Clinical Study Synopsis for Public Disclosure

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1. TITLE PAGE

<table>
<tr><td colspan="3">Title of Study
EFFECT OF CD08514 VERSUS PLACEBO, IN PATIENTS PRESENTING WITH TYPE 1 ROSACEA OVER AN 8-WEEK TREATMENT</td></tr>
<tr><td>Project Name
CD08514</td><td>Project Number
211</td><td>Clinical Phase
Phase 2</td></tr>
<tr><td colspan="2">Investigational Product
(name, formulation, concentration)
CD08514 20 mg tablet</td><td>Comparator Product
(name, formulation, concentration)
Placebo tablet</td></tr>
<tr><td>Subject Population/Indication
Male and female subjects from 18 to 65 years old, suffering from moderate to severe erythematotelangiectatic rosacea (ETR) characterized by a persistent erythema (with or without telangiectasia, flushing/blushing, edema) and without any papules and/or pustules</td><td>Treatment/Study Duration
Study duration per subject: total 13 weeks (approximately) consisting of a 4-week screening period, an 8-week treatment period and a 1-week follow-up period</td><td>Dose
CD08514 10 mg BID (total 20 mg/day) or 40 mg BID (total 80 mg/day) for 8 weeks</td></tr>
<tr><td colspan="3">Design
Multi-centre, randomized, double blind, parallel-group, placebo-controlled study.</td></tr>
<tr><td colspan="2">Study Initiation Date
(first Subject enrolled)
27th January 2010</td><td>Study Completion/Termination Date
(last Subject completed)
07 June 2010</td></tr>
<tr><td colspan="3">EUDRACT/IND No.: 2009-013111-35</td></tr>
</table>

This study was performed in compliance with Good Clinical Practice (GCP) including the archiving of essential study documents. This abbreviated Clinical Study Report (CSR), which complies with the International Conference on Harmonization (ICH) E-3 guidance, has been developed to respond to the internal reporting needs of Galderma and to conclude with the negative POC/POE studies. Therefore, this abbreviated CSR focuses on the main data. However, whole data of this study is accessible in the statistical analysis report attached in appendix. All data, either provided by the Investigator (and study staff), or collected during the study and/or reported herein will be regarded as confidential and proprietary in nature and will not be disclosed to any third party without Galderma's written consent.

2. SYNOPSIS

NAME OF COMPANY: GALDERMA R&D	***For regulatory use only***	
NAME OF FINISHED MEDICINAL PRODUCT: CD08514 20 mg tablet		
NAME OF ACTIVE INGREDIENT(S): Famotidine		

Title of study:	EFFECT OF CD08514 VERSUS PLACEBO, IN SUBJECTS PRESENTING WITH TYPE 1 ROSACEA OVER AN 8-WEEK TREATMENT
Investigator(s):	
Study centre(s):	4 centers in Germany
Clinical phase:	Phase 2
Period of study:	
Date of first enrolment:	27 January 2010
Date of last subject completed:	07 June 2010
Publication(s):	N/A
Study objective(s):	To evaluate the efficacy of CD08514 10 mg and 40 mg BID (i.e. 20 mg and 80 mg per day respectively) over 8 weeks, in a double blind placebo-controlled study, in subjects with moderate to severe erythematotelangiectatic rosacea (ETR).
Methodology:	This was a multi-centre, randomized, double-blind, parallel-group, placebo controlled study. Subjects were randomized to receive either: CD08514 10 mg BID (20 mg per day) or CD08514 40 mg BID (80 mg per day) or placebo for 8 weeks. Interim evaluation visits took place on Days 1 (Baseline), 2, 5, 12±1, 19±1, 26±1, 33±1, 40±1, 47±1 with a full clinical examination on Day 54 (last treatment visit). In addition, blood samples were taken from 7 subjects on Day 40 or 47 for determination of CD08514 plasma concentrations. Skin biopsies were also performed in 5 out of these subjects on Day 54 for quantification of CD08514 skin levels.
Number of subjects (planned and analyzed):	Up to 72 subjects were planned; 24 subjects per treatment group. 74 subjects were actually recruited and randomized into three groups.

