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

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Primary Objective:The primary objectives of the study are to demonstrate:• Superiority of LAS41008 versus placebo based on the proportion of subjects achievingPASI 75 at week 16 (a 75% reduction in the Psoriasis Area and Severity Index, PASI,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Epidermal and dermal conditions
Study type	Interventional

Summary

ID

NL-OMON39748

Source
ToetsingOnline

Brief title
Bridge study

Condition

- Epidermal and dermal conditions

Synonym
Psoriasis, psoriasis vulgaris

Research involving
Human

Sponsors and support

Primary sponsor: Almirall
Source(s) of monetary or material Support: Almirall

Intervention

Keyword: LAS41008, Psoriasis

Outcome measures

Primary outcome

Primary efficacy variables are:

- PASI 75 (= Response)

- Proportion of subjects achieving a score of "clear" or "almost clear" in the

Physician's Global Assessment (PGA)

Secondary outcome

- PASI 50, PASI 75, PASI 90, PASI 125

- Proportion of subjects achieving a score of "clear" or "almost clear" in the

Physician's Global Assessment (PGA)

- Body Surface Area (BSA)

- Treatment Success rate

- Remission rate

- Time to Relapse

- Time to Rebound (worsening of psoriasis over baseline value (PASI > 125%))

- Patient Benefit Index based on the Patient Need Questionnaire (PNQ) and the

Study description

Background summary

Psoriasis is a chronic inflammatory skin condition that is characterized by hyperproliferation and abnormal differentiation of epidermal keratinocytes, lymphocyte infiltration consisting mostly of T lymphocytes, and various endothelial vascular changes in the dermal layer, such as angiogenesis, dilation, and high endothelial venule formation. Meissner et al. demonstrated that DMF causes a decrease in tube formation in human endothelial cells in vitro. Although only formally authorized in Germany for the treatment of psoriasis, FAEs are accepted by some dermatologists as effective systemic therapies for both short-term and long-term treatment of moderate to severe psoriasis also in other countries of the EU as well as the US, in accordance with recent clinical therapy guidelines for psoriasis treatment.
Since its approval by the BfArM in 1994, Fumaderm® has become the most commonly prescribed product for the systemic therapy of psoriasis in Germany (approximately 66% of all prescriptions for systemic psoriasis therapy (EUROPSO 2002). In the S3 guideline, Fumaderm® is recommended not only for induction therapy, but also for long-term therapy in particular due to its good efficacy and safety profiles.

Fumaderm®, the reference product for this developmental program, is a prescription only medicine containing DMF and the calcium, magnesium and zinc salts of monoethylfumaric acid (MEF) as additional active ingredients. There is evidence from clinical data indicating DMF as the main active ingredient of Fumaderm® for the treatment of psoriasis.

Almirall S.A. intends to develop gastro-resistant tablet formulations of dimethyl fumarate (DMF) for the treatment of moderate to severe chronic plaque psoriasis in adult patients in need of systemic therapy. The tablets to be developed will contain the active ingredient DMF in two strengths (30 mg and 120 mg) only, without the monoethylfumaric acid salts as contained in the reference product Fumaderm®. Hence, these two tablet strengths correspond to the respective dosages of DMF in the already authorized reference product, Fumaderm®. In order to achieve an optimum efficacy and tolerability profile, a low initial dose of 30 mg DMF is recommended for the introduction of the therapy with 120 DMF. The development rationale is based on proven efficacy and safety of Fumaderm® and the evidence suggesting DMF is mainly responsible for the principal anti-psoriatic activity of the product.

Study objective

Primary Objective:
The primary objectives of the study are to demonstrate:
• Superiority of LAS41008 versus placebo based on the proportion of subjects achievingPASI 75 at week 16 (a 75% reduction in the Psoriasis Area and Severity Index, PASI, compared to baseline.
• Superiority of LAS41008 versus placebo based on the proportion of subjects achieving a score of *clear* or *almost clear* in the Physician*s Global Assessment (PGA) after 16 weeks of treatment.
• Non-inferiority of LAS41008 compared to Fumaderm® regarding PASI 75 after 16 weeks of treatment.

Secondary Objectives:
a. Superiority of LAS41008 versus placebo based on changes on PASI, PGA after 3 and 8 weeks and BSA after 3, 8 and 16 weeks.
b. Non-inferiority of LAS41008 compared to Fumaderm® regarding PASI 75 after 3 and 8 weeks of treatment.
c. Assessment of the safety of LAS41008 compared to Fumaderm® and Placebo for both treatment periods (30/120mg dimethyl fumarate).
d. - 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, angiotensin II inhibitors and statins.

