2 SYNOPSIS

Name of Sponsor/Company: DS Biopharma	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: DS107E Cream		
Name of Active Ingredient: DGLA		

Title of Study: A Prospective, Randomised, Vehicle-controlled, Double-blind, Exploratory Clinical Trial to Assess the Efficacy and Steroid-sparing Potential of DGLA Cream Topically Applied to Early Childhood Patients with Moderate to Severe Atopic Dermatitis

Investigator: Prof. Alan Irvine

Study Phase: 2A

Study Center: Our Lady's Children's Hospital Crumlin, Dublin, Ireland

Study Period:
Date of first enrollment: 08 January 2016
Date of last completed: 25 April 2016

Objectives:

Primary Objective:

To evaluate the clinical efficacy of alternating treatment with Locoid® Ointment (hydrocortisone butyrate 0.1%) and 1% topical DGLA formulation once daily (OD) compared to Locoid® Ointment (hydrocortisone butyrate 0.1%) and vehicle OD for one week, followed by eight weeks of treatment with either 1% topical DGLA formulation alone twice daily (BD) or vehicle alone BD in early childhood patients with moderate to severe Atopic Dermatitis (AD).

Secondary Objective:

To evaluate the efficacy of DGLA cream in the improvement of clinical signs and symptoms in AD including Investigator's Global Assessment (IGA), SCORing of Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI), Body Surface Area (BSA), improvement of quality of life, family impact, investigation of skin barrier function, days to relapse and rescue medication use.

Methodology:
This was a randomised, vehicle-controlled, double-blind, parallel group, exploratory study to investigate the efficacy and steroid-sparing potential of topically applied DS107E DGLA cream in early childhood patients with moderate to severe AD. Two parallel groups of patients with confirmed AD were to be investigated in this study to compare DS107E DGLA cream with vehicle over a 63-day treatment period.
The study consisted of a Screening Visit, a Baseline Visit, Day 7 Visit, Day 14 Visit (Telephone Visit), Day 21 Visit , Day 35 Visit, Day 49 Visit, a Day 63 Final Visit and a Follow-up Visit on Day 91. All patients were to undergo a tolerability patch test of DGLA at a minimum of 72 hours

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prior to treatment. Patients not receiving treatment for their AD could continue to the treatment phase of the study, as long as they met all of the entry criteria at Baseline Visit.
In the event that treatment was occurring, a wash out period of up to 28 days may have been necessary. Patients were assessed at the Screening Visit using the screening examinations after the parents/guardians had given informed consent for the patient to participate. Eligible patients with confirmed AD who met the inclusion criteria and did not meet the exclusion criteria were enrolled using the Hanifin and Rajka criteria.

During the treatment period and follow-up period patients were restricted from using any other treatment for AD or from taking new or not previously prescribed anti-histamines or any antimicrobial medication. Any medication (prescription as well as over the counter (OTC) drugs) or therapeutic intervention deemed necessary for the patient, and which in the opinion of the investigator did not interfere with the safety and efficacy evaluations, was continued. A list of "medications and therapeutic regimens excluded from the study" was defined in the protocol as concomitant medication.

Following completion of the wash-out period, before the comparative treatment period could commence, patients returned to the site for a baseline investigator assessment of the severity of their AD.

Eligible patients were randomly allocated to one of the two parallel group treatment regimens by a 1:1 randomisation:

- Locoid® ointment (hydrocortisone butyrate 0.1%) (morning) + DS107E DGLA 1% cream (evening) applied topically OD each for seven days. (As the first dose of treatment occured on the evening of Day 0, Locoid® was only applied at six time points [Day 1 – Day 6]). DGLA 1% alone was then applied topically for a further 56 days BD.
- Locoid® ointment (hydrocortisone butyrate 0.1%) (morning) + DS107E vehicle cream (evening) applied topically OD each for seven days. (As the first dose of treatment occurred on the evening of Day 0, Locoid® was only applied at six time points [Day 1 – Day 6]). Vehicle alone was then applied topically for a further 56 days BD.

The patients' parents/guardians were provided with Locoid® Ointment and either 1% DS107E cream or vehicle cream was applied liberally to the patient's whole body OD according to the randomisation schedule above.

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For the first seven days parents/guardians applied Locoid® Ointment OD (morning) and 1% DS107E cream or vehicle cream OD (evening). After seven days parents/guardians applied either 1% DS107E cream or vehicle cream BD until Day 63.