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Diagnosis and Inclusion Criteria:	Subject were male or female adults, aged 18 to 65, presenting with moderate to severe ETR characterized by: - persistent erythema on the face, - an erythema severity score graded at least 3 on a 5-point scale (from 0 to 4), on each cheek, - no history of inflammatory (papules and/or pustules) lesions during the past 3 months before Baseline (subjects with a few papules and/or pustules on non-analyzed areas could be included).	
Treatment Groups:	Subjects were randomly allocated to one of the 3 following parallel treatment groups: -CD08514 10 mg BID -CD08514 40 mg BID -Placebo - half tablet BID (half P) - 2 tablets BID (2P)	
Test Product Dosage Form:	CD08514 20 mg divisible tablet	
Route of administration:	Oral	
Dosage regimen:	-CD08514 10 mg BID (half a 20 mg tablet twice per day for 8 weeks) -CD08514 40 mg BID (2 x 20 mg tablet twice per day for 8 weeks)	
Batch/formulation number:	NA (no formulation number was given as it was a product from the market)	
Treatment duration	8 weeks	
Reference Therapy	Placebo	
Route of administration	Oral	
Dosage regimen	- half a tablet BID (half P) - 2 tablets BID (2 P)	
Batch/formulation number:	NA	
Treatment duration	8 weeks	
Efficacy assessment:	Efficacy was assessed on Days 1, 2, 5, 12, 19, 26 33, 40, 47 and 54 during the treatment period.	
Efficacy Criteria:	**Main efficacy analysis variable:**	

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	Change from baseline in cheek-combined erythema severity score (total sum score of the 2 cheeks) on Day 54. **Secondary efficacy variables:** - Cheek-combined erythema score at every intermediate visit; - Whole-face combined erythema score (total sum score of the 4 areas: cheeks, chin and forehead) at every intermediate visit; - Change from baseline in cheek-combined and whole face-combined erythema scores at every visit; - Worst post-baseline erythema severity score across the 2 cheeks; - Change from baseline in the telangiectasia Dermascore score; - Edema score at every visit; - Inflammatory lesions (papule/pustule) count at every visit; - Change from baseline in the mean a*, b* and L* colorimetric parameter at every visit; - Subject's Global Assessment of improvement at the last treatment visit; - Number of flushing/blushing per week at every visit. - Exploratory efficacy analysis variables: - Change from baseline of the mean blood flow parameter (in selected centre only); - Change from baseline of the redness intensity from photographs. **Exploratory efficacy analysis variables:** - Change from baseline of the mean blood flow parameter (in selected centre only); - Change from baseline of the percentage of occupation of the telangiectasia from photographs (will be set out in a separate report); - Change from baseline of the redness surface area from the photographs (will be set out in a separate report); Change from baseline of the redness intensity from photographs	
Pharmacokinetics	Plasma pharmacokinetic parameters (Cmax, Ctrough, Tmax,) were calculated using a non compartmental analysis in plasma and skin. CD08514 in plasma and skin levels were summarized in ng/cm². Then, CD08514 skin/plasma ratios were calculated.	
Safety:	**Primary safety criterion:** Adverse event (AE) recording at each visit	

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	Secondary safety criteria: - General physical examination and vital signs at Baseline visit (Day 1) and on Days 12, 26, 40 and 54 or before in case of early termination. - Electrocardiogram (ECG) at Screening and on Days 26 and 54 or before in case of early termination. - Laboratory safety tests at the Screening visit and on Days 26 and 54 or before in case of early termination.
Principal statistical method(s):	Erythema score of the right and the left cheeks were summed. The change from baseline in the so-called combined erythema score at Day 54 (PP) and Day 54 (ITT-LOCF) was analyzed via ANCOVA, including treatment and centre as factors and baseline score as a covariate. All tests were two-sided and the 0.05 probability level was chosen to declare significance.

