**Clinical Study Synopsis for Public Disclosure**

These results are supplied for informational purposes only in the interest of scientific disclosure. The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups. This information is not intended to substitute for informed medical advice. You should not use this information to diagnose or treat a health problem or disease without consulting with a Healthcare Professional. Before prescribing any product mentioned in this Register, Healthcare Professionals should always refer to the specific approved product labeling information in their country. The results from a single trial may not reflect the overall results and need to be considered in the context of the totality of the available clinical research results for a product.

# 1. TITLE PAGE

<table>
<tr><td colspan="3">Title of Study<br>ACTIVITY OF TWICE DAILY PER OS ADMINISTRATION OF CD06713 AT 8MG VERSUS ITS PLACEBO DURING 4 WEEKS TREATMENT, IN PATIENTS WITH ERYTHEMATO-TELANGIECTATIC ROSACEA.</td></tr>
<tr><td>Project Name<br>CD06713</td><td>Project Number<br>204</td><td>Clinical Phase<br>Phase 2</td></tr>
<tr><td colspan="2">Investigational Product<br>(name, formulation, concentration)<br>CD06713 8mg tablet</td><td>Comparator Product<br>(name, formulation, concentration)<br>Placebo tablet</td></tr>
<tr><td>Subject Population/Indication<br>Male and female subjects from 18 to 65 years, suffering from moderate to severe Erythemato-Telangiectatic Rosacea characterized by a persistent erythema, an erythema severity score graded at least 3 on a 5-point scale, on each cheek and no history of inflammatory lesions during the past 3 months before inclusion</td><td>Treatment/Study Duration<br>Total study duration per subject: nine weeks, including a 2- week screening period, a 4-week treatment period and a 3-week follow-up period.</td><td>Dose<br>8 mg tablets, twice daily oral administration over four weeks</td></tr>
<tr><td colspan="3">Design<br>This is a multi-centre, randomized, group-parallel, placebo-controlled, investigator-blinded study</td></tr>
<tr><td colspan="2">Study Initiation Date<br>(first Subject enrolled)<br>22/12/2006</td><td>Study Completion/Termination Date<br>(last Subject completed)<br>23/05/2007</td></tr>
<tr><td colspan="3">EUDRACT/IND No.: 2006-003707-40</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 to 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.

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## 2. SYNOPSIS

| | | |
|---|---|---|
| **NAME OF COMPANY:**<br>Galderma R&D | ***For regulatory use only*** | |
| **NAME OF FINISHED MEDICINAL PRODUCT:**<br>CD06713 | | |
| **NAME OF ACTIVE INGREDIENT(S):** | | |
| Ondansetron (Zofren®) | | |
| **Title of study:** | ACTIVITY OF TWICE DAILY PER OS ADMINISTRATION OF CD06713 AT 8MG VERSUS ITS PLACEBO DURING 4 WEEKS TREATMENT, IN PATIENTS WITH ERYTHEMATO-TELANGIECTATIC ROSACEA. | |

**Objectives**

The aim of this study was to evaluate the activity of twice daily per os administration of 8mg of CD06713 (Ondansetron) over four weeks versus placebo in two parallel group patients with erythemato-telangiectatic rosacea (ETR). Relapse was evaluated after a 3-week follow-up period without treatment.

**Methodology**

This was a multi-centre, randomized, group-parallel, placebo-controlled, investigator-blinded study. The planned total study duration for a given subject was 9 weeks, including a 2-week screening period, a 4-week treatment period and a 3-week follow-up period. Subjects attended one screening visit between Day -14 and Day - 4 before Day 1 visit to ensure his/her eligibility. At Day 1, Baseline clinical and biophysical evaluations were performed before the first treatment administration. In addition, screening laboratory safety tests results were to be made available to the investigator at Day1. Subjects attended weekly visits at Day 8, Day 15, Day 22 and Day 29 to assess the treatment activity. The first treatment administration was performed in the evening of Day 1 by the subject at his/her home. There was only one oral treatment administration at Baseline/Day 1. A twice daily oral treatment regimen (morning and evening administration) was to be respected from Day 2 to Day 28. A 3-week relapse follow-up period (period without treatment) to evaluate the relapse of symptoms was scheduled after the end of the 4-week treatment period. During this follow-up period, subject attended evaluation visits at D36 and D50.

