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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Skilarence

International non-proprietary name: dimethyl fumarate

Procedure No. EMEA/H/C/002157/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

a.a.	After administration
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC0-∞	Area under the plasma concentration-time curve from time zero to infinity
AUC0-t	Area under the plasma concentration-time curve from time zero to time t, where t is the time of the last concentration measured
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (the German Federal Institute for Drugs and Medical Devices)
BID	Twice Daily
BSA	Body surface area
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cmax	Maximum plasma concentration
CV	Coefficient of variation
CYP	Cytochrome P450
DLQI	Dermatology Life Quality Index
DMF	Dimethyl fumarate
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency (formerly EMEA)
EoT	End of treatment
EU	European Union
FA	Fumaric acid
FAE	Fumaric acid ester
FAS	Full analysis set
GCP	Good Clinical Practice
GSH	Glutathione
HLT	High level term
HPLC	High Performance liquid chromatography
ICH	International Conference on Harmonization
IMP	Investigational medicinal product
LAS41008	Almirall code number (DMF drug product as tablet) for Skilarence
LAS190046	Almirall code number (DMF active ingredient)
LASW1835	Almirall code number (Fumaderm commercial product, tablets with DMF in combination with MEF salts)

LASW1837	Almirall code number (Blend of active ingredients, DMF + MEF salts at the same proportion presented in the Fumaderm formulation)
LLOQ	Limit of quantification
LOCF	Last observation carried forward
LS mean	Least square mean
MAA	Marketing Authorisation Application
MTX	Methotrexate
MedDRA	Medical Dictionary for Regulatory Activities
MEF	Monoethyl fumarate (synonym: ethyl hydrogen fumarate)
MHRA	Medicines & Healthcare Products Regulatory Agency
MMF	Monomethyl fumarate
NF-κB	Nuclear factor 'kappa-light-chain-enhancer of activated B-cells'
PASI	Psoriasis Area and Severity Index
PBI	Patient Benefit Index
PBQ	Patient Benefit Questionnaire
PD	Pharmacodynamics
PGA	Physician's Global Assessment
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PNQ	Patient Need Questionnaire
PPS	Per protocol set
PT	Preferred term
QD	Once daily
SAE	Serious adverse event
SAS	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SMQ	Standardised MedDRA Queries
SOC	System organ class
SOP	Standard operating procedure
t1/2	Half-life
TESAE	Treatment-emergent serious adverse event
Th	T helper Type
tmax	Time to reach maximum plasma concentration
UK	United Kingdom
VZV	Varicella zoster virus
WBC	White Blood Cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Almirall S.A. submitted on 2 December 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Skilarence, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 May 2015. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The applicant applied for the following indication:

treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy.

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC - complete and independent application. The applicant indicated that dimethyl fumarate was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0287/2015 granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 17 February 2011 and 21 November 2013. The Scientific Advice pertained to insert quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Robert James Hemmings Co-Rapporteur: Martina Weise

- The application was received by the EMA on 2 December 2015.
- The procedure started on 31 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 March 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 March 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 1 April 2016.
- During the meeting on 28 April 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 December 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 January 2017.
- During the PRAC meeting on 6-9 February 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 23 February 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 March 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 April 2017.
- During the meeting on 18-21 April 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Skilarence.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Psoriasis is a chronic inflammatory disease, predominantly involving the skin, where it is characterised by the presence of erythematous plaques, usually covered by white silvery scales (Griffiths, 2007; Nestle, 2009), but joints may also be affected (psoriatic arthritis).

2.1.2. Epidemiology

Psoriasis is more frequent in countries further away from the equator and has an estimated worldwide prevalence of 1% to 2% (Cohen, 2012; Chong, 2013).

2.1.3. Biologic features

An altered balance between the T helper Type (Th) cells, Th1 and Th2, may play a critical role in the psoriatic lesions (Szegedi, 2003; Jacob, 2003), leading to a predominance of Th1-cell cytokines over the Th2-cell cytokines (Del Prete, 1998). The key element that seems to be initially responsible for the imbalance between inflammatory cells and the cytokine profile is a dysregulation of the NF-κB, which has been shown to be activated in lesional psoriatic skin (Gesser, 2007; Johansen, 2005). The increase in Th1 cytokines has been related to keratinocyte hyperproliferation and chemoattraction of neutrophils (Guenther, 2002; McKay, 1995; Barker, 1991). Also, stimulated keratinocytes produce vascular endothelial growth factor/vascular permeability factor (Detmar, 1994) that together with tumor necrosis factor-alpha promotes angiogenesis, dilation and tortuosity of capillaries, conferring the characteristic vascular changes to the psoriatic lesion in the dermis (Guenther, 2002). Another consequence from stimulation of Th1 cells and keratinocytes is the up-regulation of intercellular adhesion molecule 1 in vascular endothelial cells (Detmar, 1992), which enhances the inflammatory infiltrate into the affected skin.

2.1.4. Clinical presentation

Psoriasis is a stigmatising condition that can have a major impact on quality of life, to a similar extent as cancer, heart disease and diabetes (Menter, 2007; Cohen, 2012; Chong, 2013). Psoriatic lesions can be itchy and painful and cause extreme physical and emotional discomfort to patients (Menter, 2007; Nestle, 2009; Cohen, 2012; Chong, 2013). In addition, in its most severe presentations, patients with psoriasis have an increased risk of developing other comorbidities such as depression, diabetes and cardiovascular disease (Cohen, 2012; Chong, 2013), which can eventually increase the overall risk of mortality (Nestle, 2009; Salahadeen, 2015).

2.1.5. Management

At present there is no definitive cure for psoriasis. Available treatments focus primarily on the use of anti-inflammatory or immunomodulatory agents to control the symptoms of the disease and prevent further relapses. The management of mild psoriasis usually consists of topical treatments (e.g.

corticosteroids, calcipotriene, retinoids, salicylic acid, coal tar, dithranol, and emollients) (Krueger, 2005; Menter, 2007; Nestle, 2009). Treatments for patients with moderate to severe psoriasis include phototherapy and systemic treatment with oral agents (methotrexate, ciclosporin, retinoids, FAEs) and injectable biotechnology-derived products such as infliximab, etanercept, and adalimumab (Cohen, 2012; Chong, 2013). More recent additions to the therapeutic armamentarium include the biologics ustekinumab and secukinumab, and the small molecule apremilast.

The "*European S3-Guidelines on the Systemic Treatment of Psoriasis Vulgaris*" (Pathirana et al., 2009), which was supported by the European Dermatology Forum in cooperation with the European Association for Dermatology and Venereology and the International Psoriasis Council and the "*S3 – Guidelines on the treatment of psoriasis vulgaris (English version). Update*" (Nast et al. 2012) refers to the use of FAE (Fumaric acid esters), particularly to Fumaderm. Amongst others dimethyl fumarate (DMF) and monoethyl fumarate (MEF) are fumaric acid esters.

In Germany Fumaderm gastro-resistant tablet for oral use was approved in 1994 for the treatment of moderate to severe forms of psoriasis vulgaris if external treatment alone is not sufficient. Fumaderm is a fixed combination medicinal product which is available in two strengths. The tablets contain DMF 30 mg resp. 120 mg, as well as the calcium, magnesium, and zinc salts of monoethyl fumarate (MEF (also known as ethyl hydrogen fumarate (EHF) as three further active ingredients each.

Table 1 – Active substances of Fumaderm initial and Fumaderm

Active substances	Fumaderm initial	Fumaderm
Dimethylfumarate	30 mg	120 mg
Monoethylfumarate (MEF), calcium salt	67 mg	87 mg
MEF, magnesium salt	5 mg	5 mg
MEF, zinc salt	3 mg	3 mg

The gastro-resistant tablet formulation was designed to improve tolerability by avoiding dissolution in the gastric media of the stomach and enabling release of the active substance in the intestinal fluid, and it has been reported to decrease the rate of gastrointestinal adverse effects (Rostami-Yazdi, 2008).

Fumaderm initial and Fumaderm are the most commonly prescribed oral therapy in Germany for the systemic treatment of psoriasis. Current German guidelines recommend a gradual increase in FAE dosage to determine optimal efficacy and tolerability for each patient. Although Fumaderm products are only approved in Germany, special provisions allow FAEs to be prescribed in a number of other countries, e.g. UK and Ireland.

About the product

Almirall S.A., has developed dimethyl fumarate (DMF) 30 mg and 120 mg gastro-resistant tablets intended for the treatment of moderate to severe plaque psoriasis in adults in need of systemic drug therapy.

The applied and approved indication is:

Skilarence is indicated for the treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy.

The active ingredient in Skilarence 30 mg and 120 mg gastro-resistant tablets is DMF, the dimethyl ester of fumaric acid (trans-butenedioic acid), a simple, unsaturated dicarbonic acid compound that is an intermediate in the mammalian citric acid cycle. FAEs, including DMF, are immunomodulating agents that are effective in the treatment of psoriasis.

The anti-inflammatory and immunosuppressive effects of dimethyl fumarate and its metabolite monomethyl fumarate are not fully elucidated but are thought to be mainly due to the interaction with the intracellular reduced glutathione of cells directly involved in the pathogenesis of psoriasis, as dendritic cells, lymphocytes, keratinocytes and endothelial cells. This interaction with glutathione leads to the inhibition of the translocation into the nucleus and the transcriptional activity of nuclear factor 'kappa-light-chain-enhancer of activated B-cells' (NF-κB).

The development rationale for Skilarence 30 mg resp. 120 mg gastro-resistant tablets was based on the proven efficacy and safety of Fumaderm and evidence suggesting that DMF is mainly responsible for the anti-psoriatic activity of these products, as understood by the applicant from data published in literature.

Consequently, the only active ingredient in Skilarence is DMF (30 mg resp. 120 mg). Skilarence does not contain the MEF salts. The DMF content is quantitatively the same as in Fumaderm initial and Fumaderm respectively.

To improve tolerability, it is recommended to begin treatment with a low initial dose with subsequent gradual increases, i.e. starting with DMF 30 mg/day and increasing the dose week by week to a maximum of DMF 720 mg/day.

Type of Application and aspects on development

The present application for Dimethylfumarate for the treatment of psoriasis, is a full-mixed Article 8(3) application using both company-sponsored non-clinical and clinical studies including a pivotal study and evidence from published literature.

The development rationale for DMF gastro-resistant tablets in this application, was based on the proven efficacy and safety of Fumaderm and evidence suggesting that DMF is mainly responsible for the anti-psoriatic activity of these products, as supported by clinical data (Nieboer, 1989; Nieboer, 1990; Ormerod, 2004; Rostami Yazdi, 2008; Lijnen, 2015). As a result, DMF gastro-resistant tablets contains DMF alone as the active ingredient, in a gastro-resistant tablet formulation, available in two strengths (30 mg and 120 mg), corresponding to the DMF content of Fumaderm initial and Fumaderm respectively. In addition, the same dosage regimen is recommended with respect to the DMF content of Fumaderm initial and Fumaderm, and this has been used for the clinical development of DMF 30 mg and 120 mg gastro-resistant tablets.

The evaluation of new medicinal products in the indication psoriasis should follow the "Guideline on Clinical Investigation of Medicinal Products indicated for the Treatment of Psoriasis" (CHMP/EWP/2454/02 corr, 2004).

Other relevant guidelines are amongst others:

- Dose-Response Information to Support Drug Registration (ICH E4),

- Points to Consider on Application with 1. Meta-Analysis; 2. One Pivotal Study (CPMP/EWP/2330/99)

- Statistical Principles for Clinical Trials (ICH topic E9),

- Choice of Control Group in Clinical Trials (ICH E10)

Scientific Advice on the clinical development programme was received from European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP) on 17 February 2011 and 11 September 2014.

In general, the scientific advice was followed for the clinical development program. The conduct of one pivotal trial only was principally agreed to, provided the requirements set out in the CHMP "Points to Consider on Application with 1. Meta-Analysis; 2. One Pivotal Study (CPMP/EWP/2330/99)" would be met. For the non-inferiority of Skilarence compared with Fumaderm for PASI 75 after 16 weeks of treatment, a non-inferiority margin of 15% was set in line with EMA/CHMP Scientific Advice.

The phase III clinical trial was conducted and analysed in general in accordance with the "CHMP Guideline on the Clinical Investigation of Medicinal Products indicated for the Treatment of Psoriasis (CPMP/EWP/2454/02, Nov 2004)" and with the clinical scientific advice from EMA/CHMP on 17 February 2011.

With regard to evaluation of long-term efficacy the Guideline on Psoriasis recommends the randomisation of responders either to active drug or placebo in order to explore the duration of remission/response, rebound and time to relapse. EMA Scientific Advice in 2011 stated furthermore that "*placebo patients may be shifted to the test drug, but also patients on the active arms should be shifted to the placebo to allow gaining the necessary 2 further months of comparative data on maintenance of effect, safety and rebound in the end (refer to Guideline)*…"

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as gastro-resistant tablets containing 30 mg or 120 mg of dimethyl fumarate as active substance.

Other ingredients of the tablet core are lactose monohydrate, cellulose microcrystalline, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate. The film coating is composed of methacrylic acid-ethyl acrylate copolymer (1:1), talc, triethyl citrate, titanium dioxide (E171) and simethicone for both strengths. The film coating of Skilarence 120 mg also contains indigo carmine (E132) and sodium hydroxide.

The product is available in PVC/PVDC aluminium blister packs as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of dimethyl fumarate is dimethyl (E)-butenedioate corresponding to the molecular formula $C_6H_8O_4$ and has a relative molecular mass 144.13 g/mol and has the following structure:

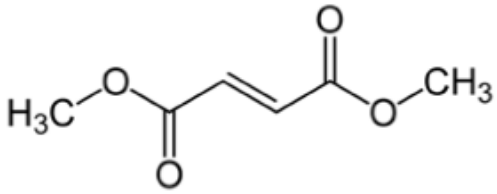


Figure 1. Structure of dimethyl fumarate

The structure of the active substance was elucidated by a combination of ^{1}H-NMR and IR spectroscopy, by elemental analysis and by the route of synthesis.

Dimethyl fumarate appears as a white crystalline powder, slightly soluble in pH range from 1-6.8, soluble in acetone, slightly soluble in ether and poorly soluble in ethanol.

Dimethyl fumarate does not contain chiral centres. Dimethyl fumarate is the trans (or E) isomer. X-Ray Powder Diffraction (XRPD) and Differential Scanning Calorimetry (DSC) data confirm the existence of only one crystal form. Polymorphism has not been observed for dimethyl fumarate.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance (AS) has been provided in the restricted part of the ASMF and it was considered satisfactory.

Dimethyl fumarate is synthesized in one synthesis step followed by crystallisation, purification and drying.

Critical steps and critical process parameters have been identified. Adequate in-process controls are applied during the synthesis.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. The fate and carry over of genotoxic impurities have been discussed satisfactorily.

All components used as primary packaging material have been described and are food grade and comply with the requirements of Ph. Eur. and European Directive 10/2011 as amended.

Specification

The active substance specification includes appropriate tests and limits for appearance (visual), clarity and colour of the solution, pH, identity (IR, HPLC), water content, sulphates, sulphated ash,, heavy metals, related substances (HPLC), assay (HPLC), particle size distribution and residual solvents (GC).

The overall control strategy for the related impurities is acceptable; sufficient information has been provided on the control of the potential impurities (including genotoxic) and to demonstrate that potential impurities arising from the described route of synthesis are adequately removed.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from three production scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability studies on three production scale batches of dimethyl fumarate from the proposed manufacturer stored in the intended commercial package under long term conditions (5 ºC ± 3 ºC) have been performed. Data up to 36 months for all primary batches except one (for which up to 24 months data are available) and for up to 6 months under accelerated conditions (25 ºC / 60% RH), according to the ICH guidelines, were provided.

In addition, supportive stability data on another three production scale batches of dimethyl fumarate from the proposed manufacturer stored in the intended commercial package for up to 48 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH, according to the ICH guidelines, were provided. The stability results indicate the material is stable for 48 months without storage conditions in the tested container closure systems.

Samples were tested for description, water content, assay, organic impurities, residual solvents and particle size distribution. The analytical methods and acceptance criteria are the same as applied for release testing and have been shown to be stability indicating.

Results on stress conditions (heat, humidity, UV radiation, basic and acidic conditions and oxidation) were also provided. The conclusion of the forced degradation studies was that dimethyl fumarate is a stable molecule that can only be degraded at extreme conditions.

Photostability information was also provided and showed that dimethyl fumarate is photostable.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months of dimethyl fumarate stored in a refrigerator (2-8 ºC) in the two proposed container closure systems. Measures are in place to ensure that the overall retest period for dimethyl fumarate, calculated from the manufacturing date onwards will not exceed the total period of 48 months established by the manufacturer of dimethyl fumarate.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as round and biconvex gastro-resistant tablets, white for 30 mg tablets and blue for 120 mg tablets, intended for oral administration.

Dimethyl fumarate is known to cause gastrointestinal irritation; hence the aim of the development was a gastro-resistant tablet product to protect the gastric mucosa. The aim was the gastro-resistant tablet cores to only contain 30 mg or 120 mg dimethyl fumarate as active substance and followed by subsequent coating.

During development, different excipients were tested and some changes in the formulation were introduced to achieve the most suitable formulation and to improve the stability and target dissolution profile of the final product. The coating composition and applied amount on the tablets has been optimised

The tablets are obtained from the same blend but tableted at different weights to obtain two proportional cores of different strengths. Each tablet is coated with a different coating dispersion to obtain the final dimethyl fumarate 30 mg and 120 mg film-coated tablets.

The influence of the particle size distribution of the active substance was studied in order to assess its impact on the manufacture and the performance of the 30 mg and 120 mg drug products. Based these test results about the manufacturability and dissolution the particle size distribution limits for the active substance were established.

The gastro-resistant coating is necessary, in order to improve the gastrointestinal tolerability by avoiding dissolution in the gastric media and enabling the release of the active substance in the intestinal tract.

The manufacturing process development was focused on 3 main stages: manufacturing of the blend (blending), blend compression into tablet cores (tableting) and coating of the tablet cores. The manufacturing process was adjusted and adapted during the scale-up stage, to afford a finished product within the proposed specifications.

A standard blending process was designed considering the rheological properties of the active substance and the excipients, in order to achieve good active content homogeneity as well as an optimal distribution of the excipients for the best process performance.

The tableting conditions were defined to obtain the optimal values of the target parameters (weight, thickness, hardness, friability, disintegration time and appearance) and to ensure suitable content and mass uniformity. Robustness studies on tableting speed and pressures have been performed to identify critical aspects impacting the different processes and to confirm the scale-up feasibility.

Enteric coating was carried out under standard conditions. The coating process is considered the most critical manufacturing step as it is the responsible of the gastro resistance performance. Therefore, during the development phase, once the formulation showed the desired dissolution profile, a set of trials applying design of experiments (DoE) were carried out to guarantee the gastro-resistance of the film-coated tablets, and to study the limits for process parameters in relation with coating solution and coating process. Taking into account all the results, the critical parameters for the coating process were defined and limits were established.

Manufacture of the product has been successfully transferred and scaled up to production scale batch size at the proposed site for manufacture of commercial batches. The clinical development batches were manufactured by the development site. The batches used in the clinical studies are of identical composition and manufactured by the same process. The *in vitro* drug dissolution profile of the batches used in the clinical study have been adequately characterised in accordance with the Bioequivalence guideline and the Guideline on quality of oral modified release products. *In vitro* dissolution equivalence of clinical batches and full scale batches manufactured at the commercial site has been demonstrated.

The choice of the routine *in vitro* dissolution test in neutral buffer after the acid stage is regarded justified. The discriminating properties of the dissolution method are deemed demonstrated.

The primary packaging of Skilarence 30 mg and 120 mg gastro-resistant tablets is PVC/PVDC-Aluminium blisters. The primary packaging is of food grade and complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process follows the conventional approach for solid dosage forms, employing widely used, non-specialized manufacturing equipment, consistent with that available within the proposed manufacturer's facilities.

The manufacturing process of gastro-resistant tablets comprises the following four main steps:

1. Blending. The active substance and the excipients are blended.

2. Tableting. This blend is compressed to manufacture cores of different strengths (30 mg and 120 mg).

3. Coating. The cores are coated with the enteric coating mixture.

4. Packaging. The coated tablets are packaged into blisters.

The pharmaceutical form is considered a specialised form as per the process validation guideline however the manufacturing process employs conventional methods for this type of product and it has been described satisfactorily.

Holding time for the bulk product is supported based on stability data.

Critical steps have been identified and critical process parameters were defined to control the critical steps. The IPCs during the manufacturing process have been presented and are adequately justified. The control strategy ensures that the manufacturing process consistently delivers a product that meets the defined criteria for all release specifications.

The manufacturing process has been satisfactorily validated. It is also considered that the manufacturing process is sufficiently robust to provide assurance that gastro-resistant tablets of consistent quality, complying with the designated specification, are produced.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for this kind of dosage form: description (visual), active substance identification (HPLC, IR), colorants identification (Ph. Eur.) assay (HPLC), degradation products (HPLC), dissolution (Ph. Eur.), uniformity of mass and content (Ph. Eur.), water content (Ph. Eur.) and microbial purity (Ph. Eur.).

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

The dissolution test has been set, based on the Guideline on Quality of oral modified release products (EMA/CHMP/QWP/428693/2013) and Ph. Eur. 2.9.3.
The microbial purity is specified according to the requirements of Ph. Eur. 5.1.4 for non-aqueous preparations for oral use. Based on the batch results and stability data, skip testing is proposed, once the validation of the manufacturing process is completed.

Batch analysis data for 6 pilot scale and 4 production scale batches of 120 mg strength and for 4 pilot scale and 3 production scale batches of 30 mg strength, manufactured with the proposed commercial formulation of Dimethyl fumarate were presented. All batches are representative of the process and the results show that the finished product meets the proposed specification limits.

Stability of the product

Stability studies on 4 pilot batches and one commercial scale batch for the 30 mg strength of the finished product and 4 pilot batches and two commercial scale batches for the 120 mg strength of the finished product, have been conducted in line with the ICH Stability Guidelines under long term conditions at 25 ºC / 60% RH for up to 36 months and accelerated conditions at 40 ºC / 75% RH for 6

months. Appropriate post-approval stability commitments are provided. The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Stability of the bulk intermediate (coated tablets) product in the proposed containers has also been investigated. The proposed holding time is supported by the presented data.

The following parameters were investigated: description, water content, assay, degradation products, dissolution test and microbial purity. The shelf-life specification, acceptance criteria and analytical procedures, which were shown to be stability-indicating, were applied. No significant change in any of the tested parameters was observed during the study, as all the parameters tested met the acceptance criteria for all samples stored at long term and accelerated storage conditions, and no appreciable differences between batches manufactured with different drug substance batches were observed for any of the parameters studied. No trends were observed.

A photostability study was conducted on one pilot scale batch of each strength according to ICH Q1B Guideline. No significant change was observed in any of the tested parameters (description, assay, degradation products and dissolution test) and the results confirm that the product is not photosensitive and the immediate pack proposed for marketing provides adequate protection to light exposure.

Based on the provided stability data, the proposed shelf life of 36 months with no special storage conditions, as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Stearic acid used in the manufacture of magnesium stearate is of animal origin and a copy of a valid certificate of suitability for the stearic acid has been provided. The TSE/BSE risk statements from the respective suppliers of lactose monohydrate and magnesium stearate were provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

All pivotal non-clinical toxicity studies with LAS190046 (DMF active ingredient) were consistent with International Conference on Harmonisation (ICH) Nonclinical Testing Guidelines and in compliance with the Good Laboratory Practice (GLP) Regulations.

The non-clinical development programme for DMF consists of company-sponsored studies complemented with publicly available published data on Fumaderm, FAEs in general, and DMF in particular.

At different stages of DMF development, the applicant has obtained scientific advice from different regulatory authorities. Non-clinical advice primarily concerned the requirements to perform additional non-clinical bridging studies to supplement the published literature on the safety profile of DMF.

Since DMF is contained within Fumaderm for which there is considered to be a long history of clinical use (19 years in Germany), the safety and efficacy of DMF was generally considered to be adequately documented and toxicologically well defined, as supported by the available literature data. A brief summary of existing non-clinical toxicology data for DMF has therefore been provided in the submission, but in order to address any gaps in the non-clinical data and to provide comparative safety data with Fumaderm, a non-clinical testing programme for DMF has also been conducted to support the marketing authorisation for Skilarence. Furthermore, supporting information was also derived from clinical studies or publications of clinical studies with DMF.

The applicant has conducted one pharmacokinetic (PK) study (absorption) of DMF (LAS190046 [DMF active ingredient]) and DMF in combination with monoethyl fumarate (MEF [i.e, LASW1837 (Blend of active ingredients, DMF + MEF salts at the same proportion presented in the Fumaderm formulation)]) in mice; and several in vitro and in vivo toxicity studies in mice, rats and dogs, with DMF, DMF + MEF salts or monomethyl fumarate (MMF), the main metabolite of DMF. All in vivo studies, except one study in dogs where a tablet administration method was investigated, were conducted via oral gavage using aqueous suspensions on 0.5% methylcellulose.

Supporting information was also derived from the literature and direct human experience via three Phase I PK clinical trials in healthy subjects and one Phase III efficacy and safety clinical trial in patients with moderate to severe chronic plaque psoriasis. In the Phase III clinical trial, DMF was administered at a starting dose of 30 mg daily and titrated up to a maximum of 720 mg daily.

2.3.2. Pharmacology

The pharmacology of fumaric acid esters (FAEs) including DMF is generally well known, and the applicant has not conducted primary/secondary pharmacodynamic, pharmacodynamic drug interaction or stand-alone safety pharmacology studies with either DMF or other FAEs. Instead, a review of the known pharmacology of DMF alone, DMF in combination with MEF salts, MMF and fumaric acid from the published literature has been provided.

There are numerous published reports supporting the proposed mechanism of action of DMF and its metabolite MMF in the treatment of psoriasis, mainly through its anti-inflammatory and immune-modulating effects on lymphocytes, keratinocytes and endothelial cells. Central to these effects is believed to be the interaction with intracellular reduced GSH, which induces hemoxygenase-1 (HO-1) and inhibits the transcriptional activity of NF-κB, which results in a shift in cytokine/chemokine profile towards an anti-inflammatory and anti-proliferative response. This includes down-regulation of pro-inflammatory cytokines (e.g. TNF-α, IFN-γ and IL-1), inhibition of keratinocyte proliferation, inhibition of expression of adhesion molecules (e.g. ICAM-1 on keratinocytes and endothelial cells), which is believed to reduce trafficking and accumulation of leukocytes within the psoriatic plaque.

No stand-alone safety pharmacology studies have been conducted, but the applicant included a functional observational battery assessment (FOB), a visual respiratory assessment, ECG evaluation and renal assessment as part of the pivotal 13 week oral (gavage) toxicity study in beagle dogs to compare any safety pharmacological effects with DMF (LAS190046) to those of DMF + MEF salts (55.8% and 44.2% respectively; the same proportion as presented in the Fumaderm formulation; LASW1837) at doses up to 30 mg/kg/day. In this study, there was no effect on the measured safety pharmacology endpoints with either DMF or DMF + MEF salts. Furthermore, clinical studies (studies 1102, 1103 and 1104) submitted by the applicant conducted with the DMF gastro-resistant tablets did not show any changes in vital signs.

2.3.3. Pharmacokinetics

The pharmacokinetics of DMF has been primarily supported by published literature, but the applicant has conducted one pharmacokinetic study in mice and several in vitro studies primarily to characterise the potential for drug interactions.

The human plasma protein binding of MMF was shown to be between 42-51% over the concentration range studied. Pharmacokinetic/toxicokinetic studies of DMF and its primary active metabolite (MMF) have been conducted in animals using protein precipitation followed by LC-MS/MS. DMF is rapidly pre-systemically hydrolysed to MMF after oral administration and therefore, PK analysis was only performed on MMF.

Absorption of DMF following administration of a single oral dose of DMF (LAS190046) or DMF + MEF salts (LASW1837) was measured as the level of MMF (and MEF in LASW1837 dose groups) in mouse plasma in a GLP-compliant pharmacokinetic study conducted by the applicant. Plasma concentrations of MMF suggested rapid absorption of DMF following oral administration (between 2-15 min post dose), and also rapid biotransformation in plasma of DMF to MMF. Several published studies have confirmed that DMF is hydrolysed to MMF in the GI tract, primarily in the small intestine. In addition, rapid conjugation of DMF with GSH further explains the lack of detectable amounts of DMF in the plasma after oral administration. GSH conjugation is likely to occur in the portal vein and/or in the small intestine. In the applicants study, there were no appreciable differences in exposure between DMF (LAS190046) or DMF + MEF salts (LASW1837) when dosed at the same dose level (140 mg/kg). DMF, MMF (and MEF in LASW1837-treated animals) were detected in the stomach content, and generally the profiles for MMF and DMF in the stomach and intestinal contents were similar following administration of DMF or DMF + MEF salts. However, DMF, MMF and MEF levels were low or absent in the duodenum contents. Absorption of FAE from the small intestine into the circulation has been reported to be dependent on the permeability of the intestinal membrane and the stability of the various FAEs in the small intestine. In addition, pre-systemic hydrolysis of DMF to MMF is dependent on the pH of the environment, the lipophilicity of the monoester fumarates themselves and the activities of esterases

such as carboxyl- and cholinesterases. Monocytes/lymphocytes have also been implicated in the hydrolysis of DMF to MMF.

Apart from the serum protein binding capacity of DMF (absent) and MMF/MEF (low), there is no non-clinical information on the distribution profile of DMF and its metabolites. The absence of this information is generally considered acceptable, given the long history of clinical experience with FAEs. There is also no information on whether DMF or its metabolites are excreted in the breast milk in animals or humans. The absence of this information is adequately reflected in section 4.6 of the SmPC.

Apart from a study to evaluate the hydrolysis process in human whole blood, the applicant has not conducted additional non-clinical metabolism studies. DMF is very rapidly hydrolysed in human blood with DMF levels below the lower limit of quantification after 5 minute incubation. Based on limited literature data, there is no evidence for the involvement of cytochrome P450 enzymes in the metabolism of FAEs in the liver. MMF is metabolised into fumaric acid and, in the tricarboxylic acid (TCA) cycle, into water and CO_2. A smaller proportion is excreted in the urine and faeces. No drug interaction studies have been conducted, and clinical drug interactions have not been reported. From a clinical perspective, further data have been requested on the possible effect of DMF and the major metabolite MMF on cytochrome P450s and on drug transporters. Fumarate has been shown to be a substrate for the renal transporter, OAT1, which is located on proximal tubular cells and its *cis* isomer, maleate, has been shown to cause proximal tubular damage in rodents, through depletion of coenzyme A, ATP and glutathione. It has been suggested that this mechanism may also be responsible for the known renal FAE side effects observed in humans. Additional data provided during the assessment shows that MMF (up to 750 µM) is not an inhibitor of P450 enzymes, or an inducer of CYP3A4 (up to 250 µM), CYP1A2 and CYP2B6 (up to 200 µM). In addition, MMF only showed inhibition of BCRP at 1000 µM, and only limited inhibition of OAT1-, OAT3-, OCT-1 and OCT-2-mediated probe transport at 1000 µM, indicating that interactions at clinically relevant concentrations are unlikely. Finally, MMF was shown not to be a P-gp substrate or inhibitor (at concentrations up to 7.38 mM)

2.3.4. Toxicology

The toxicological profile of DMF+MEF salts can be considered to be clinically well-established through long term use of FAEs (mainly Fumaderm in Germany), and the primary aim of the applicant's non-clinical acute and repeat dose toxicity studies was therefore to elucidate whether administration of DMF alone would result in a different toxicological response in comparison to DMF + MEF salts.

Single dose toxicity

The comparative acute toxicity between DMF and DMF + MEF salts was investigated by utilising information generated from in vivo genotoxicity studies in mice and exploratory toxicity studies in dogs. In mice, both components, DMF and MEF salts, appeared to contribute similarly to the observed acute toxicity. However, in dogs, slightly more severe clinical signs and body weight losses were evident in animals receiving DMF + MEF salts compared to DMF alone at equivalent doses of DMF.