During the first seven days of treatment parents/guardians sparingly applied Locoid® ointment (hydrocortisone butyrate 0.1%) topically to affected areas of skin OD (morning), as per randomisation schedule. As the first dose of treatment occured on the evening of Day 0, Locoid® was only applied at six time points (Day 1 – Day 6).

To maintain the double-blind conditions, the DS107E DGLA cream and DS107E vehicle cream was identical in appearance.

Following completion of the comparative treatment period and follow-up period there were restrictions on the treatment for AD.

Disease severity assessments were performed at the following scheduled visits at the study site: Screening (Visit 1), Baseline/Day 0 (Visit 2), Day 7 (Visit 3), Day 35 (Visit 6), Day 63 (Visit 8) and Day 91 (Visit 9).

Number of Patients (Planned and Analysed):
Planned: 40 patients (20 in each treatment group).
Randomised: 5
Analysed: Data not analysed due to the low number of patients.

Diagnosis and Main Criteria for Inclusion:
This study was to enroll male and female infants aged 3-12 months with moderate to severe AD (Hanifin and Rajka Criteria; IGA > 3); covering a minimum of 10% of their body surface area.

Test Product, Dose and Mode of Administration, Batch Number: See Appendix 16.1.6

Duration of Treatment:
Patients were dosed twice daily with study drug, for up to 63 days (seven days with Locoid® cream in the morning and DS107E/vehicle [as randomised] in the evening; the remaining 56 days both morning and evening doses with the DS107E/vehicle as per randomisation schedule).

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Criteria for Evaluation:

Efficacy:

The primary efficacy variable was change in IGA and/or change in SCORAD from Day 0/Visit 2 to Day 63/Visit 8.

Secondary efficacy variables were change in:

- Change in IGA from Baseline/Day 0 (Visit 2) to Day 7 (Visit 3), Day 21 (Visit 5), Day 35 (Visit 6), Day 49 (Visit 7), Day 63 (Visit 8) and from Day 63 (Visit 8) to Follow up Day 91 (Visit 9).
- Change in SCORAD from Baseline/Day 0 (Visit 2) to Day 7 (Visit 3), Day 21 (Visit 5), Day 35 (Visit 6), Day 49 (Visit 7), Day 63 (Visit 8) and from Day 63 (Visit 8) to Follow up Day 91 (Visit 9).
- Change in EASI from Baseline/Day 0 (Visit 2) to Day 7 (Visit 3), Day 21 (Visit 5), Day 35 (Visit 6), Day 49 (Visit 7), Day 63 (Visit 8) and from Day 63 (Visit 8) to Follow up Day 91 (Visit 9).
- Change in IDQOL from Baseline/Day 0 (Visit 2) to Day 7 (Visit 3), Day 21 (Visit 5), Day 35 (Visit 6), Day 49 (Visit 7), Day 63 (Visit 8) and from Day 63 (Visit 8) to Follow up Day 91 (Visit 9).
- Change in DFI from Baseline/Day 0 (Visit 2) to Day 7 (Visit 3), Day 21 (Visit 5), Day 35 (Visit 6), Day 49 (Visit 7), Day 63 (Visit 8) and from Day 63 (Visit 8) to Follow up Day 91 (Visit 9).
- Change in the BSA from Baseline/Day 0 (Visit 2) to Day 7 (Visit 3), Day 21 (Visit 5), Day 35 (Visit 6), Day 49 (Visit 7), Day 63 (Visit 8) and from Day 63 (Visit 8) to Follow up Day 91 (Visit 9).
- Change in the Transepidermal water loss (TEWL) from Baseline/Day 0 (Visit 2) to Day 63 (Visit 8) and from Day 63 (Visit 8) to Follow up Day 91 (Visit 9).
- Time to rescue medication use: The time elapsed between Day 7 and the necessity to use rescue medication before the end of the trial (conditional endpoint).

Safety: Safety was evaluated using:

- Parent's/guardian's assessment of local tolerability.

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- Safety laboratory parameters (haematology, clinical chemistry).
- Clinical safety examinations (vital signs, physical examination).
- Adverse event (AE) and serious adverse event (SAE) frequency and severity.

Results:

Due to difficulties experienced by the site in recruitment, the Sponsor terminated the study prematurely. In view of this, and the very few patients enrolled, it was not possible to perform formal analyses of the data. Tabulations of efficacy measures can be found in the appendices of this study report. No patients were receiving treatment at the time of study termination.

Conclusions:

Due to unsatisfactory recruitment progress, the sponsor decided to terminate the study in October 2016. Due to the small amount of data collected, and the fact that no patients completed the study, data analyses are not robust enough to draw any conclusions on safety or efficacy.

Date: 13 March 2017