Clinical Study Synopsis for Public Disclosure

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1 Title Page

Study Title	Effect of CD08100/02 3% gel versus placebo gel in subjects presenting with papulopustular rosacea over a 6-week treatment period
Protocol no.:	RD.03.SPR.40162E
EudraCT no.	2011-002058-30
Name of test drug / Product	CD08100/02
Comparator	Metrogel® (Metronidazole; CD0036)
Indication	Papulopustular rosacea (PPR) (subtype II rosacea)
Design	This was a multi-centre, randomised, intra-individual (split-face comparison), investigator-blinded, placebo-controlled study, involving approximately 50 subjects with moderate to severe PPR who met specific inclusion and non-inclusion criteria. The study incorporated an active comparator study arm (positive control group) using Metronidazole 1% gel. The two study arms were defined as follows: • CD08100/02 3% gel on one side of the face and placebo gel on the other side of the face; or • Metronidazole 1% gel on one side of the face and placebo gel on the other side of the face (positive control group). A screening period of up to 4 weeks (within 3 to 30 days prior to Baseline) was followed by a 6-week treatment period. The same placebo gel was used in both study arms; the vehicle of Metronidazole 0.75% gel.
Development Phase	Phase IIa
Sponsor	Galderma R&D Les Templiers 2400, rout des Colles 06410 Biot Phone: +33 (0)4 93 95 70 70 Fax: +33 (0)4 93 95 70 71
Coordinating Investigator	
Author of Report	

Study Initiation Date	First patient in (FPI): 12-DEC-2011
Study Completion Date	Last patient out (LPO): 23-MAR-2012
Date of Report	13-DEC-2012
This study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.	

2 Synopsis

Title of study: Effect of CD08100/02 3% gel versus placebo gel in subjects presenting with papulopustular rosacea over a 6-week treatment period
Publication (reference): Not applicable
Phase of development: IIa
Studied period (years): **Date of first subject enrolment:** 12-DEC-2011 **Date of last subject completed:** 23-MAR-2012
Objectives **Primary objective:** To evaluate the efficacy of CD08100/02 3% gel versus placebo gel after a 6-week treatment period in subjects presenting with moderate to severe PPR (subtype II rosacea). **Secondary objectives:** To evaluate the safety of CD08100/02 3% gel versus placebo gel after a 6-week treatment period in subjects presenting with moderate to severe PPR (subtype II rosacea). **Primary effectiveness criterion was:** • The raw inflammatory lesions count and its percentage change from Baseline (Day 1) at Final

Visit (Day 40).

Secondary effectiveness criteria:

Clinical evaluation:

- Change from Day 1 (Baseline) in inflammatory lesions count (papules and pustules) for each side of the face at each evaluation visit,
- Change from Day 1 (Baseline) in erythema severity score from photographic scale for each side of the face at each evaluation visit,
- Edema score for each side of the face at each evaluation visit,
- Number, severity and duration of flushing / blushing episodes per week, for each side of the face at each evaluation visit,
- Functional signs assessment for each side of the face at each evaluation visit.

Subject's and investigator's preference for PPR:

- Subject and investigator preference of overall pathology at Day 40 (Final Visit / Early Termination Visit).

Exploratory criteria:

Photographic evaluation:

- Change from Day 1 (Baseline) in telangiectasia severity score from photographic scale for each side of the face at each evaluation visit,
- Photographs taken with Visia CR at each evaluation visit (only for three centres concerned).

Secondary safety criteria:

- Adverse events (AE),
- Physical examination at Screening and Day 40 (Final Visit / Early Termination Visit),
- Vital signs and weight at visit at Screening and Day 40 (Final Visit / Early Termination Visit).

Methodology:

This was a multi-centre, randomised, intra-individual (split-face comparison), investigator-blinded, placebo-controlled study, using CD08100/02 and an active comparator (positive control group; Metrogel®; Metronidazole 1% gel; CD0036). This study comprised two different arms:

- CD08100/02 3% gel on one side of the face and placebo gel on the other side of the face; or
- Metronidazole 1% gel on one side of the face and placebo gel on the other side of the face (positive control group).

The same placebo gel was used in both study arms; the vehicle of Metronidazole 0.75% gel.

Number of centres:

Seven German investigational sites were recruited for this study.

Total number of subjects:

58 subjects were randomised in this study in a 1:1 ratio to one of the two study arms.