Approximately 48 subjects were to be randomized in two parallel equal size-groups. Subjects received either CD06713 (Batch n° R224632 and R231396) or placebo tablets (Batch n° CPM 6505).

Clinical evaluation at D1, D8, D15, D22, and D29 during the treatment period and at D36 and D50 during the follow-up period included evaluations of:

- erythema, scored on each cheek on a 5-point scale (0=None to 4=Severe);
- telangiectasia on the full face scored on a 4-point scale (0=None to 3=Severe) and on each cheek using a 6-point scale on photographic atlas to assess the Derma Score;
- an inflammatory lesions count (papules and pustules) on each cheek;
- a Subject's Global Assessment of Improvement at Day 29 and Day 50.

Biophysical evaluation at Day1, Day15, Day29 and Day50 included evaluations of:

- skin colorimetry by chromametry;
- hyperperfused area skin surface via videocapillaroscopy;
- and skin perfusion via laser scanner doppler (LSD).

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**Methodology (Cont'd)**

Other evaluations included:

- a digital standardized photographs at Day1, Day8, Day15, Day29 and Day50 to document the evaluation of improvement over the study;
- and a Flushing diary card completed by the Subject.

The primary efficacy variable was the change from Baseline in the combined erythema severity score (total sum score of both cheeks).

Secondary efficacy variables included:

- Worst erythema severity score across both cheeks
- Change from Baseline in erythema score categorized as improved, same, or worsened
- Change from Baseline in telangiectases severity score
- Inflammatory lesions (papule/pustule) count
- Change from Baseline in the mean chromametric parameter a*
- Change from Baseline in the mean chromametric parameter b*
- Change from Baseline in the mean chromametric parameter L*
- Subject's Global Assessment of Improvement
- Flushes count
- Erythema relapse rate (follow-up period),
- Erythema rebound rate (follow-up period).

Exploratory secondary efficacy analysis variables consisted in the change from Baseline in the Telangiectases DermaScore, in the mean blood flow parameter (LSD), and in the mean surface parameter (videocapillaroscopy).

Safety parameters included the incidence and multiplicity of Adverse Events (AE), as well as vital signs (blood pressure and heart rate), ECG and standard laboratory parameters.

The intent to treat (ITT) population consisted of the entire population enrolled and randomized. For the treatment period this population was analyzed at each visit using the Last Observation Carried Forward (LOCF) up to Day 29. This was the primary population for efficacy analysis. All primary and secondary efficacy variables were analyzed based on that population. The per-protocol (PP) efficacy population consisted of all enrolled and randomized subjects, except those subjects considered as not evaluable due to major protocol deviations defined after data entry and before breaking the treatment blind. For the follow-up period, all variables were analyzed using observed cases. For relapse and rebound, only subjects who had improved at the end of the treatment period were kept in the analysis, observed cases were summarised but also by imputing failure (worst case) to missing data . The safety population consisted of the ITT population, after exclusion of subjects who never took the treatment with certainty.

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**Methodology (Cont'd)**

The number of subjects included in each efficacy analyses (PP, ITT) and number of patients included in the safety analysis was presented by treatment group; usual descriptive statistics (n, mean, standard deviation, median, min, max) were used for quantitative criteria, both frequency distribution and usual statistics were used for ordinal criteria.

Erythema scores were summed across the two facial areas. The change from Baseline in the combined erythema score at Day29/LOCF (ITT,) and Day 29 (PP) were analyzed by ANCOVA model including treatment as factor, Baseline score as a covariate and analysis centre if appropriate. Other timepoints were considered secondary. Worst erythema severity score across both zones, change from Baseline in telangiectasia severity score, inflammatory lesion counts and Subject's Global Assessment were submitted at each visit to a CMH test stratified by analysis centre. Subjects with an erythema severity score worse, equal or better than baseline were also to be tabulated at each visit.