Repeat dose toxicity

In an exploratory toxicity study in dogs, tablet administration of DMF and DMF + MEF salts was generally associated with clinical signs of poor GI tolerance (mortality 1♀, diarrhoea and emesis, non-digested tablets in faeces), with detrimental effects on food consumption and body weights, and highly variable exposure. Tablet administration in dogs was not pursued further, and the subsequent studies

employed aqueous suspensions. Microscopic lesions were observed in the proximal straight tubules (minimal to moderate tubular hypertrophy, increased incidence/severity of tubular vacuolation, minimal to slight tubular degeneration) of the kidney, with tubular degeneration considered to be adverse. The findings appear to be consistent with those reported for FAEs both clinically and non-clinically, but appeared to be slightly more pronounced and was more frequently adverse in dogs treated with DMF + MEF salts than those treated with DMF. In the subsequent exploratory dog study (DMF or DMF + MEF salts, up 75 mg/kg/day for up to 8 days), clinical signs included flushing (redness of ears, redness of eyes and/or of gums), emesis and salivation. Again, clinical signs and effects on body weights (up to +3.4% for DMF, up to -17.3% for DMF + MEF salts) were generally more severe in animals given DMF + MEF salts. In the pivotal 13-week toxicity study, DMF and DMF + MEF salts were well tolerated when administered to dogs at doses up to 30 mg/kg/day. Clinical signs included emesis and abnormal faeces, together with redness of the abdomen and ears, which appeared more marked or frequent in animals given DMF + MEF salts, but were considered non-adverse. A moderate increase in kidney weights in most treated groups (up to +39% relative to body weight) was noted at necropsy, which in males given either DMF or DMF + MEF salts at 30 mg/kg/day, correlated microscopically with minimal tubular hypertrophy in the kidney. This finding was fully reversible after a 4 week treatment-free period, and was not considered adverse. Increases in NGAL values, a renal biomarker, were noted in some animals, but were not deemed toxicologically significant in the absence of morphological changes. Since NGAL is currently not considered to be a validated biomarker for early detection of renal damage in patients, its inclusion in clinical practice is not justified. In this study, the NOAEL was 30 mg/kg/day for DMF and DMF + MEF salts. The DMF exposure margins (males and females combined expressed as MMF, Day 1 and 90) compared to human exposure (assuming a human dose of 240 mg TID (720 mg total dose); C_{max} = 2151 ng/ml and AUC_{0-24} = 10497 ng·h/ml) were **6.53** for C_{max} and **2.91** for AUC_{0-24}. Similar exposure margins can be calculated for DMF + MEF salts (C_{max} = **9.7**, AUC_{0-24} = **3.0**).

Genotoxicity

The genotoxicity of DMF, DMF + MEF salts and MMF was evaluated by the applicant in in vitro and in vivo tests. There was no evidence of mutagenic activity in bacteria. However, in vitro micronucleus tests consistently showed an increased frequency in micronucleated cells in human peripheral blood monocytes at some or all experimental conditions, confirmed to be through a clastogenic mechanism. However, subsequent in vivo micronucleus studies in mice conducted with DMF (doses up to 1400 mg/kg) and DMF + MEF salts (up to 700 mg/kg), failed to reproduce the in vitro findings, and in vivo Comet studies confirmed an absence of DNA damage in the liver, stomach and duodenum.

Carcinogenicity

No carcinogenicity studies have been conducted, and the applicant has provided a position paper which reviews the available literature data with relevance to determining the potential for carcinogenicity of DMF, with particular focus on whether there could be a link between the well-characterised chronic nephrotoxicity and development of renal cell carcinomas. On the basis that fumarate has been shown to be a substrate for the basolateral organic anion transporter (OAT1) expressed on proximal tubular cells, fumarate accumulation may occur in these cells. Conversion of fumarate by fumarase to the *cis* isomer, maleate, may lead to proximal necrosis, though co-enzyme A, ATP and GSH depletion. In addition, activation of cellular pathways involved in oncogenesis (e.g. HIF-1α and Nrf2) has been described in the context of the congenital metabolic disorder, fumarate hydratase (FH) deficiency. FH has been described as a tumour suppressor, and FH deficiency leads to accumulation of endogenous fumaric acid, which has been linked to the activation of oncogenic pathways and the development of

leiomyomas and renal cells carcinomas. The mechanism of tumorigenesis may be related to the inhibition of 2-oxoglutarate-dependent oxygenases, stabilising the hypoxia inducible factor (HIF) complex and subsequent activation of oncogenic target genes, and to the activation of Nrf2 as a consequence of succination of cysteine residues, which is associated with tumour promoting activity.

Reproduction Toxicity

With respect to reproductive and developmental toxicity, the applicant has only completed embryo-fetal development studies in rats.

In the applicant's 13-week study, there was no evidence of changes in male and female reproductive organs as a result of treatment with either DMF alone or DMF + MEF salts. In addition, no signals for fertility effects have been raised from clinical use of DMF+MEF salts.

The NOAEL for DMF in the rat pivotal EFD study was 40 mg/kg/day for both maternal and embryo-fetal toxicity. At this dose level, the exposure margins compared to human exposure (assuming a human dose of 240 mg TID) were **2.0** for C_{max} and **0.2** for AUC_{0-4}.

Other toxicity studies

There are no toxicological concerns relating to drug substance and drug product impurities and excipients. While the main DMF metabolite, MMF, has been shown to induce micronuclei formation in vitro, this finding is not likely to biologically relevant, as an absence of micronuclei were confirmed in vivo for DMF and DMF + MEF salts. The proposed limit of MMF at 1% in LAS190046 is considered acceptable in the light of the absence of genotoxic potential, and the fact that it is a major metabolite of DMF.

2.3.5. Ecotoxicity / environmental risk assessment

The applicant provided an environmental risk assessment for the active ingredient dimethyl fumarate being not in line with the respective guidelines. However, the applicant agreed to perform an experimental log K_{ow} study and a Phase II, Tier A environmental risk assessment for DMF. It should be noted that in dependence on the study outcomes further investigations on the environment could be necessary. The study results will be provided post-authorisation.

2.3.6. Discussion on non-clinical aspects

Due to the established clinical experience with DMF + MEF salts, only an abridged non-clinical package of studies have been completed by the applicant, primarily to establish whether any differences exist in the toxicological profile of DMF alone compared to the combination of DMF + MEF salts, currently marketed in Germany as Fumaderm. The majority of other non-clinical information in the dossier has been supported by published literature. This approach is generally considered acceptable from the non-clinical perspective.

There are numerous published reports supporting the proposed mechanism of action of DMF and its metabolite MMF in the treatment of psoriasis. However, certain aspects of the DMF pharmacology have, not been fully elucidated. Oral administration of DMF does not result in detectable DMF plasma concentrations, which questions whether DMF actually reaches the intended site of action in the skin. MMF is, however, detected in plasma.

Overall, the applicant has provided an adequate discussion of the primary pharmacology of FAEs including DMF in relation to the treatment of psoriasis.

The pharmacokinetics of DMF has been primarily supported by published literature, but the applicant has conducted one pharmacokinetic study in mice and several in vitro studies primarily to characterise the potential for drug interactions. This is considered acceptable, and any missing non-clinical pharmacokinetic information may be superseded by clinical experience with other FAEs.

The methods of analysis to determine levels of DMF and MMF (and MEF in mouse and dog) from mouse, rat and dog plasma have been provided. Validation reports for these plasma assays are considered adequate, and the methods are considered to be suitably validated with an acceptable dynamic range.

The Pharmacokinetic data obtained is consistent with the available literature data.

Administration of DMF in repeat dose toxicity studies of up to 13 weeks duration in dogs did not reveal any new or different toxicities compared to administration of DMF + MEF salts, given at equivalent doses of DMF. Flushing and signs of local GI tolerance issues (diarrhoea, emesis, body weight decreases) were present following dosing or either DMF alone and DMF + MEF salts, with evidence of a slight worsening in animals given DMF + MEF salts. Adverse degeneration in the proximal straight tubules of the kidney was present in an exploratory toxicity study of shorter duration (up to 10 days), and appeared to be slightly more pronounced and more frequently adverse in dogs treated with DMF + MEF salts than those treated with DMF alone. The observed non-clinical findings are consistent with those reported for FAEs both clinically and non-clinically. In the RMP, flushing and gastrointestinal events have been identified as important identified risks, and renal injury and proteinuria has been identified as an important potential risk, with regular renal function monitoring required in patients.

Overall, there appears to be no significant difference in toxicological profile between DMF and DMF + MEF salts, when given at equivalent doses of DMF. It is noted that only non-adverse renal changes (tubular hypertrophy) was demonstrated in the pivotal 13 week study, where the highest dose tested was 30 mg/kg. However, adverse renal findings were observed at higher doses in an exploratory study of shorter duration, and generally systemic toxicity, as evidenced primarily renal findings, appears similar between animals given DMF and DMF + MEF salts. Importantly, nephrotoxicity has previously been reported both non-clinically and clinically with DMF + MEF salts, and kidney function should therefore be monitored in patients. In contrary to what has previously been reported, the addition of MEF salts may slightly worsen GI tolerance in dogs compared to DMF alone. Although testicular changes have previously been reported in rats treated with DMF and MEF salts, there was no evidence of macroscopic or microscopic changes in reproductive organs in the 13-week dog study conducted by the applicant. Overall, the applicant has provided sufficient evidence from their repeat dose toxicity studies to confirm that the toxicity profile between DMF alone and DMF + MEF salt does not appear to be different.

Similar to DMF + MEF salts and MMF, DMF was concluded not to be genotoxic in a series of studies conducted by the applicant.

No DMF carcinogenicity studies were conducted, and the applicant has provided a position paper which reviews the available literature data with relevance to determining the potential for carcinogenicity of DMF, with particular focus on whether there could be a link between the well-characterised chronic nephrotoxicity and development of renal cell carcinomas.

Since, DMF seems to stabilise HIF-1α and to activate Nrf2, which is also associated with tumour-promoting activity, the development of renal tumours should be considered as a potential risk of the administration of DMF. It can be agreed that while activation of these pathways as observed in FH

deficiency may substantially differ from those occurring with normally functioning Krebs cycle enzymes, a potential tumorigenic activity of exogenous administration of DMF cannot be ruled out. The potential risk relating to DMF carcinogenicity has been adequately reflected in section 5.3 of the Skilarence SmPC.

With respect to reproductive and developmental toxicity, an increased incidence of fetal variations (supernumerary liver lobes and abnormal iliac alignment) was observed in a pivotal EFD study conducted in rats by the applicant. Based on these findings, which occurred with no margins to clinical exposure, coupled with the lack of clinical experience in pregnant women, Skilarence is contra-indicated in pregnancy, and not recommended in women of child-bearing potential not taking appropriate contraception.

The absence of the fertility and early embryonic development study and the prenatal and postnatal development study is considered acceptable and their absence has been adequately reflected in section 5.3 of the SmPC.

Due to the uncertainty regarding whether DMF and/or MMF are excreted in the breast-milk, a risk to new-borns/infants cannot be excluded. This has been adequately reflected in section 4.3 and 4.6 of the SmPC.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data is considered acceptable by CHMP.

However, the environmental risk assessment for DMF is currently incomplete and does not allow a definitive conclusion on the potential risk to the environment. The CHMP recommended that additional studies shall be conducted post-authorisation and the results should be submitted by the end of Q4 2018.

2.4. Clinical aspects

2.4.1. Introduction

This is a full-mixed Marketing Authorisation Application (MAA) for Skilarence (dimethylfumarate) 30mg and 120mg gastro-resistant tablets for the treatment of moderate to severe plaque psoriasis in adult patients needing systemic therapy.

Scientific Advice on the clinical development programme was received from the European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP) on 17 February 2011 and 11 September 2014.

During scientific advice procedures, both the appropriate regulatory strategy and the planned clinical development program to support authorisation of dimethyl fumarate (DMF) 30mg and 120 mg tablets were discussed. The final outcome agreed that the strategy of an Article 8(3) – full mixed application with own clinical data supported by evidence from published literature would be acceptable. The discussed development program involved characterising the PK, efficacy and safety of the proposed product and simultaneously comparing it to Fumaderm (currently authorised in Germany, containing a mixture of DMF and other mono ethyl fumarate salts) with the objective of supporting the extrapolation of literature with Fumaderm and other fumarate products to the proposed DMF product, Skilarence. In particular, the phase III comparative clinical efficacy and safety study was discussed and

the planned study design, patient population, primary & secondary endpoints and the statistical comparisons including the interim analysis was agreed with EMA/CHMP.

In general, the scientific advice was followed for the clinical development program and there are no significant deviations from the discussed program.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- Tabular overview of clinical studies

Table 2 - Overview of Clinical Studies Type of study	**Study No.**	**Objective(s) of the study**	**Study design**	**Test Products(s); Dosage Regimen, Route of Administration**	**Number of Subjects/Patients**	**Healthy subjects or Diagnosis**	**Duration of treatment**
Efficacy and safety, phase III	1102	Efficacy (superiority) and safety of Skilarence vs. placebo and non-inferiority of Skilarence to Fumaderm	Random., DB, multi-centre, 3-arm, active, and placebo-controlled, adaptive study	DMF gastro-resistant tablets: up to 720 mg/day; oral Fumaderm up to 720 mg/day; oral Placebo; oral	DMF gastro-resistant tablets: 279 Fumaderm: 283 Placebo: 137	Moderate to severe psoriasis	16 weeks
PK, phase I, safety	1103	PK of MMF after single dose administration of 30 mg DMF and Fumaderm initial under fasted and fed conditions	Open-label, randomised, four-period crossover study	DMF 30 mg and Fumaderm Initial (30 mg DMF and 75mg MEF salts) under fasted and fed conditions	N=12[1]	Healthy Caucasian subjects (6 male and 6 female)	Single dose (four tablets)
PK, phase I, safety	1104	PK of MMF after single dose administration of 120 mg DMF and Fumaderm under fasted and fed conditions	Open-label, randomised, four-period crossover study	DMF 120 mg and Fumaderm (120 mg DMF and MEF salts) under fasted and fed conditions	N=12[2]	12 Healthy Caucasian subjects (6 male and 6 female)	A single dose (two tablets)
PK, phase I, safety	1108	PK of MMF after single dose administration of 120 mg FMF and Fumaderm under fasted and fed conditions	Open-label, randomised, four-period crossover study	DMF 120 mg and Fumaderm (120 mg DMF and MEF salts) under fasted and fed conditions	N=32[3]	30 healthy subjects (16 males and 16 females)	A single dose (one tablet)

[1] two subjects (#009, #010) were excluded from the complete PK analysis / the PK analysis of period 1 and 2, respectively

[2] two subjects had only MMF concentrations above LLOQ at 24 h a.a. of the test treatment and one subject had only concentrations above LLOQ at 16 h and 24 h a.a. of the reference treatment (page 49 study report) and - as it seems - were thus excluded from the fed analysis set. In addition, for one subject (# 006, sequence T1-R1-T2-R2),

no valid results could be obtained in Period 2 and Period 3 at 10 h a.a. and 9.5 h a.a., respectively. Thus, the subject was excluded from PK analyses at those time points.

[3] two subjects were excluded from the analysis because they did not complete all treatments. In addition, 6 subjects in the LAS41008 arm, and 10 in the Fumaderm arm, had to be excluded from the analysis for anomalous Cmax and AUC data

The first two pilot studies (study 1103 and 1104) characterise the PK and compare it to Fumaderm, while the pivotal study 1102 compares and characterises the efficacy of DMF with both placebo and Fumaderm. In addition to the above prospective, controlled studies, the applicant has submitted an overview which includes data from published literature on other DMF containing products, predominantly with Fumaderm (which contains DMF in the same quantities as in the proposed formulation and in addition contains 3 salts of monoethyl fumarate).

Table 3 – Overview of the Published Clinical Studies

Study type Author	Type of Study			
	Prospective controlled	**Prospective uncontrolled**	**Retrospective controlled**	**Retrospective uncontrolled**
Placebo-controlled studies				
Altmeyer 1994	X			
Nugteren-Huying 1990[a]	X			
Nieboer 1989, Study III[a]	X			
Comparator-controlled studies[b]				
Nieboer 1990[a]	X			
Gollnick 2002	X			
Kolbach 1992	X			
Fallah Arani 2011	X			
Prospective, non-randomised studies (including open-label/extension/follow-up studies)				
Lijnen 2015		X		
Walker 2014		X		
Wain 2010		X		
Carboni 2004		X		
Boesken 1998		X		
Mrowietz 1998		X		
Altmeyer 1996		X		
Thio 1995		X		
Nieboer 1989, Study V[a]		X		
Nieboer 1989, Study I		X		
Bayard 1987		X		
Retrospective, non-randomised studies (including open-label/extension/follow-up studies)				
Burden-Teh 2013				X
Thaçi 2013				X
Inzinger 2013			X	
Reich 2009				X
Brewer 2007				X
Fika 2006				X
Balasubramaniam 2004				X
Sladden 2006				X
Harries 2005				X
Observational studies[c]				
Boehncke 2011		X		
Litjens 2003	X			

a Severity of the psoriasis was not noted, however, inclusion criteria required involvement of at least 10% of the body surface

b Including combination therapy comparators

As the PK characterisation of Skilarence was considered to be inadequate particularly to properly characterise the PK of the proposed formulation and to support the bridging to literature evidence on Fumaderm, the applicant submitted an additional comparative PK Study (study 08) - A randomised, open label, single centre four way crossover study to investigate the pharmacokinetics of LAS41008 120 mg gastro resistant tablet and Fumaderm120 mg gastro resistant tablet under fasting and fed conditions in healthy subjects, during the procedure.

2.4.2. Pharmacokinetics

Absorption

After oral intake, no DMF was detected in plasma because it is rapidly hydrolysed by esterases to MMF and/or interacts with GSH to form conjugates.

In the Litjens (Litjens, 2004b) in vitro study, DMF was almost completely hydrolysed to MMF at pH 8, but not at an acidic pH, suggesting that this hydrolysis occurs mainly within the small intestine and not in the stomach, while MMF and MEF remained stable. Although the pH of blood and serum is the same (pH 7.4), the t1/2 of DMF in whole blood was significantly shorter than that in serum, which is explained by the presence of monocytes/lymphocytes, cells that hydrolyse DMF to MMF. The different interactions between these FAEs and the various cell types (including cells in the psoriatic lesions) may explain the beneficial effects of FAEs in psoriasis.

When taken with food the PK of DMF may be even more variable (please refer to discussion of the three PK-studies).

From the results of study 08, it is seen that the difference in exposure of MMF between Skilarence and Fumaderm in the fasted state is higher than in the fed state.

Distribution

Following oral administration, DMF arrives in the small intestine where it is mainly hydrolysed (Litjens, 2004a; Litjens, 2004b). The mucosa and intestinal alkaline milieu represent a strong pre-systemic metabolic barrier for DMF on its way into the systemic circulation, as it is evidenced that DMF cannot penetrate through this layer (Werdenberg, 2003); however, the mercapturic acid of DMF has recently been detected in urine of psoriasis patients. This suggests that in the event that any DMF penetrates through the mucosa without being metabolised, this DMF enters the portal vein blood to either be hydrolysed by esterases present in plasma, resulting in MMF, or reacts with GSH to form a GSH-conjugate (Rostami-Yazdi, 2009; Schmidt, 2007). As no DMF is detected in the plasma, this indicates the presence of strong first-pass metabolism (Rostami-Yazdi, 2008).

While MMF displays a protein binding of 50% (Mrowietz, 1999), DMF does not show any binding activity to serum proteins, which may further contribute to its rapid turnover in the circulation (Lee, 2008).

Elimination

Applicant-sponsored PK studies and published data have shown that MMF concentrations rise sharply and decline very rapidly in plasma, with a t1/2 of less than 1 hour (Litjens, 2004a; Litjens, 2004b;

Mrowietz, 2009; Rostami-Yazdi, 2008); no circulating MMF is present at 9 hours or 13 hours in the majority of subjects under fasted and fed conditions, respectively (Clinical Study Report 1103, Section 11.4.1.1). Due to the short half-life of MMF, no accumulation of MMF in plasma is expected. The mercapturic acid of DMF has been detected in urine of psoriasis patients, indicating renal excretion of DMF metabolised to GSH-conjugates (Rostami-Yazdi, 2009).

DMF is hydrolysed to MMF, then it is metabolized into FA and it is further converted to water and carbon dioxide in the tricarboxylic acid cycle (Lee, 2008). These metabolic products are primarily excreted through breathing with small amounts excreted in urine and faeces (reported by Mrowietz, 1999). There is some renal elimination of DMF as conjugates.

Following oral administration, DMF arrives in the small intestine where it is mainly hydrolysed (Litjens, 2004a; Litjens, 2004b). The mucosa and intestinal alkaline milieu represent a strong pre-systemic metabolic barrier for DMF on its way into the systemic circulation, as it is evidenced that DMF cannot penetrate through this layer (Werdenberg, 2003); however, the mercapturic acid of DMF has recently been detected in urine of psoriasis patients. This suggests that in the event that any DMF penetrates through the mucosa without being metabolised, this DMF enters the portal vein blood to either be hydrolysed by esterases present in plasma, resulting in MMF, or reacts with GSH to form a GSH-conjugate (Rostami-Yazdi, 2009; Schmidt, 2007). As no DMF is detected in the plasma, this indicates the presence of strong first-pass metabolism (Rostami-Yazdi, 2008).

Studies have shown that the metabolism of FAEs is dependent on pH and enzymes (Litjens, 2004b). Following oral administration, DMF undergoes a basic hydrolysis to MMF in the small intestine. Concurrently, DMF is exposed to various esterases associated with the intestinal lumen and mucosa (Werdenberg, 2003), which can also hydrolyse DMF to MMF (Rostami-Yazdi, 2008).

Some DMF also enters the portal vein blood. This is supported by data from Rostami-Yazdi (2010), that the mercapturic acid of DMF is excreted in the urine of psoriasis patients (Rostami-Yazdi, 2009). Some of the absorbed DMF is hydrolysed by esterases present in plasma (Werdenberg, 2003), resulting in MMF, and some reacts with GSH, forming a GSH-adduct that is metabolised further to the mercapturic acid of DMF and excreted in the urine. Finally, MMF is metabolised into FA and further metabolised to water and carbon dioxide in the tricarboxylic acid cycle (Lee, 2008).

There is no metabolism of FAEs through CYP-dependent pathways. This is in line with the fact that, to date, there are no relevant interactions with other drugs or metabolism-induced organ toxicities (Mrowietz, 2005; Mrowietz, 2009; Rostami-Yazdi, 2008).

Dose proportionality and time dependencies

No specific dose proportionality studies with DMF were conducted. Only single dose studies were performed.

Special populations

No formal studies were conducted in special populations.

Pharmacokinetic interaction studies

From the cited literature it appears that there is no relevant hepatic metabolism and renal excretion also seems to play a minor role. According to the applicant studies on the long-term use of FAEs for the treatment of psoriasis have not found any relevant interactions with other drugs including those

frequently used for comorbid conditions such as agents acting on the renin-angiotensin system, lipid modifying agents, drugs used in diabetes, calcium channel blockers, antithrombotic agents, beta-blockers and diuretics (Thaçi, 2013, Mrowietz, 2005; Rostami-Yazdi, 2008). Only one interaction with a vitamin K antagonist acenocoumarol has been described. This shall be followed in the context of routine pharmacovigilance activities such as PSURs.

Comparative Pharmacokinetics

Pilot studies 1103 and 1004 provided some data on the comparative pharmacokinetics of the DMF metabolite, MMF after administration of a single dose of Skilarence and Fumaderm in both the fed and fasted state.

Table 4 – Pharmacokinetic parameters of MMF in studies 1103 and 1104 following a single dose of drug administration under fasted and fed conditions

	120 mg of DMF 30 mg tablets				240 mg of DMF 120 mg tablets			
Parameter	DMF 30 mg		Fumaderm		DMF 120 mg		Fumaderm	
(Geometric Mean)	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed
$AUC_{0-\infty}$ [h•ng/mL]	1752	1415	1314	1229	3111	2871	3571	2824
AUC_{0-t} [h•ng/mL]	1735	1398	1187	1073	3090	2423	3534	2152
C_{max} [ng/mL]	1067	830.3	643.0	538.2	1905	1120	2139	1115
t_{max} [h][a]	2.75	6.50	3.50	9.50	4.00	7.25	3.50	7.00

a The median t_{max} is presented.

Note: subjects received a single dose (4 tablets) of DMF 30 mg and a single dose (2 tablets) of DMF 120 mg.

AUC_{0-t}: area under the plasma concentration-time curve from zero to time t, where t is the time of the last concentration measured; $AUC_{0-\infty}$: area under the plasma concentration-time curve extrapolated to infinity; C_{max}: maximum plasma concentration; DMF: dimethyl fumarate; MMF: monomethyl fumarate; t_{max}: time to reach maximum plasma concentration.

The applicant performed an additional 4–way cross-over study to compare the PK of Skilarence and Fumaderm in both fed and fasted condition . Thirty-two subjects were included and 30 completed the study. Unfortunately the time points taken were not sufficient to fully characterise the PK in all fed subjects and 6 subjects in the LAS41008 arm, and 10 in the Fumaderm arm, had to be excluded from the analysis because the characterisation of the PK is not complete. The PK results and the comparative statistics between Fumaderm and Skilarence are shown in the below tables.

Table 5 - Pharmacokinetic parameters of MMF after single dose administration of 120 mg gastro-resistant tablets of LAS41008 and Fumaderm in fasted and fed conditions in Study M-41008-08

Parameter	Units	Statistics	LAS41008		Fumaderm	
			Fasting	Fed	Fasting	Fed
C_{max}	ng/mL	N	30	25	30	21
		Mean ± SD	1325±537	1311±574	1149±637	1227±426
		CV	40.6	43.8	54.4	34.7
		Min-max	401-2880	307-2130	211-2550	380-2190
AUC_{0-t}	ng.h/mL	N	30	24	30	29
		Mean ± SD	1789±570	1743±533	1608±713	1392±860
		CV	31.8	30.6	44.4	61.7
		Min-Max	716-2966	668-2713	494-3203	39-2931
$AUC_{0-\infty}$	ng.h/mL	n	30	23	30	18
		Mean ± SD	1793± 569	1707±502	1613±713	1852±491
		CV	31.8	29.4	44.2	26.5
		Min-Max	721- 2969	673-2521	497-3206	1172-2934
$t_{1/2}$	n	n	30	23	30	18
		Mean ± SD	2.23±0.974	1.76±1.25	2.37±1.19	1.74±1.16
		CV	43.7	71.2	50.3	66.9
		Min-max	1.02-5.68	0.572-6.3	0.968-6.35	0.594-5.13
t_{max} [a]	h	n	30	25	30	21
		Median	3.5	9.0	4.5	10
		Min-max	0.5-7.5	3.5-16	2.5-11.5	4.5-16
t_{lag}	h	n	30	30	30	30
		Median	2.5	9.5	3.0	9.0
		Min-max	0.5-5	2.5-24	1.5-4.5	3-24

a The median t_{max} is presented.

AUC_{0-t}: area under the plasma concentration-time curve from zero to time t, where t is the time of the last concentration measured; $AUC_{0-\infty}$: area under the plasma concentration-time curve extrapolated to infinity; C_{max}: maximum plasma concentration; t_{max}: time to reach maximum plasma concentration; t_{lag}: Lag-time, SD: standard deviation; CV: coefficient of variation (%).

Source: ema D120responses-Q76-Appendix 2, Table 14.2.3.1

Table 6 - Statistical analysis of Study M-41008-08

Parameter	Comparison	Ratio(%)	90% confidential interval(%)
C_{max}	Fasted: LAS41008/Fumaderm	128.3	106.0 – 155.2
	Fed: LAS41008/Fumaderm	105.3	84.29 – 131.4
	Fumaderm: fed/fasted	116.6	94.01 – 144.5
	LAS41008: fed/fasted	95.65	78.10 – 117.1
AUC_{0-t}	Fasted: LAS41008/Fumaderm	118.0	91.04 – 152.8
	Fed: LAS41008/Fumaderm	174.8*	132.0 – 231.6*
	Fumaderm: fed/fasted	63.89*	49.17 – 83.02*
	LAS41008: fed/fasted	94.71	71.68 – 125.1
AUC	Fasted: LAS41008/Fumaderm	117.8	105.6 – 131.5
	Fed: LAS41008/Fumaderm	92.54	80.63 – 106.2
	Fumaderm: fed/fasted	122.9	107.7 – 140.3
	LAS41008: fed/fasted	96.52	85.54 – 108.9

Source: ema D120responses-Q76-Appendix 2, Tables 14.2.4.1 and 14.2.4.2

* Statistical analysis performed using all evaluable AUC0-t values according to the criteria previously described. However, 10 subjects showed ascending PK profiles at 24 h and, therefore, the AUC0-t values used in the analysis may be considered as truncated AUCs rather than true AUC0-t values. In a post hoc analysis these subjects were excluded and the ratio is around 1.

2.4.3. Pharmacodynamics

Mechanism of action

While the mechanism of how DMF and its metabolite MMF work clinically has not been fully elucidated, pharmacodynamic studies have shown that both interfere with intracellular and extracellular thiols, resulting in increased levels of reduced glutathione (GSH) after prolonged exposure (Nelson, 1999). Shifting the balance of oxidised to reduced GSH is known to induce the anti-inflammatory stress protein hemoxygenase-1, resulting in the attenuation of cellular damage and inflammation (Ghoreschi, 2011), and to inhibit redox-sensitive kinases, which subsequently inhibits phosphorylation and ubiquitination of IκB. This leads to a diminished translocation of NF-κB and so an inhibition of transcription of NF-κB target genes, which affects the regulation of the expression of inflammatory cytokines, chemokines and adhesion molecules (Stoof, 2001; Vandermeeren, 2001; Lehmann, 2007). This would result in the main effects by which DMF is known to improve the clinical manifestations of psoriasis including: downregulation of several inflammatory cytokines (Lehmann, 2007), inhibition of keratinocyte proliferation (Sebok, 1994; Sebok, 1998; van der Schroeff, 1989), inhibition of the expression of adhesion molecules (Stoof, 2001; Vandermeeren, 1997; Vandermeeren, 2001) and induction of proapoptotic events (Treumer, 2003; Holins, 2006; De Jong, 1996).

The reviewed literature provides ample evidence for the effects of DMF in cell types associated with psoriasis. As summarized by Meissner (Meissner, 2012), an overview of the effects of DMF in lymphocytes, dendritic cells, keratinocytes and endothelial cells is presented in the table below (table 7).

Table 7 - Overview of the effects of DMF in lymphocytes, dendritic cells, keratinocytes and endothelial cells

T cells	Dendritic cells	Keratinocyte	Endothelial cells
Th1/Th2 shift	↓ Differentiation	↓ ICAM-1, HLA-DR	↓ VACM-1, ICAM-1, E-selectin
↑ Apoptosis (e.g., Bcl-2)	↓ Formation of type II DCs	↓ CXCL1, CXCL8, CXCL9, CXCL10, IL-20	↓ NF-κB translocation
↓ TNF-α, IFN-γ, IL-1	↑ IL-10h, IL-12r, IL-23r	↓ MSK1/2	↓ Antiangiogenic VEGFR2
↑ IL-10, IL-4, IL-5 ↑	GSH depletion, ↑ HO-1	↑ p-p53, p-c-jun	
↓ NF-κB activity		↓ NF-κB translocation	
GSH depletion, ↑ HO-1			

Bcl-2=B-cell lymphoma 2; CXCL=chemokine ligand; DCs=dendritic cells; E-selectin=CD62 antigen-like family member E; GSH=reduced glutathione; HLA-DR=human leukocyte antigen DR; HO-1=heme oxygenase-1; ICAM-1=intercellular adhesion molecule 1; IFN-γ=interferon-gamma; IL=interleukin; MSK=Mitogen- and stress-activated protein kinase; NF-κB=nuclear factor 'kappa-light-chain-enhancer or activated B-cells'; Th=T helper; TNF-α=tumor necrosis factor alpha; VCAM-1 =vascular adhesion molecule-1; VEGFR2=Vascular endothelial growth factor receptor 2.

The main activity of DMF and MMF is considered to be immunomodulatory, resulting in a shift in T helper cells (Th) from the Th1 and Th17 profile to a Th2 phenotype and thus reducing inflammatory cytokine production with induction of proapoptotic events, inhibition of keratinocyte proliferation, reduced expression of adhesion molecules, and diminished inflammatory infiltrate within psoriatic plaques.

To justify supportive evidence from published literature which mainly refers to Fumaderm, the pharmacodynamics of MEF was discussed. In vitro study data indicate that DMF is considerably more potent compared to MEF in the test systems). DMF, MMF, as well as monoethyl fumarate (MEF) inhibited the proliferation of keratinocytes (*Thio, 1994).* In this study DMF was the most potent, MMF and MEF intermediate, and FA and malonic acid the least potent growth inhibitors. Also *van der Schroeff, 1989*, found a strong inhibition of keratinocyte proliferation by DMF and moderate inhibition by MMF and MEF, respectively. In the study by *Sebök, 1994*, inhibitory effects on keratinocytes were observed for MEF salts at clearly higher concentrations compared to DMF.

Primary and Secondary pharmacology

The applicant has not presented any discussion of the clinical data on the primary or secondary pharmacology of DMF except for an expert report on its potential to cause QTc prolongation. No "thorough QT" studies have been conducted by the applicant during the development of dimethyl fumarate gastro-resistant tablets. The expert report was performed by using scientific data bases information, clinical experience and data generated in 2 of the Almirall- sponsored clinical PK studies.

