam may be needed if therapy should be extended to repeated courses or continuous maintenance treatment of psoriasis vulgaris as approved for the other formulations of the combination products (Daivobet ointment and Daivobet gel).

The applicant has conducted a safety study where 37 patients with severe psoriasis (BSA 15-30% and scalp psoriasis > 30%) applied Enstilar cutaneous foam once daily for 4 weeks without significant depression of the HPA-axis and without adverse effect on calcium metabolism (MUSE trial, LEO 90100-30).

In a standardized, randomized, investigator-blind vasoconstrictor trial in 35 healthy adults that received a single dose of Enstilar cutaneous foam, Daivobet ointment, Dermovate cream (ultra-potent corticosteroid), Synalar ointment (potent corticosteroid), betamethasone in the foam vehicle and the foam vehicle, it was demonstrated that the blanching activity of Enstilar cutaneous foam induced a significantly lower degree of skin blanching compared to Dermovate cream, but a greater degree of skin blanching compared with Daivobet ointment and Synalar ointment (LP0053-69). There was no statistical difference between Enstilar cutaneous foam and betamethasone in the foam vehicle or between Daivobet ointment and Synalar ointment. This suggests that the potency of the corticosteroid component in Enstilar cutaneous foam (betamethasone) may be enhanced in the foam vehicle. It may be a potential concern if the corticosteroid activity of betamethasone in Enstilar cutaneous foam is greater than that of the marketed Daivobet ointment as bridging to long-term safety data generated for Daivobet ointment and Daivobet gel may be hampered. To address this issue, a commitment has been made to conduct a long-term efficacy and safety trial with Enstilar in adults with psoriasis vulgaris in a design as follows: a 52-week trial comparing two different ways of using Enstilar: a proactive treatment approach, using Enstilar twice weekly as long-term maintenance therapy and a conventional reactive approach, based on vehicle twice weekly, and Enstilar once-daily for 4 weeks upon relapse. As both treatment groups will receive 4-week courses of once-daily Enstilar at relapse, the vehicle arm will mimic repeated use of Enstilar according to the proposed labelling (once daily for 4 weeks).

IV.2 Pharmacokinetics

Blood samples for PK analysis were collected in the MUSE trial (LEO 90100-30), and plasma concentrations of BDP, its metabolite betamethasone 17-propionate, calcipotriol, and its metabolite MC1080 were quantified in pre-dose trough plasma samples at Day 14 and Day 28, and in samples collected 1, 2, 3, 5, and 7 hours after application of trial medication at Day 28.

BDP, calcipotriol, and MC1080 were below the lower limit of quantification in most samples; BDP was quantifiable at one or more time points in 5 subjects, calcipotriol in 1 subject, and MC1080 in 3 subjects. Betamethasone 17-propionate, was quantifiable in 27 of the 35 evaluable subjects. Only the PK parameters C_{max} and AUC_{last} could be determined for any of the four analytes, and this was

possible for only some subjects since data were scattered. These results indicate minimal systemic absorption.

IV.3 Pharmacodynamics

The pharmacological effects of calcipotriol and betamethasone dipropionate are well-known; the potential consequences of systemic absorption of the two active substances from the combination are alterations in calcium metabolism manifesting as hypercalcaemia and suppression of the HPA axis. Because the active substances of Enstilar are well-known, a limited clinical programme comprising two clinical trials to determine pharmacokinetics and pharmacodynamics relevant to Enstilar has been performed. Both trials were conducted with the intended market formulation of Enstilar.

Vasoconstrictor trial

In the vasoconstriction trial (LP0053-69), the vasoconstriction activity of Enstilar was evaluated following a 6-hour dose-duration period. The primary endpoint was visual assessment of skin blanching expressed by the AUC0-32h by treatment site. Secondary endpoints were the change from baseline in colorimetric parameter a* (the red/green balance) and the change from baseline in colorimetric parameter L* (luminance). In addition to the protocol-specified multipoint analysis, a post-hoc analysis of the visual assessment of data obtained 2 hours after removal of the investigational products from the test sites was conducted in response to a request from the FDA.

In the primary analysis based on multipoint assessment, all active products induced skin blanching, as expressed by AUC0-32h. The numerical order of the degree of skin blanching among products was identical between the methods applied (visual assessment and colorimetric assessments). Dermovate cream showed the greatest degree of skin blanching (mean AUC0-32h: 3831), followed by Betamethasone dipropionate (2595), Enstilar (2560), Daivobet ointment (2008), and Synalar ointment (1981). The comparisons of visual assessments between treatments showed that Enstilar induced a statistically significantly lower degree of skin blanching compared with Dermovate cream (mean difference: -1272; $p < 0.001$, analysis of variance [ANOVA]), but a greater degree of skin blanching compared with Daivobet ointment (mean difference: 552; $p = 0.001$, ANOVA) and Synalar ointment (mean difference: 578; $p < 0.001$, ANOVA). There was no statistically significant difference in the degree of skin blanching between Enstilar and Betamethasone dipropionate, or between Daivobet ointment and Synalar ointment.