Study design

This is a multicenter, randomized, three-arm, double-blind, adaptive, placebo and comparator controlled phase III clinical study to investigate the efficacy and safety of LAS41008 (30/120 mg) versus Fumaderm® (30/120 mg) and versus placebo. It is planned to randomize approximately 690
patients with moderate to severe chronic plaque psoriasis at 50 centres in Austria, Germany, Poland and the Netherlands (approximately 12 - 16 patients per site). Each patient will be randomized to receive either LAS41008, the comparator Fumaderm® or placebo in accordance with a randomization schedule of 2:2:1. The treatment scheme will be the same for each treatment group.

Intervention

Group 1:
LAS41008 containing 30 mg dimethyl fumarate per tablet, oral administration of up to 3 x 1 tablet per day during week 1 - 3
LAS41008 containing 120 mg dimethyl fumarate per tablet, oral administration of up to 3 x 2 tablets per day during week 4 - 16

Group 2:

Fumaderm® initial (LASW1835 initial) containing 30 mg dimethyl fumarate, oral administration of up to 3 x 1 tablet per day
Fumaderm® (LASW1835) containing 120 mg dimethyl fumarate respectively, oral administration of up to 3 x 2 tablets per day

Group 3:
Placebo

Duration of treatment:
Total duration of treatment period of 16 weeks.

Study burden and risks

Since Fumaderm® (which is marketed in Germany) contains the same active substance as LAS41008 (in addition to other active substances), it is likely that the side effects observed after intake of Fumaderm® may also occur in patients taking LAS41008.

The following side effects have been observed in patients taking Fumaderm® and are listed in the German Summary of Product Characteristics.

Contacts

Public
Almirall

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Signed and personally dated written informed consent
- Male / female
- Aged 18 years or older
- With a diagnosis of chronic plaque psoriasis for at least 12 months before enrollment in the study
- With the 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
- With general good health, or a stable medical condition not considered likely to interfere with the conduct of the clinical study, as determined by the investigator based upon results of medical history, laboratory results and physical examination
- Prior therapy with systemic drugs for psoriasis that was discontinued
e.g. due to an adverse event 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.
- Adhering to the following wash-out periods :
2 weeks : Corticosteroids, Vitamin A analogues, Vitamin D analogues, Anthracene derivatives, Tar, Salicylic acid preparations
3 months : Biologics with antipsoriatic activity
1 month : Conventional systemic antipsoriatic drugs and phototherapy
6 months: Immunosuppressive medication (if not covered by any of the above treatments)
- For females of child-bearing potential: a negative serum pregnancy test at screening and willing to use highly effective methods of birth control during the study period and for 60 days after the last dose of investigational product. Additionally they must agree to have pregnancy tests while on study medication. Highly effective methods of birth control are defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomized partner. Female patients will be considered to be of childbearing potential unless surgically sterilized by hysterectomy or bilateral tubal ligation, or post-menopausal for at least two years.
- Males (including those who have had vasectomy) must agree to use barrier contraception while on study medication
- Willing to keep sun exposure reasonably constant and not to use tanning booths or other

UV light sources for the duration of the trial

Exclusion criteria

- For females: pregnant or lactating
- With a diagnosis of guttate, erythrodermic or pustular psoriasis
- With a hematological abnormality as follows: platelet count < 100,000/mm3, WBC count < 3,000 cells/ mm3, lymphocyte count < 1.000/µl, hemoglobin, hematocrit, or red blood cell count outside 30 % of the upper or lower limits of normal for the lab
- With a history of malignancies except for non melanoma skin cancer
- Suffering from significant gastrointestinal problems (ulcers, diarrhea, etc.)
- Known to have severe renal impairment
- Are detected to have abnormal liver enzymes
(a) if an enzyme is >3x the upper limit of the normal range (AST (SGOT) ALT (SGPT), gamma-GT, alkaline phosphatase (ALP))
(b) if bilirubin is >2xULN, for the other liver enzymes >2xULN
- With active infectious disease
- On systemic therapy with drugs that may interfere with the investigational products taken within the defined wash-out period
- With a history of alcohol or drug abuse
- Known HIV-positive status or suffering from any other immunosuppressive disease
- Known to be hypersensitive to ingredients of the investigational products
- Previous enrolled in this study or participating in any other drug investigational trial within the 30 days (or five half-lives whichever is longer) prior to enrolment.
- Not willing to give consent for transmission of personal "pseudonymised" data
- Unable to comply with the requirements of the study or who in the opinion of the investigator should not participate in the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-10-2013
Enrollment:	45
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fumaderm®
Generic name:	Dimethyl fumarate
Product type:	Medicine
Brand name:	Fumaderm® initial
Generic name:	Dimethyl fumarate
Product type:	Medicine
Brand name:	LAS41008
Generic name:	Dimethyl fumarate

Ethics review

Approved WMO Date:	03-10-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-05-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-02-2014

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-000055-13-NL
CCMO	NL41945.091.12