2. SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor / Company:
Almirall, S.A.

Name of Finished Product:
Dimethyl fumarate and NB-UVB Phototherapy
Name of Active Ingredients:
N.A.</td><td>Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td>(For National Authority Use only)</td></tr>
<tr><td colspan="4">Title of Study: CLINICAL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF A COMBINATION THERAPY WITH DIMETHYL FUMARATE (DMF) AND NB-UVB PHOTOTHERAPY (VERSUS DMF MONOTHERAPY) IN ADULTS WITH MODERATE-TO-SEVERE CHRONIC PLAQUE PSORIASIS</td></tr>
<tr><td colspan="4">Investigators:
Twenty-one investigators were planned to participate in the study, however, due to the premature study termination only four investigators from two countries (Spain and Sweden) screened patients (see Appendix 16.1.4):

Spain: 1) Dr. Carrascosa, 2) Dr. Pérez
Sweden: 3) Dr. Tarsedt,4) Dr. Shayesteh

Co-ordinating Investigator: Dr. José Manuel Carrascosa; Hospital Universitari Germans Trias I Pujol, Badalona (Spain)</td></tr>
<tr><td colspan="4">Study centre (s):
Twenty-one centres were planned to participate in the study, but to the premature study termination only six centres accepted to participate: Hospital Germans Trias y Pujol, Hospital General de Universitari de Valencia, Hospital de Alicante, Karlskoga Lasaret, Hud- och STD-kliniken Norrlands Universitetssjukhus NUS and Centro Hospitalar e Universitário de Coimbra.

Due to the premature study termination only 4 centres from two countries (Spain and Sweden) screened patients (see Appendix 16.1.4):

Spain: 1) Hospital Universitari Germans Trias i Pujol, Badalona, 2) Hospital General Universitari de Valencia, Valencia
Sweden: 3) Karlskoga Lasaret, Karlskoga, 4) Hud- och STD-kliniken Norrlands Universitetssjukhus NUS, Län</td></tr>
<tr><td colspan="4">Publication (reference):
None</td></tr>
<tr><td colspan="3">Studied period (years):
Date study initiated (first screening): 18 December 2019
Date study finalised (last patient last visit): 02 July 2020</td><td>Phase of development: IV</td></tr>
</table>

OBJECTIVES:

Primary objective

To assess the efficacy of a DMF/NB-UVB PT combination regimen and DMF treatment alone in patients with moderate-to-severe chronic plaque psoriasis, as assessed by PASI 75 or PASI ≤3.

Secondary objectives

1. To assess the efficacy of a DMF/NB-UVB PT combination regimen and DMF treatment alone (as assessed by PASI, BSA, and PGA.
2. To assess the time to achieve a clinically meaningful improvement (as assessed by PASI) of a DMF/ NB-UVB PT combination regimen and DMF treatment alone.
3. To assess the efficacy of DMF/ NB-UVB PT combination regimen and DMF treatment alone according to patient-reported outcomes (PRO) (DLQI, Skindex-16, pruritus-VAS, and WPAI).
4. To assess cost-effectiveness (as assessed by health resources utilisation [HRU] and EQ-5D) of a DMF/ NB-UVB PT combination regimen and DMF treatment alone.
5. To assess the safety and tolerability of a DMF/ NB-UVB PT combination regimen and DMF treatment alone.
6. To assess adherence rate and patient satisfaction of a DMF/ NB-UVB PT combination regimen and DMF treatment alone.

METHODOLOGY:

This was a multicentre, randomised, parallel group, open label, and active comparator-controlled phase IV study to evaluate the efficacy and safety of DMF in combination with PT versus DMF alone. Patients were randomised (1:1) to Arm A (oral DMF + NB-UVB PT) or Arm B (oral DMF treatment alone). The study included a total of 8 visits distributed in three study periods: screening period (visit 1), treatment period (visit 2 to 7, visit 3 will be a virtual visit), and safety follow-up period (virtual visit 8). At the last visit of PT treatment (week 8 or when DMF+PT achieves complete clearance if before the planned 8 weeks), an unscheduled visit was done.