Number of subjects (planned and analysed):	planned: 50 screened: 64	randomised: 58 completed: 58	analysed efficacy: 58 analysed safety: 58

Diagnosis and main criteria for inclusion:

Male and female subjects, >18 years of age, with the diagnosis of moderate to severe PPR were included. Eligible subjects had to present at least 15 inflammatory facial lesions (papules and / or pustules) to allow a sufficient number to detect an effect of treatment. Lesions located on the central part of the face (nose, chin and middle forehead) were not included in this count because of the split-face design that did not allow any product application on these areas.

Test product, dose and mode of administration, batch number:
Solaraze® (diclofenac sodium; CD08100/02) Batch number(s): 109292/11.01608
109292/11.01864
109292/11.02171

The quantity of product to be applied on each half face (approx. 200 cm^2) was determined on the basis of a dose of 2 mg/cm², i.e. 400 mg equivalent to 0.4 ml which was taken with a tuberculin syringe of 1 ml. The treatments were applied at the investigational study centre by a qualified person other than the investigator, once daily (except on Saturdays and Sundays). The appropriate quantity of products was applied on each side of face and massaged gently with a gloved hand to enhance penetration. Gloves were changed between each application. Study drugs were applied to each side of face for the entire 6-week treatment period, even if the rosacea cleared.

Name of active ingredient: diclofenac sodium

Duration of treatment:
Duration of subject participation:
Total study duration for one subject was approx. 10 weeks including a screening period of up to 4 weeks and a 6-week treatment period. The treatment period had consisted in applications on 5 days per week (Mondays to Fridays) during the first 5 weeks and from Monday to Thursday during the sixth week (total of 29 applications).

Study duration:
Approximately 5 months from the First Patient In (FPI) to the Last Patient Out (LPO).

Reference therapy, dose and mode of administration, batch number:
Active comparator
Metrogel® (Metronidazole; CD0036) Batch number(s): 082682/11.01773

Placebo
Vehicle of Metronidazole 0.75% gel (CD0036NF gel placebo)
Batch number(s): 0569.0005P/11.01564

The dose and mode of administration for the active comparator as well as placebo was the same as for the test product.

Criteria for evaluation:
Efficacy assessments:
The efficacy analysis was performed on the per protocol (PP) and intent-to-treat (ITT) population.
Clinical assessment:
The following evaluations were performed for both sides of the face, for each subject.

- Inflammatory lesions (count of papules and pustules including cheeks and left and right side of forehead, but not nose, chin or middle forehead),
- Erythema (severity score),
- Telangiectasia (severity score),
- Edema (severity score),
- Flushing / blushing (frequency, severity and duration): reporting on a daily basis by the subject and recording by the investigator every week,
- Functional signs (scores of itching, dryness sensation, and stinging / burning).

Subject's and investigator's preference for PPR:

- The subject and the investigator compared the left and right sides of the face and gave their preference regarding pathology on Day 40 (Final Visit / Early Termination Visit).

Photographic evaluation:

- Standardised photographs of the subject's face (front, left and right sides) were taken in cross-polarised lighting in three study centres only.

Safety assessments:

The safety analysis was based on the safety analysis population (SA).

- Documentation of AEs throughout the clinical investigation,
- Physical examination at Screening and Day 40 (Final Visit / Early Termination Visit),
- Vital signs and weight at visit at Screening and Day 40 (Final Visit / Early Termination Visit).

Statistical methods:

In general, data were listed, sorted by site, subject, treatment and visit within subject (when appropriate).

All efficacy variables were summarised at each visit up to Day 40, using observed data in PP analysis. Additionally, all efficacy variables were analysed in the ITT population using the last observation carried forward (LOCF) within the treatment period.

The efficacy analyses performed for CD08100/02 3% gel versus placebo was also be performed for the active comparator (Metronidazole 1% gel) versus placebo.

The efficacy endpoints inflammatory lesions count, edema severity score, number, duration and severity of flushing / blushing, functional signs (itching, dryness sensation and stinging / burning), telangiectasia severity score and pathology preference by the investigator and the subject were analysed using a two-sided Wilcoxon signed rank test at a 5% significance level. Calculated changes from Baseline (Day 1) and percent changes from Baseline (Day 1) were evaluated in the same way.

The change from Baseline (Day 1) in erythema severity score was analysed using Student's t-test for paired data at a two-sided 5% significance level.