The results of the post-hoc analysis requested by the FDA were comparable to those obtained in the analyses of AUC0-32h of visual assessments. All active products led to a skin blanching effect at 2 hours after removal of the trial medications. Dermovate cream showed the greatest degree of skin blanching (mean: 2.34), followed by Enstilar (1.56), Betamethasone dipropionate (1.53), Daivobet ointment (1.14), and Synalar ointment (0.92). Enstilar induced a statistically significantly lower degree of skin blanching compared with Dermovate cream (mean difference: -0.78; $p < 0.001$, ANOVA), but a greater degree of skin blanching compared with Daivobet ointment (mean difference: 0.43; $p = 0.001$, ANOVA) and Synalar ointment (mean difference: 0.64; $p < 0.001$, ANOVA). There was no statistically significant difference in the degree of skin blanching between Enstilar and BDP, or between Daivobet ointment and Synalar ointment.

The results of both analyses indicate that Enstilar showed a greater skin blanching effect than Daivobet ointment and Synalar ointment, but less effect than the super-potent corticosteroid Dermovate cream.

IV.4 Clinical efficacy

Study population

The patient populations included in the three clinical trials that support the efficacy of Enstilar – Trial LP0053-1001, Trial LEO 90100-7, and Trial LEO 90100-35 – were adult subjects with psoriasis vulgaris

on the body (i.e. trunk and limbs) and, in Trial LEO 90100-7, also on the scalp, attending hospital outpatient clinics or the private practice of a dermatologist. The main inclusion and exclusion criteria were almost identical across the trials. In all three trials, subjects were required to have psoriasis vulgaris on the body of at least 'mild' disease severity by the Investigator's Global Assessment (IGA), a modified Psoriasis Area and Severity Index (m-PASI) score of at least 2, and psoriasis lesions involving a BSA of at least 2%. No important patient groups to be considered for treatment after approval were excluded.

Adults in all age groups were included in each trial. Elderly subjects were not excluded; pooling data from the three trials, the proportion of subjects aged ≥ 65 years ranged from 11.8% (6 subjects) in the ointment vehicle group to 19.8% (20 subjects) in the calcipotriol group (17.2% [97 subjects] in the Enstilar group), and subjects aged ≥ 75 years were represented in all treatment groups except the ointment vehicle group (3.7% [21 subjects] in the Enstilar group). Children and adolescents (below 18 years of age) were not included in the trials.

More than half the subjects in each treatment group in the pooled controlled trials (61.0% [344 subjects] in the Enstilar group) were men, but at least 35% in each treatment group were women. The majority of subjects in each treatment group were white (ranging from 82.2% [83 subjects] in the Betamethasone group to 91.1% [92 subjects] in the calcipotriol group; 87.1% [491 subjects] in the Enstilar group) and not Hispanic or Latino. Black or African American and Asian subjects, as well as Hispanic or Latino subjects, were also represented in all treatment groups.

Each treatment group in each of the three trials included subjects with a range of disease severity levels at baseline, from 'mild' to 'severe' according to the IGA. Pooling across the trials, approximately 75% of subjects in each treatment group were assessed as having 'moderate' disease (IGA) on the body at baseline, and more than half of the remaining subjects were assessed as having 'mild' disease on the body; in the Enstilar group 8.5% (48 subjects) had 'severe' disease. Thus it is anticipated that the effect demonstrated would be applicable to the population considered for treatment in clinical practice across all levels of disease severity.

In summary, the population studied is considered representative of the target population; the different subgroups with regard to age, sex, ethnicity, and disease severity were adequately represented.

Study design

The design of the clinical trials in the development programme was consistent with the recommendations in the CHMP psoriasis guideline. The pivotal phase 3 trial LP0053-1001 and the proof-of-concept trial LEO 90100-7 were double-blind, and the comparative trial LEO 90100-35 was investigator-blinded; full double-blinding was not possible in this trial because of the difference in formulation, but for each active treatment arm a corresponding vehicle control was also included in order to blind the subjects as to whether active treatment or vehicle had been applied. Wash-out periods for treatments that could affect subjects' psoriasis were included in the eligibility criteria for all trials.