It was planned to randomise 150 patients across 21 study centres in Europe (approximately 7 patients per centre): Spain, Italy, Portugal, and Sweden. However, due to premature termination of the study (see detailed reason on Section 9.4.9 Early study termination), a total of 11 patients were screened and 9 patients were randomised (4 in Spain and 5 in Sweden). All patients in the DMF + NB-UVB PT arm were recruited in Sweden and, in the DMF treatment alone arm, four patients were recruited in Spain and one patient in Sweden. At the time of study termination, the protocol was not yet approved in Italy and the recruitment had not started in Portugal.

Name of Sponsor / Company: Almirall, S.A **Name of Finished Product:** Dimethyl fumarate and NB-UVB Phototherapy **Name of Active Ingredients:** N.A.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Number of patients (planned and analysed):

	DMF+NB-UVB PT	DMF	Total
Planned:	75	75	150
Screened:			11
Randomised:	4	5	9
Completed the study:	0	0	0
Evaluated for safety:	4	5	9
Evaluated for efficacy:	4	5	9

Diagnosis and main criteria for inclusion:
Please see Section 9.3.

Test product, dose and mode of administration, batch number, expiry date:

Dimethyl fumarate

Name: Dimethyl fumarate, DMF (Skilarence®)
Administration route: Oral
Unit dose/strength: Skilarence® 30 mg and Skilarence® 120 mg
Dosage form: Gastro-resistant tablet
Dose and regimen: Daily and as per treatment scheme
Batch number: IE2037383, IE2058644, IE2037524, and IE2058680

NB-UVB PT

NB-UVB PT were done 2 times per week for a maximum of 8 weeks (up to 16 sessions in total). Irradiation was done to their full body (face and genitals covered) under the care of the study dermatologist. Phototherapy (PT) dose (mJ/cm^2) per session was done according to the phototype as described in protocol.
NB-UVB PT is a routine therapy for patients with psoriasis. If complete clearance (defined as PASI 100) was achieved before completing the first 8 weeks treatment, PT was discontinued.

The active comparator was DMF alone.

Duration of treatment:
The Treatment Period included 7 visits. Moreover, patients with PT had an unscheduled visit at the end of PT treatment (week 8 or when DMF+PT achieves complete clearance before the planned 8 weeks).

Reference therapy, dose and mode of administration, batch number, expiry date:
N/A

Criteria for evaluation:

Efficacy:

For all endpoints, baseline values were defined as values collected at Week 1 (Visit 2).

Primary Endpoint

-Proportion of patients achieving “PASI 75 response **OR** PASI ≤3” at 24 weeks of treatment (composite endpoint.

Secondary Endpoints

Efficacy endpoints

-Proportion of patients achieving a PASI 75 response at 24 weeks of treatment.

-Proportion of patients achieving an absolute PASI score of ≤3 at 24 weeks of treatment.

-Proportion (and number) of patients achieving PASI 75, PASI 90 responses as well as absolute PASI score of ≤5, ≤3 and ≤1 all visits*.

-Absolute PASI score and percentage change from baseline in the absolute PASI score at all visits*.

-Proportion (and number) of patients with a PGA score of 0 or 1 ('clear' or 'almost clear') at all visits*.

-Absolute PGA score and change from baseline in the absolute PGA score at each visit*.

-Absolute BSA score and change from baseline in the absolute BSA score at each visit*.

-Time to achieve the primary composite endpoint (PASI 75 response **OR** to PASI score ≤3).

-Time to PASI 75 response.

-Time to PASI score ≤ 3.

-Absolute DLQI score and percentage change from baseline in the absolute DLQI score at all visits*.

-Proportion of patients achieving a DLQI score of 0 or 1 at all visits*.

-Absolute Skindex-16 score and change from baseline in the absolute Skindex-16 score at all visits*.

-Absolute pruritus-VAS score and change from baseline in the absolute pruritus-VAS score at all visits*.

-Absolute WPAI score and change from baseline in the absolute WPAI score at all visits*.