Relapse and rebound rates analyzed, at each follow-up visit, only on those subjects having improved at the end of the treatment period compared to baseline. Relapse was defined as an erythema score during the follow-up period greater to the one at the end of treatment period. Rebound was defined as an erythema score during the follow-up period greater to the one at Baseline/Day1. The rates were analyzed by a Chi2 test. If at least one theoretical value was inferior to "5", Fisher's exact test was performed.
Biophysical measurements were averaged at each visit by subject to provide with one value per subject.

Change from Baseline in mean chromametric parameters "a*", "b*", and "L*", Telangiectasis DermaScore, blood flow (LSD) and surface (Videocapillaroscopy) were analyzed by ANCOVA model including Baseline as a covariate, treatment as factor and analysis centre, if appropriate.
Adverse Events (AE) were tabulated in frequency tables by System Organ Class (SOC) and Preferred Term (PT) based on the MedDRA dictionary. Additional summary tables were provided for Serious Adverse Events (SAE), adverse events related to the study drug, AE of special interest, and AE leading to discontinuation. Incidence and multiplicity of AE was summarized by period.
Laboratory parameters were summarized with descriptive statistics by treatment group. Vital signs, physical findings and other observations related to safety were descriptively summarized by treatment group at each intermediate visit using observed cases. Premature discontinuation during treatment period was summarized with Day29 data. In case of discontinuation during the follow-up period, data was to be summarized for Day50/Final visit.

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**Results**

In this study, a total of 68 subjects were screened and 50 were enrolled in six European centres in France (four centres) and Germany (two centres). The ITT population consisted of all 50 enrolled and randomised subjects: 24 in the CD06713 group and 26 in the placebo group. Forty eight (48) Subjects completed the study as expected; two subjects in the CD06713 group discontinued the study medication prematurely, one for AE (#9004) and one due to pregnancy (#9011). A total of 46 Subjects enrolled in the study were considered eligible for the PP analysis. Four subjects, all in the CD06713 group had at least one major protocol deviation, leading to the exclusion from the PP population (see Blind review minutes).

**Table 1 Demographic data**

| | | CD06713 | PLACEBO | Total |
|---|---|---|---|---|
| **Gender** | **N** | 24 | 26 | 50 |
| | **Female** | 20 (83.3%) | 22 (84.6%) | 42 (84.0%) |
| | **Male** | 4 (16.7%) | 4 (15.4%) | 8 (16.0%) |
| **Race** | **N** | 24 | 26 | 50 |
| | **Caucasian** | 24 (100.0%) | 26 (100.0%) | 50 (100.0%) |
| **Skin Phototype** | **N** | 24 | 26 | 50 |
| | **I** | | 1 (3.8%) | 1 (2.0%) |
| | **II** | 9 (37.5%) | 7 (26.9%) | 16 (32.0%) |
| | **III** | 15 (62.5%) | 18 (69.2%) | 33 (66.0%) |
| **Age (in Years)** | **N** | 24 | 26 | 50 |
| | **Mean±STD** | 47.2±10.1 | 46.8±11.7 | 47±10.9 |
| | **Median** | 46 | 48.5 | 47.5 |
| | **Min~Max** | 32~63 | 24~63 | 24~63 |

Demographic characteristics were similar in both treatment groups.

No imbalance was observed at Baseline between the two groups. All subjects included in the study, except subject #9072 (Erythema score of 2 at Screening, considered as a major protocol deviation), presented an erythema severity score at least of 3 on each cheek as defined in the protocol. The median erythema score was “6” in both groups with means ranging from 6.13 in the CD06713 group to 6.46 in the placebo group. None of the subjects presented with papules or pustules. Baseline disease characteristics were similar for the two treatment groups for Dermascore and telangiectasia. Colorimetric parameters were similar for the two treatment groups. On the affected area, mean values “a*” ranged from 20.80 for the placebo to 21.31 for CD06713, 12.85 to 13.05 for “b*” and 57.45 to 56.73 for “L*”. The non affected areas were similar between both groups for all three colorimetric parameters. The video-capillaroscopy was similar between both groups with means of about 14.9.