Duration of studies

Based on the trials conducted with Daivobet ointment, which showed that the main improvement occurred during the first 4 weeks, a treatment duration of 4 weeks was chosen for the phase 2 trials with Enstilar. The results of these trials indicated that most subjects will attain a clinically relevant improvement within 4 weeks. The benefits of a 4-week treatment duration were confirmed in the pivotal phase 3 trial, which showed that 53% of subjects achieved 'treatment success' ('clear' or 'almost clear', with at least a 2-step improvement) according to the IGA at Week 4.

Choice of endpoints

Psoriasis vulgaris on the body was evaluated using both the IGA and the extent and severity of clinical signs, from which the modified Psoriasis Area and Severity Index (m-PASI) was calculated. The m-PASI is a version of the Psoriasis Area and Severity Index (PASI), modified to include only the body (i.e. trunk and limbs).

In line with the CHMP recommendations ‘treatment success’ according to the IGA at Week 4 was chosen as the primary efficacy endpoint in all three efficacy and safety trials, and ‘treatment success’ according to the IGA at Week 4 is also the primary efficacy endpoint for the integrated analysis of efficacy. In all three trials, as well as in the integrated analysis, ‘treatment success’ (called ‘controlled disease’ in Trials LEO 90100-7 and LEO 90100-35) was defined as ‘clear’ or ‘almost clear’ for subjects who were classified as having disease of at least ‘moderate’ severity by IGA at baseline, whereas subjects with ‘mild’ disease severity by IGA at baseline had to achieve ‘clear’ to be considered as having achieved ‘treatment success’. ‘Treatment success’ according to the IGA at Week 1 was analyzed as a secondary or further (synonymous with tertiary) endpoint in all three trials, and is a secondary endpoint in the integrated analysis.

In addition to assessment by a validated, standardized global score such as the IGA, the use of PASI is also recommended by the CHMP psoriasis guideline as one of the clinically relevant measures to evaluate efficacy. Therefore, m-PASI at Week 4 and m-PASI at Week 1, assessed as secondary or further endpoints in all three trials as reported in the CSRs, are assessed as secondary endpoints in the integrated analysis. The percentage of subjects with at least a 75% reduction in m-PASI (PASI75) at Week 4 is assessed as a tertiary endpoint in the integrated analysis.

In accordance with the CHMP psoriasis guideline, several subject-assessed measures of symptoms and health-related quality of life were used to provide a more complete picture of the benefits achieved by the treatment. These included the Patient’s Global Assessment of disease severity (PaGA), assessment of itch and itch-related sleep loss by visual analogue scale (VAS), as well as the Dermatology Life Quality Index (DLQI) and the Euro Qol Group 5-dimension, 5-level questionnaire (EQ-5D-5L). ‘Treatment success’ according to the PaGA was defined as ‘clear’ or ‘very mild’, and was assessed at Week 4. The changes from baseline in itch and itch-related sleep loss were assessed at each visit (and, in Trial LP0053-1001, additionally Day 3 and Day 5); in Trial LP0053-1001, analyses of responder rates for itch and itch-related sleep loss were also performed (where response was defined as a $\geq 70\%$ reduction from baseline). The change in DLQI score from baseline to each visit was analyzed in Trials LP0053-1001 and LEO 90100-7, and change in EQ-5D-5L from baseline to Week4 was analyzed in Trial LP0053-1001.

Control groups

In accordance with the CHMP Guideline on Fixed Combination Medicinal Products, the efficacy trials included comparisons required to provide confirmatory evidence of efficacy for a combination product, i.e. comparisons with both active constituents and with the vehicle. The pivotal phase 3 trial (LP0053-1001) was controlled with the foam vehicle; the phase 2 proof-of-concept trial (LEO 90100-7) was controlled with active treatment (betamethasone and calcipotriol, each as monotherapy, so as to allow simultaneous evaluation of the contribution of each component to the effect of Enstilar); and the phase 2 comparative trial (LEO 90100-35) was controlled with an active treatment (Daivobet ointment). Betamethasone dipropionate and calcipotriol were formulated in the same vehicle as Enstilar to ensure the scientific integrity of the comparison. The foam vehicle was chosen as inactive control. Daivobet ointment was chosen as the marketed comparator because it is an approved psoriasis treatment that contains the same active substances as Enstilar, at the same concentrations.

Statistical methods

No significant modifications that might have had an impact on the overall conclusions were made to the trial conduct or assessments described in the original trial protocols.

In the phase 3 trial LP0053-1001, missing data for the primary and secondary endpoints were handled using the MI method as the primary method of imputation; LOCF was performed as one of the sensitivity analyses. In the two phase 2 trials LEO 90100-7 and LEO 90100-35, LOCF was used as the primary method of imputation. The primary method for handling missing data was changed for the phase 3 trial in response to a recommendation by the FDA issued after the phase 2 trials had been completed.