Up to now, there is no evidence in medical scientific data bases (Pubmed; Cochrane; 3 January 2014) that FAE-induced prolongation of ventricular repolarisation (QT or QTC interval prolongation) or even arrhythmias such as torsades de pointes tachycardia. Furthermore, 9 suspected cases of undesirable side effects have been reported so far to the Federal Institute for Drugs and Medical Devices (BfArM) after taking Fumaderm which have been associated with syncope, collapse-like states or arrhythmias. The "surrogate symptoms" of torsades de pointes tachycardias reported in these patients do not show in any of the cases a direct indication of QT interval prolongation or torsades de pointes tachycardia. In

the majority of cases, the states of collapse can be explained by the flush and/or gastrointestinal symptoms. In the remaining cases, the symptoms /cardiac arrhythmia can be explained by the underlying cardiovascular disease, the cardiovascular co-medication or by accidental intoxication. The Expert (Professor Bonnemeier) concluded that, on the basis of the current literature and the cases with adverse events reported to the BfArm, it is not possible to identify any causal relationship between the use of FAEs and QT prolongation, or even the induction of torsades de pointes tachycardia.

In addition, the effects of 30 mg and 120 mg of dimethyl fumarate on the stimulus conduction and repolarisation in the 12-lead standard electrocardiogram were analysed in 2 independent Phase I PK studies. In both studies, 12 healthy subjects were exposed to a single dose of multiple tablets of 30 mg (Study 1103) or 120 mg (Study 1104) of Fumaderm and DMF. Under respective dose ingestion, as well as before and after the series of tests, a 12-lead ECG was carried out in each case and stimulus conduction and repolarisation times determined. Heart rate, PR interval duration, QRS complex duration, QT interval duration, Bazett's corrected QT interval duration (QTC interval) and RR interval were recorded. The Expert (Professor Bonnemeier) was not able to find in either study any significant influence of Fumaderm or DMF ingestion on the duration of the ventricular repolarisation. Neither after the ingestion of Fumaderm nor after the ingestion of DMF is QTc interval prolongation observed. The Expert (Professor Bonnemeier, 2014) concluded that the systemic therapy with either Fumaderm or DMF gastro-resistant tablets did not suggest any concern with respect to the potential development of life-threatening arrhythmias such as torsades de pontes tachycardias.

Given the lack of publications in the scientific data bases and that the data obtained from the Phase I studies show no significant cardiovascular safety concerns, no other studies to investigate cardiovascular safety of DMF, such as a "thorough QT" study, are warranted.

No data or discussion on the relationship between, dose-plasma-concentration-response for the effects of DMF has been provided. However in the context of the vast clinical experience with fumarates in psoriasis as evidenced from the submitted literature, this lack of information is considered acceptable by CHMP.

Only one possible drug-drug interaction has been suggested between DMF (a pharmacy DMF monotherapy preparation) and the vitamin K antagonist, acenocoumarol, which was observed in a 56-year-old female patient (Lijnen, 2015). This patient was regularly treated with 2 to 3 mg acenocoumarol daily but required substantially higher doses after commencing DMF treatment; this normalised after discontinuation of DMF. It was not clear whether this was caused by the excipients and no further reports of drug-drug interaction between DMF-containing products and vitamin K antagonists have been reported in published literature.

Studies on the long-term use of FAEs for the treatment of psoriasis have not found any relevant interactions with other drugs including those frequently used for comorbid conditions such as agents acting on the renin-angiotensin system, lipid modifying agents, drugs used in diabetes, calcium channel blockers, antithrombotic agents, beta-blockers and diuretics (Thaçi, 2013, Mrowietz, 2005; Rostami-Yazdi, 2008). Metabolic organ toxicities have also not been observed (Werdenberg, 2003).

2.4.4. Discussion on clinical pharmacology

In line with the legal basis of the application (Article 8(3) of Directive of 2001/83/EC, full mixed) the PK data is based on three applicant sponsored PK studies (1103, 1104 and 08) and supporting published literature on PK data. The three PK studies 1103, 1104 (pilot studies) and 08 provide data on the characterisation of the PK of DMF from the proposed formulations (Skilarence 30 mg and 120 mg tablets) in healthy volunteers after administration in both fed and fasted state and comparative PK to

Fumaderm. The remaining aspects of the pharmacokinetics of the active substance are mainly from published studies and there is indirect support on the adequacy of the pharmacokinetics of the active substance from the number of years of clinical use of DMF containing products (mainly Fumaderm) in psoriasis.

For an Article 8(3) – full mixed application, demonstration of bioequivalence to Fumaderm is not required. However, the PK studies that were requested should allow adequate comparison of two differently composed products in terms of their biopharmaceutical characteristics, in particular since recommendations concerning the dosing and the intake with food are the same for Fumaderm and Skilarence. It is agreed that the primary PK-focus is on MMF and not DMF as DMF may not be detected systemically due to the rapid pre-systemically cleavage to MMF. It is noted that PK of MEFs was not determined in the two PK studies.

The applicant had performed two comparative PK studies initially to compare the exposure of Skilarence with Fumaderm, however the conclusions of two these studies were not clear due to the small sample size of these studies and the high variability in pharmacokinetics seen. So the applicant conducted another comparative PK study in a relatively larger sample size to better characterise the PK and relative bioavailability of Skilarence in comparison to Fumaderm.

The PK results from three prospective PK studies would not meet the criteria for bioequivalence and nor was this the objective of these PK studies. For an Article 8(3) – full mixed application, it is acknowledged that it is not necessary to demonstrate bioequivalence to a comparator and as such this is not an issue in this application.

It is noted that the results from PK study 1103 (30mg DMF) (higher overall exposure in fed and fasted state) and study 1104 (120mg DMF) (lower overall exposure in fasted state) point into different directions. The applicant commented that the individual plasma concentrations after intake of both formulations differed highly between subjects. However, in cross-over designs the intra-subject rather than inter-subject variability is most relevant.

Moreover the 90% confidence intervals are quite broad in these studies, which is due to the low number of subjects (n=11 in study 1103 and n=12 in study 1104) in these studies. Therefore any inferences drawn from these studies are not very robust. These results cannot exclude with confidence the potential for a different efficacy/safety of DMF as compared to Fumaderm at equivalent doses. The details of the validation of the PK macros or the equations used in these studies have been provided and these are appropriate.

Although bioequivalence assessments are not required here as the PK characterisation against Fumaderm is meant to be supportive information to strengthen the applicability of the public literature on this product for Skilarence, general requirements to fully characterize newly developed modified release products are to be considered. This includes comprehensive biopharmaceutic characterization, all the more as the applicant's product has no MEFs as compared to the reference used in the pivotal clinical Phase 3 study but the same dosing recommendations. To address these issues, the applicant provided the results of a new PK study (study 08) during the procedure. In the recently conducted, more robust PK study (study 08) in a larger sample size with the 120mg DMF formulation, it is seen that the exposure with Skilarence is relatively higher than Fumaderm in both fasted and fed states. A review of the complete study documentation shows that the study was well conducted and the results are reliable. The clinical overview and the relevant clinical summaries have been updated to include the results of the study 08.

In addition, to the above three PK studies and in order to support the PK of the active substance DMF, the applicant had submitted published studies (Litjens, 2004a; Rostami-Yazdi, 2010). There is no intravenous data available and so absolute bioavailability is not known. In order to show that the

published data from Fumaderm is relevant to Skilarence the applicant addressed the point whether the MEFs also impact on the PK/PD of DMF. A review of the in-vitro, ex-vivo and in-vivo studies of MEFs showed that they do not have a clinically significant effect at least in the systemic exposure levels of MMF anticipated in psoriasis patients.

Food appears to delay absorption. In addition data is more variable which is attributed to the enteric coated formulations. From the results of the recently conducted PK study it appears that the food effect on the Skilarence formulation is higher than in the Fumaderm formulation. This however tends to bring the relative systemic exposure closer to each other in the recommended administration state, which is with/after food. This recommendation is in order to improve gastric tolerability which is acceptable in spite of the higher variability as the dose is individually titrated based on patient's tolerability and the effects seen (section 4.2 of the proposed SmPC: "Skilarence tablets must be swallowed whole with fluid during or immediately after a meal.").

After oral intake, no DMF was detected in plasma because it is rapidly hydrolysed by esterases to MMF in the intestine and/or interacts with GSH to form conjugates. The active metabolite MMF is measured in the plasma and it is seen after oral administration, the tmax is around 3.5 hours in the fasted state and 9 hours in the fed state. MMF concentrations rise sharply and decline rapidly in plasma with a half-life of 1 hour and MMF has a moderate-low protein binding of 50%. Due to this short half-life, no circulating MMF is present at 9 hours or 13 hours in the majority of subjects under fasted and fed conditions, respectively. However no data (either own or from literature) is available on the exposures following multiple dosing. However based on clearance and short elimination half-life, time dependency in PK is unlikely.

MMF is then metabolized to fumaric acid and further converted to water and CO2, and these metabolic products are primarily excreted through breathing and small amounts of mercapturic acid of DMF are excreted through urine and faeces.

The applicant asserts that as DMF is not metabolised through CYP enzymes the potential for drug interactions is low. The applicant also proposes that due to the rapid hydrolysis of DMF in the gastrointestintestinal tract inhibition of CYP 3A4, Pgp and BCRP would not impact on DDIs. This is not acceptable, particularly given the apparent permeability of DMF. Data should be provided to exclude DMF as an inhibitor of Pgp, BCRP and CYP 3A4 at concentrations relevant for CYP3A4 inhibition. However, the risk of this uncertainty is considered acceptable and the issue will be followed up post authorisation (recommendation).

The data provided for inhibition of OATP1B3 can be accepted to exclude MMF as an inhibitor of OATP1B3. As MMF does not induce CYP enzymes, the applicant's assertion that an interaction study with oral contraceptives is not necessary is accepted in the context of the large clinical experience with fumarates.

However, it is recognised that a potential loss in efficacy of contraceptive could occur due to GI side effects and therefore appropriate warning statements have been included in the SmPC (see section 4.5) and an important potential risk has been included in the RMP.

Based on the understanding of the PK of DMF, it is not anticipated to be greatly affected by mild to moderate renal or hepatic impairment. As such no dose-alterations are recommended. However due to the lack of data in severe hepatic and severe renal impairment, the use of DMF in these patients is contra-indicated.

Age has not been adequately explored and an analysis of under and above 40 years and ≥65 years was performed. This is reflected in section 4.2 of the SmPC: 'Clinical studies of Skilarence had limited exposure to patients aged 65 years and above, and did not include sufficient numbers of patients to

determine whether they respond differently than patients under 65 years (see section 5.2). Based on the pharmacology of dimethyl fumarate, no need for dosage adjustments in the elderly is expected.'

No data is available in children. This is considered acceptable as Skilarence is only indicated for adults.

A PK-PD relationship for DMF in psoriasis is not established and small differences in PK between Skilarence and Fumaderm are unlikely to result in interpretable differences in efficacy or safety.

The mechanism of action of DMF/MMF has not been well elucidated. However, DMF containing medicinal products have been in clinical use for the treatment of psoriasis for a number of years where it has proven efficacy. There are a number of published reports on the in-vitro and ex-vivo effects of DMF and MMF which show that they are immunomodulators with effects on various cell types associated with inflammation. They can interfere with intracellular and extracellular thiols shift the balance of oxidised and reduced GSH which affects the expression of inflammatory cytokines, chemokines and adhesion molecules through IκB and NF-κB. The overall effect of DMF/MMF is thought to be a shift in T helper cells from the Th1 and Th17 profile to a Th2 phenotype which has an anti-inflammatory and pro-apoptotic effect in addition to inhibition of keratinocyte proliferation, reduced expression of adhesion molecules and diminished inflammatory infiltrate within psoriatic plaques.

Overall, the in vitro data presented for FAEs indicate that the antipsoriatic activity of fumaric therapies is mainly driven by DMF.

No specific pharmacodynamic studies on possible interactions of DMF with other medicinal products or substances were performed or submitted from literature. The applicant has found one reported interaction with vitamin K antagonist in literature; however it is not clear if this is a PK or PD interaction. Although a review of the available literature has not found any reports of other clinically relevant interactions which is reassuring, this does not exclude the potential for interactions. However DMF containing products have been used in the treatment of psoriasis for a number of years and the absence of any significant reports of interactions provides sufficient reassurance to not require further specific studies in this regard. The lack of information on interactions and the appropriate precautions have been appropriately reflected in the SmPC (see section 4.5).

2.4.5. Conclusions on clinical pharmacology

The applicant has performed three PK studies to compare the exposure of their product with Fumaderm. The initially conducted two comparative PK studies were small and the relative bioavailability between Skilarence and Fumaderm were inconsistent in these studies. So the applicant conducted and submitted a larger, more robust PK study during the procedure which showed that the exposure of MMF with Skilarence is relatively higher than Fumaderm in both fasted and fed states. A strict bioequivalence approach was not planned and not needed for this full-mixed application. Nevertheless it is agreed that the comparable exposure demonstrated in these studies contribute to the bridging to Fumaderm literature.

The available data can be considered adequate, in combination with the knowledge on the PK of DMF from published literature, to support this application. This is especially so as Fumaderm and other DMF containing products have been used in psoriasis with this knowledge base. In this context, the three PK studies submitted by the applicant can be deemed sufficient to characterise the PK from the presented formulation and to support the bridging to the literature data on Fumaderm.

The available data on the pharmacodynamics is limited to published literature and the exact mechanisms are still unknown. However, there is adequate data to suggest that DMF can modulate the immune system by influencing the inflammatory cell types and other cytokine mediators of

inflammation. Although the exact mechanism of action of DMF for its beneficial effects on psoriasis is not known, these immunomodulatory effects provide an acceptable biological basis to support the observed clinical effects in psoriasis. Given that DMF is a known active substance and there is significant clinical experience with Fumaderm and other DMF containing products, the lack of detailed information on its PD activity and interactions is considered acceptable. There are no outstanding concerns on pharmacodynamics of DMF.

Overall, the data submitted is acceptable to support this application.

However, as the potential for drug interaction of DMF has not been satisfactorily addressed, the CHMP recommended that a study will be conducted post-authorisation in order to exclude DMF as an inhibitor of CYP3A4, Pgp and BCRP at concentrations relevant to those in the intestine (recommendation).

2.5. Clinical efficacy

2.5.1. Dose response studies

No dose-response study has been conducted with Skilarence (DMF). The DMF content in Skilarence and Fumaderm is the same. The dosing scheme used in the pivotal study was based on the dosing recommendation of the comparator product Fumaderm. Both Skilarence and Fumaderm are gastro-resistant tablets. DMF 30 mg is the starting dose, which is increased week by week. The maximum dose is DMF 720 mg/day. According to pharmacodynamic and clinical data the main antipsoriatic effect is driven by DMF resp. its metabolite MMF. Moreover, in the pivotal study Skilarence was compared to Fumaderm. Therefore, in the context of this full-mixed application a dose-response study with Skilarence is not considered necessary, particularly as the dosing regimen is individualised. There is sufficient evidence from literature to support the proposed starting dose, the maximum daily dose and the proposed weekly dose-escalation regimen. In addition, the conclusive evidence of acceptability of this dose is based on the results of the pivotal study (study 1102) where similar dosing regimens was used for Skilarence and Fumaderm. Therefore and because the dose is titrated based on treatment response and tolerability, an independent dose finding study was not considered necessary for Skilarence.

2.5.2. Main study

The applicant has submitted a placebo and active (Fumaderm) comparator, randomized, controlled, pivotal study (study 1102) in support of the efficacy and safety of the proposed DMF formulation supported by published literature.

The outline of the pivotal study is given in the table below.

Table 8 – Overview of clinical studies providing efficacy data on fumaric acid esters in treating psoriasis

Study identifier	No. of study centres Locations	Study start Study end	Study design and type of control	Objective	Test product(s); Dosage regimen; Route of admin	No. of patients treated by arm	Diagnosis of patients	Duration of treatment	Primary endpoint
Almiral Clinical Programme									
1102	57 Austria, Germany, Poland, Netherlands	07 Jan 2013 23 Dec 2014 (completion of first follow-up visit [F1], 2 months after stopping treatment) The study is ongoing	Phase III, randomised, multicentre, double-blind, 3-arm, active and placebo-controlled, adaptive study	Efficacy, safety	Weeks 1-3: *DMF:* 1-3 x 30 mg tablets/day and Fumaderm initial placebo *Fumaderm:* 1-3 x 30 mg tablets/day and DMF placebo *Placebo:* DMF placebo and Fumaderm initial placebo Week 4-16: *DMF:* 1-6 x 120 mg tablets/day *Fumaderm:* 1-6 x 120 mg tablets/day *Placebo* matching tablets Oral administration	DMF: 279 Fumaderm: 283 Placebo: 137	PASI >10 BSA >10% PGA moderate to severe	16 weeks	Co-primary: proportion of patients achieving PASI 75 at Week 16 and the proportion of patients achieving a PGA score of "clear" or "almost clear" at Week 16

BSA = body surface area; DMF = dimethyl fumarate; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment

The publications in support of efficacy include Altmeyer 1994, Altmeyer 1996, Balasubramaniam 2004, Bayard 1987, Boehncke 2011, Boesken 1998, Brewer 2007, Burden-The 2013, Carboni 2004, Fallah Arani 2011, Fika 2006, Harries 2005, Inzinger 2013, Lijnen 2015, Litjens 2003, Nieboer 1989 (study I, III and V), Nieboer 1990, Nugteren-Huying 1990, Reich 2009, Sladden 2006, Thaci 2013, Thio 1995, Walker 2014 and Wain 2010. Most of these studies were either open-labelled or retrospective, uncontrolled studies.

Table 9 – Overview of publications submitted in support of efficacy

Author	Patients	Design	Study treatment and dose regimen	No. of patients treated	Duration of treatment	Key efficacy findings
Altmeyer 1994	• Chronic plaque, exanthematic guttate, pustular psoriasis, or psoriatic erythroderma for at least 2 years • No longer or only insufficiently responsive to external therapy • BSA >10%	Randomised, multicentre, double-blind, placebo-controlled	**Fumaderm** *Week 1:* 30 mg DMF *Week 2:* 120 mg DMF *Week 3 to 16:* dose increased up to 720 mg/day **Placebo** Corresponding numbers of placebo tablets	Fumaderm: ~50 Placebo: ~50	16 weeks	**PASI** • Fumaderm group: decrease in PASI scores from 21.57 at Baseline to 10.77 at Week 16 • Placebo group: PASI remained practically constant from Baseline to Week 16 • The difference in PASI between the groups at Week 16 was significant ($p<0.0001$) **Remission** • Fumaderm group: 71.3% had complete remission to slight improvement • Placebo group: 18% had complete remission to slight improvement • The difference between the groups for remission was significant ($p<0.0001$)

Author	Patients	Design	Study treatment and dose regimen	No. of patients treated	Duration of treatment	Key efficacy findings
Fallah Arani 2011	• Moderate to severe chronic plaque type psoriasis • PASI ≥10	Randomised, non-blinded, multicentre active-controlled	**DMF/MEF:** Initial dose of 30 mg/day and standard progressive dosage regimen. After week 9, therapy was continued at the maximum dose of 720 mg/day. or **Methotrexate** Initial dose of 5 mg/week, thereafter dose gradually increased up to 15 mg/week (3 doses of 5 mg each 12 h apart). Dose was tapered to 12.5 mg weekly at Week 13, 10 mg weekly at Week 14, 5 mg weekly at Week 15 and 2.5 mg weekly at Week 16.	DMF/MEF: 27 Methotrexate: 27	16 weeks Week 12: primary endpoint	**PASI** • DMF/MEF group: Mean PASI decreased from 18.1 at Baseline to 10.5 at Week 12 • 11 (42%) had ≥50% reduction, 5 (19%) had ≥75% reduction and 1 (4%) had ≥90% reduction in PASI from Baseline to Week 12 • Methotrexate group: Mean PASI decreased from 14.5 at Baseline to 6.7 at Week 12 • 15 (60%) had ≥50% reduction, 6 (24%) had ≥75% reduction and 2 (8%) had ≥90% reduction in PASI from Baseline to Week 12 • The effectiveness of FAEs was similar to that of methotrexate

Nieboer 1989 Study III	• Stable, nummular and plaque psoriasis • ≥10% BSA	Double-blind, placebo-controlled	**DMF or Placebo:** 60 mg DMF capsules, up to 240 mg/day.	DMF: 22 Placebo: 20	4 months observation time	**Average final total score** • DMF group: decrease to 60% • Placebo group: increase to 105% **Extent of eruption** • DMF group: decrease to 67% • Placebo group: increase to 123%

Author	Patients	Design	Study treatment and dose regimen	No. of patients treated	Duration of treatment	Key efficacy findings
Nieboer 1990	• Psoriasis of the plaque, macular and guttate type	Randomised, double-blind, active-controlled	**DMF:** 120 mg tablets or **DMF/MEF:** tablets with 120 mg DMF, 87 mg Ca MEF, 5 mg MEF, 3mg Zn MEF Initial dose 1 tablet/day, increased weekly up to 4 tablets/day (480 mg/day DMF) in 2 administrations	DMF: 22 DMF/MEF: 23	4 months	**Improvement in psoriasis** • DMF group: 5 (22%) had <25% improvement, 3 (14%) had 25-50% improvement and 10 (45%) had >50% improvement • DMF/MEF group: 1 (4%) had <25% improvement, 2 (9)% had 25-50% improvement and 12 (52%) had >50% improvement **Improvement in joint pain** • DMF group: 2 (33%) had considerable improvement, 1 (17%) some improvement and 3 (50%) deteriorated or remained unchanged • DMF/MEF group: 2 (40%) had considerable improvement, and 3 (60%) slight improvement • Treatment of psoriasis with FAE combination therapy (DMF/MEF) did not result in a better therapeutic result compared with DMF monotherapy

Author	Patients	Design	Study treatment and dose regimen	No. of patients treated	Duration of treatment	Key efficacy findings
Nugteren-Huying 1990	• Psoriasis patients • ≥10% BSA • Stable disease • Normal kidney and liver function • No cardiac or GI problems	Randomised, double-blind, placebo-controlled	**DMF/MEF:** 120 mg DMF, 87 mg Ca MEF, 5 mg Mg MEF, 3mg Zn MEF **Octyl hydrogen fumarate:** 284 mg octyl hydrogen fumarate, 5 mg Mg MEF, 3mg Zn MEF **Placebo** Gradual increase in dose from 1 to 6 tablets daily. All patients received topical treatment with 5% salicylic acid in white petrolatum	DMF/MEF: 13 Octyl hydrogen fumarate: 13 Placebo: 13	16 weeks	**Mean body surface affected** • DMF/MEF group: decrease in mean body surface affected with psoriasis from 21% at Baseline to 6.7% at Week 16 • Effect was significantly different from the octyl hydrogen fumarate and placebo groups ($p<0.01$) **Clearance and improvement** • DMF/MEF group: 6 patients showed complete clearance and 3 showed improvement • Octyl hydrogen fumarate group: no patients showed improvement • Placebo group: 1 patient showed improvement

A multi-center, randomized, double-blind, three-arm, 16 week, adaptive phase III clinical study to investigate the efficacy and safety of LAS41008 vs LASW1835 and vs placebo in patients with moderate to severe chronic plaque psoriasis

Methods

Study Participants

The study participants included:

- Male and female patients aged 18 years or older with a diagnosis of chronic plaque psoriasis for at least 12 months before enrolment in the study
- No diagnosis of guttate, erythrodermic or pustular psoriasis
- Severity of psoriasis defined as moderate to severe, as reflected in meeting all the following criteria:
    - PASI >10
    - BSA (body surface area) >10 %
    - PGA moderate to severe (score of 3 = moderate, 4 = moderate to severe; or 5 = severe)
- Prior therapy with systemic drugs for psoriasis that was discontinued e.g. due to an adverse event (AE) or insufficient effect, or naïve to systemic treatment but identified as a candidate for systemic treatment
- With a complete record of at least 12 months of other previous topical and systemic treatments, if any.
- Not on systemic therapy with drugs that may have interfered with the investigational products taken within the defined wash-out period

In addition, the following were excluded

- Patients suffering from significant gastrointestinal problems (Ulcers, diarrhoea, etc.)
- Patients with active infectious disease
- Patients with known HIV positive status or suffering from other immunosuppression
- Patients with haematological abnormality as defined
- Patients with severe liver or kidney disease

Treatments

The treatment scheme was the same for each treatment group. In order to achieve an optimum efficacy and tolerability profile, tablets containing 30 mg DMF were administered during the first three treatment weeks. During the subsequent 13 weeks (Week 4 until Week 16) the patients received up to 3 x 2 visually identical tablets each containing 120 mg DMF, either as LAS41008 or as Fumaderm, leading to a maximum of 720 mg/day, or matching placebo. In case of individual intolerability of the increased dosage the patient was to receive the last tolerated dose, which was then to be maintained until the end of the treatment period, i.e. individual doses were applied. During the first week of treatment with the maintenance dose (week 4) no dose reduction was possible. If treatment success (patient achieved a score of “clear” = 0 or ”almost clear” = 1 in the PGA or >90% improvement in PASI from baseline) was reached before administration of the maximum dose of 720 mg/day, no

further dose increase was necessary and the dosage was to be steadily reduced to an individual maintenance dose.

During the treatment period the patients visited the study centre at baseline (Day 1, Visit 1) and at Weeks 1 (Visit 2), 3 (Visit 3), 5 (Visit 4), 8 (Visit 5), 12 (Visit 6) and 16 (Visit 7). After the 16 week visit, treatment was stopped and the patients were to be followed up for a further 12 months including 3 visits after 2, 6 and 12 months (F1, F2 and F3, respectively). In case of relapse and a need for new systemic therapy during the follow-up period, a final follow-up visit would be conducted prior to initiation of the therapy.

The same dosing schedule as shown in table 10 was used in each treatment group.

Table 10 – Dosing schedule

Week	Dose of 30 mg DMF per tablet Double-dummy			Daily dose of DMF (mg)
	Morning	Noon	Evening	
1	-	-	2 (1 large and 1 small tablet)	30
2	2 (1 large and 1 small tablet)	-	2 (1 large and 1 small tablet)	60
3	2 (1 large and 1 small tablet)	2 (1 large and 1 small tablet)	2 (1 large and 1 small tablet)	90
	Dose of 120 mg DMF per tablet			
	Morning	Noon	Evening	
4	-	-	1	120
5	1	-	1	240
6	1	1	1	360
7	1	1	2	480
8	2	1	2	600
9-16	2	2	2	720

Objectives

The primary objectives of Study 1102 were:

- To demonstrate superiority of DMF gastro-resistant tablets vs. placebo based on the Psoriasis Area Severity Index (PASI) 75 and Physician's Global Assessment (PGA) after 16 weeks of treatment and
- To demonstrate non-inferiority of DMF gastro-resistant tablets to Fumaderm based on the PASI 75. This was in accordance with the EMA guideline for the treatment for psoriasis.

The secondary objectives were:

- Superiority of LAS41008 versus placebo based on changes in PASI, PGA after 3 and 8 weeks and body surface area (BSA) after 3, 8 and 16 weeks.
- Non-inferiority of LAS41008 compared to Fumaderm regarding PASI 75 after 3 and 8 weeks of treatment.
- Assessment of the safety of LAS41008 compared to Fumaderm and placebo for both treatment periods (30/120mg DMF).

- Assessment of the safety and efficacy of LAS41008 and Fumaderm when administered concomitantly with medicines known to have potential nephrotoxic effects, e.g. angiotensin converting enzyme inhibitors, angiotensin II inhibitors and statins.

Outcomes/endpoints

Primary efficacy variables

- PASI 75 at Week 16
- Proportion of patients achieving a score of “clear” = 0 or ”almost clear” = 1 in the PGA at Week16

Both these endpoints were tested to show superiority of LAS41008 over placebo but only PASI 75 was tested to show non-inferiority of LAS41008 versus Fumaderm.

Secondary efficacy variables

- Proportion of patients achieving PASI 75 at Week 3 and 8
- Proportion of patients achieving PASI 50 and PASI 90 at Week 3, 8, and 16
- Proportion of patients achieving a score of “clear” = 0 or ”almost clear” = 1 in the PGA at Week 3 and 8
- Percent change in PASI at Week 3, 8, 16 and F1
- PGA score at Week 3, 8, 16 and F1
- BSA at Week 3, 8, and 16
- Treatment success rate at Week 3, 8, and 16
- Treatment success was defined as patients achieving either a “clear” or “almost clear” score in the PGA and/or PASI 90.
- Remission rate at Week 3, 8, and 16 - Remission was defined as a score of “clear” in the PGA.
- Time to relapse - Relapse was defined as the event when the achieved maximal improvement from baseline was subsequently reduced by ≥ 50% based on PASI. Two time-to-relapse analyses were conducted: a) relapse occurring at any time during the study duration (on-treatment + 12 months off treatment [in the initial report only data up to F1 were available]) and b) relapse occurring within 2 months after last study drug intake.
- Time to rebound - Rebound was defined as a worsening of psoriasis over baseline value (PASI≥ 125%)
- Patient Benefit Index (PBI) based on the Patient Need Questionnaire (PNQ) and Patient Benefit Questionnaire (PBQ) at Week 16 and F1

Health-related quality of life variable

- Dermatology Life Quality Index [DLQI] score (also as categorical variable) after 16 weeks of treatment and at the 2 month follow-up visit (F1)

Safety outcomes

- Physical examination
- Vital signs
- Laboratory assessments (blood and urine analysis)
    - Clinical chemistry parameters: Creatinine, total bilirubin, aspartate amino transferase (AST), Alanine amino transferase (ALT), gamma-glutamyl-transferase (gamma-GT), alkaline phosphatase (ALP)
    - Haematology parameters: Haemoglobin, red blood cell count (erythrocytes), haematocrit, platelet count (thrombocytes), total white blood cells (WBC) count (leucocytes), neutrophils, granulocytes, lymphocytes, monocytes, eosinophils, basophils
    - Urinalysis (dipstick) parameters: pH, blood (leukocytes and erythrocytes), protein, glucose, ketones, nitrite.
- AEs

Sample size

The multiple primary hypotheses were to be tested each on a 5% significance level based on the testing procedure. A power of 90% was required in the sample size calculation. The ratio between LAS41008 and placebo patients was 2:1. For PASI 75, a difference of 40% between LAS41008 versus placebo was assumed, based on a LAS41008 response rate of 50% and a placebo response rate of 10%. This would have required a sample size of 44 patients for the LAS41008 and 22 patients for the placebo group.

For the proportion of patients achieving a score of “clear” or ”almost clear” in the PGA, a difference of 30% between LAS41008 versus placebo was assumed based on a LAS41008 response rate of 40% and a placebo response rate of 10%. This would have required a sample size of 70 patients for the LAS41008 and 35 patients for the placebo group.

For the non-inferiority for LAS41008 compared to Fumaderm regarding PASI 75 after 16 weeks of treatment a non-inferiority margin of 15% was set in line with the EMA Scientific Advice. This margin was well within the effect size compared to placebo but was also considered a reasonable maximal difference that was judged to be not clinically relevant. Based on a proportion of patients achieving PASI 75 of 50% for LAS41008, an expected difference to Fumaderm of 0, a power of 90% and a significance level of 5%, this would have given a sample size of 234 patients per treatment group.

A sample size of 234 + 234 + 117 (2:1 ratio between active and placebo groups) of 585 patients was necessary. Based on an estimated drop-out rate of 15% during the treatment phase, a total sample size of 690 patients was set.

The assumptions for the effect size of the proportions achieving PASI75 and PGA of ‘clear; or ‘almost clear’ were based on literature research for Fumaderm.

Randomisation

The randomization list was drawn up for 1400 patients by SynteractHCR using blocks of 5 and no stratification factors.

Blinding (masking)

Double-blind study.

Statistical methods

Primary endpoint

One-sided p-values (for further use in the adaptive interim analysis) for the superiority testing were calculated. The decision was based on the one-sided p-values for superiority at Week 16 comparing LAS41008 and placebo.

For the non-inferiority testing, one-sided p-values for the test decision were calculated comparing Fumaderm and LAS41008.

Additional descriptive CIs with adjusted confidence level were calculated. The CIs and p-values were calculated based on an asymptotic Wald test.

A hierarchical approach was used to deal with multiple comparisons. The non-inferiority testing for PASI 75 was ordered hierarchically after the two primary superiority endpoints, i.e., only if both superiority comparisons led to a rejection of the null hypothesis (in the FAS and PPS population), non-inferiority for PASI 75 was to be tested (a priori-order of hypotheses). As long as the first two primary hypotheses could be rejected, this non-inferiority testing could be done at a 5% significance level.

This approach was combined and integrated into the adaptive design concept. The Bauer P. and Köhne method, based on the Fisher's combination test, was used to combine the results of each of the two stages. The statistical significance threshold was set to 0.00380 according to this method. This was a conservative approach as no penalty was needed as no adaptation of sample size was done.

Interim analysis

An interim analysis was planned after data from at least 1/3 of the 690 subjects (i.e. 230 evaluable subjects) were available for the two primary efficacy variables.

