Clinical Study Synopsis for Public Disclosure

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1. TITLE PAGE

Title of Study		
Exploratory study to evaluate the efficacy and safety of CD5789 in subjects with acne		
Project Name	**Project Number**	**Clinical Phase**
CD5789	P219	2a
Investigational Product *(name, formulation, concentration)*	**Comparator Product** *(name, formulation, concentration)*	
CD5789 Gel at 0.005 and 0.01%	CD5789 Gel vehicle Epiduo®	
Subject Population/Indication	**Treatment/Study Duration**	**Dose**
Subjects with acne vulgaris Aged from 18 to 35 years	Screening phase: 4 weeks Treatment phase: 4 weeks Follow up phase: 10 days	Once daily application, during 4 weeks, 5 days per week
Design		
Multi-centre study, controlled, randomized, investigator blinded, intra-individual comparison (right versus left).		
Study Initiation Date *(first Subject screened)*	**Study Completion/Termination Date** *(last Subject completed)*	
17Mar2009	03Dec2009	
EUDRACT/IND No.: 2008-007981-44		

This study was performed in compliance with Good Clinical Practice (GCP) including the archiving of essential study documents. This Clinical Study Report (CSR) complies with the International Conference on Harmonization (ICH) E-3 guidance.

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.

Appropriate Investigator and/or Responsible Medical officer's signature(s) are in Appendix 16.1.5

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Summary: All signatories

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1. SYNOPSIS

NAME OF COMPANY:	*For regulatory use only*
Galderma	
NAME OF FINISHED MEDICINAL PRODUCT:	
Not applicable	
NAME OF ACTIVE INGREDIENT(S):	
CD5789	
Title of study:	Exploratory study to evaluate the efficacy and safety of CD5789 in subjects with acne

▪ Study centers

Five study sites in France, 3 recruited subjects.

▪ Clinical phase

Phase 2a

▪ Study period

- Date of first subject screened: 17Mar2009
- Date of last subject completed:03Dec2009

▪ Study objectives

- Efficacy Objective :
  - Evaluation of efficacy on acne lesions
- Safety Objectives :
  - Evaluation of the local tolerance of the study product.
  - Evaluation of the systemic safety by adverse event reporting, physical examination, vital signs and laboratory safety tests follow-up.

▪ Study design

Multi-center study, controlled, randomized, investigator-blinded, intra-individual comparison (right versus left).

- **Total number of subjects**

Approximately 70 randomized subjects.

- **Diagnosis and key inclusion and non-inclusion criteria**
  - Key inclusion criteria
    - Male or female subjects aged from 18 to 35 years;
    - Subject had a medical diagnosis of *acne vulgaris* on the face;
    - Subjects had, on the face, at least 15 inflammatory lesions and 25 non-inflammatory lesions but no more than 2 nodules;
    - Subjects had a severity grade 2 through 5 according to the Leeds Revised Acne Grading System.
  - Key non-inclusion criteria
    - Subjects had severe forms of acne (acne conglobata, acne fulminans) or secondary acne form (chloracne, drug-induced acne, etc.);
    - The number of inflammatory or non inflammatory lesions on half-face was greater than twice the number on the other half-face;

- **Test product dosage form**

		Investigational Product		Comparator Product	Vehicle Product
Name of active ingredient/ Concentration		CD5789 0.01%	CD5789 0.005%	Epiduo®	Vehicle of CD5789
Dosage form		Gel			
Dose regimen	Route of administration	Topically on half faces			
	Frequency of administration	Once daily application, during 4 weeks, 5 days per week			
	Duration of administration	27 days (20 applications in total)			

- **Efficacy assessment**
  - **Efficacy measurements**
    - Inflammatory lesions count (papules, pustules and nodules);
    - Non inflammatory lesions count (whiteheads and blackheads);
    - Total lesions count (including inflammatory and non inflammatory lesions);
    - Efficacy preference at the end of treatment by the Investigator and by the Subject.