To ensure a uniform way of reporting for the integrated analysis of efficacy, the results of the phase 2 trials LEO 90100-7 and LEO 90100-35 were reanalyzed using MI. The original reporting based on LOCF is presented and the analysis based on MI is presented as additional supportive data. Hence, for the primary and secondary endpoints and PASI75 two sets of tables are presented: one showing the analysis based on MI and one based on LOCF for missing values.

In the three controlled trials evaluating efficacy, Enstilar, applied once daily for 4 weeks, was statistically significantly superior to the foam vehicle alone, betamethasone, calcipotriol, and Daivobet ointment when assessed by the primary endpoint ('treatment success' according to the IGA at Week 4), using the primary method of imputation for missing data. The percentage of subjects in the Enstilar group with 'treatment success' at Week 4 was very similar in Trials LP0053-1001 and LEO 90100-35 (53.3% and 54.6% respectively); in Trial LEO 90100-7 the percentage was lower (45.0%), but this was most likely due to random variation, since the 95% confidence interval (CI) for the frequency of 'treatment success' in this trial (35.2 to 54.8%) contains the estimated frequencies for the other two trials. At Week 1, Enstilar was statistically significantly superior only to the foam vehicle with regard to 'treatment success' according to the IGA (secondary endpoint). The percentage of subjects in the Enstilar group with 'treatment success' at Week 1 was 8.5% in Trial LP0053-1001, 6.0% in Trial LEO 90100-7, and 3.5% in Trial LEO 90100-35.

The results for the secondary endpoints m-PASI at Week 4 and Week 1 were consistent across the three trials and supported the results for 'treatment success' according to the IGA; Enstilar was statistically significantly superior to all of the comparators at Week 4, and to the foam vehicle, calcipotriol, and Daivobet ointment at Week 1. The least squares (LS) mean m-PASI in the Enstilar group at each of the two time points, using the primary method of imputation, was similar across trials. The results for the tertiary endpoint PASI75 at Week 4 were also consistent across the three trials. Enstilar was statistically significantly superior to the foam vehicle and calcipotriol.

The results for 'treatment success' by PaGA were consistent across the three trials and supported the results for the investigator-assessed endpoints. In all three trials, subjects treated with Enstilar also reported a substantial mean decrease in itch severity by Week 1, and continued improvement in itch was seen from Week 1 to Week 4. In Trial LP0053-1001, responder rates for itch increased successively during the course of the trial in the Enstilar group, and were statistically significantly superior to those in the foam vehicle group at all time points: by Week 4, 83.5% of subjects had achieved a $\geq 70\%$ itch reduction, compared with 40.6% in the foam vehicle group. Similar results were seen in the responder analysis for itch-related sleep loss.

The results for change in DLQI were consistent between Trials LP0053-1001 and LEO 90100-7, showing a statistically significantly greater improvement in quality of life for Enstilar than for foam vehicle at all visits in Trial LP0053-1001 and for calcipotriol, but not betamethasone, at all visits in Trial LEO 90100-7.

The efficacy of Enstilar on the scalp has been evaluated in one trial (Trial LEO 90100-7). There is extensive experience with the use of Daivobet gel on the scalp, and the results in Trial LEO 90100-7 are consistent with the results for Daivobet gel, showing that the combination product is more effective on the scalp than either component alone. Enstilar was associated with a higher rate of 'treatment success' by the IGA on the scalp at Week 4 than both betamethasone and calcipotriol, but the trial was not powered to show statistical significance. However, Enstilar was statistically significantly superior to calcipotriol.

Consistency across subgroups

The efficacy of Enstilar as assessed by the primary endpoint ('treatment success' according to the IGA at Week 4) was examined in subpopulations based on sex, age, race, ethnicity, and baseline disease severity.

Enstilar was shown to be effective in both men and women, and in all age groups. The majority of subjects in the pooled controlled trials were white and not of Hispanic or Latino ethnicity, and some race

subgroups were very small, but the results in the larger subgroups were generally consistent with those for the overall population. In all subgroups ‘treatment success’ was more frequent with Enstilar than with the foam vehicle, even though the response rates varied across subgroups. In summary, the efficacy of treatment with Enstilar in subjects with psoriasis appears to be insensitive to sex, age, race, and ethnicity.

Although the response rate was highest in subjects with ‘moderate’ disease severity at baseline, ‘treatment success’ was achieved regardless of whether baseline disease severity according to the IGA was ‘mild’, ‘moderate’ or ‘severe’, supporting use in all disease severity categories.

Long-term efficacy

The applicant has not conducted any long-term trials investigating efficacy with this product. The long-term efficacy of the calcipotriol/betamethasone combination has, however, been investigated as a secondary objective in the long-term safety trials (52 weeks) conducted with both the ointment and gel formulations.