It was agreed to include all patients randomised until 31 July 2013 into the interim analysis (~240patients). The interim analysis was based on the PPS population as well as the FAS population. Prior to unblinding by the independent statistician undertaking the interim analysis, a data review meeting was performed by the sponsor to classify patients into the various population subsets.

Two possible outcomes were possible as a result of this interim analysis:

a) to increase the sample size up to a maximum of 1160 patients if the initial sample size of 690 patients was considered insufficient to meet the primary efficacy objectives (resulting p-values of the interim between 0.0090 and 0.6). By contrast, if success seemed likely even with a smaller sample size, no early termination at lower subject numbers was allowed in order to continue to collect safety data.

b) to stop the study for futility if the (resulting p-values of the interim >0.6)

Adjusted confidence intervals and combined final analysis

The following adjusted confidence intervals for descriptive purposes were used:

1st stage: Two-sided confidence intervals at a 1-2*0.0090 = 0.982 (or 98.2%) confidence level

2nd stage: Two-sided confidence intervals at a 95% confidence level

Overall combined confidence intervals at a 1-2*0.00380 = 0.9924 (or 99.24%) confidence level

It should be noted that the 95% CI given at the second part and final (first and second parts combined) are for reference only and not decisional.

One-sided p-values resulting from analysis of stage 1 and stage 2 are combined based on the Fisher's combination test as the product of both p-values and comparing this product with a significance level of 0.00380. The overall significance level by using this method is controlled and limited at 5%.

Secondary endpoints:

For the comparisons of proportions of patients with PASI 75 at Week 3 and 8 and PASI 50 and PASI 90 at Week 3, 8, and 16 and the proportions of patients with a score of “clear” or “almost clear” in the PGA at Week 3 and 8, two-sided 95% CIs for the differences between treatments were calculated. Corresponding one-sided p-values were also presented. The CIs and p-values were calculated based on an asymptotic Wald test for the risk difference.

An ANCOVA using LOCF with factors treatment and centre and baseline as covariate was used to test differences between treatments for the percent change in PASI from baseline.

The PGA score (LOCF) was compared between treatments using the Cochran-Mantel-Haenszel test.

BSA at Week 3, 8 and 16 was compared between treatments using an Analysis of Covariance (ANCOVA) with factors treatment and centre and BSA at baseline as covariable.

The treatment success and remission rates at Week 3, 8 and 16 were compared between treatments using the Cochran-Mantel-Haenszel test stratified by centre.

Time to rebound and time to relapse was based on the observed cases of PASI score. Time to relapse (since first intake of study drug) and time to rebound (since stop of study drug) was analysed using Kaplan-Meier estimates.

The PBI score was analysed with an ANCOVA model including treatment and centre as factors and baseline values as covariate.

Analysis Populations

Definitions of the analysis sets used in this study are provided in table 11.

Table 11 – Analysis sets

Analysis set	Definition
Safety analysis set (SAS)	All patients who were randomized and received at least one dose of the investigational medicinal product.
Full analysis set (FAS)	All patients of the SA set with at least one measurement of the primary variables PASI and PGA after Week 0.
Per protocol set (PPS)	All patients of the FA set for whom no relevant protocol deviations were documented.

The decision whether or not a protocol deviation was relevant for the exclusion of patients from the per protocol set (PPS) set was made in the blind data review meetings (BDRM) prior to the interim and final analyses.

The efficacy analysis was based on the full analysis set (FAS) and the PPS with both being of equal importance. The safety analysis was based on the safety set (SAS).

Missing values

In case of drop-outs, for all efficacy analyses derived from PASI and PGA assessments the last assessment prior to withdrawal was carried forward for the subsequent (missing) assessments (last observation- carried-forward [LOCF]).

If the last visit (excluding the follow-up visits) was done more than 7 days after last intake, then assessments for the primary efficacy parameters, PASI and PGA, from such visits were not used for the analysis of on-treatment study visits. LOCF up to Week 16 was applied using the last on-treatment assessment or assessment where the visit took place $\leq$ 7 days after the last IMP intake.

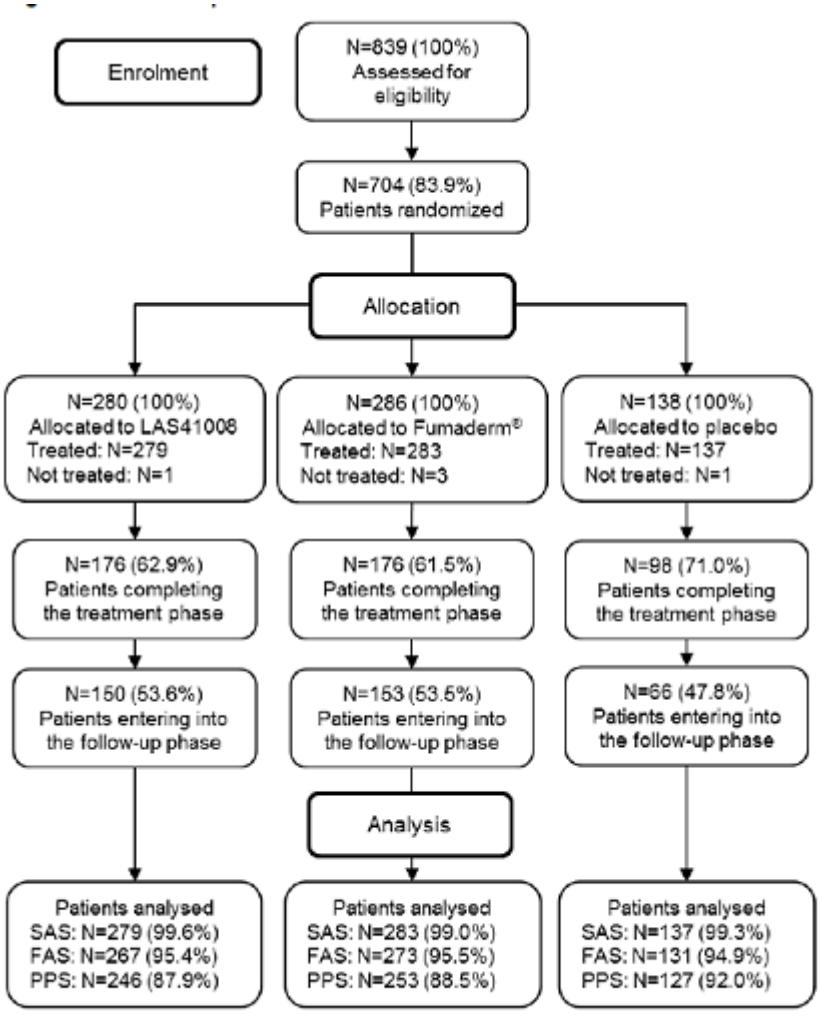
For the primary efficacy analysis of responders, an alternative approach for handling missing data was applied, setting patients with missing examinations as non-responders (sensitivity analysis). Additionally, analyses of the total PASI score (continuous data) and the percent change from baseline and the PGA were performed based on observed cases.

Analysis of other efficacy variables was done on observed cases approach, i.e., no imputation technique was applied for missing observations.

Results

Participant flow

Figure 6 – Patient disposition



SAS: Safety analysis set; FAS: Full analysis set; PPS: Per protocol analysis
Note: The percentage in the second row is based on the enrolled patients: subsequent percentages are based on the randomized patients per each treatment group, respectively.

Recruitment

This was a multi-centre study involving 57 study sites across Germany, Austria, Netherlands and Poland. The study was initiated on 7 Jan 2013 and the last patient to complete first follow-up visit (F1), two months after last dose of study treatment was on 23 Dec 2014.

Conduct of the study

Four amendments to study protocol version 1.0 dated 25 July 2012 were issued. Relevant changes introduced in Amendments 1 to 4 related to

- Clarification on prior therapy
- Clarification on contraceptive measures
- Assessments at follow-up and screening
- Permitted use of concomitant medications with known harmful influence on kidneys and a secondary objective to assess safety and efficacy in this sub-group
- Detailed definition of renal impairment and abnormal liver enzymes included
- Clarification that full study report will be written after 2 months follow-up and the data on 6 & 12 month follow-up would be included as addendum.

Protocol deviations that were considered major as determined in a Blind Data Review Meeting (BDRM) and in consultation with the coordinating investigator included are listed in table 12.

Table 12 – Major protocol deviations

Deviation	Number of patients[1]
Deviations against eligibility criteria	6
Incorrectly allocated randomization number	3
Deviation against visit windows (major if performed more than ± 14 days from planned time) Visit 7 (Week 16 ± 3 days), i.e. < 109 or > 115 days after baseline	3
Use of prohibited concomitant medications (topical treatments)	13
Use of prohibited concomitant medications (systemic treatments)	2
Use of prohibited concomitant medications (immunosuppressive treatments)	2
Lack of compliance (major if <80% and >120%)	25

[1] A patient with more than one deviation per category was only counted once

Baseline data

The demographic and baseline characteristics were well balanced between the treatment groups (Table 13).

Table 13 – Demographic and baseline characteristics of patients in study 1102 (FAS population)

Characteristic	DMF N=267	Placebo N=131	Fumaderm N=273	Total N=671
Age[a]				
Mean (SD)	43.97 (15.17)	44.27 (14.37)	45.21 (13.65)	44.53 (14.40)
Median (range)	44.00 (18.0, 80.00)	44.00 (18.0, 78.0)	45.00 18.0, 87.0)	45.00 (18.0, 87.0)
Age group, n (%)				
≤18 – <40 years	114 (42.70)	49 (37.40)	98 (35.90)	261 (38.90)
≤40 – <65 years	127 (47.57)	70 (53.44)	154 (56.41)	351 (52.31)
≥65 years	26 (9.74)	12 (9.16)	21 (7.69)	59 (8.79)
Gender, n (%)				
Male	167 (62.55)	88 (67.18)	177 (64.84)	432 (64.38)
Female	100 (37.45)	43 (32.82)	96 (35.16)	239 (35.62)
Race, n (%)				
Caucasian	263 (98.50)	131 (100.0)	271 (99.27)	665 (99.11)
Black or African American	1 (0.37)	0	0	1 (0.15)
Asian	1 (0.37)	0	2 (0.73)	3 (0.45)
Other	2 (0.75)	0	0	2 (0.30)
PASI score				
Mean (SD)	16.34 (5.71)	16.18 (4.89)	16.43 (6.79)	16.35 (6.02)
Median (range)	14.80 (10.1, 62.1)	14.90 (10.1, 31.9)	14.40 (10.1, 61.9)	14.70 (10.1, 62.1)
PASI group[b], **n (%)**				
Moderate	223 (83.52)	108 (82.44)	224 (82.05)	555 (82.71)
Severe	44 (16.48)	23 (17.56)	49 (17.95)	116 (17.29)
PGA group[c], **n (%)**				
Moderate	162 (60.67)	79 (60.31)	164 (60.07)	405 (60.36)
Severe	105 (39.33)	52 (39.69)	109 (39.93)	266 (39.64)
BSA,%				
Mean (SD)	21.93 (11.61)	21.90 (12.25)	21.27 (12.45)	21.66 (12.07)
Median (range)	18.00 (10.1, 75.0)	17.50 (10.5, 70.0)	18.00 (10.2, 90.0)	18.00 (10.1, 90.0)
DLQI				
n	266	131	270	667
Mean (SD)	11.32 (6.26)	10.93 (6.49)	11.98 (7.04)	11.51 (6.64)
Median (range)	11.00 (0.0, 29.0)	10.00 (0.0, 27.0)	11.00 (0.0, 30.0)	11.00 (0.0, 30.0)
DLQI categories, n (%)				
No effect at all on patient's life	9 (3.38)	5 (3.82)	7 (2.59)	21 (3.15)
Small effect on patient's life	51 (19.17)	27 (20.61)	48 (17.78)	126 (18.89)
Moderate effect on patient's life	66 (24.81)	36 (27.48)	71 (26.30)	173 (25.94)
Very large effect on patient's life	117 (43.98)	52 (39.69)	116 (42.96)	285 (42.73)
Extremely large effect on patient's life	23 (8.65)	11 (8.40)	28 (10.37)	62 (9.30)
Missing	1	0	3	4

a Age at signing the informed consent form.
b PASI severity at baseline: moderate = PASI >10 to ≤20%, severe = PASI >20%.
c PGA severity at baseline: moderate = PGA score 3; severe = grouping of the categories moderate to severe (PGA score 4) with severe (PGA score 5).
BSA=body surface area; DMF=dimethyl fumarate gastro-resistant tablets; DLQI=Dermatology Quality of Life

Numbers analysed

Table 14 – Analysis populations

	LAS41008 N=280[1]	Fumaderm N=286[1]	Placebo N=138[1]
	n (%[2])		
Number of patients included into safety set	279 (99.6)	283 (99.0)	137 (99.3)
Number of patients included into full analysis set	267 (95.4)	273 (95.5)	131 (94.9)
Number of patients included into per-protocol set	246 (87.9)	253 (88.5)	127 (92.0)

Outcomes and estimation

An interim analysis was performed after data for the two primary efficacy variables for 1/3 of the planned 690 patients, i.e., 230 evaluable patients, was available in order to address the implications of continuing with the original sample size and to check if there were any safety concerns. After consideration of this interim analysis, the decision was that no change would be made. This period from study start to the time of the interim analysis is defined as stage 1 of the study.

The Data Monitoring Committee suggested increasing the sample size from 690 patients up to 1070 patients. The recommendation was not implemented and the original sample size remained. In spite of not conducting any adaptation into the sample size the threshold for statistical significance was penalised to be less or equal than 0.0038.

After the interim analysis the study continued: the period comprising the remaining treatment period up to Week 16 for all subjects continuing in the study was defined as stage 2. Data of a further 441 patients was available for this stage.

Results of the primary variables for the individual stages are provided in table 15. Otherwise, the following results derive from the final analyses only, i.e. when data from both stages have been combined.

Table 15 – Proportion of patients with PASI 75/PGA score (almost) clear at week 16 (LOCF), FAS and PPS Populations

Variable	Set		LAS41008	Fumaderm	Placebo
			n (%)		
Proportion of patients with PASI 75 at Week 16	FAS	Stage 1	34 (34.0)	36 (42.9)	7 (15.2)
		Stage 2	66 (39.5)	74 (39.2)	13 (15.3)
		Combined	100 (37.5)	110 (40.3)	20 (15.3)
	PPS	Stage 1	32 (35.6)	35 (45.5)	7 (15.9)
		Stage 2	61 (39.1)	73 (41.5)	12 (14.5)
		Combined	93 (37.8)	108 (42.7)	19 (15.0)
Proportion of patients with a "clear" or "almost clear" score in PGA at Week 16	FAS	Stage 1	25 (25.0)	29 (34.5)	7 (15.2)
		Stage 2	63 (37.7)	73 (38.6)	10 (11.8)
		Combined	88 (33.0)	102 (37.4)	17 (13.0)
	PPS	Stage 1	23 (25.6)	28 (36.4)	7 (15.9)
		Stage 2	57 (36.5)	72 (40.9)	9 (10.8)
		Combined	80 (32.5)	100 (39.5)	16 (12.6)

The results of the superiority testing between DMF and placebo for PASI75 and PGA in the full analysis set, per protocol set and safety analysis set are provided in the table below.

Table 16 – Superiority test for proportion of patients with PASI 75 and clear/almost clear PGA at week 16: DMF vs. Placebo treatment difference in study 1102

Analysis population	Missing approach	RD	Adjusted 99.24% CI	Non-adjusted 95% CI	p-value
PASI 75					
FAS	LOCF	22.2	10.7, 33.7	13.7, 30.6	<0.0001
	Non-responders	21.8	10.5, 33.2	13.5, 30.2	<0.0001
PPS	LOCF	22.8	11.0, 34.7	14.2, 31.5	<0.0001
	Non-responders	22.0	10.2, 34.8	13.4, 30.7	<0.0001
SAS [a]	LOCF	21.6	10.3, 32.9	13.3, 29.9	<0.0001
	Non-responders	22.0	11.0, 33.0	13.9, 30.0	<0.0001
PGA Clear /Almost clear					
FAS	LOCF	20.0	9.0, 31.0	11.9, 28.0	<0.0001
	Non-responders	19.2	8.5, 30.0	11.3, 27.2	<0.0001
PPS	LOCF	19.9	8.7, 31.1	11.7, 28.1	<0.0001
	Non-responders	19.1	8.0, 30.3	10.9, 27.3	<0.0001
SAS [a]	LOCF	20.2	9.6, 30.8	12.4, 28.0	<0.0001
	Non-responders	19.5	9.1, 29.9	11.9, 27.2	<0.0001

a Post-hoc analyses requested in pre-submission meetings.
Note: CI=confidence interval; DMF=dimethyl fumarate gastro-resistant tablets; FAS=full analysis set; LOCF=last observation carried forward; PASI 75=a 75% reduction in Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; PPS=per protocol set; RD=risk difference; SAS=safety analysis set

The results for the comparison of Fumaderm versus placebo in the primary variables with LOCF in both the FAS and PPS are as below.

Table 17 – Statistical test for superiority of fumaderm vs placebo in primary variables (LOCF) – combined analysis, FAS and PPS populations

Variable	Set	Fumaderm-Placebo Difference	99.24% CI	P-value[1] for superiority
Proportion of patients with PASI 75 at Week 16	FAS	25.0%	13.5%, 36.6%	<.0001
	PPS	27.7%	15.9%, 39.6%	<.0001
Proportion of patients with a "clear" or "almost clear" score in PGA at Week 16	FAS	24.4%	13.3%, 35.5%	<.0001
	PPS	26.9%	15.6%, 38.3%	<.0001

[1] P-values are derived from the Wald test for risk differences and a combination of the p-values from stage 1 and 2 (p-value stage 1 x p-value stage 2) according to the Bauer & Köhne procedure; the p-value is significant if <0.0038
Note: Significant p-values are shaded.

As the superiority of LAS41008 to placebo in both the proportion of patients achieving PASI 75 and the proportion of patients achieving a score of "clear" or "almost clear" in the PGA at Week 16 was confirmed in the FAS and PPS populations, in a second step the non-inferiority of LAS41008 to Fumaderm in the proportion of patients achieving PASI 75 at Week 16 was assessed using a non-inferiority margin of -15% (see Table below).

Table 18 – Non-inferiority test[a] for proportion of patients with PASI 75 at week 16: DMF vs. Fumaderm treatment differences in study 1102

Analysis population	Missing approach	RD	Adjusted 99.24% CI	Non-adjusted 95% CI	p-value
PASI 75					
FAS	LOCF	-2.8	-14.0, 8.4	-11.1, 5.4	0.0003
	Non-responders	-2.9	-14.0, 8.3	-11.0, 5.3	0.0003
PPS	LOCF	-4.9	-16.6, 6.8	-13.5, 3.7	0.0024
	Non-responders	-4.5	-16.2, 7.1	-13.1, 4.0	0.0019
SAS [b]	LOCF	-2.0	-12.9, 9.0	-10.0, 6.1	<0.0001
	Non-responders	-2.0	-12.8, 8.9	-9.9, 6.0	0.0001

a Non-inferiority test based on a 15% margin of non-clinically relevance. The non-inferiority test is based on p-values (cut-off for statistical significance=0.0038) and 99.24% CI is for exploratory purposes.
b Post-hoc analyses requested in pre-submission meetings.
Note: CI=confidence interval; DMF=dimethyl fumarate gastro-resistant tablets; FAS=full analysis set; LOCF=last observation carried forward; PASI 75=a 75% reduction in Psoriasis Area and Severity Index; PPS=per protocol set; RD=risk difference; SAS=safety analysis set

The results of the sensitivity analysis for the primary efficacy variables with missing data imputed as 'non-responders' were also consistent with the findings of the primary analysis with LOCF.

Secondary Endpoints

Table 19 shows the proportions of patients who achieved PASI 50 or PASI 90 at Weeks 3, 8, and 16 in each treatment group based on the FAS and PPS population.

Table 19 – PASI 50, PASI 90 (LOCF) at week 3, 8 and 16, FAS and PPS populations

Population		Visit	LAS41008	Fumaderm	Placebo
			n (%)		
FAS	PASI 50	Week 3	15 (5.6)	16 (5.9)	3 (2.3)
		Week 8	71 (26.6)	87 (31.9)	23 (17.6)
		Week 16	143 (53.6)	169 (61.9)	38 (29.0)
	PASI 90	Week 3	0 (0.0)	0 (0.0)	0 (0.0)
		Week 8	4 (1.5)	4 (1.5)	0 (0.0)
		Week 16	49 (18.4)	61 (22.3)	6 (4.6)
PPS	PASI 50	Week 3	15 (6.1)	15 (5.9)	2 (1.6)
		Week 8	66 (26.8)	81 (32.0)	22 (17.3)
		Week 16	132 (53.7)	159 (62.8)	37 (29.1)
	PASI 90	Week 3	0 (0.0)	0 (0.0)	0 (0.0)
		Week 8	4 (1.6)	4 (1.6)	0 (0.0)
		Week 16	45 (18.3)	61 (24.1)	6 (4.7)

Table 20 shows the mean change from baseline in the body surface area in the FAS population.

Table 20 – Change from baseline in Body Surface Area, FAS Population

Analysis visit		LAS41008 N=267	Fumaderm N=273	Placebo N=131
Week 3	Mean (%)	-0.5	-0.5	-0.7
	SD	5.02	3.63	4.73
	n	267	273	129
Week 8	Mean (%)	-4.1	-3.5	-2.3
	SD	7.56	6.20	7.59
	n	243	252	128
Week 16	Mean (%)	-13.2	-11.3	-4.9
	SD	12.07	10.25	10.76
	n	190	197	112

Quality of Life endpoint

In Study 1102, after 16 weeks of DMF treatment, a significantly lower mean DLQI was observed in the DMF group (5.4) compared with the placebo group (8.5) with an LS Mean difference of -3.23 (p-value <0.0001) (Table 21).

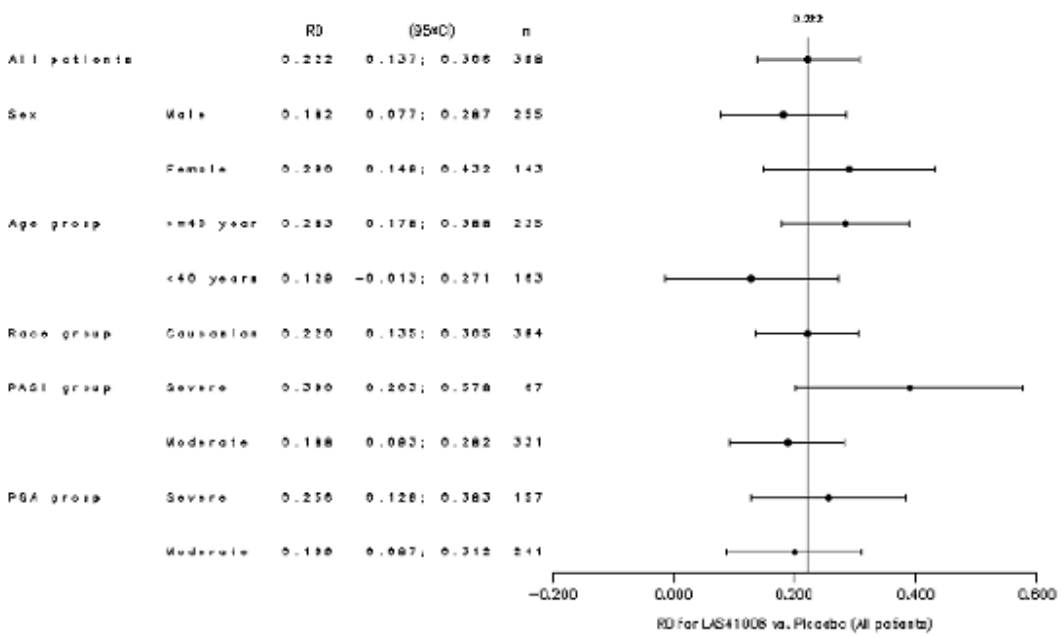
Table 21 – Dermatology Life Quality Index in Study 1102 from Baseline to week 16 (FAS population)

Time point	DMF N=267	Placebo N=131	Fumaderm N=273
Baseline			
n	266	131	270
Mean (SD)	11.3 (6.26)	10.9 (6.49)	12.0 (7.04)
Week 16			
n	253	118	258
Mean (SD)	5.4 (6.07)	8.5 (6.88)	6.0 (7.17)
LS Mean difference (95% CI)	-3.23 (-4.69, -1.78) [a]	--	-0.64 (-1.79, 0.51) [b]
p-value	<0.0001 [a]	--	0.2733 [b]
F1 follow-up visit (2 months post treatment)			
n	139	60	142
Mean (SD)	4.8 (5.57)	7.8 (5.98)	5.4 (6.12)
LS Mean difference (95% CI)	-3.02 (-4.89, -1.16) [a]	--	-0.64 (-2.12, 0.74) [b]
p-value	0.0016 [a]	--	0.3415 [b]

a p-value and CI for DMF - placebo
b p-value and CI for DMF - Fumaderm
CI=confidence interval; DMF=dimethyl fumarate gastro-resistant tablets; FAS = Full Analysis Set; LS Mean=least square mean; n=number of patients with available data; N=total number of patients; SD=standard deviation

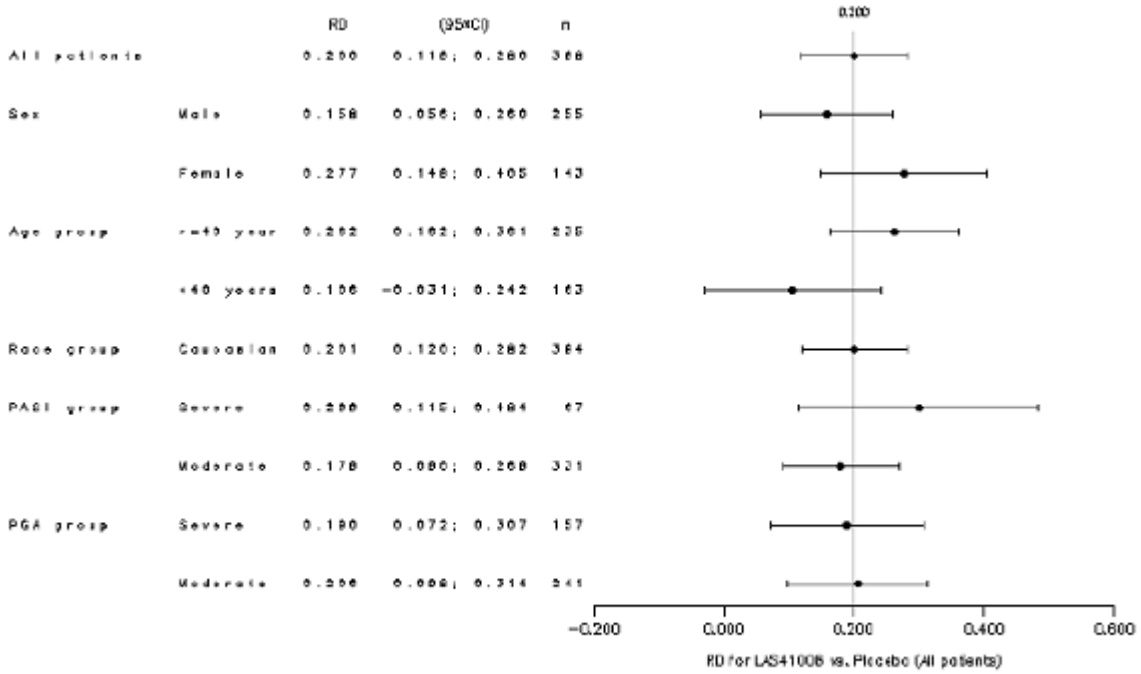
The results of the sub-group analyses for the two co-primary endpoints of PASI75 and PGA are depicted in the figures below:

Figure 7 – Number of patients with PASI 75 at weeks 16 by subgroup in study 1102



CI=confidence interval; n=number of patients; PASI=Psoriasis Area and Severity Index; PGA=Physicians' Global Assessment; RD=risk difference

Figure 8 – Number of patients with clear or almost clear PGA at week 16 by subgroup in study 1102



CI=confidence interval; n=number of patients; PASI=Psoriasis Area and Severity Index; PGA=Physicians' Global Assessment; RD=risk difference

Long-term follow-up

Patients in this study went off treatment at week 16, but were followed up for recurrence (time to relapse), success rate and remission rate.

The treatment phase was completed by 450 of the 699 patients and 369 of these have entered into the follow-up phase. A total of 110 patients – that means only 24.4% of those who completed the treatment phase - completed the 1-year follow-up. Common reasons given for premature study termination after completion of the treatment phase were lack of efficacy (numerically more frequent in the Fumaderm group compared to LAS41008; 32% vs. 25%), withdrawal of consent for personal reasons, and reasons within the category "other".