- **Efficacy criteria**
- *Primary efficacy criteria:*
  - Total acne lesion count and percent reduction at end of treatment (D27) evaluated clinically.
- *Secondary efficacy criteria*
  - Clinical inflammatory, non-inflammatory and total lesions count and percent reduction at each visit;
  - Efficacy preference at the end of treatment by Investigator and Subject.
- *Exploratory criteria*
  - Photographic evaluation:
    - Inflammatory lesions count at each visit;
    - Inflammatory lesions reduction at end of treatment;
    - Severity measurement at each visit;
    - Severity measurement reduction at end of treatment;
  - Evaluation of treatment on *Propionibacterium acnes* by UVA reflectance photographs analysis.

- **Safety assessment**

- **Adverse Events**

Adverse events recording at each visit after the screening visit.

- **Local Tolerance**

Clinical irritation was assessed, on each treated area, every day from Day 2 to Day 27/End of treatment visit and Day 36/Follow-up visit or before in case of early termination, using a 5-point skin reaction scale.

- **General Physical examination**

Physical examination and Vital signs were conducted at Screening, Day 1, Day 27/End of treatment visit and Day 36/Follow-up visit or before in case of early termination.

- **Laboratory Safety Tests**

Laboratory tests were conducted at Screening and Day 27/End of treatment visit or before in case of early termination.

- **Systemic exposure measurement**

Blood sampling was performed one and 16 hours after the last treatment application.

- **Principal statistical methods**

Clinical lesion counts (inflammatory, non inflammatory and total) and percent reductions in lesion counts were descriptively summarized by visit and by treatment received. The bilateral differences between treatments were summarized and analyzed by visit using a Wilcoxon rank signed test.

Investigator and subject's preferences were analyzed using a sign test.

All tests were two-sided and the 5% probability level was chosen to declare significance.

Local tolerance, general physical examination, vital signs and laboratory parameters were summarized by descriptive statistics.

- **Results**

  - Demographics and baseline disease characteristics

Ninety-three (93) subjects were screened at 5 study sites and 3 sites randomized 76 subjects.

Among the 76 randomized subjects (ITT population), 2 in CD5789 0.005% Gel/Vehicle group withdrew prematurely due to treatment unrelated adverse events. The PP population comprised 66 subjects, 21 in the CD5789 0.01% Gel/Vehicle as well as in the CD5789 0.005% Gel/Vehicle and 24 subjects in the Epiduo®/Vehicle. The safety population comprised all 76 randomized subjects.

A total 40 (5.26%) female and 36 (47.4%) male subjects were randomized into the study. Seventy-five (75, 98.7%) Caucasians and one Hispanic subject were randomized. The mean age was 22.3 years, with a min/max of 18/35 years. The majority (45, 59.2%) had Phototype III.

There was no difference for any lesion type between the active and vehicle controlled treatment side, in any of the groups and between treatment groups.

Detailed baseline disease characteristics are presented in Table 1 below.

Table 1 Baseline disease characteristics - Clinical evaluations D01 (ITT population)

		CD5789 0.01%/Vehicle		CD5789 0.005%/Vehicle		Epiduo®/Vehicle	
		Active (N=25)	Vehicle (N=25)	Active (N=25)	Vehicle (N=25)	Active (N=26)	Vehicle (N=26)
Inflammatory lesions	N	25	25	25	25	26	26
	Mean±SD	13.2 ± 8.3	13.1 ± 8.0	16.2 ± 15.4	16.9 ± 15.5	15.4 ± 7.8	16.0 ± 6.7
	Median	10.0	11.0	11.0	12.0	14.0	14.0
	(Min,Max)	(7,49)	(6,44)	(7,79)	(8,76)	(7,34)	(8,38)
Non inflammatory lesions	N	25	25	25	25	26	26
	Mean±SD	26.8 ± 15.6	27.8 ± 13.6	23.5 ± 11.6	24.1 ± 13.3	24.5 ± 8.6	26.7 ± 9.7
	Median	21.0	23.0	20.0	18.0	23.5	26.5
	(Min,Max)	(11,61)	(14,67)	(12,49)	(12,53)	(12,49)	(13,45)
Total lesions	N	25	25	25	25	26	26
	Mean±SD	40.0 ± 16.6	40.8 ± 14.1	39.7 ± 22.8	41.0 ± 25.3	39.9 ± 11.8	42.6 ± 12.2
	Median	36.0	38.0	30.0	30.0	38.5	42.5
	(Min,Max)	(20,76)	(23,73)	(22,121)	(20,129)	(23,77)	(24,75)

- Efficacy
  - Primary efficacy criteria: total acne lesion count and percent reduction at end of treatment (Day27)

After a 4-week treatment period CD5789 Gel at 0.01% and 0.005% demonstrated a statistically significant superiority, compared to vehicle, in the primary efficacy criteria, total acne lesion count and percent reduction.