SUMMARY

DEMOGRAPHIC DATA

Subjects screened	105
Subjects enrolled	74

	CD08514 10mg BID (n=23)	CD08514 40mg BID (n=24)	PLACEBO (half P) (n=14)	PLACEBO (2 P) (n=13)	TOTAL (n=74)
Mean age (±SD) years	43.30±8.8	51.92±10.6	42.93±13.8	49.62±8.4	47.14±11.0
Female	19 (82.6%)	20 (83.3%)	14 (100.0%)	11 (84.6%)	64 (86.5%)
Male	4 (17.4%)	4 (16.7%)	-	2 (15.4%)	10 (13.5%)
Discontinued	1	3	0	1	5
Assessable for efficacy (PP)	19	22	12	11	64
Assessable for safety	23	24	14	13	74

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EFFICACY RESULTS

Primary efficacy variable

The cheek-combined erythema severity score at Day 54 was reduced in each treatment group compared to baseline, with the strongest effect seen in the placebo group (see table below). The mean (±SD) change from baseline for placebo (-2.35±1.5) was not significantly different to that of the CD08514 10 mg BID group (1.84±1.4; p=0.197) or the CD08514 40 mg BID group (1.95±1.5; p=0.362).

Change from baseline in cheek-combined erythema severity score (total sum score of the 2 cheeks) on Day 54

		CD08514 10mg BID	CD08514 40mg BID	PLACEBO
Day 54-LOCF(ITT)	N	23	24	27
	Mean ± SD	-1.91±1.3	-1.96±1.5	-2.07±1.5
	LS-Mean	-1.88	-1.91	-2.11
	Median	-2.00	-2.00	-2.00
	Min~Max	-4~0	-4~0	-6~0
	Q1~Q3	-3~-1	-4~0	-3~-1
Day 54-(PP)	N	19	22	23
	Mean ± SD	-1.84±1.4	-1.95±1.5	-2.35±1.5
	LS-Mean	-1.79	-1.96	-2.30
	Median	-2.00	-2.00	-2.00
	Min~Max	-4~0	-4~0	-6~0

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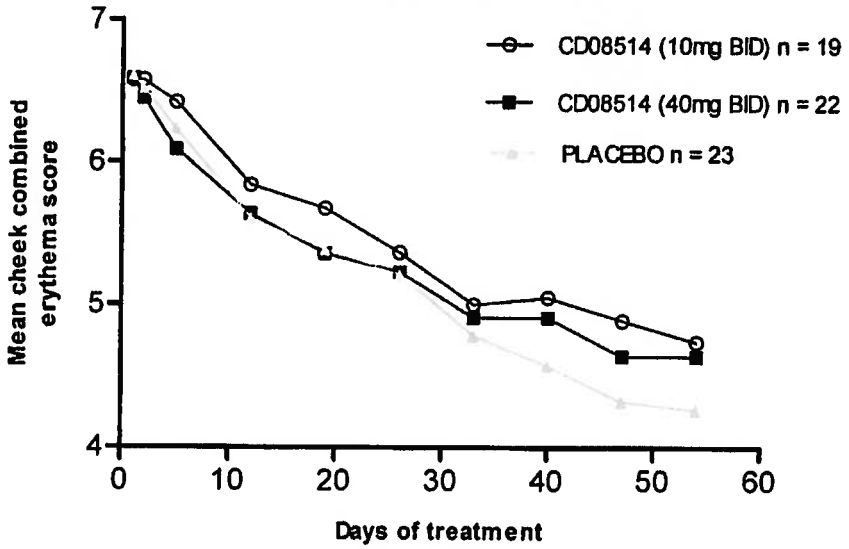
Cheek combined erythema score (PP Population)



Secondary efficacy variables
No statistically significant differences were seen between the CD08514 groups and the placebo group for any of the secondary efficacy variables.

Exploratory efficacy variables
These results will be addressed in a separate report.

Pharmacokinetics (PK)
Blood samples were taken from 5 subjects in the CD08514 10 mg BID group and from 2 subjects in the CD08514 40 mg BID group. Out of the subjects who gave blood samples, 5 subjects also had skin biopsies taken from the lower back on Day 54: 3 subjects in the CD08514 10 mg BID group and 2 subjects in the CD08514 40 mg BID group.
CD08514 plasma concentrations were proportional to the dose administered and were nearly 4-fold higher in the CD08514 40 mg BID group (138.1 ± 6.22 ng/ml) than in the CD08514 10 mg BID group (38.92 ±16.56 ng/ml).
CD08514 was quantifiable in skin biopsies from both groups but concentrations were not dose proportional. Skin levels were about 2-fold higher in the CD08514 40 mg BID group (3.48 ± 2.02 ng/ml) than in the CD08514 10 mg BID group (1.76 ± 1.34 ng/ml).
In addition, plasma/skin ratios showed that CD08514 plasma concentrations were approximately 10-fold higher than skin concentrations in both CD08514 10 mg and 40 mg BID groups.