If possible, summary tables were grouped by study arm and treatment. Summary tables of adverse events were additionally grouped by intensity and relationship to study medication and summarised by system organ class (SOC) and preferred term (PT) respectively.

According to the level of measurement variables were summarised by mean, median, standard deviation, range and numbers and percentages respectively.

Results and conclusions:

In this study, subjects with moderate to severe PPR were treated over a period of 6 weeks once daily (except Saturdays and Sundays) with CD08100/02 3% gel on one half of the face. The other half of the face was treated with placebo gel. In addition, an active comparator arm was included with treatment with Metronidazole 1% gel on one side of the face and placebo gel on the other side of the face.

58 subjects were randomised and received study treatment. All randomised subjects completed the study.

Primary efficacy results:

Total inflammatory lesion count at Day 40 and percent change from Baseline (Day 1)

The mean and median of **total inflammatory lesions count at Day 40** were lower in the hemi face treated with CD08100/02 3% gel respectively with Metronidazole 1% gel than in the Placebo-treated hemi face. The null hypothesis of no treatment effect could be rejected at a 5% significance level for both study arms.

The mean as well as median absolute **percent change from Baseline of inflammatory lesion count at Day 40** were higher in the hemi face treated with CD08100/02 3% gel respectively with Metronidazole 1% gel than in the Placebo-treated hemi face. The null hypothesis of no treatment effect could be rejected at a 5% significance level for CD08100/02 3% gel, but could not be rejected for Metronidazole 1% gel.

Secondary efficacy results:

Inflammatory lesions count at each visit

The mean inflammatory lesions count at each visit for the CD08100/02 3% gel study arm is clearly higher for the Placebo-treated hemi face than for the CD08100/02 3% gel-treated hemi face or for the

Metronidazole 1% gel-treated hemi face (starting after Day 5). The null hypothesis of no treatment effect could be rejected at a 5% significance level for Days 5 to 40 for CD08100/02 3% gel and for Days 12 and 40 for Metronidazole 1% gel. The absolute median percent change in inflammatory lesions count from Baseline is clearly higher in the hemi face treated with CD08100/02 3% gel than in the Placebo-treated hemi face at each evaluation visit and it is also higher in the hemi face treated with Metronidazole 1% gel than in Placebo-treated hemi face after Day 5. The null hypothesis of no treatment effect could be rejected at a 5% significance level for Days 12, 26, 33 and 40 in the CD08100/02 3% gel study arm. For Metronidazole 1% gel the null hypothesis could not be rejected for each evaluation visit. The absolute median change in inflammatory lesions count for the CD08100/02 3% gel study arm is clearly higher for the hemi face treated with CD08100/02 3% gel than for the hemi face treated with Placebo and it is also higher for the hemi face treated with Metronidazole 1% gel than for the Placebo-treated hemi face after Week 2 - Day 12. The null hypothesis of no treatment effect could be rejected at a 5% significance level for each evaluation visit except for Day 19 for CD08100/02 3% gel. For Metronidazole 1% gel the null hypothesis could not be rejected for each evaluation visit.

Erythema severity score

The null hypothesis of no treatment effect could not be rejected at a 5% significance level for each evaluation visit for CD08100/02 3% gel. For Metronidazole 1% gel the null hypothesis could not be rejected for Days 1 to 33 but could be rejected at Day 40 where the score for the Metronidazole 1% gel-treated hemi face was significantly better than for the Placebo-treated hemi face. For the change in erythema severity score from Baseline the null hypothesis of no treatment effect could not be rejected at a 5% significance level for Days 5 to 26 but could be rejected at Day 33 and Day 40 for CD08100/02 3% gel where the change from Baseline was significantly better for the CD08100/02 3% gel-treated hemi face than for the Placebo-treated hemi face. For Metronidazole 1% gel the null hypothesis could not be rejected at each evaluation visit.

Edema severity score

The null hypothesis of no treatment effect could not be rejected at a 5% significance level for each evaluation visit for both study arms.

Flushing / blushing

For mean number of flushing / blushing episodes per week, the null hypothesis of no treatment effect could be rejected at a 5% significance level for Week 1 and Week 2 but could not be rejected for Week 3 to Week 6 for CD08100/02 3% gel. The mean number of flushing / blushing episodes is higher for the CD08100/02 3% gel-treated hemi face than for the Placebo-treated hemi face until Week 5 thereafter the mean number of episodes is slightly lower for the hemi face treated with CD08100/02 3% gel. For Metronidazole 1% gel the null hypothesis of no treatment effect could not be rejected for all time points. For severity and duration of flushing / blushing episodes the null hypothesis of no treatment effect could not be rejected at a 5% significance level for each week for both study arms.