The topline results are provided below:

Table 22 – Psoriasis area and severity index: total score (LOCF), percent change from baseline, FAS population

		LAS41008 N=267	Fumaderm N=273	Placebo N=131
Week 3	Mean	-11.8	-12.3	-8.2
	Median	-11.1	-10.1	-5.9
	SD	24.19	22.14	18.11
	Min	-87	-78	-58
	Max	127	112	44
	N	267	273	131
Week 8	Mean	-30.9	-33.1	-20.0
	Median	-33.3	-36.4	-20.0
	SD	33.36	31.77	31.20
	Min	-100	-96	-82
	Max	176	113	97
	N	267	273	131
Week 16	Mean	-50.8	-54.1	-27.0
	Median	-57.5	-64.4	-22.5
	SD	41.78	39.94	37.62
	Min	-100	-100	-100
	Max	214	137	74
	N	267	273	131
F1 2 months	Mean	-48.5	-51.6	-27.5
	Median	-56.0	-59.7	-24.6
	SD	41.72	39.87	39.28
	Min	-100	-100	-97
	Max	233	151	70
	N	267	273	131
F2 6 months	Mean	-42.7	-44.2	-25.2
	Median	-47.6	-50.8	-22.8
	SD	41.38	40.60	39.46
	Min	-100	-100	-97
	Max	233	167	70
	N	267	273	131
F3 12 months	Mean	-40.6	-43.6	-27.5
	Median	-44.1	-48.8	-30.3
	SD	41.93	39.19	39.91
	Min	-100	-100	-98
	Max	233	151	70
	N	267	273	131

Table 23 – Treatment success rate, FAS population[7]

Analysis visit	LAS41008 N=267	Fumaderm N=273	Placebo N=131	P-value[1] LAS41008-Placebo	P-value[1] LAS41008-Fumaderm
	n (%)				
Week 3	1 (0.4)	0 (0.0)	0 (0.0)	0.513	0.317
Week 8	15 (5.6)	19 (7.0)	3 (2.3)	0.178	0.415
Week 16	89 (33.3)	104 (38.1)	17 (13.0)	<.001	0.218
F1 2 months	73 (27.5)	89 (32.6)	20 (15.3)	0.009	0.187

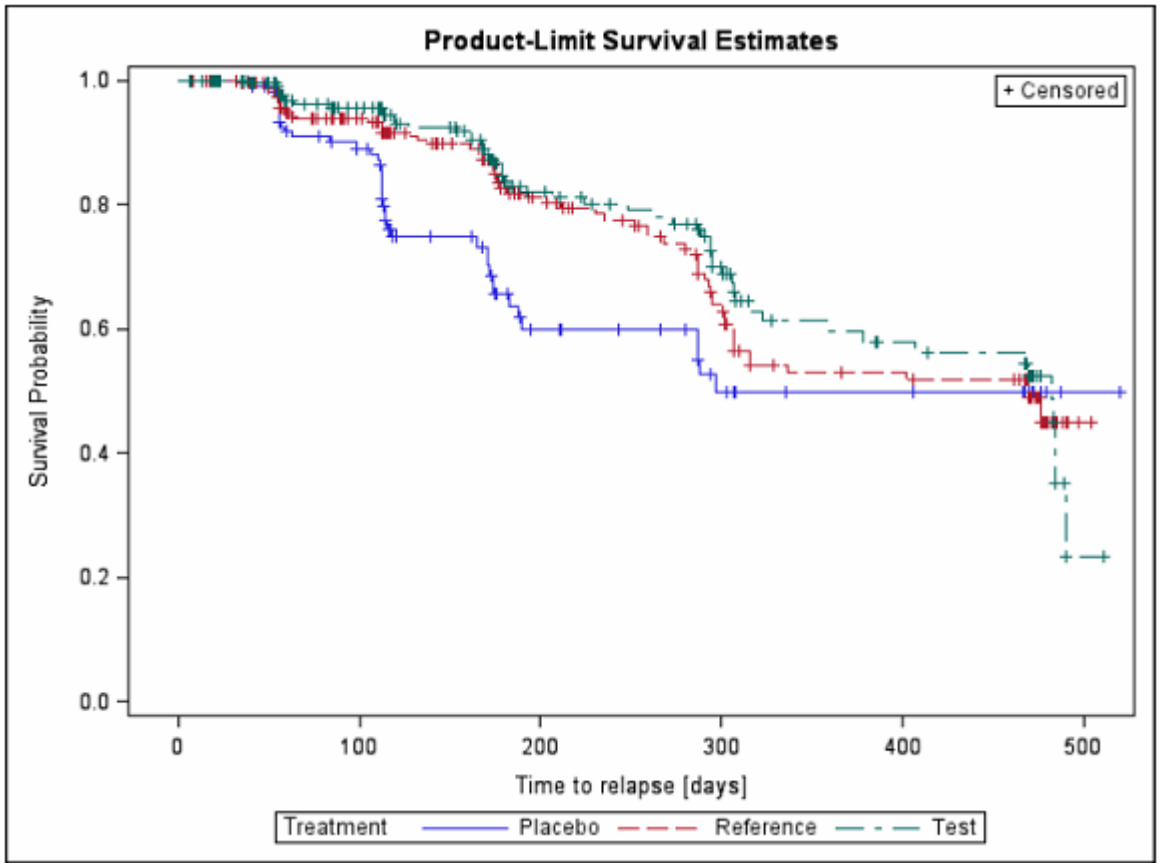
[1] Two-sided p-values derived from Cochran-Mantel-Haenszel test stratified by center

Table 24 – Remission rate, FAS population[8]

Analysis visit	LAS41008 N=267	Fumaderm N=273	Placebo N=131	P-value[1] LAS41008-Placebo	P-value[1] LAS41008-Fumaderm
	n (%)				
Week 3	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Week 8	1 (0.4)	0 (0.0)	0 (0.0)	0.513	0.317
Week 16	17 (6.4)	21 (7.7)	1 (0.8)	0.019	0.563
F1 2 months	16 (6.0)	19 (7.0)	0 (0.0)	0.005	0.602

NA: not applicable
[1] Two-sided p-values derived from Cochran-Mantel-Haenszel test stratified by centre

Figure 7 – Time to relapse, Kaplan-Meier curve, FAS population



Ancillary analyses

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 25 - Summary of Efficacy for trial 1102

Title: A multi-center, randomized, double-blind, 3-arm, 16 week, adaptive phase III clinical study to investigate the efficacy and safety of LAS41008 vs LASW1835 and vs placebo in patients with moderate to severe chronic plaque psoriasis		
Study identifier	1102	
Design	Randomized, double-blind, 3-arms (Skilarence vs. active control and vs. placebo) phase III study; randomization 2:2:1, parallel groups, double dummy technique until week 3 for the 30 mg tablets. Adaptive design with 1 planned interim analysis. After 16 weeks treatment (short-term efficacy) subsequently 12 months of off treatment for follow up. In case of relapse and need for new systemic treatment, a final follow-up visit would be conducted prior to initiation of therapy. Analysis of time to relapse and time to rebound by Kaplan-Meier estimates.	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	16 weeks not applicable 12 months (off treatment)
Hypothesis	Primary Objectives: The proportion of subjects achieving PASI 75 and the proportion of subjects achieving a score of “clear” or ”almost clear” in PGA (Physician’s Global Assessment) at Week 16 were tested to show **superiority** of **Skilarence versus placebo**. Further, PASI 75 was tested to show **non-inferiority** of **Skilarence versus Fumaderm.**	
Treatments groups	test product Skilarence (DMF)	DMF, tablets, 16 weeks, n= 280 (randomized) The dosing-scheme in regard to DMF was identical for the test drug and the active control: Daily dose Week 1 30 mg DMF Week 2 60 mg DMF Week 3 90 mg DMF Week 4 120 mg DMF Week 5 240 mg DMF Week 6 360 mg DMF Week 7 480 mg DMF Week 8 600 mg DMF Week 9-16 720 mg DMF Nevertheless in both the test product and active control group individual doses were applied. The maximum dose was DMF 720 mg/day. In case of intolerance reduction to the last tolerated dose and maintenance of this dose until week 16. In case of treatment success before DMF 720 mg (PGA “clear” or “almost clear”) → then no further increase and reduction to individual maintenance dose. In week 1 to 4 no dose reduction was possible.

	active control Fumaderm (DMF/MEF)		DMF/MEF, tablets, 16 weeks, n= 286 Same dosing-scheme in regard to DMF as for the test drug: Daily dose Week 1 30 mg DMF Week 2 60 mg DMF Week 3 90 mg DMF Week 4 120 mg DMF Week 5 240 mg DMF Week 6 360 mg DMF Week 7 480 mg DMF Week 8 600 mg DMF Week 9-16 720 mg DMF
	placebo		Placebo, tablets, 16 weeks, n= 138
Endpoints and definitions	Co-Primary endpoints	week 16 compared to baseline	• Superiority of DMF vs placebo by proportion of patients achieving PASI 75 (= a 75% reduction in PASI) • Superiority of DMF vs placebo by proportion of patients achieving a score of “clear” or ”almost clear” in PGA • Non-inferiority of DMF vs DMF/MEF by proportion of patients achieving PASI 75

	Secondary endpoints		• Proportion of patients achieving PASI 75 at Week 3 and 8 • Proportion of patients achieving PASI 50 and PASI 90 at Week 3, 8, and 16 • Proportion of patients achieving a score of “clear” = 0 or ”almost clear” = 1 in the PGA at Week 3 and 8 • Percent change in PASI at Week 3, 8, 16 and F1 (=follow-up visit 2 months after end of treatment) • PGA score at Week 3, 8, 16 and F1 • BSA (Body Surface Area) at Week 3, 8, and 16 • Treatment success rate at Week 3, 8, and 16 (treatment success = patients achieving either “clear” or “almost clear” score in PGA and/or PASI 90) • Remission rate at Week 3, 8, and 16 (remission= “clear” in PGA) • Time to relapse (relapse = reduction of the maximal improvement by ≥50% based on PASI). Two time-to-relapse analyses were conducted: a) relapse occurring at any time during the study duration (on-treatment + 12 months off treatment [in this initial report only data up to F1 are available]) b) relapse occurring within 2 months after last study drug intake. • Time to rebound (rebound = worsening of psoriasis over baseline value (PASI≥125%) • Patient Benefit Index (PBI) based on the Patient Need Questionnaire (PNQ) and Patient Benefit Questionnaire (PBQ) at Week 16 and F1 Quality of life variable: • Dermatology Life Quality Index [DLQI] at week 16 and F1
Database lock	The last patient completed the follow-up visit F1 (which was 2 months after the end of treatment) on 23 December 2014. On this date the database was closed for an analysis up to visit F1 (Clinical Study Report, version 1.0). An updated integrated study report was submitted after analysis up to the last follow-up visit at month 12 (last patient last visit on 19 Oct 2015; Integrated Clinical Study Report, 27 June 2016).		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Per protocol and FAS (full analysis set= randomized patients with at least one dose of study medication and at least one measurement of PASI and PGA) Evaluation after 16 weeks of treatment compared to baseline			
Descriptive statistics	Treatment group	Skilarence (DMF)	Fumaderm (DMF/MEF)	Placebo
	Number of subject	267 (FAS) 246 (PPS)	273 (FAS) 253 (PPS)	131 (FAS) 127 (PPS)
	PASI 75 (% responders)	37.5% (FAS) 37.8% (PPS)	40.3% (FAS) 42.7% (PPS)	15.3% (FAS) 15.0% (PPS)
	PGA (% responders)	33.0% (FAS) 32.5% (PPS)	37.4% (FAS) 39.5% (PPS)	13.0% (FAS) 12.6% (PPS)
Effect estimate per comparison		Comparison groups	Skilarence (DMF) vs. Placebo	
	Co-Primary: PASI 75	Difference in responder proportions	22.2% (FAS) 22.8% (PPS)	
		99.24% confidence interval	10.7%, 33.7% (FAS) 11.0%, 34.7% (PPS)	
		P-value	< 0.0001 (FAS, PPS)	
	Co-Primary: PGA	Difference in responder proportions	20.0% (FAS) 19.9% (PPS)	
		99.24% confidence interval	9.0%,31.0% (FAS) 8.7%,31.1% (PPS)	
		P-value	< 0.0001 (FAS, PPS)	
		Comparison groups	Skilarence (DMF) vs. Fumaderm (DMF/MEF)	
	Co-Primary: PASI 75	Difference in responder proportions	-2.8% (FAS) -4.9% (PPS)	
		99.24% confidence interval	-14.0%,8.4% (FAS) -16.6%,6.8% (PPS)	
		P-value (NI test)	0.0003 (FAS) 0.0024 (PPS)	
Notes	The study had an adaptive two-stage design applying the Bauer and Köhne method allowing for sample size adjustment after stage 1. One-sided p-values resulting from analysis of stage 1 and stage 2 were combined based on the Fisher's combination test as the product of both p-values and comparing this product with a significance level of 0.0038. The 99.24% Wald confidence intervals are provided for descriptive purposes and are not consistent with Fisher's combination test. The analyses based on the FAS and PP were considered of equal importance. Missing values were replaced by last observation carried forward (LOCF). The non-inferiority margin for the comparison of Skilarence (DMF) vs. Fumaderm was -15%.			
Analysis description	**Secondary analysis**			

Descriptive statistics	Treatment group	Skilarence (DMF)	Fumaderm (DMF/MEF)	Placebo
	PASI 75 at week 8 (% responders)	7.5 (FAS) 6.9 (PPS)	8.4 (FAS) 8.7 (PPS)	5.3 (FAS) 4.7 (PPS)
	PGA at week 8 (% responders)	5.6 (FAS) 4.9 (PPS)	7.0 (FAS) 7.5 (PPS)	2.3 (FAS) 1.6 (PPS)
	Remission rate at week 16	6.4 (FAS) 6.5 (PPS)	7.7 (FAS) 8.3 (PPS)	0.8 (FAS) 0.8 (PPS)
	DLQI at week 16/ EoT (mean, SD)	n=253 5.4 (6.1)	n=258 6.0 (7.2)	n=118 8.5 (6.9)
	DLQI at F1 (mean, SD)	n=139 4.8 (5.6)	n=142 5.4 (6.1)	n=60 7.8 (6.0)
Effect estimate per comparison		Comparison groups	Skilarence (DMF) vs. Placebo	Skilarence (DMF) vs. Fumaderm (DMF/MEF)
	PASI 75 at week 8	Difference in responder proportions (%)	2.1 (FAS) 2.2 (PPS)	-0.9 (FAS) -1.8 (PPS)
		95% CI	-2.8, 7.1 (FAS) -2.7, 7.1 (PPS)	-5.5, 3.6 -6.5, 2.9
		P-value	0.42 (FAS) 0.41 (PPS)	0.69 (PPS) 0.46 (PPS)
	PGA at week 8	Difference in responder proportions	3.3 (FAS) 3.3 (PPS)	-1.3 (FAS) -2.6 (PPS)
		95% CI	-0.4, 7.1 (FAS) -0.2, 6.8 (PPS)	-5.4, 2.7 (FAS) -6.8,1.6 (PPS)
		P-value	0.13 (FAS) 0.11 (PPS)	0.52 (FAS) 0.22 (PPS)
	Remission rate at week 16	Difference in remission proportions	5.6 (FAS) 5.7 (PPS)	-1.3 (FAS) -1.8 (PPS)
		95% CI	Not reported	Not reported
		P-value	0.02 (FAS) 0.02 (PPS)	0.56 (FAS) 0.52 (PP)
	DLQI at week 16/ EoT	Difference in LS Means	-3.23	-0.64
		95% CI	-4.69, -1.78	-1.79,0.51
		P-value	< 0.0001	0.27
	DLQI at F1	Difference in responder LS Means	-3.02	-0.69
		95% CI	-4.89,-1.16	-2.12,0.74
		P-value	0.0016	0.34
	Analyses of missing DLQI values were done using an observed cases approach, i.e., no imputation technique was applied for missing observations. In addition, as a post-hoc analysis for DLQI, 2 different methods for handling missing data were applied as sensitivity analyses (baseline observation carried forward [BOCF] and multiple imputation).			

Analysis performed across trials (pooled analyses and meta-analysis)

There is only one pivotal study (study 1102) evaluating efficacy and safety of DMF gastro-resistant tablets, as such no pooled analyses and meta-analysis were performed.

Clinical studies in special populations

There are no clinical studies in special populations (e.g. elderly, children) and no discussion in this regard has been presented as there is no significant data in special populations from published literature as well.

Supportive studies

Placebo controlled studies with DMF

Nieboer 1989, study III – is a double-blind, 16-week study that assessed the efficacy and safety of DMF 240 mg/day (22 patients) with placebo (20 patients) for the treatment of plaque psoriasis (Nieboer, 1989, Study III). All patients in the DMF group were treated with capsules filled with 60 mg enteric coated granulate of DMF. The proportion of patients with improved psoriasis measured by PASI 25 to 50 and PASI >50 scores was significantly greater in the DMF group (27% and 27%, respectively) compared with placebo (5% and 0%, respectively; $p<0.01$), and improvement started within 6 weeks of treatment. Two of 3 patients with psoriatic arthritis also reported improvement. Pre-existing nail lesions were observed in 9 patients in the DMF group; an improvement was observed in 2 patients.

Another study by the same author Nieboer (Nieboer, 1990) which was not a placebo controlled study but compared DMF to DMF/MEF, using a higher dose of 480 mg/day DMF in both groups. This study is an active-controlled study, but has been discussed here as it was useful to compare and present the results of the studies from the same author together. This study showed that roughly 50% of patients achieved PASI 50 in both the DMF and DMF/MEF groups (table 26), which was higher than the response to DMF 240mg/day. There were no statistically significant differences between the DMF group (22 patients) and the DMF/MEF (87 mg calcium, 5 mg magnesium and 3 mg zinc) group (23 patients) in the proportion of patients with improved psoriasis from baseline to Week 16, measured by PASI <25 (22% vs. 4%, respectively), PASI 25-50 (14% vs. 9%, respectively), and PASI >50 (45% vs. 52%, respectively) (the p-value was not provided in the article).

Table 26 – Percentage improvement in PASI after Treatment with DMF or DMF/MEF (Nieboer studies)

Author	Treatment Duration	Percentage of Patients		
		PASI >50% Improvement	PASI 25-50% Improvement	PASI <25% Improvement
Nieboer 1989 – Study III	16 weeks			
DMF 240 mg/day (n=22)		27%	27%	18%
Placebo (n=20)		0%	5%	60%
Nieboer 1990	16 weeks			
DMF 480 mg/day (n=22)		45%	14%	22%
DMF/MEF 480 mg/day (n=23)		52%	9%	4%
Nieboer 1989 – Study V (open label)	4-9 months			
DMF 240 mg/day (n=56)		33%	22%	25%

DMF=dimethyl fumarate, MEF=mono ethyl fumarate; n=number of patients evaluated, PASI=Psoriasis Area and Severity Index

Placebo controlled studies with Fumaderm and/or other preparations containing DMF

The Altmeyer (1994) study was a German multicentre randomized, double-blind study conducted in 100 patients with psoriasis (predominantly male) randomised (1:1) to either Fumaderm or placebo. Patients were treated with ascending doses of Fumaderm (30 mg in Week 1, 60 mg in Week 2, 120 mg in Week 3, up to a maximum of 720 mg in Week 16) or matching placebo. In the Fumaderm group, the reduction in PASI score from baseline (21.57) to Week 16 (10.77) was statistically significant compared with placebo (approximately 24 at baseline to approximately 23 at endpoint; $p<0.0001$). A significant improvement in clinical symptoms of arthralgia was observed in the Fumaderm group by the end of the study compared with the placebo group ($p<0.002$); however, no statistically significant differences were observed between treatment groups for changes in nail deformities

Table 27 – Decrease in PASI after treatment in controlled studies with DMF/MEF combinations

Treatment group	Treatment Duration	Mean PASI score		Between-treatment difference
		Baseline	Endpoint	
Altmeyer 1994				
Fumaderm up to 720 mg/day (n=49)	16 weeks	21.57	10.77	p<0.0001
Placebo (n=50)		~24	~23	

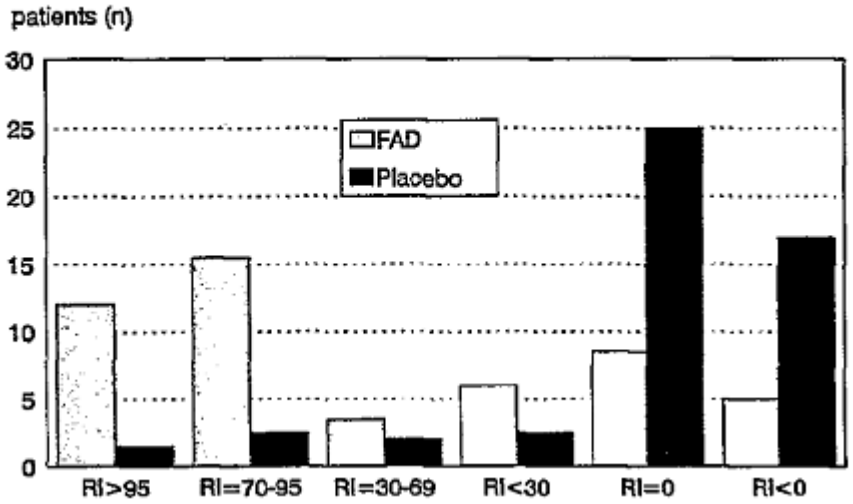
The remission index based on PASI score was defined as below for this study

Table 28 – Remission indexes based on the PASI score

	Remission index
Complete remission	>95%
Good improvement	70%-95%
Moderate improvement	30%-69%
Slight improvement	<30%
No change	0%
Deterioration	<0%

The results from this study on the above remission index is graphically shown as below

Figure 8 – Physician's judgment of the therapeutic effect of fumaric acid derivatives (FAD) an placebo. RI, Remission index



The Nugteren-Huying (1990) study was conducted in 39 patients randomised to a non-specified DMF/MEF combination (120 mg DMF, 87 mg calcium MEF, 5 mg magnesium MEF and 3 mg zinc MEF) or an octyl hydrogen fumarate (OHF)/MEF combination (284 mg OHF, 5 mg magnesium MEF, and 3 mg zinc MEF) or placebo. However the dose of DMF evaluated is not in line with the proposed dose. Further a comparison of the proposed formulation to the formulation studied is not available. The number of patients randomised to each arm was not reported. Of the 34 patients who completed the study, the mean percentage of the BSA with psoriasis was reduced in the DMF/MEF group from 21% at baseline to 6.7% at Week 16; this effect was significantly larger than the reductions obtained in the other treatment groups ($p<0.01$). At Week 16, the mean scores for infiltration and scaling were significantly lower in patients in the DMF/MEF group compared with the other treatment groups ($p<0.01$). Complete clearance was achieved in 6 DMF/MEF-treated patients and 3 patients showed an improvement, whereas no placebo or OHF/MEF patients had complete clearance, and only 1 placebo patient showed improvement

Active comparator controlled studies with DMF or other DMF-containing preparations

In the Kolbach (Kolbach, 1992) 2-year, non-randomised study comparing the efficacy and safety of DMF monotherapy (240 mg/day, 129 patients) with Fumaderm (480 mg/day, 67 patients), PASI >75 was achieved in 48% of the Fumaderm patients and 32% of DMF patients after 3 to 6 months of treatment. The percentage of responders declined to 18% in the DMF group after 24 months but remained about the same in the Fumaderm group (46%). These differences were statistically significant. The first signs of improvement were noted after 3 weeks. Improvement of nail dystrophy occurred in about half the patients after several months of therapy. A decrease in arthralgias was noted in 27% of the DMF group and 50% of the Fumaderm group.

Table 29 – Results of treatment with DMFAE or FAC per observation after 3 months

Period (mo)	DMFAE treatment			FAC treatment		
	No.	Results		No.	Results	
		Sufficient*	Insufficient†		Sufficient	Insufficient
3-6	104	41 (32%)‡	63 (49%)	60	32 (48%)	28 (42%)
6-12	68	41 (32%)	27 (21%)	51	31 (46%)	20 (30%)
12-18	45	34 (26%)	11 (9%)	48	34 (51%)	14 (21%)
18-24	30	23 (18%)	7 (5%)	39	31 (46%)	8 (13%)

*Sufficient: Improvement more than 75%.
†Insufficient: Exacerbation, no improvement, or improvement less than 75%.
‡Percentages of the entire patient population.

Table 30 – Data of patients treated with DMFAE (n=129) and FAC therapy (n=67)

Period (mo)	DMFAE treatment*			FAC treatment†		
	Treated (per period)	Discontinued (per period)	Discontinued (cumulative)	Treated (per period)	Discontinued (per period)	Discontinued (cumulative)
3	129 (100%)	25 (19%)	25 (19%)	67 (100%)	7 (11%)	7 (11%)
6	104 (81%)	36 (28%)	61 (47%)	60 (90%)	9 (13%)	16 (24%)
12	68 (53%)	23 (18%)	84 (65%)	51 (76%)	3 (4%)	19 (28%)
18	45 (35%)	15 (12%)	99 (77%)	48 (72%)	9 (13%)	28 (42%)
24	30 (23%)	9 (7%)	108 (84%)	39 (58%)	2 (3%)	30 (44%)

*Dimethylfumaric acid ester, 120 to 240 mg/day.
†Fumaric acid combination (see text). Dosage of DMFAE: 240 to 480 mg/day.

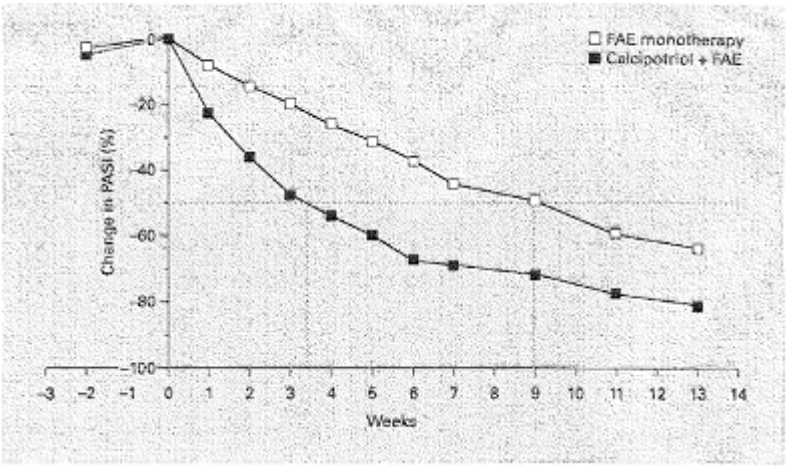
In the Fallah Arani (2011**)** study, Sixty patients with moderate to severe psoriasis vulgaris were randomly assigned to treatment for 16 weeks with either methotrexate (30 patients; 15 mg per week) or fumarates (30 patients; 30 mg, followed by 120 mg according to a standard progressive dosage regimen) and were followed up for 4 weeks. The primary endpoint with respect to the efficacy was the difference in mean change from baseline in Psoriasis Area and Severity Index (PASI) after 12 weeks of treatment. There were no statistically significant differences between the DMF/MEF group and MTX groups for the change in PASI score from baseline to Week 12 or the proportion of patients with PASI ≥ 50, PASI ≥ 75 or PASI ≥ 90 from baseline to Week 12. A total of 24 patients (89%) treated with DMF/MEF and all MTX patients reported AEs during the study. More DMF/MEF patients (48%) than MTX patients (7%) reported flushing, while more MTX patients (26%) than DMF/MEF patients (4%) reported influenza-like symptoms. Four (15%) MTX patients had to stop treatment due to highly elevated liver enzymes (200-300% over baseline), which returned to normal within 4 to 8 weeks after stopping treatment.

Table 31 – Overview of results for the Fallah Arani (2011) study

Author	Treatment duration	Percentage of patients			
		PASI ≥90%	PASI ≥75%	PASI ≥50%	PASI <50% or worsening
Fallah Arani 2011					
DMF/MEF 720 mg/day (n=26)	12 weeks	4%	19%	42%	NR
MTX 15 mg/week (n=25)		8%	24%	60%	NR
DMF/MEF 720 mg/day (n=18)	20 weeks	6%	39%	72%	0%
MTX 15 mg/week (n=19)		11%	32%	53%	16%

Gollnick (2002) reported a prospective, randomised, double-blind, 13-week, multicentre (Germany and the Netherlands) study assessing Fumaderm treatment (up to 1075 mg/day) with or without calcipotriol ointment in 134 patients with severe psoriasis. In both treatment groups the PASI was lower at the end of treatment compared with baseline. The mean percentage change in PASI (adjusted for the effect of centre and baseline PASI) was -76.1% in the combination group and -51.9% in the group with Fumaderm alone ($p<0.001$ for the difference between groups). While both treatment groups improved based on the investigators' assessment and the patient's assessments at the end of treatment, the results showed that Fumaderm plus calcipotriol had a more favourable effect than Fumaderm alone ($p\leq 0.001$ for the difference between groups).

Figure 9 – Percentage change in PASI at each visit (ITT population)



Persistence of efficacy and/or tolerance effects

There is no evidence of tolerance and/or reduction in the effect achieved with DMF gastro-resistant tablets over 16 weeks of treatment in Study 1102, nor in any of the published long-term studies with FAEs. The percentage reduction in PASI total score over time that was achieved during the 16 weeks of treatment with DMF in Study 1102 persisted after stopping treatment for a further 8 weeks of follow-up (Figure 2.7.3-3). Published reports confirmed the ability of FAEs to achieve and maintain the beneficial effects for up to 5 years of treatment, by looking at clinical assessments, reductions in PASI, and improvements in PGA and/or BSA (Kolbach, 1992; Thio, 1995; Lijnen, 2015; Raschka, 1999; Thaçi, 2013; Reich, 2009; Brewer, 2007; Fika, 2006; Harries, 2005). In addition, some of the retrospective studies reported on patients who had been refractory to previous anti-psoriatic treatments and who achieved full clearance of their psoriasis with FAE treatment that persisted over years of continuous treatment (Fika, 2006; Harries, 2005). The brief overview of published studies providing long-term efficacy data is provided below.

Table 32 - Overview of published studies providing long-term efficacy data

Author	Patients	Design	Study treatment and dose regimen	No. of patients treated	Duration of treatment	Key efficacy findings
Altmeyer 1996	• Severe psoriasis vulgaris	Open, single-centre, prospective, long term, study	**Fumaderm** Initial dose of 30 mg/day, increasing by 1 tablet each week for 3 weeks. If tolerated, 120 mg tablets up to 720 mg/day	83	12 months	• **PASI:** Mean reduction of 76% in PASI from Baseline to 12 months • **Complete remission** in 35 (42.2%) patients, improvement in 24 (28.9%) patients
Balasubramaniam 2004	• Severe psoriasis • Failed to respond to topical therapy and/or to phototherapy alone.	Retrospective	The existing treatment regimen in each patient was supplemented with **Fumaderm.** The dose was adjusted according to the regimen derived from the published guidelines, patient response and tolerability	12	3-19 months	• 8 patients had improved **clinical change** in psoriasis as assessed by an investigator, 2 were well controlled and 1 was worse (this patient interrupted the treatment due to overseas travel and diarrhoea, having previously improved) • 9 patients received FAE in combination with other systemic therapies. 7 achieved useful overall reductions in the dose of the other drugs • There was no evidence of drug interactions
Burden-Teh 2013 (abstract)	• Refractory to conventional therapy	Retrospective, single centre	**Fumaderm** Dose NR	35	8 months	• 54% had an **excellent response** • 28% had a **partial response** • 6% had a **poor response**
Inzinger 2013	• Patients treated systemically for chronic plaque psoriasis.	Observational retrospective, cohort study of clinical data extracted from the Psoriasis Registry Graz	**FAE**: patients dosed according to a standard progressive regimen-initial dose of 30 mg daily increased to a maximum of 720 mg DMF daily in week 9, depending on individual tolerance **or** **Methotrexate** used either orally or subcutaneously Oral methotrexate: median initial dose was 10 mg after which the dose was gradually increased to a maximum median dose of 20 mg once a week Subcutaneous methotrexate: median initial dose was 10 mg after which the dose was gradually increased to a maximum median dose of 20 mg once a week	FAE: 200 Methotrexate: 72	12 months	In the ITT population, the proportion of FAE-treated patients (n = 200) who had shown efficacy after 3 months was as follows: • **Complete remission:** 1% of patients • **PASI 90:** 5% of patients • **PASI 75:** 27% of patients • **PASI 50:** 44% of patients • There were no statistically significant differences in the efficacy of methotrexate vs FAE treatment at any time point

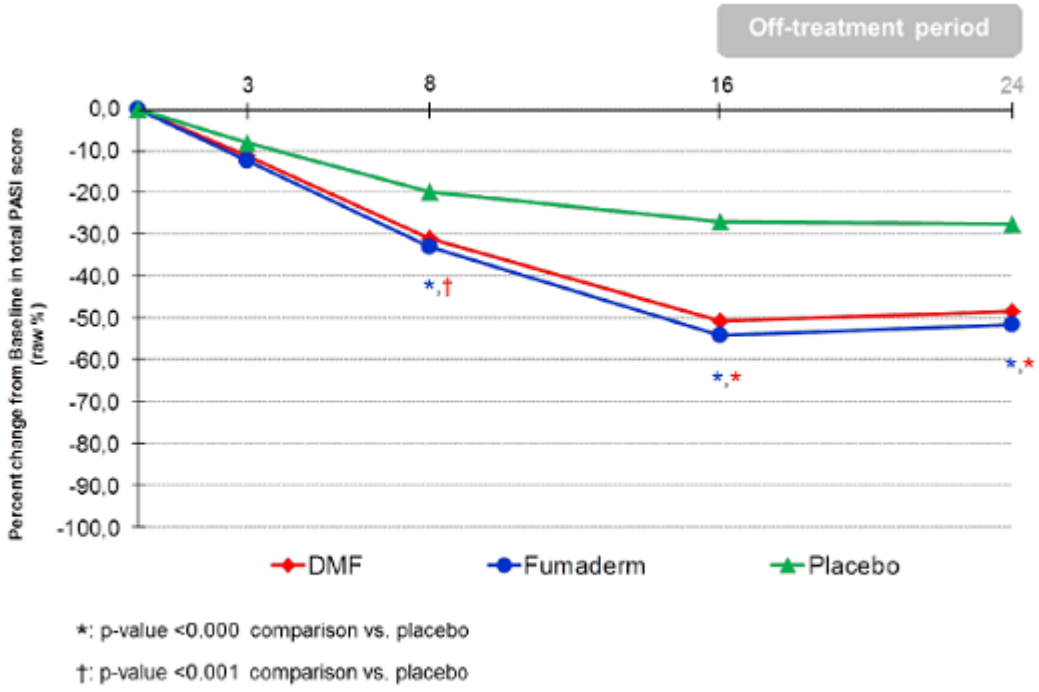
Lijnen 2015	• Moderate to severe psoriasis • Insufficient clinical response to topical therapies, phototherapy, and/or systemic oral anti-psoriasis treatments • Adults (≥18 years)	Prospective, single-blinded, follow-up study	**DMF**: Initial dose of 30 mg/day. Daily dose was increased by 30 mg every week, up to a dose of 240 mg/day. Thereafter, daily dose was increased by 120 mg every third week until a sufficiently satisfactory effect. Dosage was then gradually reduced to a minimum maintenance dose (ie, maintenance phase). Maximum daily dose was 1680 mg.	176	Median duration of 28 months	• For the 122/176 patients with available **PGA** scores, the mean PGA score decreased from 3.3 at baseline to 1.6 at the maintenance phase. This improvement was significant by 1.7 out of 5 points ($p<0.001$).
Litjens 2003	• Moderate or severe psoriasis	Open, prospective, longitudinal cohort study	**DMF/MEF:** 120 mg DMF, 87 mg Ca MEF, 5 mg Mg MEF, 3mg Zn MEF Dose was increased to a daily max of 720 mg at 10 weeks. After remission, the dosage was reduced to a lower level, usually 240 mg-360 mg daily	12	24 months	• The **PASI** scores of all patients significantly decreased after 3 months of FAE therapy • In 11 of 12 patients the max. decrease in **PASI** score was reached within 6 months of therapy, after which the PASI score remained more or less constant, at about 20% of its initial value
Reich 2009	• Psoriasis patients treated continuously with FAE for at least 24 months, or for 36 months with interruptions of no longer than 6 months.	Retrospective, multi centre, cross-sectional	In the initial phase (therapy weeks 1–3) 96.3% prescribed **Fumaderm** initial according to the recommended standard dosage scheme with an increase of 1 tablet per week. In the subsequent dosage phase (therapy weeks 4–9) an increase of Fumaderm by 1 tablet per week was performed in 86.4% of patients. At the end of the dosage phase 12.6% of patients were being treated with less than 3 tablets daily, 25.2% with 3 tablets, 16.6% with 4 tablets, 10.3 with 5 tablets. 34.9% with 6 tablets and 0.4% with more than 6 tablets daily	984	24 months continually or at least 36 months with interruptions (sum of therapy interruptions totalling not more than 6 months)	• After 3 months of therapy, 30.8% of patients were "**markedly improved**" or "**clear**" and an additional 50% of patients "slightly improved" • After 6 months of therapy 67% of patients were "markedly improved" or "clear"; after 1 year this degree of improvement was documented in 76% of patients • At the end of the documentation time period (24 months or >36 months) 80% of patients were markedly improved or clear • Among patients with additional **nail psoriasis** this proportion was 63%, among patients with additional **joint involvement** 40% (markedly improved or clear) • A reduction of mean PASI from 22.7 before initiation of therapy to 4.8 after 36 months
Thaçi 2013	• Psoriasis patients treated continually for at least 6 weeks with FAE • Had at least 1 comorbidity requiring treatment	Multi centre, retrospective, cross-sectional study.	**Fumaderm** plus at least 1 co-medication Dose NR	69	Mean duration of 27.4 months of continuous treatment	• After 3 months of therapy, using Physician's Global Assessment, psoriasis was rated as "**marked improved**" or "**clear**" in 33% of the patients and in a further 55 as "slightly improved" • After 1 year this degree of improvement was achieved in 77% • After 2 years this degree of improvement was achieved in 75% • Efficacy proved to be independent of the number of co-medications administered

Thio 1995	• Stable plaque type psoriasis	Long-term, follow-up study	**Fumaderm** 120 mg tablets. Dosage gradually increased to a max of 720 mg/day Additional topical antipsoriatic therapy/UVB phototherapy was used.	83	≥6 months uninterrupted	• 26/52 patients had very good **improvement**, 15 patients had good improvement, 10 patients had moderate improvement and1 patient had no improvement • There was a significant decrease in the percentage of **involved BSA** from baseline to final evaluation
Walker 2014	• Mild, moderate, or severe psoriasis • Adults ≥18 years	Prospective, multicentre	The mean dosage of **Fumaderm** was 2.8 tablets per day	249	12 months	• The mean **PASI** score decreased from 16.83 to 5.61 after 12 months of investigation (overall PASI reduction of 66.6%) • The overall mean **DLQI** score improved 67.2% from a baseline score of 9.95, whereby the quality of life correlated with the severity of the psoriasis • The mean **PGA** score decreased from 2.74 at baseline to 1.52 after 12 months of treatment

In fact, the published literature provides data that indicate sufficient treatment duration is needed to achieve the full effect of DMF treatment. The Kolbach (1992), Brewer (2007), and Harries (2005) papers reported that an initial response became apparent after between 3 weeks and 3 months. However, several studies have reported that the efficacy continues to improve over time. After an initial response, Harries (2005) reported a mean time to clearance of 15.2 weeks. Boesken (1998) reported that the skin status improved from grade 6 for all patients to grade 2.5 within 3 months and to grade 1.8 after 6 months. The Lijnen (2015) paper reports that patients had achieved sufficient effect and established a maintenance dose after 8 months of treatment with DMF monotherapy. The Inzinger (2013), Reich (2009), and the Kolbach (1992) studies show that the proportion of patients achieving PASI 75/PASI 90 or a PGA score of markedly improved or clear peaked only after 12 months and persisted with long-term treatment.