Similarly, the occurrence of rebound and relapse of disease after discontinuation of treatment was investigated for both the ointment and the gel formulations (Daivobet ointment and Daivobet gel), in accordance with the CHMP psoriasis guideline. A commitment has been made to conduct a 52 week long-term efficacy and safety trial with Enstilar in adults with psoriasis vulgaris in which both proactive treatment (Enstilar twice weekly as long-term maintenance therapy) and reactive treatment (once-daily for 4 weeks upon relapse) will be assessed.

IV.5 Clinical safety

Overall, 13.8% (78) of the subjects in the pooled Enstilar group reported at least one AE, compared with 8.6% (13 subjects) in the foam vehicle group. The percentage of subjects experiencing at least one adverse drug reaction (ADR, i.e. an AE for which the investigator had not described the causal relationship to trial medication as not related) was 2.7% (15 subjects) in the Enstilar group, and 1.3% (2 subjects) in the foam vehicle group. Lesional/perilesional AEs were reported by 2.5% (14 subjects) in the Enstilar group and 2.0% (3 subjects) in the foam vehicle group. AEs of severe intensity were reported in the Enstilar group (in 1.1% [6 subjects]), but not in the foam vehicle group.

The most frequent AE that occurred in the Enstilar group was nasopharyngitis (in 1.1% [6 subjects]); it was not reported in the foam vehicle group. Nasopharyngitis is a common condition and is not considered a typical reaction for the pharmacological class of either of the active ingredients. Therefore the applicant does not consider this to be an adverse reaction to Enstilar.

Adverse events seen in between 0.1% and 1% of subjects treated with Enstilar included hypertension, application site pain, nausea, application site irritation, application site pruritus, contusion, diarrhoea, excoriation, flank pain, flushing, hordeolum, and influenza (each occurring in ≥ 2 subjects), as well as a number of further events each occurring in a single subject only. All AEs were evaluated in order to identify potential adverse reactions. The vast majority of the events are not typical reactions for the pharmacological class and occurred in only one subject, so are not considered to be adverse reactions to Enstilar. Nausea, contusion, diarrhoea, excoriation, flank pain, flushing, hordeolum, and influenza each occurred in ≥ 2 subjects in the pooled Enstilar group, but are not typical class effects and occurred in few subjects, so are also not considered to be adverse reactions.

The following events were each reported in one subject in the Enstilar group, and are considered typical reactions for the pharmacological class: abscess, cellulitis, contact dermatitis, fungal skin infection, and tinea. In each of these cases, however, the event was distant from the treated psoriasis lesions (i.e. located >2 cm from the lesion border), so the sponsor does not consider any of these events to be an adverse reaction to Enstilar. In addition, folliculitis, which is also a typical reaction for the pharmacological class, was reported in one subject in the Enstilar group, and was recorded as distant (>2 cm) from the application site. However, this event was assessed by the investigator as being possibly related to Enstilar.

While the causal relationship to Enstilar for this particular event is unclear, taking into account that in the dermal safety trial folliculitis was observed after application of Enstilar (in 20 [9.2%] subjects and all events were assessed by the investigators as probably related to Enstilar) but not after application of foam vehicle, LEO regards folliculitis as an adverse reaction to Enstilar.

Application site pain was reported in 4 subjects (0.7%) in the Enstilar group, but had a higher incidence in the foam vehicle group (2 subjects [1.3%]) and so is not considered to be an adverse reaction to Enstilar.

Impetigo was reported in 1 subject (0.2%) in the Enstilar group. Impetigo can be a typical reaction to the pharmacological class, and the reported case was lesional/perilesional (i.e. located ≤ 2 cm from the border of a treated psoriasis lesion). However, impetigo is a rare condition in psoriasis lesions. Furthermore, as recorded in the case report form (CRF), the impetigo was not verified by the investigator. The AE was self-reported by the subject and self-treated with an antibiotic between Visit 3 and Visit 4; at Visit 4 the impetigo had resolved. The investigator assessed the event as not related to trial medication. The sponsor does not consider impetigo to be an adverse reaction to Enstilar.

Hypertension was reported in 4 subjects (0.7%) in the Enstilar group and no subjects in the foam vehicle group (MedDRA preferred term: blood pressure increased [3 subjects], hypertension [1 subject]). Blood pressure increase is a typical reaction for the pharmacological class of corticosteroids; however, fluctuations in blood pressure are common and have many causes. Three of the subjects who experienced a blood pressure increase or hypertension during the trials already had elevated blood pressure at baseline, and the fourth had borderline elevated blood pressure. None of the subjects experienced a substantial increase in blood pressure between baseline and the end of the trial. None of the subjects had a medical history or concurrent diagnosis of hypertension.