Functional signs

The null hypothesis of no treatment effect could not be rejected for dryness sensation and itching for all time points for CD08100/02 3% gel. For stinging / burning the null hypothesis of no treatment effect could be rejected for Week 1 - Day 5 and Week 2 - Day 12 but could not be rejected for the other time points. The stinging / burning was significantly better for the Placebo-treated hemi face for Week 1 - Day 5 and Week 2 - Day 12 than for the CD08100/02 3% gel-treated hemi face. For Metronidazole 1% gel the null hypothesis of no treatment effect could not be rejected for itching, dryness sensation and stinging / burning for all time points.

Pathology preference of the investigator and subject

The null hypothesis of no preference of a hemi face could be rejected for CD08100/02 3% gel: 14 investigators and 16 subjects evaluated the side of the CD08100/02 3% gel-treated side of the face as better or much better than the Placebo-treated side, 14 investigators and 10 subjects saw no differences between the sides of the face and only 2 investigators and 4 subjects evaluated the Placebo-treated side

as better or much better as the CD08100/02 3% gel-treated side. The null hypothesis that investigators and subjects did not prefer a hemi face could not be rejected at a 5% significance level for Metronidazole 1% gel.

Telangiectasia score

The null hypothesis of no treatment effect could be rejected for Week 6 - Day 40 and could not be rejected for the other time points for CD08100/02 3% gel. At Week 6 - Day 40 the Telangiectaisa score was significantly better for the hemi face treated with CD08100/02 3% gel than for the Placebo-treated hemi face. For Metronidazole 1% gel the null hypothesis of no treatment effect could be rejected at a 5% significance level for Week 5 - Day 33 and could not be rejected for the other time points. For Week 5 - Day 33 the Telangiectasia score is significantly better for the Metronidazole 1% gel-treated hemi face than for the Placebo-treated hemi face. For its change from Baseline the null hypothesis of no treatment effect could not be rejected for all time points for CD08100/02 3% gel. For Metronidazole 1% gel the null hypothesis could be rejected for Week 5 - Day 33 and could not be rejected for the other time points. At Week 5 - Day 33 the change from Baseline of Telangiectasia score was better for the Metronidazole 1% gel-treated hemi face than for the Placebo-treated hemi face.

Secondary safety results:

All 58 randomised subjects were included in the safety population.

Adverse Events

A total of 36 AEs occurred in 25 subjects of the SA population. In the CD08100/02 3% gel study arm 17 AEs occurred in 10 subjects of which one subject had two AEs (‘Paraesthesia’) assessed as related to treatment with CD08100/02 3% gel. In the Metronidazole 1% gel study arm 19 AEs occurred in 15 subjects of which one had a severe AE (‘Gastrointestinal infection‘) assessed as not related. None of the observed AEs led to discontinuation of the study.

During the study no deaths, SAEs, AEs of special interest and dermatologic AEs occurred.

Vital signs

No relevant changes were noticed between screening and final visit in both study arms.

Physical examination

Three abnormalities each were detected in the CD08100/02 3% gel study arm (abnormal skin at screening (twice), abnormal lower extremities at screening) and in the Metronidazole 1% gel study arm (abnormal skin at screening and final visit and abnormal left leg at final visit, abnormal abdomen at final visit, abnormal skin at screening).

Overall conclusions:

Once daily treatment with CD08100/02 3% gel respectively with Metronidazole 1% gel of one hemi-face in comparison with the other hemi-face treated with placebo gel showed a statistically significant effect on total inflammatory lesions after 6 weeks of treatment and percentage change from Baseline, but only in the CD08100/02 3% gel treatment arm.

Overall, a treatment effect of both, CD08100/02 3% gel and Metronidazole 1% gel, was shown with CD08100/02 3% gel being more effective. The positive comparator (Metronidazole 1% gel) confirmed the usability of a split-face, placebo-controlled design for clinical studies in PPR.

In general, CD08100/02 3% gel and Metronidazole 1% gel treatment was very well tolerated by the subjects, although two AEs in the CD08100/02 3% gel arm were assessed as related (‘Paraesthesia’).

Date of report: 13-DEC-2012