Data on the incidence of relapse and rebound up to the F1 follow-up visit, 2 months after stopping treatment showed that the DMF gastro-resistant tablets group had a similar incidence of either a relapse (10.1%) or a rebound (1.1%) to that of the Fumaderm group (relapse: 12.5%, rebound: 2.2%) and the incidence in both active treatment groups was much less that that with placebo (relapse: 27.5%, rebound: 9.3%). The percent change in PASI total score in study 1102 is depicted in the below diagram. Additional follow-up data for up to one year showed a similar trend with substantial efficacy retained up to 12 months follow-up off-treatment (treatment stopped-week16); however this should be interpreted with caution as only a small proportion (around 24%) of patients completed one year follow-up.

Figure 10 – Percentage change in PASI total score in study 1102



Patients did not receive study treatment after Week 16.
DMF=dimethyl fumarate gastro-resistant tablets; PASI=Psoriasis Area and Severity Index

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

This application is supported by a single pivotal study.

The dosing regimen in both the LAS41008 and Fumaderm arms was identical and in line with the approved dose of Fumaderm and included a dose-titration phase to improve tolerability. The maximum dose allowed was 720mg/day of DMF for both active treatments. There are no dose-finding studies conducted by the applicant. The dose regimen of Fumaderm appears to be empirical and there is sufficient evidence from literature to support the proposed starting dose, maximum daily dose and the weekly dose-escalating regimen. Nevertheless, as according to in vitro and clinical data the main antipsoriatic activity is driven by DMF, LAS41008 and Fumaderm have the same content of DMF and the pivotal study compares LAS41008 to Fumaderm, a dose-finding study is not considered necessary.

The study design is appropriate for the objectives. It is generally in line with the CHMP guideline on psoriasis and is in line with the design agreed in the Scientific Advice procedures. Although Fumaderm is only approved in Germany and not as widely used as other authorised systemic therapies like methotrexate, ciclosporin and retinoids, the choice of the active comparator is understood and accepted as the objective is to establish a bridge to the existing literature with Fumaderm to support extrapolation of certain aspects of this evidence. The proposed treatment duration of 16 weeks is adequate for demonstration and comparison of efficacy.

The study was in moderate to severe psoriasis with minimum criteria for baseline severity based on PASI, PGA and BSA. The study excluded patients with significant gastrointestinal problems, active infectious disease, immunosuppression, severe liver or kidney disease, haematological abnormality and if on systemic treatment without adequate washout. While these are appropriate in terms of avoiding confounding of the findings due to the known safety profile of DMF, the applicant has appropriately reflected the available information from literature in the SmPC.

The study sample size for demonstration of superiority was around 175, however to fulfil the objective of demonstrating non-inferiority, the study planned to include a far greater sample size of 690 patients.

The efficacy analyses based on the full analysis set (FAS) including all patients with at least one post-baseline measurement of PASI, PGA and the per protocol set (PPS) excluding major protocol violators were considered of equal importance. Discontinuation of study was not considered a protocol violation. A completer analysis for the primary endpoints as an additional sensitivity analysis was provided during the procedure.

The co-primary efficacy variables (the proportion of patients achieving PASI 75 at Week 16 and the proportion of patients achieving a score of “clear” or “almost clear” in the PGA at Week 16) were analysed using the Wald test for risk differences (difference in the proportion of responders). The study had a two-stage adaptive design applying the Bauer and Köhne method with two stages allowing for sample size adjustment after stage 1. The Bauer and Köhne method controls the type 1 error adequately taking the two-stage design into account. Further, confidence intervals taking the two-stage design into account consistent with the Bauer-Köhne method were provided during the procedure.

Superiority of DMF vs. placebo in both co-primary endpoints and non-inferiority of DMF vs. Fumaderm in PASI 75 were the primary comparisons (only if both superiority comparisons led to a rejection of the null hypothesis (in the FAS and PPS population), non-inferiority for PASI 75 was to be tested). For the non-inferiority of DMF compared with Fumaderm for PASI 75 after 16 weeks of treatment, a non-inferiority margin of 15% was set in line with EMA/CHMP Scientific Advice. A similar non-inferiority margin was used for PGA.

As substantial drop-out was observed, Kaplan-Meier plots of time to drop-out by treatment arm were provided during the procedure to support assessment of the influence of missing data on the results. Last observation carried forward (LOCF) up to Week 16 was used for missing data from PASI and PGA assessments. For the primary efficacy endpoints, a sensitivity analysis was performed setting patients with missing data as non-responders, which yielded similar results as the analysis using the LOCF method. As considering drop-outs as non-responders does not assume benefit from treatment after treatment discontinuation and most drop-outs for DMF and Fumaderm were due to adverse events, which probably reflect clinical reality, considering drop-outs as non-responders is probably most adequate both for superiority and NI analysis.

Missing values for the secondary endpoint DLQI were not replaced in the statistical analysis, however, for the dropouts the DLQI values reported at Week 16 represent the data obtained from the last visit. A sensitivity analysis where DLQI values for all patients who discontinued treatment before week 16 was replaced by BOCF was submitted during the procedure. In addition, a placebo multiple imputation analysis was also submitted.

The randomisation was not stratified by centre and there is no requirement to adjust the analysis by centre either, particularly if the number of subjects per centre is quite small. The applicant also submitted the analyses for absolute and percent change in PASI and for DLQI scores without adjusting for centre.

Overall, the statistical analyses were conducted in the following data sets with the Full analysis set pre-designated as the primary analysis.

Table 33 – Analysis sets

Analysis set	Definition
Safety analysis set (SAS)	All patients who were randomized and received at least one dose of the investigational medicinal product.
Full analysis set (FAS)	All patients of the SA set with at least one measurement of the primary variables PASI and PGA after Week 0.
Per protocol set (PPS)	All patients of the FA set for whom no relevant protocol deviations were documented.

Although a number of published studies with DMF containing formulations including Fumaderm were submitted, these studies were varied in design and many of these studies did not have all the information that is needed to do a robust assessment. Many of these studies were uncontrolled or open-labelled or retrospective observational studies which cannot provide pivotal evidence in support of the proposed DMF formulation. Only two studies Altmeyer 1994 and Gollnick 2002 were randomized, double blind controlled studies. While Altmeyer 1994 was a placebo controlled study, Gollnick 2002 compared Fumaderm monotherapy against a combination treatment of Fumaderm+calcipitriol. Further the Gollnick 2002 study did not have a placebo arm and allowed higher than the proposed maximum of 720mg/day.

Although these studies have been selected for discussion under main studies, these published studies do not have sufficient details and the study designs are not adequately robust to provide pivotal data on efficacy. While these limitations of published studies are acknowledged, it is also recognised that a number of studies by different investigators, across different centres and over the years are available to support the efficacy of fumarates in psoriasis. Therefore, these are considered as useful supportive studies for replication of results, extent of clinical experience, evidence of maintenance of efficacy at relevant dose-range in a wider patient population. In conclusion, the overall evidence on efficacy is deemed adequate particularly for a known active substance, especially as the single pivotal study is adequately large to provide compelling evidence of superiority in efficacy over placebo.

Efficacy data and additional analyses

The overall treatment discontinuation rate was around 36% which is higher than the 15% planned during the sample size estimation, which is a concern particularly for the non-inferiority comparison to Fumaderm. Although the overall rate of patients completing the treatment is lower (63.1%) in the LAS41008 as compared to placebo (71.5%), this is comparable to the completion rate in the active control, Fumaderm arm (62.2%). The main reasons for discontinuation in the active treatment arms were adverse events and in the placebo arm it was lack of efficacy. The baseline characteristics in the three treatment arms appeared to be balanced.

Co-Primary Endpoints

All 3 primary objectives of the pivotal study in moderate to severe chronic plaques psoriasis at week 16 were met. The study demonstrated that Skilarence (DMF) is statistically significant superior to placebo in regard to PASI 75 responders (37.5% vs. 15.3%) and clear/almost clear PGA responders (33.0% vs. 13.0%). Additionally, it was demonstrated that Skilarence (DMF) is non-inferior to Fumaderm (DMF/MEF) according to the pre-specified non-inferiority margin, in the proportion of patients achieving PASI 75 at Week 16 (37.5% vs. 40.3%). In a post-hoc comparison of PGA response

between Skilarence (DMF) and Fumaderm (33.0% vs. 37.4% (FAS)), the lower limit of the one-sided 97.5% CI for the difference was at the size of -13% (FAS) and -16% (PP).

For the comparison of PASI75 responders against placebo the 99.24% CI (10.7, 33.7) and the p-value (<0.0001) provided convincing evidence of superiority. For the comparison of PGA against placebo the 99.24% CI (9.0, 31) and the p-value (<0.0001) provided convincing evidence of superiority. These results were consistently seen in the FAS, SAS and PPS with two different approaches for missing data (designated as LOCF or non-responders). The observed risk difference between LAS41008 and placebo is 22.2. This is much lower than the risk difference of 40 that was anticipated in the sample size calculation which was based on review of literature of the efficacy of Fumaderm. Although formally non-inferiority can be claimed based on the pre-specified margins, this may not be considered robust given the lower than anticipated effect size. However for this full mixed application, where the evidence of short-term efficacy of Skilarence is convincingly demonstrated in comparison to placebo and where the non-inferiority comparison is to bridge to the information from Fumaderm for aspects like maintenance of efficacy and long term safety, this level of comparability is considered adequate. It is agreed that the evidence from literature on Fumaderm is relevant for this product.

The inferences drawn on the primary endpoints were generally supported by the results in the secondary endpoints of change in PASI 75 and PGA at week 3 and 8 as well as assessments on BSA and DLQI with one exception. A slight numerical advantage of Fumaderm compared to LAS41008 in the primary and most secondary efficacy parameters is noted, whereas the change from baseline in the affected BSA was more favourable in Skilarence, and mean PASI and Patient Benefit Index at week 16 were identical in both active treatment groups. However the applicant attributes this to the subjective nature of the scales and justifies that this is within the normal range of variability for this scale. This efficacy is much lower than the efficacy reported with biological agents where PASI75 responses of up to 80% have been reported. Further the biological agents are supported by larger clinical database of good quality. Nevertheless the demonstrated efficacy of DMF is considered clinically meaningful. The results of study 1102 are adequate in themselves for inferring the short-term efficacy of the proposed DMF product without replication of evidence, particularly in the context of the existing knowledge of the efficacy of DMF containing products from published literature.

For the non-inferiority comparison between LAS41008 and Fumaderm, the difference in proportion of patients achieving PASI 75 was -2.8 (99.24% CI -14.0. 8.4; p-value -0.0003) with the lower limit of the confidence interval within the pre-specified non-inferiority limit of 15%. Given the absolute difference in proportion of responders by PASI 75 between LAS41008 and placebo was 22.2%, the non-inferiority margin of 15% in this parameter (which constitutes 68% of the response) may not be appropriate. Nevertheless, it is agreed that this demonstrates sufficient comparability to support bridging to the evidence from literature on Fumaderm. This is probably due to the less than anticipated effect size [anticipated a benefit of 40% over placebo on PASI 75 while the observed benefit was 22.2% over placebo] and the decision of not accepting the recommendation to increase the sample size from 690 to more than 1000 patients based on the results at the interim analysis.

Overall the results from study 1102 can be accepted to demonstrate a convincing evidence of superior efficacy of LAS41008 as compared to placebo and a comparable efficacy to Fumaderm. Further sufficient comparability in terms of efficacy has been demonstrated between Skilarence and Fumaderm to contribute to the bridging to the evidence from literature on Fumaderm.

The follow-up of 2 months after stopping treatment showed that the rebound or loss of treatment response was lower in the treatment arms as compared to placebo. Further follow-up visits until one year also demonstrated that considerable maintenance of effects was retained for this follow-up period, nevertheless these results have to be interpreted with caution due to substantial drop-out and replacement of missing values by LOCF.

Despite the individual short-comings with the published studies, collectively these studies with different formulations containing DMF (but mainly including Fumaderm), conducted by different investigators across different centres/countries across time, consistently have reported significantly better efficacy as compared to placebo or clinically significant improvement from baseline. Around 28 published studies have evaluated the efficacy of DMF containing products in nearly 2700 psoriasis patients which is substantial. Many of these studies followed up patients for beyond 12 months and it was seen that there was no tolerance or loss in efficacy with long-term treatment. Some studies even demonstrated that the peak effects of treatments can take up to 12 months thus supporting the efficacy of long-term treatment.

The evidence to bridge the data (efficacy and safety) from Fumaderm to this product is based on comparability of quantitative composition of DMF coupled with relative bioavailability studies and the pivotal study comparing Skilarence to Fumaderm showing non-inferiority/comparability. Given this strength of evidence to bridge between Skilarence and Fumaderm it is accepted that the literature evidence on efficacy and safety of Fumaderm is highly relevant and supportive for Skilarence.

Despite the number of years of clinical use, the acceptability of the use of DMF containing products with concomitant medications or co-morbidities have not been well documented in literature. However the absence of significant safety concerns with long-term clinical use offers indirect reassurance. Given this situation, the applicant has clearly described the limitations of the data in the SmPC and provided appropriate cautionary advice.

A total of 28 patients aged ≥65 years were included in the pivotal study. The efficacy of LAS41008 seen in the study's main analysis was also demonstrated in the elderly subpopulation. Statistically significant superiority was shown for LAS41008 vs. placebo, as well as a comparable effect in the elderly (PASI 75 response in 38.5% resp. 33.3% of the elderly).

In study 1102, a follow-up visit two months after stop of treatment showed the treatment effects to be maintained as assessed by PASI and PGA. Additional follow-up data at 6 months and 12 months after stopping treatment at 16 weeks, showed the benefits were substantially maintained. Nevertheless the results have to be interpreted with caution due to substantial drop out during the follow up phase. A significantly greater mean percentage change from baseline in PASI was observed in the Skilarence compared to the placebo group at week 16 (-50.8 vs. -27.0) and at the 2 months follow-up visit (-48.5 vs. -27.5).

Thus, results of the follow-up have to be interpreted with caution due to substantial drop-out and replacement of missing values by LOCF for the most of the analyses. However, as deterioration during the follow-up without treatment appears plausible, LOCF may lead to imputation of too optimistic values, particularly for active treatment arms where larger improvements than under placebo were observed during the treatment phase. Therefore, deterioration may be larger for active treatment such that the difference between active treatments and placebo after 12 months follow-up may have been overestimated.

The percentage of patients with a PGA "clear" or "almost clear" was significantly greater in the Skilarence compared to the placebo group at week 16 (33% vs. 13%) and at the 2 months follow-up visit (27% vs. 15,3%). Both the mean percentage change in PASI and the percentage of patients with a PGA "clear" or "almost clear" at each of these visits was numerically slightly greater with Fumaderm compared to Skilarence (non-significant).

In general, for the long-term maintenance of treatment effects, placebo controlled direct comparison data is not needed. Usually single arm open-label extension studies with long term treatment showing maintenance of efficacy observed at the end of controlled phase is considered sufficient. In this dossier although there is no long-term data with the proposed formulation beyond 16 weeks, the active

substance is DMF and the long-term efficacy of DMF/MEF as well DMF is clearly supported by published literature. There are several studies with DMF/MEF covering treatment duration of up to 24 months, some studies even cover longer treatment duration. The studies indicated maintenance of treatment effects during long-term treatment with acceptable tolerability and there were no signs of development of tolerance to benefits. Moreover, some of them evaluated effects over several years and they indicated that with long-term treatment an increase of the effect can be anticipated beyond treatment duration of 3 months and peak of the effect is anticipated after 12 months of treatment (e.g. Thaci et al., 2013). Given that the proposed product also contains DMF in the same quantities as in Fumaderm and has shown comparable systemic exposures when administered in the fed state (particularly at the 120mg dose strength) which taken in consideration with the evidence from study 1102 showing comparable short-term efficacy, it is considered reasonable to extrapolate the long-term maintenance of treatment effects seen with different DMF containing formulations to the proposed DMF formulation. Moreover, the open-label study by Linjen et al, 2016, investigated long-term safety and efficacy of DMF monotherapy. Median treatment duration was 28 months. DMF monotherapy reduced PGA from 3.3/5 to 1.6/5 in 122 patients (69%) that reached the median maintenance dose of 480 mg/day after a median of 8 months.

Therefore, it is agreed that the proposed formulation can be expected to maintain the treatment benefits seen at 16 weeks in the patients if treated over the long term of up to 24 months. From the clinical study 1102, it is seen that the majority of the patients who completed the treatment phase of week 16 were on the maximum dose of 720 mg (72.5% for LAS41008 and 71.02% for Fumaderm). A detailed analysis of the doses used in both the treatment arms shows that these were comparable, providing support for the extrapolation of efficacy and safety from Fumaderm to Skilarence.

There is a lack of direct comparator data with other first-line systemic therapies, with only one small study comparing Fumaderm to methotrexate available from the literature. In addition, there is a high rate of treatment discontinuations (36% in study 1102 and exceeding 40% in published studies) with Fumaderm and lack of substantial evidence from studies of high quality to compare against other more widely established first line systemic therapies of psoriasis. In this context, the proposed indication which implies a first line systemic therapy for Skilarence was questioned. However from the applicant's justification, it is seen that Fumaderm is widely used in the first line systemic therapy of psoriasis in Germany, where it is authorised. Importantly, the European treatment guidelines also recommend the use of fumarates in first line systemic therapy. The predominant evidence of efficacy and safety for the use of Fumaderm in published literature and in study 1102 is also in patients receiving first line systemic therapy. Further the data on the efficacy of DMF containing products in patients who were treatment resistant to other systemic therapies is not available. Taking in to consideration these factors, a first line systemic therapy for Skilarence is agreed.

2.5.4. Conclusions on the clinical efficacy

In the pivotal study 1102, LAS41008 has convincingly demonstrated superior efficacy to placebo and similar but numerically slightly lower efficacy than the active comparator, Fumaderm. The superiority over placebo was with very significant p-values <0.0001. The secondary endpoints also indicated superiority of LAS41008 over placebo. The superiority of LAS41008 to placebo in various sub-group analyses was also significant, as the study sample size was based on the objective of demonstrating non-inferiority to Fumaderm, which resulted in a large study for the comparison against placebo. Taking all this into account the results are compelling enough to be acceptable as a single pivotal study.

A formal conclusion of non-inferiority of the proposed DMF formulation to Fumaderm was demonstrated. However, considering the observed effect size a strict non-inferiority cannot be concluded. Nevertheless it is agreed that adequate comparability of efficacy has been demonstrated to support bridging to the evidence from literature on Fumaderm. The evidence to support comparability includes a) the equal quantities of DMF in both Fumaderm and Skilarence b) relative bioavailability and c) comparable efficacy and safety seen in study 1102. Therefore, it is agreed that the evidence of efficacy and safety of Fumaderm in the published literature is highly relevant and supportive of the efficacy and safety of Skilarence.

This is especially so as the dosing in both treatment arms were not fixed equal doses but were titrated based on tolerability and response but nevertheless was comparable in both treatment arms. Further it was seen that the majority of the patients in the two treatment arms were on the maximum dose of 720mg/day by week 16, which provides adequate support for the upper end of the proposed dosing regimen.

Taking in to consideration the established information on the active substance - DMF, the comparable exposure and efficacy to Fumaderm and the supporting literature on the long-term efficacy from other DMF containing products, it is reasonable to infer that the demonstrated efficacy at 16 weeks of treatment in study 1102 would be maintained in patients on long-term treatment. Further in study 1102, 16 weeks of treatment were followed by a period of 12 months without treatment in order to asses relapse, rebound and maintenance of effects. It was seen that a considerable extent of the treatment effects are retained during this extended off-treatment follow-up period; however these results have to be interpreted with caution as there were a number of drop-outs.

An indication in the first line systemic therapy for psoriasis is adequately justified by the evidence of efficacy, the fact that Fumaderm is approved as first line systemic treatment of moderate to severe psoriasis in Germany and the use of fumarates are established in first line systemic therapy in clinical practice. Further support is provided by the recommendation of European S3-gudeline on psoriasis where DMF containing products are recommended for first line systemic therapy for both induction and long-term treatment. More importantly, the pivotal study was pre-dominantly in systemic therapy naïve patients.

2.6. Clinical safety

The data which provide the basis for the safety assessment of DMF gastro-resistant tablets in this clinical development programme are derived from 4 clinical studies with DMF (3 Phase I studies [Study 1103, Study 1104 and Study 08] and 1 pivotal Phase III study [Study 1102]) and 52 published studies and case reports in patients with psoriasis.

Patient exposure

A total of 3659 patients and 56 healthy subjects were treated with FAEs (DMF alone and DMF/MEF combinations including Fumaderm) in the 4 clinical studies and 56 published studies and case reports presented in this dossier: 562 in the pivotal Study 1102 (Table 34); 56 healthy subjects in the PK Studies 1103, 1104, and 08; and 3097 patients in the published articles.

Table 34 – Extent of Exposure in study 1102 (SAS)

Treatment duration	DMF N=279	Placebo N=137	Fumaderm N=283
Days exposure			
Mean (SD)	87.8 (35.3)	98.6 (27.4)	89.0 (34.2)
Median (min, max)	112.0 (1, 131)	112.0 (4, 119)	112.0 (5, 142)
Number (%) of patients [patient years]			
≥1 day	279 (100) [67.1]	137 (100) [37.0]	283 (100) [69.0]
≥1 week	275 (98.6) [67.0]	136 (99.3) [37.0]	282 (99.6) [68.9]
≥4 weeks	257 (92.1) [66.2]	131 (95.6) [36.8]	259 (91.5) [67.8]
≥8 weeks	212 (76.0) [61.3]	123 (89.8) [35.9]	220 (77.7) [63.4]
≥12 weeks	189 (67.7) [57.4]	114 (83.2) [34.3]	193 (68.2) [58.5]
≥16 weeks	165 (59.1) [50.7]	92 (67.2) [28.3]	170 (60.1) [52.3]

Note: Treatment duration is the date of last dose of IMP - date of first dose of IMP + 1. Patient-year of exposure is the total amount of time exposed to investigational product, expressed in years

DMF=dimethyl fumarate; IMP=investigational medicinal product; max=maximum; min=minimum; N=number of patients in the SAS; SAS=safety analysis set; SD=standard deviation

The overall safety population in the published literature comprised subjects aged ≥ 11 years, who were healthy or who had a medical history of psoriasis (mild, moderate or severe). The population available for the assessment of safety from the published literature was broader than the target population. In the prospective controlled and uncontrolled studies in patients with psoriasis, patients were exposed to study treatment up to 6 years. In retrospective studies, exposure data are available for up to 14 years of treatment.

In addition, there is a considerable clinical experience with Fumaderm (> 5 million packs sold in the last 15 years).

However, the number of patients exposed to the proposed formulation alone is small and includes 279 patients exposed with 189 exposed for 3 months or more.

Adverse events

In Study 1102, more patients reported any TEAEs in the DMF gastro-resistant tablets (83.9%) and Fumaderm (84.1%) groups compared with the placebo group (59.9%).

Table 35 – Summary of treatment-emergent adverse events in study 1102

Category of TEAE	Number (%) of Patients [inc]		
	DMF N=279 ET=67.1	Placebo N=137 ET=37.0	Fumaderm N=283 ET=68.9
At least one TEAE	**234 (83.9) [3489]**	**82 (59.9) [2218]**	**238 (84.1) [3452]**
Any mild TEAE	186 (66.7) [2773]	72 (52.6) [1947]	190 (67.1) [2756]
Any moderate TEAE	133 (47.7) [1983]	30 (21.9) [811.4]	135 (47.7) [1958]
Any severe TEAE	42 (15.1) [626.2]	10 (7.3) [270.5]	34 (12.0) [493.1]
Any related TEAE	206 (73.8) [3071]	54 (39.4) [1461]	209 (73.9) [3031]
Any TEAE leading to discontinuation	67 (24.0) [998.9]	8 (5.8) [216.4]	69 (24.4) [1001]
Any TESAE	9 (3.2) [134.2]	5 (3.6) [135.2]	8 (2.8) [116.0]
Any death during treatment period	0	0	1 (0.4) [14.5]

Note: Version 15.1 of MedDRA was used to code the adverse events. Percentages are calculated as 100 x (n/N); Patients are counted only once within each category. Table includes deaths recorded during the treatment phase or within 30 days of last dose of investigational product

ET=total exposure time in years; inc=incidence: number of patients in the specific category per 1000 patient years of exposure (n/ETx1000); MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in the Safety Population; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event

The majority of TEAEs were of mild to moderate intensity. A TEAE of severe intensity was reported by 15.1% of DMF gastro-resistant tablets patients and 12.0% of Fumaderm patients, compared to 7.3% of placebo patients.

Related Treatment Emergent Adverse Events

The proportion of patients with related TEAEs was also higher in the DMF gastro-resistant tablets (73.8%) and Fumaderm (73.9%) groups compared to placebo (40.1%); again, this was mainly attributable to gastrointestinal disorders.

The percentage of related TEAEs to the investigational product as per investigator judgment that were reported in at least 2% of patients by SOC and PT is presented in Table 36.

Table 36 – Related treatment-emergent adverse events in ≥2% (in any treatment group) of patients by system organ class and preferred term in study 1102

System Organ Class Preferred Term	Number (%) of Patients		
	DMF N=279	Placebo N=137	Fumaderm N=283
Any event	206 (73.8)	55 (40.1)	209 (73.9)
Gastrointestinal disorders	169 (60.6)	37 (27.0)	170 (60.1)
Diarrhoea	103 (36.9)	20 (14.6)	109 (38.5)
Abdominal pain upper	55 (19.7)	10 (7.3)	59 (20.8)
Abdominal pain	54 (19.4)	6 (4.4)	43 (15.2)
Nausea	30 (10.8)	5 (3.6)	24 (8.5)
Flatulence	15 (5.4)	7 (5.1)	16 (5.7)
Vomiting	12 (4.3)	2 (1.5)	17 (6.0)
Abdominal discomfort	8 (2.9)	2 (1.5)	11 (3.9)
Abdominal distension	4 (1.4)	2 (1.5)	9 (3.2)
Dyspepsia	6 (2.2)	2 (1.5)	4 (1.4)
Constipation	6 (2.2)	0 (0.0)	4 (1.4)
Gastrointestinal disorder	2 (0.7)	0 (0.0)	8 (2.8)
Skin and subcutaneous tissue disorders	60 (21.5)	12 (8.8)	55 (19.4)
Erythema	26 (9.3)	3 (2.2)	22 (7.8)
Pruritus	19 (6.8)	7 (5.1)	19 (6.7)
Skin burning sensation	21 (7.5)	3 (2.2)	18 (6.4)
Vascular disorders	60 (21.5)	3 (2.2)	48 (17.0)
Flushing	51 (18.3)	2 (1.5)	44 (15.5)
Hot flush	7 (2.5)	1 (0.7)	5 (1.8)
Blood and lymphatic system disorders	46 (16.5)	1 (0.7)	47 (16.6)
Lymphopenia	25 (9.0)	0 (0.0)	28 (9.9)
Eosinophilia	25 (9.0)	0 (0.0)	15 (5.3)
Investigations	30 (10.8)	8 (5.8)	25 (8.8)
Hepatic enzyme increased	6 (2.2)	3 (2.2)	9 (3.2)
Alanine aminotransferase increased	7 (2.5)	1 (0.7)	5 (1.8)
Gamma-glutamyltransferase increased	4 (1.4)	1 (0.7)	7 (2.5)
General disorders and administration site conditions	25 (9.0)	5 (3.6)	20 (7.1)
Fatigue	10 (3.6)	2 (1.5)	5 (1.8)
Feeling hot	6 (2.2)	2 (1.5)	6 (2.1)
Nervous system disorders	26 (9.3)	6 (4.4)	15 (5.3)
Headache	11 (3.9)	5 (3.6)	9 (3.2)
Paraesthesia	10 (3.6)	0 (0.0)	3 (1.1)

Published studies

There were 5 prospective controlled studies that reported on overall incidence of AEs in which patients were treated for between 12 and 16 weeks. The incidence of patients with any AE was similar in all groups treated with DMF/MEF or Fumaderm, which was higher than in patients treated with placebo and lower than patients treated with MTX (Table 37).

Table 37 - Summary of adverse events in prospective controlled published studies in psoriasis

Author	Treatment duration	Number of patients treated	Percentage of Patients		
			Any AE	Discontinuation due to AEs	SAEs
Altmeyer 1994	16 weeks				
Fumaderm 720 mg/day		~50	75.5	8.0	NR
Placebo		~50	16.0	2.0	NR
Peeters 1992	16 weeks				
DMF/MEF (240 mg/day)		13	NR	15.4	NR
Placebo		14	NR	0	NR
Balak 2015	12 weeks				
DMF/MEF (720 mg/day)		25	84	24	NR
DMF/MEF (720 mg/day) plus cetirizine		25	84	32	NR
Gollnick 2002	13 weeks				
Fumaderm (360-600 mg/day)		66	78.8	NR	0
Fumaderm (360-600 mg/day) plus calcipotriol		68	82.4	NR	1
Fallah Arani 2011	16 weeks				
DMF/MEF (720 mg/day)		27	88.9	7.4	0
MTX (15 mg/week)		27	100	14.8	0

AE=adverse event; DMF=dimethyl fumarate; MEF=monoethyl fumarate; MTX=methotrexate; NR=not reported; SAE=serious adverse event

In general, the relationship of the AE to the investigational product was not reported in the published studies and therefore the treatment emergent adverse events reported in published studies are presented below.