Based on the above considerations, the applicant does not consider hypertension to be an adverse reaction to Enstilar. None of the blood pressure increases/hypertension reports was considered related to treatment by the investigator.

In addition to folliculitis, the following were identified as adverse reactions to Enstilar, and will be included in the product labelling. The reactions are regarded as typical for the pharmacological class of the active ingredients of Enstilar, and the local events occurring in the clinical trials were recorded as lesional/perilesional: application site irritation, application site pruritus, application site discolouration (skin hypopigmentation), blood calcium increased (hypercalcaemia), hypersensitivity, and psoriasis (rebound effect). The adverse reactions are all in the frequency category Uncommon ($\geq 1/1,000$ and $< 1/100$), calculated based on the 564 subjects in the pooled Enstilar treatment group.

Serious and significant adverse events

No deaths were reported in any of the clinical trials with Enstilar.

In the pooled controlled trials, serious AEs (SAEs) were reported in 3 subjects (0.5%) in the Enstilar group and 2 subjects (1.5%) in the Daivobet ointment group, but not in any other treatment group. One of the SAEs in the Enstilar group (hypersensitivity) was considered by the investigator to be possibly related to treatment and led to permanent discontinuation of treatment and withdrawal from the trial. The other two were considered not related to trial medication; one of them (substance-induced psychotic disorder) led to permanent discontinuation of treatment. One further SAE (rectal haemorrhage) was reported in the dermal safety trial. This SAE was not considered by the investigator to be related to trial medication, and led to withdrawal from the trial. No SAEs occurred in the MUSE trial, the vasoconstriction trial (LP0053-69), or the exploratory psoriasis plaque test trial (LEO 90100-01).

In the pooled controlled trials, AEs were recorded as a reason for permanent discontinuation of treatment with trial medication for 3 subjects (0.5%) in the Enstilar group, 3 subjects (3.0%) in the calcipotriol group, and 1 subject (0.7%) in the Daivobet ointment group, but none in the foam vehicle group. No AE (preferred term) led to permanent discontinuation of treatment for more than one subject in the Enstilar group. The SAE of hypersensitivity was assessed by the investigator as possibly related to trial medication, but the other 2 AEs leading to permanent discontinuation in the Enstilar group were considered not related to trial medication. In the dermal safety trial, the SAE of rectal haemorrhage

was the only AE that led to permanent discontinuation of treatment and withdrawal from the trial (LP0053-66). No AEs led to permanent discontinuation of treatment or withdrawal from the trial in the MUSE trial, the vasoconstriction trial (LP0053-69), or the exploratory psoriasis plaque test trial (LEO 90100-01).

AEs that would be of concern in relation to this product are systemic effects related to calcipotriol absorption (hypercalcaemia, blood calcium increased, and urine calcium increased) and local and systemic effects related to topical corticosteroid use. There was one AE of blood calcium increased in the Enstilar group in the pooled controlled trials; two further subjects in this group developed serum calcium values above the reference range at Week 4 which were not reported as AEs. None of the high values was considered clinically relevant, and all returned to 'normal' or 'low' at the follow-up visit.

Events potentially related to corticosteroid use were identified by the review of the AEs reported in the pooled controlled trials as follows. Application site discolouration (verbatim term: perilesional hypopigmentation) was reported for 1 subject (0.2%) in the Enstilar group. There were no AEs of tachyphylaxis. Psoriasis on the lesional/perilesional area or assessed as treatment-related (verbatim term: psoriasis flare) was reported for 1 subject (0.2%) in the Enstilar group (this event was considered a rebound event) and 1 subject (0.7%) in the Daivobet ointment group. Lesional/perilesional or treatment-related infections of any type were reported for 6 subjects, including 2 in the Enstilar group (1 case of folliculitis and 1 of impetigo). Hypertension/blood pressure increased was reported for 4 subjects (0.7%) in the Enstilar group, one of whom experienced two separate episodes, as well as for 1 subject (1.0%) in the BDP group and 1 subject (0.7%) in the Daivobet ointment group.

Given the low incidence of each of these events across the pooled treatment groups, there is no clear evidence to suggest an increased incidence of any of these AEs due to the treatment with Enstilar compared with the other treatments.

In summary, no safety issues were identified in the short-term trials based on a review of deaths, SAEs and withdrawals due to AEs. The incidence of potentially calcipotriol- or corticosteroid-related AEs was low and in line with previous experience from trials with marketed calcipotriol/betamethasone products, and gave no indication of any new concerns.

Systemic safety

Calcium homeostasis and HPA axis suppression are particular safety concerns with all products containing a potent steroid such as betamethasone and a vitamin D analogue. In the MUSE trial (LEO 90100-30), the effect on HPA axis function was assessed, and a rigorous assessment of calcium metabolism was performed. In addition, clinical laboratory evaluations of calcium metabolism were performed in each of the three pooled controlled trials (LP0053-1001, LEO 90100-7, and LEO 90100-35).