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**Results (Cont'd)**

**Primary criterion**

In terms of mean score, both treatments reduced erythema: by 1.13 points (CD06713) and by 1.69 (placebo). The variability in the CD06713 group was 1.6, and 0.88 for the placebo, indicating that the spread of values was twice as high in the CD06713 than in the vehicle group and above the expected standard deviation of the hypotheses (1.35). According to the initial hypotheses the mean difference at Week 5/Endpoint between the change from baseline of CD06713 and the Placebo was expected to be 1.35, whereas it was 0.43 (ITT/LOCF) and 0.24 (PP) in favour of the Placebo. These differences were not statistically differences with respectively p>0.23 (ITT/LOCF) and p>0.53 (PP).

**Table 2 Descriptive Results of the Combined Erythema Score at Day29 / Endpoint**

| | | **CD06713** | | **Placebo** | |
|---|---|---|---|---|---|
| | | **Raw Data** | **Change From Baseline** | **Raw Data** | **Change From Baseline** |
| **Day29 / LOCF (ITT)** | **N** | 24 | 24 | 26 | 26 |
| | **Mean±STD** | 5.00±1.53 | -1.13±1.60 | 4.77±1.24 | -1.69±0.88 |
| | **Median** | 6.00 | 0.00 | 4.00 | -2.00 |
| | **Min/Max** | 2/7 | -4/1 | 3/8 | -3/0 |
| **Day 29 (PP)** | **N** | 20 | 20 | 26 | 26 |
| | **Mean±STD** | 4.90±1.62 | -1.35±1.66 | 4.77±1.24 | -1.69±0.88 |
| | **Median** | 6.00 | -1.00 | 4.00 | -2.00 |
| | **Min/Max** | 2/7 | -4/1 | 3/8 | -3/0 |

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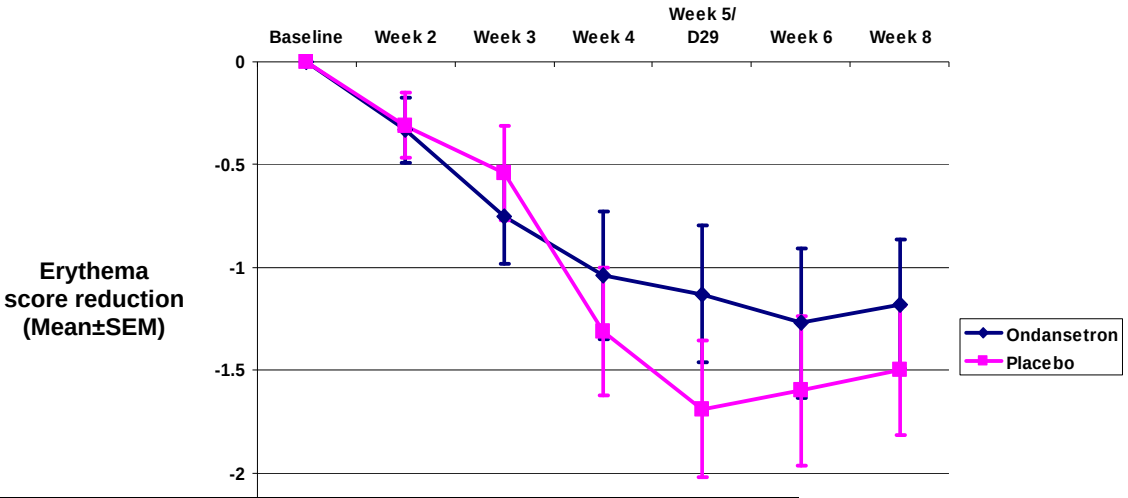
**Results (Cont'd)**

**Secondary criteria**

*Erythema*

There were no significant differences between the two treatments at any time during the treatment period. Erythema scores remained stable during the follow-up period and were similar between groups (see figure 1).

