SYNOPSIS

Name of Company: Dompé s.p.a. (Dompé)	**Individual Study Table Referring to Part of the Dossier:** **Volume:**	*(For National Authority Use Only)*
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Title of Study: A phase 2, multi-center, single-arm, pilot study to assess the efficacy and the safety of 150 mg twice a day oral DF2156A in patients with active bullous pemphigoid.

Investigator(s) and Study Center(s): Four sites (1 in Italy and 3 in Germany) were recruited to enroll patients.

Publication (reference): None

Study Period (years): 29 February 2012 to 05 July 2012

Phase of Development: 2

Objectives: The objective of this clinical trial was to evaluate whether DF2156A has a potential in improving the clinical outcome in patients with active blistering bullous pemphigoid (BP) to warrant its further development. The safety of DF2156A in the specific clinical setting was also evaluated.

Methodology: This was a Phase 2, multi-centre, single-arm, pilot study. A total of 12 BP patients were planned for inclusion in the study and were to be administered DF2156A 150 milligrams (mg) orally twice a day for a maximum of 14 days.

Recruitment was to be competitive among the study sites until the planned number of patients was enrolled. Competitive recruitment was chosen to increase the speed of recruitment and to account for any unexpected occurrence at a site that could have negatively impacted the rate of enrollment.

The single-arm design was chosen as an appropriate tool for this study because BP is a rare disease where a placebo control is not acceptable. Moreover, as there is no spontaneous acute recovery from the active blistering condition, any improvement in patient outcome can be attributed to a positive effect of the investigational product.

Each patient was planned to be involved in the study for a screening period, for 14 days of treatment, for all required measurements up to hospital discharge (planned on day 8$\pm$1 of treatment) and for 1 assessment occasion on day 15$\pm$1, either during the hospital stay or after hospital discharge (out-patient visit). An optional post-treatment visit could have been scheduled at day 30$\pm$3.

Number of Patients (planned and analyzed): Twelve patients were planned for inclusion in the study. Overall, 5 patients were screened for the study and 4 patients were enrolled into the study and included in the safety population.

Diagnosis and Main Criteria for Inclusion: Male and female patients aged ≥50 years of age with newly diagnosed or relapsing BP based on clinical diagnosis confirmed by direct immunofluorescence and indirect immunofluorescence on salt-spit skin (or BP180 and/or BP230 ELISA). Patients with mild to moderate active blistering disease (total number of blisters between 1 and 30) whether associated or not with urticarial/eczematous lesions.

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Test Product, Dose and Mode of Administration, Batch Number: DF2156A provided as 75-mg hard gelatin white opaque capsules (size 3) in a patient box with 14 treatment-day sachets (2 x 75 mg capsules each, 1 for morning and 1 for evening administration). Batch Number: PPD

Duration of Treatment: 14 days

Criteria for Evaluation:

Efficacy:

No tables were generated for efficacy and no efficacy population was used for evaluation.

Safety:

The Safety population consisted of all patients who received any study medication. The Safety population was used to present the demographic and baseline data, and all safety data.

Statistical Methods:

As the study was abandoned after 4 subjects were enrolled, the data were summarized via listings only.

Efficacy Endpoints:

- Total number of blisters and percent change from baseline (time frame: day 0/1 [pre-dose], day 8 and day 15).
- Modified Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) score and percent change from baseline (time frame: day 0/1 [pre-dose], day 8 and day 15).
- Physician's Global Assessment (PGA) score measured on a 0-10 scale. Absolute value and percent change from baseline (time frame: day 0/1 [pre-dose], day 8 and day 15).
- Pruritus measured on a 10 cm visual analogue scale. Absolute value and percent change from baseline (time frame: day 0/1 [pre-dose], day 8 and day 15).
- Eosinophil blood count. Absolute number and percent change from baseline (time frame: screening and day 15).
- Number and percentage of patients with treatment failure (drug discontinuation due to lack of improvement [time frame: day 8]).
- Number and percentage of patients completely free from blisters (time frame: day 15).
- Number of patients who were still free from blisters without requiring any systemic or topical rescue treatment - Optional (time frame: day 30).

Pharmacokinetic Endpoint:

Plasma levels of DF2156A and its major metabolites (DF2227 and DF2108) at steady state conditions (time frame: day 5 and day 8).

Safety Endpoints:

- Vital signs (blood pressure and heart rate) (time frame: screening and day 15 [or withdrawal]).

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- Routine laboratory tests (hematology, clinical chemistry) (time frame: screening and day 15 [or withdrawal]).
- Corrected QT interval using Fredericia's formula (QTcF). Absolute value and change from baseline (time frame: day 0/1 [pre-dose], day 1, 5, 8 and 15).
- Incidence of Adverse Events (AEs) and Serious Adverse Events (SAEs) (time frame: throughout the study up to day 15 or day 30).

Summary and Conclusions:

Disposition and Demographics: Four white male patients with BP between the ages of 65 and 75 were included in the safety population.

Efficacy Results: The study was terminated early due to lack of efficacy. Of the 4 enrolled patients, only 1 patient completed the 14-day treatment period. The remaining 3 patients were discontinued from the study early (1 patient due to treatment failure and 2 who were discontinued and admitted to rescue therapy).

Pharmacokinetic Results: Blood samples to determine plasma levels of DF2156 and its major metabolites (DF2227 and DF2108) at steady state conditions were taken and were under analysis during the writing of this abbreviated clinical study report.

Safety Results: Three patients experienced a total of 4 AEs during the study. The AEs reported were PPD (1 patient), PPD and PPD (1 instance each in the same patient), and PPD (1 patient). All of the AEs were mild and considered either possibly, probably, or highly probably related to study treatment with the exception of 1 AE in 1 patient PPD) which was considered unrelated to study treatment. Two patients had a series of abnormal ECGs at baseline that continued throughout the study neither of which were considered clinically significant by the investigator. There were no other safety findings deemed clinically significant by the investigator. There were no deaths, SAEs, or discontinuations from the study due to AEs.

Conclusion: The objective of this clinical trial was to evaluate whether DF2156A has a potential in improving the clinical outcome in patients with active blistering BP to warrant its further development. The safety of DF2156A in the specific clinical setting was also explored. Overall, DF2156A did not prove efficacious at the tested dose and schedule (150 mg twice a day for a maximum of 14 days). Only 1 of the 4 enrolled patients completed the study's 14-day treatment period. The remaining 3 patients were discontinued from the study early (1 patient due to treatment failure and 2 patients who were discontinued and admitted to rescue therapy). While DF2156A appeared to be safe and was generally well-tolerated with only mild AEs reported in 3 patients (and no deaths, SAEs, or discontinuations from the study due to AEs), the limited sample size of the safety population prevents any overall conclusions of safety regarding the investigational product.

Date of the Report: 20 December 2012