Effects on the HPA axis

The HPA axis testing in Trial LEO 90100-30 was conducted by means of the adrenocorticotropic hormone (ACTH) challenge test, a well-established standard for detecting adrenal suppression. Serum cortisol concentrations at 30 and 60 minutes after injection of the synthetic subunit of ACTH were measured in order to assess the maximum stimulated cortisol level. The primary endpoint for evaluation of HPA axis function was the percentage of subjects with a serum cortisol concentration of ≤ 18 mcg/dl at 30 minutes after ACTH challenge at Week 4.

None of the 35 subjects who completed 4 weeks of treatment as per protocol had a serum cortisol level ≤ 18 mcg/dl either 30 minutes or 60 minutes after the ACTH stimulation test at Week 4 (LEO 90100-30).

Effects on calcium metabolism

In Trial LEO 90100-30, the primary calcium metabolism endpoints were the changes from baseline to Week 4 in albumin-corrected serum calcium, 24-hour urinary calcium excretion, and urinary calcium:creatinine ratio (Module 2.7.4, Section 3.1.2.1), and the secondary calcium metabolism endpoints were the changes from baseline to Week 4 in serum phosphate, serum alkaline phosphatase,

plasma parathyroid hormone, 24-hour urinary phosphate excretion, and urinary phosphate:creatinine ratio.

The mean and median values for each of the primary and secondary calcium metabolism parameters were within the reference ranges at both baseline and Week 4, and the mean and median changes from baseline to Week 4 were small and not considered clinically significant.

None of the 35 subjects who completed 4 weeks of treatment as per protocol had a shift from normal at baseline to above the normal range at Week 4 for any of the primary parameters. A small number of subjects had shifts from normal to high for 24-hour urinary phosphate excretion (1 subject), urinary phosphate:creatinine ratio (1 subject), serum alkaline phosphatase (1 subject), and plasma parathyroid hormone (4 subjects), and 1 subject had a shift from a normal 24-hour urinary phosphate excretion value at baseline to a low value at Week 4. None of these shifts was considered clinically relevant.

Data for the primary calcium metabolism endpoints were analyzed by 25-hydroxy vitamin D classification at baseline to assess whether there was an association between vitamin D levels at baseline and changes in calcium metabolism parameters. The mean and median changes from baseline to Week 4 (LOCF) in albumin-corrected serum calcium, urinary calcium:creatinine ratio, and 24-hour urinary calcium excretion were small regardless of whether 25-hydroxy vitamin D levels were low, normal, or high at baseline.

Albumin-corrected serum calcium levels and the urinary calcium:creatinine ratio (from spot urine samples) were also assessed at baseline and Week 4 in each of the three controlled trials (LP0053-1001, LEO 90100-7, and LEO 90100-35). The data supported the conclusions drawn from the MUSE trial: the mean and median changes for these parameters from baseline to Week 4 in all treatment groups were small and not considered clinically relevant. Three subjects in the pooled Enstilar group and 1 in the Daivobet® ointment group had shifts from normal albumin-corrected serum calcium values at baseline to values above the reference range (2.15 to 2.55 mmol/l) at Week 4; one of the high values in the Enstilar group was reported as an AE of mild intensity and assessed by the investigator as possibly related to trial medication. The high levels in the Enstilar group were only 0.08 mmol/l, 0.03 mmol/l, and 0.05 mmol/l above the upper limit of the normal range, and all returned to 'normal' or 'low' at the follow-up visit. Dietary calcium intake was not restricted in subjects in these trials. No values above the LEO-defined threshold ('high': > 2.9 mmol/l) for clinically important laboratory changes were seen. None of these subjects with high serum calcium values experienced a concurrent increase in the urinary calcium:creatinine ratio. Shifts from a normal urinary calcium:creatinine ratio at baseline to a high ratio at Week 4 (LOCF) were seen in 17 (3.1%) subjects in the Enstilar group and in broadly comparable proportions of subjects in the other pooled treatment groups.

In summary, there was no indication that treatment with Enstilar is associated with a disturbance of calcium metabolism as measured by albumin-corrected serum calcium and urinary calcium:creatinine ratio.

Dermal safety

Dermal safety was assessed in a phase 1 trial combining a 21-day cumulative irritancy assessment with a repeat insult patch test (Trial LP0053-66). This trial showed Enstilar to have a low skin irritation potential in healthy subjects, and the foam vehicle alone to be non-irritant. Both Enstilar and the foam vehicle alone showed no skin sensitization potential in healthy subjects.