**Figure 1 Erythema (Mean change from baseline)**




| | | CD06713 | PLACEBO | CD06713 vs Placebo |
|---|---|---|---|---|
| Week 5/LOCF (ITT) | LSmean(SE) | **-1.22 (0.26)** | **-1.66 (0.25)** | 0.43 (0.36) |
| | 95%CI | [-1.75;-0.70] | [-2.16;-1.16] | **[-0.30;1.17]** |
| | p-value(1) | . | . | 0.2385 |
| Week 5 (PP) | LSmean(SE) | **-1.46 (0.29)** | **-1.69 (0.25)** | 0.24 (0.38) |
| | 95%CI | [-2.03;-0.88] | [-2.19;-1.19] | **[-0.53;1.00]** |
| | p-value(1) | . | . | 0.5352 |

Combined erythema score= total sum score of the right and left cheek
(1) p-value are based on ANCOVA model including baseline as covariate and treatment and pseudo-center as factors

Erythema scores were also summarized as worsening, same or improved from Baseline. At Day29/LOCF, 22 (84.6%) subjects had improved with the placebo and only 10 (41.7%) with CD06713.

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Relapse and rebound rates could be based on 10 subjects who had improved with CD06713 and 22 subjects with the placebo.
However, since no effect could be demonstrated with the active, this analysis was considered useless.

**Results (Cont'd)**

*Telangiectases*
For the telangiectases severity score, expressed in terms of change from Baseline, there was no statistical significant difference between the two groups at any time on the ITT population. Severity of telangiectases remained unchanged in both treatment groups. Also, there were no statistical differences between the two treatments at any time in terms of mean change from Baseline in telangiectases DermaScore

*Inflammatory lesions count*
Subjects did not present with any lesions at Baseline. Few lesions appeared over time and median counts remained "0" for both groups over time; there were no significant differences between treatments at any time.

*Colorimetry*
The efficacy in terms of mean change at Day29/LOCF from Baseline in chromametry parameters "a*", showed that CD06713 (-0.98) was slightly superior to the placebo (-0.13). However, this gain was not significant and not considered clinically relevant.

*Subject's global assessment of improvement*
At the end of the treatment period (Day29) seven subjects (30.4%) rated their rosacea as moderately or markedly improved with CD06713 compared to 10 (38.5%) subjects with the placebo; the difference was not statistically significant.

*Flushes count*
Flush counts were similar during the first week with means ranging from 4.31 for the placebo to 5.17 for CD06713. During the treatment period the number of flushes slightly decreased similarly in both groups to reach 3.38 for CD06713 and 2.62 with the placebo. At the end of the study mean flush counts were 2.08 for CD06713 and 1.52 for the placebo.

**Exploratory secondary criteria**
*Dermascore*
There was no statistical difference between the two groups at any time in terms of mean change from baseline (all p-values $> 0.45$).

*Laser scanner doppler*
Laser scanner doppler was collected in four centres, three in France (#5074, #5078, and #5562) and

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one (#5560) in Germany with different calibrations. No global evaluation was performed.

*Videocapillaroscopy*
At Day29/ LOCF videocapillaroscopy values change from Baseline was numerically higher for CD06713 (-6.76) compared to -5.02 for the placebo. However, the difference was not statistically significant.

**Results (Cont'd)**

**Safety**
During the treatment period 20 (83.3%) subjects experienced 51 AE in the CD06713 group and 15 (57.7%) subjects experienced 27 AE in the placebo group.