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SAFETY RESULTS

Summary of adverse events

	CD08514 10mg BID (N=23)	CD08514 40mg BID (N=24)	PLACEBO (N=27)	Total (n=74)
All AEs	18 (78.3%)	16 (66.7%)	17 (63.0%)	51 (68.9%)
Related AEs	3 (13.0%)	5 (20.8%)	4 (14.8%)	12 (16.2%)
All dermatologic AEs	4 (17.4%)	2 (8.3%)	2 (7.4%)	8 (10.8%)
Related dermatologic AEs	1 (4.3%)	0	1 (3.7%)	2 (2.7%)
All serious AEs	0	0	0	0
Severe AEs	1 (4.3%)	1 (4.2%)	0	2 (2.7%)
Related severe AEs	0	1 (4.2%)	0	1 (1.4%)
AEs of Special Interest	1 (4.3%)	4 (16.7%)	1 (3.7%)	6 (8.1%)
Related AEs of Special Interest	1 (4.3%)	2 (8.3%)	0	3 (4.1%)
AEs leading to discontinuation	1 (4.3%)	3 (12.5%)	1 (3.7%)	5 (6.8%)
Related AEs leading to discontinuation	1 (4.3%)	1 (4.2%)	0	2 (2.7%)

In the safety population (n=74), 12 subjects experienced treatment-related AEs; 3 subjects (13.0%) in the CD08514 10 mg BID group, 5 subjects (20.8%) in the CD08514 40 mg BID group and 4 subjects (14.8%) in the placebo group. Gastrointestinal disorders were the most common.

Study drug was permanently discontinued by 2 subjects due to treatment-related AEs (1 subject in each of the CD08514 treatment groups) and by 3 subjects due to unrelated AEs (2 subjects in the CD08514 40 mg BID group, 1 subject in the placebo group).

No clinically significant changes in weight, vital signs or physical examination were observed. Two subjects had clinically relevant laboratory results reported as AEs (raised GGT in both cases) which led to discontinuation of drug: one subject in the CD08514 40 mg BID group and one subject in the placebo group. A few abnormal ECG results were observed in all 3 treatment groups.

No SAEs or deaths occurred in this study.

CONCLUSION

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This was a multi-centre, randomized, double-blind, parallel-group, placebo controlled study to evaluate the efficacy of CD08514 10 mg and 40 mg BID over 8 weeks in subjects with moderate to severe ETR.

74 subjects were enrolled in the study, all of whom were included in the safety and ITT populations. There were 10 protocol deviations; therefore the PP population comprised 64 subjects. Efficacy was evaluated in the PP population.

The primary efficacy variable, the change from baseline in cheek-combined erythema severity score (total sum score of the 2 cheeks) on Day 54, was reduced in each treatment group compared to baseline, with the strongest effect seen in the placebo group. The mean change from baseline for the CD08514 10 mg BID group or the CD08514 40 mg BID group were not statistically different to that of the placebo; moreover the two doses were not statistically different from each other. Additionally, no differences were observed between the treatment groups and the placebo for any of the secondary variables analyzed.

The PK assessments showed that CD08514 plasma concentrations were dose proportional. CD08514 was quantifiable in skin biopsies taken on Day 54 but concentrations were not dose proportional. Plasma concentrations were approximately 10-fold higher than skin concentrations in both CD08514 groups.

The results of the safety assessments did not raise any cause for concern. Treatment-related AEs were reported for 3 subjects (13.0%) in the CD08514 10 mg BID group, 5 subjects (20.8%) in the CD08514 40 mg BID group and 4 subjects (14.8%) in the placebo group. Gastrointestinal disorders were the most common. Only 2 subjects permanently discontinued the study drug due to treatment-related AEs (1 subject in each of the CD08514 treatment groups). There were no SAEs.

In conclusion, CD08514 10 mg and 40 mg BID orally over 8 weeks did not demonstrate superior efficacy to placebo in subjects with moderate to severe ETR although PK assessments showed that the CD08514 was detectable in the plasma and skin. The results of the safety assessments did not raise any cause for concern.