Long-term safety

The safety of the calcipotriol/betamethasone combination for long-term use has been well established for the marketed products Daivobet ointment and Daivobet gel. Long-term safety of the combination treatment has been investigated in three long-term trials with Daivobet ointment and/or Daivobet gel, including over 900 subjects on Daivobet therapy for up to 52 weeks. In addition, substantial post-marketing safety data are available for both products. Enstilar contains the same active ingredients as the ointment and the gel formulations, and its safety profile in the seven completed trials was similar to that of the Daivobet products.

Comparisons of safety data between the Enstilar and Daivobet ointment treatment groups in two head-to-head trials indicated that, while the corticosteroid potency of Enstilar is slightly higher than that of Daivobet ointment, the short-term AE profiles of the two formulations are similar. Further analyses of pooled safety data from the Enstilar, Daivobet ointment, and Daivobet gel treatment groups in four MUSE trials and 11 short-term trials provide additional supportive evidence that the systemic safety profile and short-term AE profile of Enstilar are similar to those of Daivobet ointment and Daivobet gel, and that no new safety concerns have emerged for Enstilar beyond those already described for the calcipotriol/betamethasone combination product in the ointment and gel formulations

Long-term safety profiles for both single components, calcipotriol and betamethasone, as well as for the combination in the ointment and gel formulations are well established. The types of adverse reactions observed during long-term treatment with the ointment and gel products were predictable pharmacological class effects typically associated with calcipotriol and topical corticosteroids. There were no ADRs that increased in frequency or severity with time, and there were no serious ADRs associated with repeated treatment with Daivobet ointment or Daivobet gel as needed for up to 1 year, as compared with 4 or 8 weeks.

Enstilar is effective and safe when used in patients with plaque type psoriasis for up to 4 weeks. The product may be a more cosmetically acceptable and more efficacious alternative to Daivobet ointment, which contains the same active ingredients at the same concentrations.

A benefit-risk assessment based on the available efficacy and safety data support an approval of the product for short-term therapy of psoriasis of 4 weeks duration, as approved for potent and ultra-potent corticosteroids.

LEO has committed to conduct a long-term efficacy and safety trial with Enstilar in adults with psoriasis vulgaris designed as described in the 120 day response i.e., a 52-week trial which will compare two different ways of using Enstilar: a proactive treatment approach, using Enstilar twice weekly as long-term maintenance therapy and a conventional reactive approach, based on vehicle twice weekly, and Enstilar once-daily for 4 weeks upon relapse. As both treatment groups will receive 4-week courses of once-daily Enstilar at relapse, the vehicle arm will mimic repeated use of Enstilar according to the proposed labeling (once daily for 4 weeks). The intention with this trial is to document long term safety and efficacy with maintenance therapy and repeated use, and to support an extension of the indication to include maintenance treatment in the EU label. The outcome of the trial will be reported by submitting the appropriate variation.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Enstilar.

The agreed summary list of safety concerns with no additional pharmacovigilance or risk minimisation measures is as follows:

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • Skin atrophy • HPA axis suppression • Rebound phenomenon • Secondary infections • Hypercalcaemia
Important potential risk	<ul style="list-style-type: none"> • Potential enhancement of UV radiation induced skin cancer

Summary of safety concerns	
Missing information	<ul style="list-style-type: none"> • Safety and efficacy in children below 18 years • Safety and efficacy in patients with severe renal insufficiency or severe hepatic disorders

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Enstilar cutaneous foam has a proven chemical-pharmaceutical quality and is effective and safe when used for topical treatment of psoriasis vulgaris in adults for up to 4 weeks. The product may be a more cosmetically acceptable and more efficacious alternative to Daivobet ointment, which contains the same active ingredients at the same concentrations.

A benefit-risk assessment based on the available efficacy and safety data support an approval of the product for short-term therapy of psoriasis of 4 weeks duration, as approved for potent and ultra-potent corticosteroids. However, the Applicant has committed to conduct a long-term efficacy and safety study with Enstilar cutaneous foam especially in order to evaluate the risk of corticosteroid related cutaneous adverse reactions and possible systemic effect during prolonged or repeated use of the product. This is based on the previously mentioned concern of a potentiation of the strength of the corticosteroid component of the product seen in the vasoconstrictor test and which may have contributed to the increased efficacy seen in the comparative clinical trial. This also means that treatment with Enstilar should not exceed 4 weeks, as sufficient long-term data are currently not available.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that a marketing authorisation for Enstilar could be granted. The decentralised procedure was finalised on 18 March 2016. Enstilar was authorised in Denmark on 27 April 2016.

According to the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs), the PSUR submission cycle is 9 years with next DLP on 01-01-2021.

The date for the first renewal will be: 18 March 2021.