**Table 3 Overview of adverse events (Safety population)**

| | **Treatment Period** | | | | **Follow-up period** | | | |
|---|---|---|---|---|---|---|---|---|
| | **CD06713 (N at risk= 24)** | | **Placebo (N at risk= 26)** | | **CD06713 (N at risk= 22)** | | **Placebo (N at risk= 26)** | |
| | **nb events** | **Nb (%) subjects** | **nb events** | **Nb (%) subjects** | **nb events** | **Nb (%) subjects** | **nb events** | **Nb (%) subjects** |
| **All AE** | 51 | 20 (83.3%) | 27 | 15 (57.7%) | 4 | 3 (13.6%) | 9 | 5 (19.2%) |
| **Related AE** | 42 | 19 (79.2%) | 10 | 6 (23.1%) | 0 | 0 | 0 | 0 |
| **All dermatologic AE** | 2 | 2 (8.3%) | 2 | 2 (7.7%) | 0 | 0 | 0 | 0 |
| **Related dermatologic AE** | 2 | 2 (8.3%) | 2 | 2 (7.7%) | 0 | 0 | 0 | 0 |
| **All serious AE** | 0 | 0 | 1 | 1 (3.8%) | 0 | 0 | 0 | 0 |
| **AE of special interest** | 2 | 2 (8.3%) | 0 | 0 | 0 | 0 | 0 | 0 |
| **Related AE of special interest** | 1 | 1 (4.2%) | 0 | 0 | 0 | 0 | 0 | 0 |
| **AE leading to discontinuation** | 2 | 1 (4.2%) | 0 | 0 | 0 | 0 | 0 | 0 |
| **Related AE leading to discontinuation** | 2 | 1 (4.2%) | 0 | 0 | 0 | 0 | 0 | 0 |

Forty-two (42) AE were considered related to CD06713 and concerned 19 (79.2%) subjects; two events (Constipation and then Haemorrhoids) led to permanent discontinuation of one subject (#9004). In the placebo group 10 adverse events concerning six (23.1%) subjects were considered related to the study drug.

In the placebo group, one subject (#9057) experienced one serious adverse event (bilateral inguinal hernia), considered as not related to treatment by the investigator.

During the follow-up period the number of adverse events had decreased: three (13.6%) subjects experienced four adverse events in the CD06713 group and five (19.2%) subjects experienced nine

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adverse events in the placebo group. None of them were related or serious or led to permanent discontinuation.
During the treatment period, constipation was the most frequent related adverse event, and its incidence was more than four times higher in the CD06713 group, 13 (54.2%) subjects than it was in the placebo group (3 subjects, 11.5%). There were no related AE during the Follow-up period.

Assessments of vital signs, ECG and standard laboratory parameters did not show any significant abnormalities

**Discussion and Conclusion**

The primary objective of the study was to compare the change from Baseline at Day29/LOCF of the combined erythema score (Left + Right cheek scores). A difference of 1.35 point was expected in favour of CD06713 compared to the placebo. The study demonstrated that the difference was numerically in favour of the placebo (0.43 (ITT/LOCF) and 0.24 (PP)) but not statistically significant. There were no differences between the two treatments for all clinical scores, except on the worst erythema score across the two cheeks at Day15/LOCF (p=0.037)

Concerning the biophysical assessment, the efficacy in terms of mean change from baseline at Day29/LOCF in colorimetry “a*” and videocapillaroscopy were slightly superior in the CD06713 group (-0.98 and -6.76 respectively) than in the placebo group (-0.13 and -5.02, respectively) but not statistically significant.

In terms of safety, the incidence rate of related AE was more than three times higher in the CD06713 group (19, 79.2% subjects experienced 42 related AE) than in the placebo group (6, 23.1%) subjects experienced 10 related AEs). Constipation was the most frequent related AE observed during the treatment period, with an incidence more than four times higher in the CD06713 group, (13, 54.2%) subjects) compared to the placebo group (3, 11.5%) subjects). This was expected considering the dose regimen and treatment duration, constipation being the most frequent side effect reported with Ondansetron.

One subject (#9004) in the CD06713 group had two AE considered related by the investigator (Constipation and Haemorrhoids) leading to permanent discontinuation of the treatment. One subject (#9057) in the placebo group had a SAE (Bilateral inguinal hernia) considered not related by the investigator.

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# 14.TABLES, FIGURES, AND GRAPHS

## 14.1. Demographic Data

## 14.2. Efficacy Data

## 14.3. Safety Data

## 15.REFERENCE LIST