Table 38 – Common adverse events in the prospective controlled studies

Author	Treatment Duration	No. of patients treated	Proportion of Patients (%)			
			GI events	Flushing	Lympho-penia	Eosino-philia
Balak 2015	12 weeks					
DMF/MEF (720 mg/day)		25	64	48	16	32
DMF/MEF (720 mg/day) plus cetirizine		25	68	60	20	40
Gollnick 2002	13 weeks					
Fumaderm (360-600 mg/day)		66	36	26	0	3.0[a]
Fumaderm (360-600 mg/day) plus calcipotriol ointment		68	32	34	0	2.9[a]
Fallah Arani 2011	16 weeks					
DMF/MEF (720 mg/day)		27	NR	48	4	19
MTX (15 mg/week)		27	NR	7	0	0
Nugteren-Huying 1990	16 weeks					
DMF/MEF (720 mg/day)		13	100	92	31	38.5
OHF/MEF (1704 mg/week)		13	92	NR	0	0
Placebo		13	NR	NR	NR	NR
Nieboer 1989, Study III	16 weeks					
DMF (240 mg/day)		22	73	27	64	0
Placebo		20	NR	NR	NR	0
Nieboer 1990	16 weeks					
DMF (480 mg/day)		22	55	86	12	35
DMF/MEF (480 mg/day)		23	61	87	8	13
Kolbach 1992	≤24 months					
DMF (240 mg/day)		129	NR[b]	NR	86	NR
Fumaderm (480 mg/day)		67	NR[b]	NR	81	NR

a Only the incidence of eosinophilia leading to withdrawal from the study was reported.
b GI events were the most frequent complaint in the first 6 months in both groups (no data given).
DMF=dimethyl fumarate; GI=gastrointestinal; MEF= monoethyl fumarate; MTX=methotrexate; NR=not reported; OHF=octyl hydrogen fumarate

The safety profile from prospective uncontrolled published studies and in retrospective published studies was also presented. These were consistent with the safety profile as established in other studies but showed much more variability in the frequency of reported events

Immunological events

No cases of hypersensitivity have been reported in the prospective clinical studies and none have been described by the applicant in the published literature.

Adverse events of special interest

Based on the known safety profile of Fumaderm and other DMF containing products, TEAEs considered to be of special interest were decrease in total leukocyte and lymphocyte counts, flushing, gastrointestinal events, serious and opportunistic infections, malignancies, renal injury and proteinuria, and hepatic injury. These events were specifically monitored and reported in study 1102. All reported TEAEs of special interest in Study 1102 were assessed as non-serious.

Decreases in Leukocyte and Lymphocyte Count

Leukocytopenia and lymphopenia were common during treatment with either of the DMF containing treatments. The proportion of patients who reported decreased leukocyte and lymphocyte count TEAEs in the DMF gastro-resistant tablets (13.3%) and Fumaderm (13.1%) groups were higher compared to placebo (1.5%). Lymphopenia was the most commonly reported TEAE in the DMF gastro-resistant tablets (10.0%) and Fumaderm (10.6%) groups, of which 89.3% and 93.3% were assessed as related to study treatment, respectively. No TEAEs of lymphopenia were reported in the placebo group.

Lymphopenia was not defined in a standardized way across publications and for the purpose of full disclosure, whatever publications referred to as lymphopenia is reported here. The reported incidence of patients with lymphopenia in published studies is highly variable with no apparent dose relationship, and ranged from 0% to 64% in studies with treatment duration of between 12 and 16 weeks, and 86% with treatment duration of up to 24 months. As the incidence of the AEs was not reported for placebo groups, a comparison to placebo is not possible.

Flushing

The proportion of patients who reported flushing TEAEs (flushing or hot flush TEAEs) in the DMF gastro-resistant tablets (20.8%) and Fumaderm (17.3%) groups were higher compared to placebo (2.2%). All but 2 TEAEs of flushing were assessed as related to study treatment. Most patients experienced flushing during the early treatment phase/weeks. Flushing was also one of the most common AEs reported in the published studies, with an incidence of up to 92% of patients that generally increased with increasing dose. Flushing usually occurred in the first few months of treatment and resolved or became less problematic with time.

Gastrointestinal Disorders

The proportion of patients who reported gastrointestinal disorder TEAEs in the DMF gastroresistant tablets (62.7%) and Fumaderm (63.3%) groups were higher compared to placebo (29.9%). The majority of gastrointestinal disorders were assessed as related to study treatment.

Gastrointestinal disorders were one of the most common AEs reported in the published studies, with an incidence of up to 100% of patients that generally increased with increasing dose. The gastrointestinal disorders usually occurred in the first few months of treatment and resolved or became less problematic with time.

Hepatic Injury

The proportion of patients who reported hepatic injury TEAEs in the DMF gastro-resistant tablets (7.5%) and Fumaderm (9.2%) groups were similar to the placebo (7.3%) group. The majority of hepatic injury TEAEs were assessed as related to study treatment and the majority were mild or moderate in intensity in the DMF gastro-resistant tablets (20/21 patients) and Fumaderm (25/26 patients) groups.

Malignancies

A systematic literature review with meta-analysis was performed on the risk of cancer in psoriasis, accompanied by evidence-based recommendations (Beyaert, 2013). The authors concluded that there is a slightly increased risk of some cancers in patients with psoriasis (upper aero-digestive tract, liver, lung, pancreatic and urinary tract cancers), that the highest increased risk is for skin carcinoma, that there is no increased risk of melanoma and that regarding lymphoma, misdiagnosis of primary skin lymphoma as psoriasis might have overestimated the risk.

Very few malignancies were reported with DMF-containing treatments. Only 1 patient (22- 005 in the Fumaderm group) in Study 1102 had a TEAE of malignancy (dysplastic naevus assessed as mild, non-serious and not related to treatment). Few published studies reported malignancies. Squamous cell carcinoma was reported in 1 patient who had been treated with Fumaderm for 6 weeks (Jennings, 2009), carcinoma of the breast was reported in 1 patient shortly after starting Fumaderm treatment (Brewer, 2007), and malignancies including breast cancer, prostate cancer, basal cell carcinoma and an oligodendroglioma were reported by 3% of patients in the long-term with treatment of up to 74 months (Lijnen, 2015). No malignancies were reported in any of the other long-term studies with treatment of up to 14 years (Thio, 1995; Reich, 2009; Hoefnagel, 2003). There is thus no indication that long-term FAE treatment is associated with an increased risk of malignancies.

Renal Injury and Proteinuria

The proportion of patients who reported renal injury and proteinuria TEAEs was low (<3%) in all treatment groups, and the majority of TEAEs were assessed as not related to study treatment. Between 1972 and 2013, 12 individual cases have been published as case reports describing the development of renal toxicity associated with local and systemic FAE treatment (Reid, 2013; Ogilvie, 2011; Raschka, 1999; Dalhoff, 1990; Stühlinger, 1990; Roodnat, 1989; Dubiel, 1972). Several of these cases of renal toxicity occurred with doses of FAEs that are much higher than the dose recommended for the DMF gastro-resistant tablets. In all of these cases, the renal function returned to normal after stopping treatment.

Serious and Opportunistic Infections

The proportion of patients who reported infection TEAEs was low (<5%) in all treatment groups in Study 1102. None of the patients in the DMF gastro-resistant tablets group, 2/6 patients in the Fumaderm and 3/6 patients in the placebo groups had TEAEs assessed as related to study treatment. All infection TEAEs had resolved by the end of the study or the 2-month follow-up period. No relationship was found between blood disorders such as leukopenia and lymphopenia and the onset of infections during the 16 weeks of treatment duration of Study 1102.

Serious adverse event / deaths / other significant events

Deaths

One patient in the Fumaderm group died due to recent sub endocardial ischaemia which was assessed as 'not related' to the study drug by the investigator and sponsor.

Among the 52 published studies and case reports included in the safety section there were 2 deaths reported. One patient died due to oligodendroglioma during treatment with DMF monotherapy in the long-term Lijnen (2015) study. No further details were provided in the publication. The second death was due to Progressive multifocal leukoencephalopathy (PML) in a psoriasis patient treated with DMF and presented in a case report (Nieuwkamp, 2015). This was a 64-year-old female patient with psoriasis who presented treatment-related PML that occurred after receiving DMF (Psorinovo pharmacy preparation) for 2 years in which lymphocyte numbers were not monitored for nearly 2 years. The patient was discontinued from treatment after being diagnosed with PML, which was considered as DMF-associated.

Other serious adverse events

Study 1102 **-** A total of 22 non-fatal TESAEs were reported in 22 patients in Study 1102: 9 (3.2%) DMF gastro-resistant tablets patients, 8 (2.8%) Fumaderm patients, and 5 (3.6%) placebo patients. The only TESAE reported for more than 1 patient in any treatment group was atrial fibrillation (2 patients in the DMF gastro-resistant group). Two patients had TESAEs assessed as related to study treatment (both in the Fumaderm group): gastritis erosive and gastro duodenitis.

Published studies **-** Only 7 publications with 456 patients treated with FAEs explicitly mentioned the incidence of SAEs (Fallah Arani, 2011; Gollnick, 2002; Wain, 2010; Schmieder 2015; Altmeyer 1996; Burden-Teh, 2013; Harries, 2005): no patients were reported to have SAEs in 6 of these studies and in the other study (Gollnick 2002), only 1 patient was reported as having an SAE (adnexitis) during treatment with a combination of Fumaderm plus topical calcipotriol.

Other publications did not give a comprehensive overview of all SAEs that occurred, but did report some individual events of sufficient medical interest to be considered SAEs. These were cardiovascular events including myocardial infarction, angina pectoris, percutaneous coronary intervention, atrial fibrillation and heart valve replacement (3% of patients in the long-term Lijnen study [2015], 8% [4/50] of patients in the Balak study [2015]), and malignancies including breast cancer, prostate cancer, basal cell carcinoma and an oligodendroglioma (3% of patients in the long-term Lijnen study [2015]).

In addition, among case report studies, squamous cell carcinoma was reported in 1 patient who had been treated with Fumaderm for 6 weeks (Jennings 2009), and tuberculosis was reported in 1 patient after treatment with FAEs for 7 months (Ahmad, 2007). PML was reported in 8 case reports in patients treated with FAEs (Stoppe, 2014; Ermis, 2013; Dammeier, 2015; Sweetser 2013; van Kester, 2015; Bartsch, 2015; Nieuwkamp, 2015; Hoepner, 2015; van Oosten 2013).

Table 39 – Details of PML reports in psoriasis patients treated with DMF / MEF or DMF alone

Paper	Treatment Received (years)	Age/ Race/ Sex	Prior Immuno-suppressive treatment	Monitoring intervals for lymphocytes	Onset of lymphopenia[a] after FAE start	Lymphocyte levels during treatment with FAEs	Duration of lymphopenia[a] at start of PML symptoms	Time on FAEs at start of PML symptoms	Outcome
Bartsch, 2015	**Fumaderm**: up to 600 mg/day DMF (Jul 2010 through Sep 2014)	68/ White/ Male	Radiochemotherapy (8 yrs before), levothyroxine, citalopram	Regular (varying between monthly and every 2-3 months)	2-3 months	0.5 – 1.0 x10^9/L	2 yrs	2.5 yrs	Stabilised
Dammeier, 2015	**Fumaderm**: up to 360 mg/day DMF, reduced to 120 mg/day DMF with severe lymphopenia (May 2013 to Dec 2014)	53/ White/ Female	None	Regular (every 2 months)	2 months	0.45 – 0.7 x10^9/L (<0.8 x10^9/L persistently after 2 months, nadir of <0.5 x10^9/L at 11 months)	1.4 yrs	1.5 yrs	Stable course of disease
Ennis, 2013	**Fumaderm**: up to 240 mg/day DMF (mid 2007 through Aug 2010)	74/NR/ Male	Methotrexate (in the 1 yr prior to DMF), concomitant tamsulosin	Every 2 months for 1st year, every 5-6 months for 2nd yr, monthly at time of PML diagnosis	9 months	0.62 x10^9/L after 9 months, <0.5 x10^9/L persistently from 11 months (nadir 0.28 x10^9/L)	2.25 yrs	3 yrs	Recovered

Paper	Treatment Received (years)	Age/ Race/ Sex	Prior Immuno-suppressive treatment	Monitoring intervals for lymphocytes	Onset of lymphopenia[a] after FAE start	Lymphocyte levels during treatment with FAEs	Duration of lymphopenia[a] at start of PML symptoms	Time on FAEs at start of PML symptoms	Outcome
Hoepner, 2015	**Fumaderm**: 360 to 720 mg/day DMF (Dec 2008 to May 2013)	69/ White/ Male	None	Regular (every 1-3 months)	NR	0.724 – 0.738 x10^9/L at the onset of PML symptoms (and not <0.6 x 10^9/L in the 5 months prior to that)	at least 1.5 yr	4.25 yrs	Recovered
Stoppe, 2014	**Fumaderm**: dose not reported (2007 to Aug 2010)	NR/ White/ Male	Efalizumab (in the 1 yr prior to DMF), steroid tablets	No apparent measurement for 2-yr period prior to PML onset	NR	≤0.8 x10^9/L at time of PML start (nadir 0.5 x10^9/L)	NR	2.75 yrs	Recovered
Sweetser 2013[b], Buttmann 2013	**Fumaderm**: 480 mg/day DMF reduced to 60 mg/day due to lymphopenia (Aug 2006 to Oct 2009)	57/NR/ Female	Prednisolone and methotrexate (to treat sarcoidosis 3 yrs before PML onset), steroids	NR	Early	Grade 2 to 3 developed early, persisted during therapy (nadir 0.45 x10^9/L)	>2.5 yrs	3 yrs and 1 month	Recovered with mild to moderate residual symptoms
Nieuwkamp 2015; Mark 2015	**Psorinovo**: 720 mg/day DMF for 1 yr, 480 mg/day DMF for 2nd yr (Jun 2012 through Jul 2014)	64/NR/ Female	None	Sporadically	2 yrs	0.792 x10^9/L at 1 month before PML diagnosis; >1.0x10^9/L in the 6 months before that	1 month	2 yrs and 1 month	Died

Paper	Treatment Received (years)	Age/ Race/ Sex	Prior Immuno-suppressive treatment	Monitoring intervals for lymphocytes	Onset of lymphopenia[a] after FAE start	Lymphocyte levels during treatment with FAEs	Duration of lymphopenia[a] at start of PML symptoms	Time on FAEs at start of PML symptoms	Outcome
van Oosten 2013	**Psorinovo**: 420 mg/day DMF (Apr 2007 through Nov 2012)	42/NR/ Female	None	Regular (every 3 months)	6 months	0.3 – 0.6 x10^9/L for 5 years, then 0.2 x10^9/L at PML diagnosis	5 yrs	5.5 yrs	Recovered

[a] Moderate or severe lymphopenia, i.e. any value of <0.8 x10^9/L

[b] The 2nd patient reported by Sweetser is the same patient reported in detail by Stoppe, 2014, so only the first case is listed here to avoid duplication.

DMF: dimethyl fumarate; MEF: monoethyl fumarate; MS: multiple sclerosis; NR: not reported; PML: progressive multifocal leukoencephalopathy

Of the 8 case reports, there was one fatality, 2 had stable disease, 1 recovered with mild to moderate residual symptoms and the rest recovered fully. All of these PML patients had lymphocyte levels of <0.8 x109/L prior to the onset of PML symptoms. Except for 1 patient where the duration of lymphopenia was stated to be 1 month (where monitoring was sporadic), all other cases had recorded a duration of lymphopenia which was more than a year.

Laboratory findings

In Study 1102, blood samples for safety laboratory tests were taken at all visits throughout the study (screening, Visits 1-7 over the 16 weeks of treatment, and follow-up visits F1, F2, and F3).

Mean serum creatinine levels decreased slightly during the study in all treatment groups. Additionally, neither the estimated glomerular filtration rate nor the results of urinalysis indicate a decrease in kidney function in any of the 3 treatment groups.

A transient increase in eosinophils was observed with DMF gastro-resistant tablets and Fumaderm treatment, and the mean changes from baseline after 16 weeks of treatment were generally comparable between the DMF gastro-resistant tablets (100/µL) and Fumaderm groups (40/µL), although there were some numerical differences in favour of Fumaderm at some time points of measurement. Such eosinophilia has been noted in respect of Fumaderm treatment previously and has not been associated with clinical consequences. However, it was seen that there was a higher incidence of potentially eosinophil-related disorders: GI disorders (diarrhoea, abdominal pain nausea and vomiting), skin and subcutaneous tissue disorders (erythema and pruritus), vascular disorders (flushing) and general disorders (asthenic conditions) in patients with eosinophilia.

Treatment with DMF gastro-resistant tablets and Fumaderm also led to comparable decreases in leukocytes (DMF: -730/µL and Fumaderm: -690/µL) and lymphocytes (DMF: -520/µL and Fumaderm: -520/µL). Twelve months after stop of treatment (=F3 visit) where data were available, all patients (n=30) had leukocyte counts above the lower limit of normal ($3.0x10^9$/L). However, lymphocyte levels had still not recovered and were below the lower limit of normal ($1.0x10^9$/L) in 3/28 patients (10.7%), which would represent 3/279 (1.1%) of the patients started on Skilarence. For lymphocytes, the LAS41008 mean baseline was 1.98 to 1.53 at F3 (n=28/272, 10%) and for Fumaderm the mean baseline was 2.02 to 1.70 at F3 (n=38/277, 14%).

Severe lymphopenia (<500 lymphocytes/mm3) is associated with a higher risk of developing PML. A Rote Hand (“Dear Doctor”) letter was issued by BfArM in June 2013 warning of a suspected association between severe lymphopenia known to occur with Fumaderm treatment and PML. Although PML was not reported in Study 1102, the BfArM database reports 9 cases of PML in association with Fumaderm treatment and there are 6 case reports of PML in patients treated with FAEs (Stoppe, 2014; Ermis, 2013; Dammeier, 2015; van Kester, 2015; Bartsch, 2015; Nieuwkamp, 2015).

Vital signs: In Study 1102, there were no clinically meaningful changes in blood pressure, pulse, or body temperature

From published studies, the reported laboratory findings include leucopenia, lymphopenia, eosinophilia, liver abnormalities, creatinine abnormalities and proteinuria.

Safety in special populations

Subgroup analyses by intrinsic factors were only performed for Study 1102. Subgroup analyses of TEAEs were performed to identify any safety concerns associated with age (<40 years vs. >40 to <65 years, and ≥ 65 years), race (Caucasian vs. non Caucasian), and disease severity at baseline assessed

by PASI (moderate vs. severe [PASI >10]) and PGA (moderate [score of 3] vs. severe [score of 5]). No new safety concerns were identified in any of the subgroup analyses.

Table 40 – Subgroup analyses of TEAEs in study 1102

Subgroup	DMF		Placebo		Fumaderm	
	N	Number (%) of Patients [inc]	N	Number (%) of Patients [inc]	N	Number (%) of Patients [inc]
Age (years)						
≤18 to <40	119	96 (80.7) [3307]	52	31 (59.6) [2219]	103	88 (85.4) [3566]
≤ 40 to <65	132	115 (87.1) [3584	73	44 (60.3) [2252]	158	129 (81.6) [3212]
≥65	28	23 (82.1) [3857]	12	7 (58.3) [2018]	22	21 (95.5) [5110]
Gender						
Male	174	138 (79.3) [3230]	93	52 (55.9) [2062]	185	147 (79.5) [3111]
Female	105	96 (91.4) [3943]	44	30 (68.2) [2551]	98	91 (92.9) [4195]
PASI						
Moderate	234	195 (83.3) [3562]	113	68 (60.2) [2204]	232	205 (88.4) [3637]
Severe	45	39 (86.7) [3161]	24	14 (58.3) [2290]	51	33 (64.7) [2623]
PGA						
Moderate	167	138 (82.6) [3461]	80	47 (58.8) [2110]	167	145 (86.8) [3423]
Severe	112	96 (85.7) [3529]	57	35 (61.4) [2381]	116	93 (80.2) [3498]

PGA score of 3=moderate; PGA score of 5=severe
Note: Version 15.1 of MedDRA was used to code the adverse events. Percentages are calculated as 100 x (n/N); Patients are counted only once within each category. Table includes deaths recorded during the treatment phase or within 30 days of last dose of investigational product.
DMF=dimethyl fumarate; ET=total exposure time in years; inc=number of patients in the specific category per 1000 patient years of exposure (n/ETx1000); MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in the Safety Population; PASI=Psoriasis Area and Severity Index; PGA= Physician's Global Assessment; TEAE=treatment-emergent adverse event

During the Phase III Study 1102, a 32-year-old female in the DMF gastro-resistant tablets group realised she was pregnant after receiving study treatment for 3 days. The study treatment was stopped immediately. After 38 weeks gestation, the patient gave birth to a healthy boy (weight 3,790 grams, height 54.0 cm).

The safety of DMF in human pregnancy or in nursing mothers has not been established in controlled clinical studies. Pregnancy was an exclusion criterion in the published studies. There were 2 pregnancies reported in the published literature during treatment with FAEs and treatment was stopped during the course of pregnancies in both cases (Reid 2013; Balak, 2015).

Table 41 – Safety information for the older population

MedDRA Terms	Number (%) of subjects			
	Age <65 N=251	Age 65-74 N=21	Age 75-84 N=7	Age 85+ N=0
Total AEs	211 (84.1)	17 (81.0)	6 (85.7)	0
Serious AEs – Total	8 (3.2)	1 (4.8)	0	0
- Fatal	0	0	0	0
- Hospitalization/prolong existing hospitalization	7 (0.3)	1 (4.8)	0	0
- Life-threatening	1 (0.4)	0	0	0
- Disability/incapacity	0	0	0	0
- Other (medically significant)	0	0	0	0
AE leading to drop-out	58 (23.1)	5 (23.8)	4 (57.1)	0
Psychiatric disorders	5 (2.0)	1 (4.8)	0	0

MedDRA Terms	Number (%) of subjects			
	Age <65 N=251	Age 65-74 N=21	Age 75-84 N=7	Age 85+ N=0
Nervous system disorders	39 (15.5)	2 (9.5)	0	0
Accidents and injuries	3 (1.2)	1 (4.8)	0	0
Cardiac disorders	3 (1.2)	0	0	0
Vascular disorders	59 (23.5)	3 (14.3)	0	0
Cerebrovascular disorders	1 (0.4)	0	0	0
Infections and infestations	41 (16.3)	3 (14.3)	0	0
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	1 (0.4)	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	5 (2.0)	1 (4.8)	0	0

TEAE: treatment-emergent adverse event including all events that occurred up to 30 days after the last IMP intake.

Safety related to drug-drug interactions and other interactions

No drug-disease interactions were reported in patients from any of the clinical studies or published studies.

Due to the potential risk for DMF to cause kidney damage, MTX, retinoids, psoralens, cyclosporin, immunosuppressive agents, cytostatic agents and drugs with known harmful effect on kidneys must not be administered concomitantly with DMF.

No drug-drug interactions were reported in patients from any of the clinical studies. One case of a possible drug-drug interaction between DMF and vitamin K antagonist acenocoumarol was observed in a 56-year-old female patient (Lijnen, 2015). This patient was regularly treated with 2-3 mg acenocoumarol daily but required substantially higher doses after commencing DMF monotherapy treatment, which normalised after discontinuation of DMF. No information was available on the type of DMF product used.

Discontinuation due to adverse events

TEAEs leading to study drug withdrawal were reported in 144 patients (20.6%). The incidence was similar in the DMF gastro-resistant tablets (67 patients [24.0%]) group and the Fumaderm (69 patients [24.4%]) groups, and lower in the placebo group (8 patients [5.8%]).

The most common TEAEs (≥ 2% of patients) by SOC were gastrointestinal disorders (17.9% of DMF gastro-resistant tablets patients and 14.8% of Fumaderm patients vs 2.2% of placebo patients), and skin and subcutaneous tissue disorders (2.2% of DMF gastro-resistant tablets patients and 3.2% of Fumaderm patients vs 0.7% of placebo patients).

In the 4 prospective controlled studies that reported on the incidence of discontinuation due to AEs, treatment duration was between 12 and 16 weeks and the incidence in DMF treatment groups ranged from 7% to 32%. In general, the most common AEs leading to withdrawal of DMF, Fumaderm or other DMF combination treatments in the psoriasis studies were gastrointestinal events.

Post marketing experience

There is no post-marketing experience with Skilarence. However the safety profile of DMF containing products is relevant to Skilarence and the submitted information from published literature has been reviewed under each section above.

2.6.1. Discussion on clinical safety

The evidence on safety comes from the prospective studies with Skilarence and published studies where the latter predominantly includes studies with Fumaderm. Treatment with FAEs (DMF+MEFs; Fumaderm) is an established treatment for psoriasis and as such has been widely used in Germany. The main safety issues refer to GI-AE, flushing, leuko- and lymphopenia with the risk of opportunistic infections and renal AEs. The applicant has developed a gastro-resistant tablet (Skilarence) that contains only DMF in the same amount as Fumaderm.

It is pointed out that Skilarence and Fumaderm contain the same amount of DMF i.e. 30mg or 120 mg per tablet, respectively. However, Fumaderm in addition contains monoethylfumaric acids (MEFs), i.e. each Fumaderm 120 mg tablet contains 95 mg of MEFs (120 DMF + 95 MEFs = in total 215 mg FAEs). Therefore, if comparing the (adverse) effects of Skilarence containing equal amounts of DMF (i.e. 120 mg DMF) to Fumaderm, it has to be considered, that Fumaderm in addition contains MEFs (95 mg per 120 mg tablet), which may additionally to DMF impact on the safety/tolerability/PK profile of Fumaderm. Based on the comparative quality, PK, efficacy and safety data between Skilarence and Fumaderm, it is agreed that the main effects in psoriasis seem to be from the DMF component and therefore the evidence on efficacy and safety of Fumaderm from literature is highly relevant and supportive of Skilarence.

Patient exposure

A total of 3659 patients and 56 healthy subjects (3 PK studies 1103, 1104, and 08) were treated with FAEs (DMF alone and DMF/MEF combinations including Fumaderm) in the 4 clinical studies and 56 published studies and case reports presented in this application: i) 562 in the pivotal study 1102 (plus n=137 in the placebo arm (SAS)), and ii) 3.097 in the published articles.

The vast majority of the safety data from literature refers to Fumaderm (DMF+MEF). The population which was treated with DMF-only in studies published mostly about 25 years ago (except for the Lijnen study (2015)) was also small (around n=375) if compared to Fumaderm which contains DMF+MEF. Hence, the long term safety data for DMF mono-treatment in psoriasis may be considered to be associated with some uncertainties and thus the long term safety profile is considered missing information in the proposed safety specification. In this regard a PASS, included in the RMP, will be conducted.

Adverse events

In the pivotal study 1102 a similar proportion of patients reported at least 1 TEAE in the DMF group (83.9%) and the Fumaderm group (84.1%), compared to a smaller proportion of patients in the placebo group (59.9%): however, this was mainly attributable to gastrointestinal disorders (such as diarrhoea, abdominal cramps, and nausea), which are known, common AEs that occur during

treatment with DMF mono- and combination treatments, and are consistent with the established safety profile of DMF treatment, with essentially no difference in either the profile or the frequency of the AEs reported.

The same accounts for treatment-related TEAEs in the DMF group (73.8%) and the Fumaderm group (73.9%), compared to a smaller proportion (40.1%) of the patients in the placebo group.

With regard to published literature it is noted that most of the studies refer to Fumaderm and not DMF monotherapy. However, the range of the incidence of AEs reported in the different (types of) studies (62-100%) is broadly in accordance with the incidence reported in study 1102 (DMF: 83.9%; Fumaderm: 84.1%).

In the pivotal study 1102 the most frequently reported ADRs refer among others to GI-events (TEAEs by SOC: 62.7% (DMF) vs. 63.3% (Fumaderm)) and flushing (TEA by PT (DMF: 18.3% vs. Fumaderm: 16.3%)).

Decreases in lymphocytes (in varying degrees) are known for Fumaderm and were seen in DMF treated (10%) and Fumaderm treated patients (10.6%) in study 1102 [concerning the parameter “at any visit” numerically more often with DMF (54/266 (20.3%) than with Fumaderm (45/276 (16.3%)]. It is noted that there were cases of decrease in lymphocytes in the placebo group during the follow up period and the reason for this is not clear. The applicant clarified that none of these patients were known to be on other immunosuppressive therapy and so the reasons remain unclear.

However, it is clear that lymphopenia is an expected side effect of treatment with DMF gastro-resistant tablets. Clinically, lymphopenia is a risk factor for serious and/or opportunistic infections, and therefore blood cell counts should be monitored regularly as per the recommendations in the Summary of Product Characteristics in order to minimise the risk.

The applicant presented analyses with different definitions for decreased leukocytes (<3000/mm3 and <4000/mm3) and the relative leukopenia in both treatments were comparable regardless of the definition. With a definition of <3000/mm3, transient leukopenia ccurred in 9% (DMF) and 6% (Fumaderm) [31.2% (DMF) vs. 27.9% (Fumaderm) at any visit].

The clinical concern due to the occurrence of decrease in lymphocytes relates to the occurrence of serious opportunistic infections and the main identified risk includes PML. Based on the evidence from literature submitted by the applicant, there have been 8 case reports of PML occurring after use of fumarates in psoriatic patients. All these cases were associated with lymphopenia $<0.8x10^9$/L and most of them (7 out of 8) for prolonged lymphopenia. Of the 8 case-reports, there was 1 fatality and 2 stable diseases, with the rest recovering. A review by the CHMP for PML risks associated with fumarates irrespective of the indication, made recommendations for risk mitigation by regular monitoring for lymphocyte counts and treatment stop.

For this application, the applicant proposes monitoring periods for complete blood count with differential of 3 months for people with normal lymphocyte count and a more frequent (once every 4 weeks) monitoring for patients with lymphocyte count below $1x10^9$/L. This is less conservative than the recommendations from the CHMP review (which recommends every 4 weeks), however this is considered a more rational approach to provide a practical and adequate risk mitigation measure, particularly as a more conservative criterion for stopping treatment is proposed.

The thresholds of lymphocytes for stopping the treatment is $0.7x10^9$/L (see SmPC section 4.4). If the lymphocyte count falls below $0.7x10^9$/L, the blood test must be repeated and if the levels are confirmed to be below $0.7x10^9$/L, then treatment must be stopped immediately. This is more conservative as compared to the CHMP recommendations which recommends halving the dose when the levels are below $0.7x10^9$/L and stopping treatment only if after 4 weeks at half the dose, the

lymphocyte levels remain below $0.7x10^9$/L. In these recommendations, the threshold for a straight stop without any dose reduction is $<0.5x10^9$/L.

In the different types of published studies the percentage of patients experiencing GI disorders, flushing, lymphopenia, and eosinophilia is rather heterogenous between the studies. Due to the wide ranges reported in the different types of studies, the percentages reported for common AEs in study 1102 fit in the percentages that have been reported for the different published studies. The applicant states that GI (gastrointestinal) AEs were most frequent in the first 2 months after starting therapy and subsided thereafter.

In general the adverse events reported with LAS41008 in the pivotal study 1102, their frequency, severity and causality assessment were along expected lines based on the known safety profile of Fumaderm and other DMF containing products.

The most common adverse events associated with DMF treatment are gastrointestinal disturbance (including diarrhoea, abdominal pain, nausea, flatulence and vomiting), skin and subcutaneous disorders (pruritus, erythema and skin burning sensation), flushing and haematological abnormalities (lymphopenia and eosinophilia). Other common adverse events included headache, paraesthesia, fatigue, decreased appetite and raised hepatic enzymes. Other uncommon adverse events include proteinuria. Some events/potential safety concerns based on safety information of Fumaderm which have not been identified in the limited data from study 1102 include increased serum creatinine, renal failure, serious opportunistic infections especially PML, malignancies and Fanconi syndrome. All of these have now been included in the proposed safety profile of the proposed DMF product. For the safety events of haematological abnormalities, renal injury and hepatic injury recommendations are made in the SmPC to have regular monitoring and appropriate treatment discontinuation if significant changes are noted to prevent unacceptable consequences (see SmPC section 4.4).

Most of the discontinuations early in treatment are due to tolerability issues leading to GI disturbances, flushing and skin related adverse events. This is planned to be managed by the gradual dose-titration which has kept the discontinuation rates to acceptable limits with Fumaderm. A similar dose-titration scheme is therefore proposed with this product. Overall the incidence of adverse events was 83.9% with LAS41008 as compared to 59.9% in placebo. Most of them were mild; however adverse events were the reason for 24.4% of patient discontinuing treatment in LAS41008 as compared to 5.8% in placebo. The discontinuation rate due to adverse events in published literature is wide and ranges from 7 to > 40% (even up to 80% in some reports) but a reasonable expectation from the diverse literature would be up to 40%.

There were no deaths considered related to study treatment or any serious adverse events that occurred in more than 2 patients. Likewise, the reports from published literature have not given rise to any significant concerns in relation to serious adverse events. However, there are potential significant safety concerns particularly with long-term use of malignancies and serious opportunistic infections like PML. These potential concerns have been identified with Fumaderm and other DMF containing products as well and there are case-reports of PML in the literature after Fumaderm treatment. There is a strong mechanistic basis for the potential for serious opportunistic infections as there have been some reports of severe lymphopenia with long-term treatment. However, from literature it is not clear if Fumaderm can increase the risk of PML to an unacceptable level as the data is from spontaneous reporting. This is of particular importance as a substantial amount of the safety data from published literature is with Fumaderm and as most of these data is by spontaneous reporting and probably from patients who have not used recently authorised monoclonal antibodies that also modulate the immune system, and the risks of DMF in the current therapeutic setting could well be different. A post-authorisation registry based safety study to evaluate the rare but significant risks over long-term use will be performed.