** When the data was collected*

-HRU related to psoriasis collected at Week 24:

- Number of visits related to psoriasis (including unscheduled).
- Treatments related to psoriasis (including dose, route, frequency, duration, onset date, end date, and reasons for onset and discontinuation.
- Number of hospitalisation/s related to psoriasis (if any, number of hospitalisations and length [days]).
- Number of unscheduled/emergency room visits to the general practitioner/dermatologist related to psoriasis (if any, number [days]).
- Diagnostic procedures related to psoriasis (clinical examination, laboratory controls, biopsy [if any], others).
- Percentage of HRU related to adverse reactions (ARs) to psoriasis-treatments generating costs (i.e. concomitant treatments, etc.).

- Quality Adjusted Life Year (QALY) for 24 weeks of treatment using the EQ-5D score.

Safety:

Safety and tolerability endpoints

-Safety and tolerability as assessed by vital signs, physical examination, safety laboratory, and

Treatment-Emergent Adverse Events (TEAEs).

Other endpoints

-Proportion of patients withdrawing from the trial at each visit and overall (and reasons for withdrawal), as well as time from Baseline to withdrawal.

-Treatment compliance.

-Proportion of patients achieving a score ≥ 7 in the numerical rating scale (NRS) treatment satisfaction-NRS at Week 24.

-Proportion of patients using topical corticosteroids (TCS) at each visit and overall, as well as the duration of the TCS treatment.

Statistical methods:

Analysis populations

The following different data sets to be analysed:

Safety Analyses Set (SAF) was defined as all patients who were randomised and took at least one dose of the study medication or received 1x PT.

The intent-to-treat (ITT) population in this study was defined as all randomised patients.

The modified intent-to-treat (mITT) population in this study was defined as all randomised patients who applied at least one-time study medication or received 1x PT and had at least one baseline value (e.g. PASI, BSA, or PGA).

Per-Protocol (PP) population was defined as a subset of mITT/ITT population (in Spain and Sweden, respectively) constituted by those patients who did not have any major protocol violations that could affect the main efficacy analyses.

The mITT/ITT population was the primary population (in Spain and Sweden, respectively) for the efficacy analysis while the PP population was used to assess the robustness of the findings from the mITT/ITT population, respectively. The precise reasons for excluding patients from the PP population were fully defined and documented in the statistical report (see more details in Section 9.7.).

Demographic and other baseline characteristics were analysed using the SAF.

All safety outcomes and other variables (i.e., concomitant medication, number of withdrawals) were analysed using the SAF.

SUMMARY – CONCLUSIONS

Efficacy Results:

Due to the early study termination, only 11 patients were screened and 9 of them were randomised, and none of them could finalize the 24 weeks of treatment. Therefore, efficacy of DMF/NB-UVB PT combination regimen and DMF treatment alone could not be analysed. As a result, there are no efficacy conclusions.

Safety Results:

Throughout the study, 6 patients reported TEAEs (total 9 TEAEs) (7 in the DMF + NB-UVB PT arm and 2 in the DMF arm). There were 3 AEs leading to discontinuation of the study (2 in the DMF + NB-UVB PT arm and 1 in the DMF arm), 2 of them possibly related to the study drug (diarrhoea and lymphocytopenia). A SAE was also reported in the DMF arm that led to drug discontinuation and was not related to the study drug (duodenal neuroendocrine tumour).

There were no deaths reported during the study.

CONCLUSIONS:

This was a phase IV study with the objective of evaluating the efficacy of DMF/NB-UVB PT combination regimen and DMF treatment alone in patients with moderate-to-severe chronic plaque psoriasis. The study was terminated prematurely with 9 patients randomised at that time. The reason for premature

termination was the irruption of the SARS-CoV-2 pandemic. As the study was going on, it was realized that with the situation of most hospitals across the European Union, the willingness of the patients to avoid frequent visits to the sites as well as the difficulty in accessing the phototherapy equipment increased quite remarkably. As these factors had a great impact in the quality of the clinical trial, in its data, and therefore in its results, Almirall decided to prematurely terminate the study. Premature termination was not based on any safety or efficacy concerns (for more details see Section 9.9).

Due to the early study termination and limited data, efficacy and overall safety profile of DMF/NB-UVB PT combination regimen and DMF treatment alone in patients with moderate-to-severe chronic plaque psoriasis could not be analysed; therefore, this study could not report any conclusion.

DATE OF REPORT:
24th November 2020