The overall clinical experience with the proposed DMF product is limited (279 patients treated with 189 patients treated for 3 months or more). Although reassurance can be obtained from published literature with Fumaderm (literature describes around 3200 patients treated with Fumaderm and it is known that more than 5 million packs of Fumaderm have been sold in Germany in the last 15 years) that the anticipated uncommon and rare events are likely to be acceptable, the frequency and severity of these events reported with Fumaderm cannot be extrapolated directly to the proposed DMF product due to Fumaderm containing monoethylfumarate salts in addition to DMF which can potentially alter the safety profile. Therefore to address the long-term safety concerns and to evaluate the frequency of rare but serious adverse events, a PASS is required. The applicant has submitted the PASS protocol and the draft timelines for agreement.

With respect to interactions, there were only 6 published studies that provided general details of concomitant medication use in patients treated with DMF (Lijnen, 2016) or DMF/MEF (Schmieder, 2015; Ismail, 2014; Thaçi, 2013; Reich, 2009; Harries, 2005), all of which were uncontrolled studies. The concomitant medications most commonly reported were treatments for hypertension, coagulation disorders and dyslipidaemia, which is consistent with the medical history and co-morbidities described in these patients. In addition, as the PK and PD interactions data have not been well characterised and the available clinical data with Fumaderm from published literature is not detailed, the clinical data from special sub-groups of population like elderly, patients with hepatic or renal impairment, immunosuppressed patients, patients with other concomitant co-morbidities especially those that were excluded from the pivotal clinical study is limited and the applicant will address these in the post-marketing safety study and/or by appropriate wording in the SmPC. This is acceptable.

According to the applicant the extent of exposure for patients with renal impairment based on GFR was n=117 patients (mild renal impairment), and n=12 (moderate renal impairment). Taking in to consideration the known PK of DMF, the applicant asserts that there is no need for change in dose in these patients. With regard to patients with severe renal impairment a contraindication has been proposed. This was considered to be appropriate.

Likewise there were only 3 patients with medical history of hepatic impairment that were included in the trial. Nevertheless based on the PK of DMF, a dose-modification is not proposed for mild to moderate hepatic impairment. For patients with severe hepatic impairment, a contraindication was proposed and considered to be appropriate.

2.6.2. Conclusions on the clinical safety

The safety profile of the proposed DMF product as characterised in the pivotal study 1102 is acceptable and comparable to the safety profile of Fumaderm. In addition, this safety profile is consistent with the known safety profile of other DMF containing products including Fumaderm as evidenced from published literature. However the safety data with the proposed DMF product is limited (n=279) and is inadequate to sufficiently characterise uncommon and rare adverse events. In addition, the potential significant safety concerns of increased risk of serious and opportunistic infections including PML and malignancies with long-term treatment have not been accurately ascertained with the clinical use of fumarates. Educational materials will be distributed to the health care professionals, about the risk of serious infections, mainly opportunistic infections such as progressive multifocal leukoencephalopathy (PML), and to provide guidance on the monitoring of lymphocyte and leukocyte count abnormalities.

Although it is acknowledged that there is considerable safety experience with Fumaderm and other DMF-containing products and that this experience is relevant to Skilarence, it cannot be excluded that the lack of MEF salts in Skilarence and the small differences in exposure to MMF may result in some differences in long-term safety profiles and/or rare ADRs. However, despite this inadequate

characterisation of the safety profile with the proposed DMF product there is reassurance on the acceptability of its safety profile as it is in general similar to that of Fumaderm, for which the safety profile is well characterised including the long-term safety profile as evidenced from published literature. In addition, based on the overall evidence vis-a-vis Fumaderm that has been submitted in this dossier, it is agreed that the established safety profile of Fumaderm is highly relevant for this product. However as the characterisation of the rare but serious adverse events of Fumaderm are not well characterised in the published literature, the applicant is required to conduct a post-authorisation safety study included in the RMP.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Decreases in leukocyte and lymphocyte counts • Serious infections (including opportunistic infections such as PML) • Gastrointestinal events • Flushing • Proteinuria
Important potential risks	• Malignancies, including renal carcinoma • Renal injury, including Fanconi syndrome • Hepatic injury • Eosinophilia related conditions • Interaction with oral contraceptives
Missing information	• Safety profile in patients over 65 years old • Safety profile in children and adolescents • Safety profile in pregnant and lactating woman • Safety profile in patients with renal impairment • Safety profile in patients with hepatic impairment • Safety profile in immunosuppressed patients • Safety profile in patients with gastrointestinal disease • Safety profile in patients with pre-existing/concurrent infections • Long term safety profile

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Skilarence Post-	To evaluate the	Serious infections	Planned	Protocol

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Authorisation Safety Study in European Psoriasis Registries Category (3)	long-term safety of Skilarence used for the treatment of patients with moderate to severe psoriasis.	Malignancies Renal impairment		Submission: Q4 2017 First annual report: In line with PBRER starting in 2018 End of data collection: Q1 2027[c] Study report: Within 1 year of availability of final data set.
Retrospective chart Review to assess the effectiveness of the Skilarence risk minimisation activities in daily practice. Category (3)	Assessment the effectiveness of the risk minimization measures for Skilarence in daily practice	Risk of PML Lymphopenia	Planned	Protocol submission: Q4 2017 Final study report: TBD

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Decreases in leukocyte and lymphocyte counts	**Label in patient information and SmPC** Proposed texts in SmPC Sections: • 4.4 Special warnings and precautions for use. • 4.8 Undesirable effects. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	Educational material

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Serious infections (including opportunistic infections such as PML)	**Label in patient information and SmPC** Proposed texts in SmPC Sections: • 4.4 Special warnings and precautions for use. • 4.8 Undesirable effects. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	Educational material
Flushing	**Label in patient information and SmPC** Proposed texts in SmPC Sections: • 4.4 Special warnings and precautions for use. • 4.8 Undesirable effects. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None
Gastrointestinal events	**Label in patient information and SmPC** Proposed texts in SmPC Sections: • 4.3 Contraindications • 4.4 Special warnings and precautions for use. • 4.5 Interaction with other medicinal products and other forms of interaction. • 4.8 Undesirable effects. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None
Proteinuria	**Label in patient information and SmPC** Proposed texts in SmPC Sections: • 4.4 Special warnings and precautions for use. • 4.8 Undesirable effects. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Malignancies	**Label in patient information and SmPC** Proposed texts in SmPC Section: • Section 5.3 Preclinical safety data. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None
Renal injury, including Fanconi syndrome	**Label in patient information and SmPC** Proposed texts in SmPC Sections: • 4.2 Posology and method of administration. • 4.3 Contraindications. • 4.4 Special warnings and precautions for use. • 4.8 Undesirable effects. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None
Hepatic injury	**Label in patient information and SmPC** Proposed texts in SmPC Sections: • 4.2 Posology and method of administration. • 4.3 Contraindications. • 4.4 Special warnings and precautions for use. • 4.8 Undesirable effects. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None
Eosinophilia related conditions	**Label in patient information and SmPC** Proposed texts in SmPC Sections: • 4.8 Undesirable effects. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Interaction with oral contraceptives	**Label in patient information and SmPC** Proposed texts in SmPC Sections: • 4.5 Interaction with other medicinal products and other forms of interaction. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None
Safety profile in patients over 65 years old	**Label in patient information and SmPC** Proposed texts in SmPC Section: • 4.2 Posology and method of administration. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None
Safety profile in children and adolescents	**Label in patient information and SmPC** Proposed texts in SmPC Sections: • 4.1 Therapeutic indications • 4.2 Posology and method of administration. • 5.1 Pharmacodynamic properties. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None
Safety profile in pregnant and lactating woman	**Label in patient information and SmPC** Proposed texts in SmPC Section: • 4.3 Contraindications. • 4.6 Fertility, pregnancy and lactation. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Safety profile in patients with renal impairment	**Label in patient information and SmPC** Proposed texts in SmPC Sections: • 4.2 Posology and method of administration. • 4.3 Contraindications. • 4.4 Special warnings and precautions for use. • 5.2 Pharmacokinetic properties. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None
Safety profile in patients with hepatic impairment	**Label in patient information and SmPC** Proposed texts in SmPC Sections: • 4.2 Posology and method of administration. • 4.3 Contraindications. • 4.4 Special warnings and precautions for use. • 5.2 Pharmacokinetic properties. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None
Safety profile in immunosuppressed patients	**Label in patient information and SmPC** Proposed texts in SmPC Sections: • 4.4 Special warnings and precautions for use. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None
Long term safety profile	Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Safety profile in patients with gastrointestinal disease	**Label in patient information and SmPC** Proposed texts in SmPC Section: • 4.3 Contraindications. • 4.4 Special warnings and precautions for use. Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None
Safety profile in patients with pre-existing/concurrent infections	**Label in patient information and SmPC** Proposed texts in SmPC Sections: • 4.4 Special warnings and precautions for use Prescription-only medicine. Use restricted to physicians experienced in the treatment of psoriasis.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Skilarence is intended for the treatment of moderate to severe plaque psoriasis in adults in need of systemic drug therapy.

Dimethyl fumarate is a fumaric acid ester (FAE).

Psoriasis is a chronic inflammatory disease, predominantly involving the skin, where it is characterised by the presence of erythematous plaques, usually covered by white silvery scales, but joints may also be affected (psoriatic arthritis). Psoriasis is more frequent in countries further away from the equator and has an estimated worldwide prevalence of 1% to 2%.

Psoriasis is a stigmatising condition that can have a major impact on quality of life, to a similar extent as cancer, heart disease and diabetes. Psoriatic lesions can be itchy and painful and cause extreme physical and emotional discomfort to patients. In addition, in its most severe presentations, patients with psoriasis have an increased risk of developing other comorbidities such as depression, diabetes and cardiovascular disease, which can eventually increase the overall risk of mortality.

3.1.2. Available therapies and unmet medical need

At present there is no definitive cure for psoriasis. Available treatments focus primarily on the use of anti-inflammatory or immunomodulatory agents to control the symptoms of the disease and prevent further relapses. The management of mild psoriasis usually consists of topical treatments. Treatments for patients with moderate to severe psoriasis include phototherapy and systemic treatment with oral agents and injectable biotechnology-derived products.

3.1.3. Main clinical studies

This is an Article 8(3)- full mixed application and is supported by the applicant's own studies and substantial supportive evidence from published literature where the efficacy/safety of Fumaderm has been well documented.

Table 42 – Overview of clinical studies with DMF gastro-resistant tablets

Phase of Study	Study Identifier	Objective of the Study
I	Study 1103	Assess the pharmacokinetic profiles of DMF 30 mg gastro-resistant tablets and Fumaderm 30 mg in healthy subjects
I	Study 1104	Assess the pharmacokinetic profiles of DMF 120 mg gastro-resistant tablets and Fumaderm 120 mg in healthy subjects
I	Study 08	A randomised, open label, single center four way crossover study to investigate the pharmacokinetics of LAS41008 120 mg gastro resistant tablet and Fumaderm120 mg gastro resistant tablet under fasting and fed conditions in healthy subjects
III	Study 1102	Pivotal study in patients with moderate to severe psoriasis to assess the superiority of DMF gastro-resistant tablets to placebo and the non-inferiority of DMF gastro-resistant tablets to Fumaderm

3.2. Favourable effects

In the pivotal study, treatment with the proposed DMF product using the proposed dose-titration scheme resulted in 37.5% of the treated patients achieving PASI 75 (a >75% reduction in the PASI score from baseline) after 16 weeks of treatment as compared to placebo where 15.2% of the patients achieved PASI 75. Twenty percent more patients in the treatment arm achieved a clear or almost clear score in PGA (33.0% vs. 13.0%) at week 16 as compared to placebo. The proportion of patients with PASI 90 was 18.4% with LAS41008 as compared to 4.6% with placebo. The mean DLQI score at baseline of 11.3 (indicating a very large effect of the disease on patient's life) was improved to a mean of 5.4 (indicating a moderate effect on patient's life). The probability of relapse within two months after end of treatment was smaller than 20% in the Skilarence and the Fumaderm group. Additionally, it was demonstrated that Skilarence (DMF) is comparable to Fumaderm (DMF/MEF) in the proportion of patients achieving PASI 75 at Week 16 (37.5% vs. 40.3%).

Most of the patients who completed treatment of 16 weeks had been titrated to the maximum 720mg/day dose in both treatment arms (72.25% for LAS41008 and 71.02% for Fumaderm).

In addition to the benefits as ascertained in the pivotal study with the proposed DMF product, there are also supportive studies from published literature ranging over a wide time-span with different DMF containing formulations (most of them referring to Fumaderm, but also DMF-monotherapy) by different authors from different centres which all suggest a clinically relevant and significant treatment benefit in psoriasis. In two published randomised, double-blind, controlled studies with grade A_2 evidence level (high-quality comparative study) according to the S3-guidelines a reduction of PASI of 50.2% at week 16 resp. 51.9% at week 13 was reported with Fumaderm.

The onset of treatment effects was seen at weeks 3/8 in some of the sensitive endpoints but not in all the endpoints. With continued treatment the benefits of treatment continued to increase as compared to placebo showing a maximum difference at week 16 in this pivotal study. In this study the benefits of DMF were seen to be comparable to Fumaderm (which contains DMF in the same quantities and in addition three other salts of monoethyfumarate). Published literature suggests with other DMF containing products show that there is maintenance of treatment effects with long-term treatments > 24 months. Some published studies also suggest that the peak effect of treatment could take up to 12 months to achieve.

3.3. Uncertainties and limitations about favourable effects

Given the small size of the overall efficacy data available with the proposed DMF product, there are a number of specific sub-groups of the patient population with co-morbidities (renal and hepatic impairment) who were excluded from these studies.

The potential for PK and PD interactions has not been well characterised. Only indirect assurance from the long-term clinical use of other DMF products (mainly Fumaderm) is available. As this predominantly depends on publications and spontaneous reporting there are uncertainties about the extent of benefit that can be seen in different sub-groups of the target population.

It is acknowledged that there is considerable published literature to support the efficacy, however, the estimates of the efficacy (effect size) varies widely and there are limitations with respect to the lack of detailed data to allow precise description of the effect size in various sub-groups of patients other than those studied in the study 1102.

Non-inferiority of DMF vs. Fumaderm was evaluated for PASI75 and PGA. A formal non-inferiority was established based on the pre-specified non-inferiority margin; however although the pre-specified

margin of +/-15% has been generally accepted in this setting, this is considered broad particularly due to the observed effect size in this study.

The effects in regard to the co-primary endpoints were numerically slightly lower in the Skilarence group compared to Fumaderm although this could be due to variability, a limited PD and the efficacy effect of MEFs in Fumaderm may also be contributing to an anti-psoriatic effect.

The evidence for long-term efficacy has been extrapolated from the evidence in published literature with other DMF containing products mainly Fumaderm and there is no direct evidence for long-term maintenance of effect with the proposed product.

3.4. Unfavourable effects

Around 84% of treated patients experienced an adverse event with the proposed DMF product as compared to 60% of patients on placebo. The majority of TEAEs were of mild to moderate intensity. The common adverse events included gastrointestinal (GI) disorders (diarrhoea, abdominal pain, nausea, vomiting, dyspepsia, constipation, flatulence), flushing, erythema, pruritus, skin burning sensation, fatigue, decreased appetite, haematological abnormalities (lymphopenia, eosinophilia, leukopenia) and increase in hepatic enzymes. The most frequently reported ADRs were among others to GI-events (TEAEs by SOC: 62.7% (DMF) vs. 63.3% (Fumaderm) in study 1102) and flushing (TEAE by PT (DMF: 18.3% vs. Fumaderm: 16.3%) in study 1102).

Decreases in lymphocytes (in varying degrees) are known for Fumaderm and were reported in DMF treated (10%) and Fumaderm treated patients (10.6%) in study 1102 [concerning the parameter “at any visit” numerically more often with DMF [54/266 (20.3%) than with Fumaderm 45/276 (16.3%)]. From literature it is known that the decrease in lymphocytes can be stopped on stopping treatment and the time for the lymphocytes to return to baseline can be long. From the results of the long-term follow up study 1102, the time for lymphocyte count to return to baseline can be longer than 46 weeks as evidenced by the mean number of lymphocytes at 52 week follow-up visit. However despite the high incidence of decrease in lymphocyte counts, the number of ‘clinical events’ due to the low lymphocyte count is very low.

The most significant clinical event due to reduced lymphocyte count is PML and 8 case reports have been found in the literature with the use of fumarates in psoriasis. These events of PML described in association with Fumaderm treatment have generally occurred when treatment was continued despite significant reduction in low lymphocyte counts contrary to the current recommendations to stop treatment. Of the 8 reports, the clinical outcomes reported were 1 fatality, 2 stable disease, 1 recovered with mild sequelae and the remaining recovered. Serious infections (including opportunistic infections such as PML) are currently classified as important identified risks in the safety specification for Skilarence.

Other uncommon/rare/very rare/frequency unknown events based on safety information of Fumaderm include proteinuria, increased serum creatinine, renal failure, other serious opportunistic infections and Fanconi syndrome. Twelve cases of renal toxicity associated with local or systemic FAE treatment have been described in the literature. In the Lijnen (2015) study which investigated DMF-mono therapy with higher DMF doses, proteinuria was reported in 25/176 (14%) of patients which compares poorly with regard to proteinuria of 4/279 (1.4%) in DMF patients and 6/283 (2.1%) of Fumaderm patients reported in the study 1102. Renal injury and proteinuria is currently classified as an important potential risk in the proposed safety specification of Skilarence.

Treatment related adverse events resulted in treatment discontinuation in 24% of the patients in the DMF treatment group as compared to around 6% in the placebo group; however most of the adverse events resolved on discontinuation of treatment.

Based on literature, the intolerability to GI disorders and flushing can be reduced by dose-titration, which has resulted in the proposed dose-titration scheme at treatment initiation. The risk of serious consequences of renal, hepatic and haematological abnormalities can be managed by regular monitoring of the function of these organ systems and appropriate actions with respect to treatment withdrawal have been included in the SmPC.

Overall, the submitted clinical data from the phase III study and from the few and limited published studies that refer to DMF mono therapy as well as the substantial literature of Fumaderm (which contains DMF+MEF salts) do not indicate critical differences in the ADR profile of Skilarence compared to the DMF containing products, although some numerical differences are noted.

3.5. Uncertainties and limitations about unfavourable effects

The overall safety data set with the proposed DMF product is around 280 patients with around 190 patients exposed for 12 weeks or more. The overall treatment duration was for 16 weeks and this number is too small to detect rare ADRs or adverse events which occur after long-term treatments.

Although there is sufficient information (around 3200 patients exposed) on safety with other DMF containing products including Fumaderm, which can provide reassurance with respect to an acceptable safety profile for this product, data from published literature is not fully reliable. With regard to published literature, 483/3.051 (16%) of treated patients were included in prospective controlled studies, 787/3.051 (26%) in prospective uncontrolled studies, and the majority 1.781/3.051 (58%) in retrospective and observational studies. In addition, only a small number of these patients was exposed to DMF-only treatment of psoriasis (around n=375). Hence, the long term safety data for DMF mono-treatment of psoriasis may be considered missing and has been included as such in the proposed safety specification and will be further investigated in a PASS as outlined in the RMP.

In addition, there is the safety data from spontaneous reports due to the long duration of clinical use (more than 20 years) of DMF containing products, mainly Fumaderm in Germany but also from other EU countries. However these data by their very nature cannot provide a fully accurate description of the safety profile of DMF containing products. However it is acknowledged that these data provide very useful supportive data to give reassurance on an acceptable profile.

With regards to the frequent adverse reactions of GI upset, flushing, erythema, pruritus, skin burning sensation, fatigue, decreased appetite, haematological abnormalities (lymphopenia, eosinophilia, leukopenia) and increase in hepatic enzymes, the frequency is reasonably characterised but not fully accurate as there is a range of incidences that is reported.

With respect to the lymphopenia, from the limited data available from the long-term follow-up study 1102, it is noted that although the treatment was stopped at week 16, the lymphocyte levels had still not recovered and were below the lower limit of normal ($1.0x10^9$/L) in 3/28 patients (10.7%) at 12 months after stopping treatment. However there were a number of drop-outs and only around 15% of the patients stayed in the study till week 52. This persistent low lymphocyte count is taken into account in the design of the PASS study to evaluate the occurrence of events of interest due to lymphocyte count even after stopping treatment with DMF containing products.

The important clinically significant consequence of persistent, prolonged lymphopenia is the occurrence of serious opportunistic infection of PML. Although the total number of case reports in psoriasis

patients with use of fumarates is low (n=8) over the number of years of its clinical use, the denominator with regards to the total number of patient exposure years for this incidence is not known and the reliability of the actual number of case reports is also not robust as these are from spontaneous case reports. In addition, there are more cases of PML reported with use of DMF in multiple sclerosis. However, the risk cannot be directly extrapolated as the risk is probably different in patients with multiple sclerosis, where patients are treated with other immunomodulators and the risk acceptance for the occurrence of PML is different. Nevertheless this provides additional information to support the fact that occurrence of PML is an identified risk with use of DMF.

In addition, the long-term safety for potential significant safety concerns of serious opportunistic infections including PML and malignancies are not well characterised in the published literature for Fumaderm. In any case, the safety profile of Fumaderm cannot be directly attributed to the proposed DMF product because of the difference in the therapeutic moieties as Fumaderm contains DMF and 3 other salts of monoethyl fumarate. Therefore a postmarketing safety study will be conducted to address the above deficiencies.

3.6. Effects Table

Table 43 - Effects Table for Skilarence in the treatment of psoriasis

Effect	Short Description	Unit	DMF	Fumaderm	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects							
PASI -75	Patients with PASI 75 after 16 weeks of treatment	Proportion (%)	37.5	40.3	15.3	The actual dose used by patients to have this effect and the data to support the maximum 750mg/day dose are not clear The efficacy in patients naïve to systemic therapies and patients who have failed/intolerant to other systemic therapies not clear	Study 1102
PGA	Patients with PGA score clear/almost clear after 16 weeks of treatment	Proportion (%)	33.0	37.4	13.0	As above	As above
DLQI	Change from baseline in Dermatology Life Quality Index at week 16	Mean DLQI reduction	5.9	6.0	2.4	As above	As above
Unfavourable Effects							
Gastrointestinal effects	Diarrhoea, Abdominal pain, Nausea, Flatulence, Vomiting, Dyspepsia, Constipation	%	60.6	60.1	27.0	Placebo and active comparator incidence from a randomized controlled study – strong evidence	Study 1102

Effect	Short Description	Unit	DMF	Fumaderm	Placebo	Uncertainties/ Strength of evidence	References
Skin and subcutaneous disorders	Erythema, Pruritus, Skin burning sensation	%	21.5	19.4	8.8	As above	As above
Vascular disorders	Flushing, hot flush	%	21.5	17.0	2.2	As above	As above
Blood disorders	Lymphopenia, Esoinophilia	%	16.5	16.6	0.7	As above	As above
Raised hepatic enzymes	ALT, GGT, AST	%	10.8	8.8	5.8	As above	As above
Discontinuation	Adverse events leading to treatment discontinuation	%	24.0	24.4	5.8	As above	As above
Malignancies	Mechanistic possibility/pre-clinical signal, some events reported but not sufficient data to conclude increased risk – potential safety concern	%	Not Known	Not known	Not known	From published literature over many years with DMF containing products – denominator of use not clear, not sure all cases have been identified and reported – so estimates not possible	Literature
Serious opportunistic infections particularly PML	Mechanistic possibility, some events reported,– potential safety concern	%	Not Known	Not known	Not Known	As above	Literature

Abbreviations:

PASI -75 – psoriasis area severity index -75 (patients with 75% improvement from baseline on PASI)

PGA – Physician's global assessment

DLQI – Dermatology Life Quality Index

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pivotal study has demonstrated that the proposed DMF product has a statistically significant and clinically relevant benefit over placebo on co-primary endpoints of PASI75 (proportion of patients showing >75% reduction in baseline PASI score) and PGA (greater proportion of patients who had clear/almost clear) after 16 weeks of treatment. The beneficial effects were slow in onset and evidence from literature suggests that there will be continued improvement beyond week 16 week with continued treatment. Similar superiority was shown on other secondary endpoints including PASI 90 (proportion of patients showing >90% reduction from baseline PASI score) and in the mean reduction of the affected body surface area from baseline. In addition, the patients' quality of life improved significantly as compared to placebo. Moreover from literature it is seen that fumarates can be used for

both induction and long-term maintenance treatment of psoriasis and there are reports of successfully managing psoriasis with fumarates over a period of a number of years with acceptable tolerability.

With regard to safety, the study showed that common adverse events were gastrointestinal (GI) disorders (diarrhoea, abdominal pain, nausea, vomiting, dyspepsia, constipation, flatulence), flushing, erythema, pruritus, skin burning sensation, fatigue, decreased appetite, haematological abnormalities (lymphopenia, eosinophilia, leukopenia) and increase in hepatic enzymes. Twenty four percent of the patients discontinued treatment due to adverse events. However, most events were resolved following treatment discontinuation. Furthermore these events are easily detected by clinical monitoring or lab investigations and have generally not led to clinically unacceptable sequelae. There is some uncertainty on the rates of these events as a range of incidence rates have been reported in literature. Nevertheless, this uncertainty is acceptable due to the fact that these can be monitored by routine investigations and development of undesirable clinical consequences can be prevented. Appropriate information to the prescriber in order to control these risks is given in the SmPC.

While lymphopenia is quite common and this could be a risk factor for serious opportunistic infections, the number of events of serious infection including PML is low as seen from published literature (especially considering the number of years of use of fumarates). However, compared to the high incidence of lymphopenia reported with fumarate use, the number of cases of serious infections is very low. Further, it is seen that after stopping treatment, the lymphocyte counts gradually increased and moreover the persistent decreased lymphocyte count did not result in clinically significant adverse events in the study 1102 or as seen from literature.

The number of cases of PML with use of fumarates in psoriasis patients that is reported in literature is low (n=8) with one case report of fatality and one case report of ‘recovery with sequelae’. This is in comparison to the reported mortality rate of 30-50% within first three months of diagnosis, if PML is not managed. Therefore, from the case-reports it is seen that the PML cases after treatment with fumarates were manageable and the unacceptable consequences can be limited. It is acknowledged by the nature of the reports, the reliability of the total cases of PML with use of fumarates in psoriatic patients and the uncertainty on the total exposure of patients for this incidence rate, no reliable estimate on the incidence rate of this significant clinical event cannot be currently estimated.

The risk of PML with other DMF containing products was reviewed recently by CHMP and appropriate recommendations for monitoring and treatment initiation, maintenance & discontinuation were made. The applicant has taken in to consideration these recommendations and proposed appropriate risk mitigation measures including educational materials for the healthcare professionals. Considering the implementation of these risk minimization measures, regular monitoring and treatment withdrawal (please see SmPC), the risk of increased incidence of PML with use of fumarates is considered acceptable given the current knowledge of its rate of incidence.

On efficacy and safety parameters, DMF (Skilarence) was shown overall to have a comparable effect to Fumaderm (which contains DMF in the same quantities as in this proposed product and additionally contains 3 other salts of monoethyl fumarate). Although a conclusion on non-inferiority to Fumaderm cannot be reliably drawn based on the data of the pivotal study, supporting literature suggests that DMF is the main active component with respect to its efficacy and safety profile in psoriasis which explains the comparability of the two products observed in study 1102. Further the dossier has shown the systemic exposure of the active metabolite of DMF is comparable between the proposed product and Fumaderm, although bioequivalence was not demonstrated.

Literature shows that Fumaderm and other DMF containing products maintain efficacy with long term treatment for periods greater than 24 months. Some studies suggest that the peak treatment benefits need treatment duration of 1 year. The prospective, open-label study by Linjen et al, 2016,

investigated long-term safety and efficacy of DMF monotherapy. Median treatment duration was 28 months. DMF monotherapy reduced PGA from 3.3/5 to 1.6/5 in 122 patients (69%) that reached the median maintenance dose of 480 mg/day after a median of 8 months.

The uncommon/rare/very rare/frequency unknown events based on safety information available with Fumaderm include proteinuria, increased serum creatinine, renal failure, serious opportunistic infections especially PML and Fanconi syndrome. Although the safety profile indicates potential for renal and hepatic injury as well as haematological abnormalities which may have potential serious consequences of infection, it has been shown with Fumaderm that these have been managed by regular monitoring and treatment withdrawal as appropriate. Given the extent of comparability between Skilarence and Fumaderm that was presented in this dossier (comparative PK, efficacy & safety data) and overall evidence to suggest that DMF is the main substance for the efficacy and safety in psoriasis, this evidence on long-term maintenance of efficacy and safety with Fumaderm is considered relevant and supportive of Skilarence, at least in broad terms.

Because of the small dataset with this product there are remaining uncertainties on the incidence of safety events. Also supporting information on potentially serious safety concerns such as malignancy and increased risk of serious opportunistic infections including PML on long-term use with other DMF containing products is sparse. Whereas the risks can be managed by appropriate warnings and recommendations included in the SmPC further characterisation of Skilarence in terms of uncommon, rare and very rare events (with respect to frequency, severity and any potential differences from other DMF containing products including Fumaderm) in the post authorisation phase will be done by means of a Post-authorisation safety study (PASS) as outlined in the RMP.

3.7.2. Balance of benefits and risks

Short-term efficacy of Skilarence is considered to have been convincingly demonstrated in comparison to placebo. All 3 primary objectives of the pivotal study in moderate to severe chronic plaques psoriasis at week 16 were met.

The long-term maintenance of efficacy with continued treatment comes from published literature of DMF containing products (mainly Fumaderm).

There are some uncertainties for the proposed DMF product in that although comparability to Fumaderm has been shown a strict bioequivalence has not been demonstrated nor is it required for an Article 8(3) application. However, any impact is likely to be only on some numerical differences in effect size and a major difference in effects is not anticipated, as these effects have been demonstrated consistently by different DMF containing formulations in literature and sufficient comparability between Skilarence and Fumaderm have been demonstrated in the studies submitted in this dossier.

The safety profile of Skilarence after 16 weeks of treatment has been characterised and has been shown to be comparable to that of Fumaderm in study 1102. The majority of TEAEs were of mild to moderate intensity. The common adverse events included gastrointestinal (GI) disorders (diarrhoea, abdominal pain, nausea, vomiting, dyspepsia, constipation, flatulence), flushing, erythema, pruritus, skin burning sensation, fatigue, decreased appetite, haematological abnormalities (lymphopenia, eosinophilia, leukopenia) and increase in hepatic enzymes. The most common reasons for treatment discontinuation were GI disturbances and flushing.

Most of the reported adverse events resolved without sequelae. More importantly most of these events are easily identified clinically or by laboratory monitoring and patients can be appropriately managed including measures of treatment withdrawal. These measures prevent development of unacceptable clinical consequences.

The long-term safety profile with continued treatment comes from published literature of Fumaderm. The significant clinical adverse events that have been reported with treatment of fumarates in psoriasis include serious opportunistic infections like PML. However, the risk can be mitigated by monitoring for lymphopenia and stopping treatment when appropriate.

It is also considered that fumarates may have the potential to increase the incidence of rare but clinically significant events like renal damage, malignancies and other serious infections. However, the numbers of case reports are very low in comparison to the extent of use and these potential risks are yet to be confirmed despite a number of years of clinical use of fumarates. To address the identified risk of PML and the uncertainties with regards the incidence rate of PML and other serious infections as well as the incidence of other potential rare adverse events, the applicant is committed to conduct a PASS. This is considered adequate.

Based on the overall evidence of benefits, which are clearly significant and meaningful for a significant proportion of the treated patients and the known safety profile which can generally be monitored and appropriate risk mitigation measures can be used including treatment withdrawal to successfully prevent unacceptable clinical consequences, the benefit-risk balance of Skilarence in the treatment of moderate to severe psoriasis is considered to be positive.

3.8. Conclusions

The overall B/R of Skilarence is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Skilarence is favourable in the following indication:

Skilarence is indicated for the treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of European Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Skilarence in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The objectives of the educational programme are to inform health care professionals about the risk of serious infections, mainly opportunistic infections such as progressive multifocal leukoencephalopathy (PML), and to provide guidance on the monitoring of lymphocyte and leukocyte count abnormalities.

The MAH shall ensure that in each Member State where Skilarence is marketed, healthcare professionals who are expected to prescribe and dispense Skilarence have access to the following educational package.

- **The guide for healthcare professionals** shall contain the following key elements:
    - Relevant information on PML (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable)
    - Details of the population at higher risk for PML

- Details on how to minimise the risk of PML through appropriate monitoring and management, including laboratory monitoring of lymphocyte and leukocyte prior to and during treatment, and criteria for treatment discontinuation
- Key messages to convey in counselling of patients