Table 2 and Table 3 below provide detailed information on the primary efficacy criteria.

Table 2 Clinical Evaluation: Total Lesions Count at Day 27

		CD5789 0.01%/Vehicle			CD5789 0.005%/Vehicle			Epiduo®/Vehicle		
		Active	Vehicle	A-V	Active	Vehicle	A-V	Active	Vehicle	A-V
Day 27/PP	N	21	21	21	21	21	21	24	24	24
	Mean±SD	11.8±9.8	28.4±13.8	-16.6±10.7	16.2±12.1	26.2±10.8	-10.0±10.8	16.8±11.5	29.0±16.7	-12.2±14.7
	Median	8.0	30.0	-17.0	12.0	28.0	-7.0	15.0	28.0	-10.0
	(Min,Max)	(1.0,32.0)	(5.0,62.0)	(-37.0,6.0)	(4.0,44.0)	(7.0,47.0)	(-25.0,12.0)	(0.0,44.0)	(5.0,86.0)	(-53.0,16.0)
	P-value*			<0.001			<0.001			<0.001
Endpoint/IT TLOCF	N	25	25	25	25	25	25	26	26	26
	Mean±SD	12.2±9.4	27.2±14.0	-15.0±10.9	19.4±17.5	29.0±18.7	-9.6±10.6	16.6±11.1	28.3±16.2	-11.7±14.3
	Median	9.0	30.0	-15.0	14.0	27.0	-7.0	15.0	27.5	-9.5
	(Min,Max)	(1.0,32.0)	(4.0,62.0)	(-37.0,6.0)	(4.0,84.0)	(7.0,105.0)	(-25.0,12.0)	(0.0,44.0)	(5.0,86.0)	(-53.0,16.0)
	P-value*			<0.001			<0.001			<0.001

* p-value by two-sided Wilcoxon rank signed test
A - V is Active – Vehicle

Percent decrease from Baseline for total lesions at Day 27 paralleled these results.

Table 3 Clinical evaluation: Total lesion percent reduction from Baseline

		CD5789 0.01%/Vehicle			CD5789 0.005%/Vehicle			Epiduo®/Vehicle		
		Active	Vehicle	A-V	Active	Vehicle	A-V	Active	Vehicle	A-V
Day 27/PP	N	21	21	21	21	21	21	24	24	24
	Mean±SD	72.1±20.3	24.2±41.6	47.9±34.8	56.2±30.7	26.5±28.2	29.6±34.7	54.9±32.1	26.2±41.9	28.7±33.8
	Median	75.0	29.4	46.0	64.3	29.8	21.5	59.2	27.9	22.9
	(Min,Max)	(11.8,97.2)	(-59.3,88.1)	(-0.2,134.3)	(-46.7,86.7)	(-45.0,72.0)	(-40.0,118.9)	(-33.3,100.0)	(-68.6,87.5)	(-51.0,107.5)
	P-value*			<0.001			<0.001			<0.001
Endpoint/IT TLOCF	N	25	25	25	25	25	25	26	26	26
	Mean±SD	70.6±19.2	29.4±40.7	41.1±35.9	51.7±30.3	26.1±26.0	25.7±33.5	56.0±31.1	28.6±41.1	27.4±32.8
	Median	74.3	31.8	29.8	57.1	25.8	20.3	62.3	40.9	20.9
	(Min,Max)	(11.8,97.2)	(-59.3,88.1)	(-14.0,134.3)	(-46.7,86.7)	(-45.0,72.0)	(-40.0,118.9)	(-33.3,100.0)	(-68.6,87.5)	(-51.0,107.5)
	P-value*			<0.001			<0.001			<0.001

* p-value by two-sided Wilcoxon rank signed test
A - V is Active – Vehicle

- Secondary efficacy criteria
  - Total lesion count at all visits and percent reduction over time

At Day27, the total lesion count with CD5789 Gel at 0.01% and 0.005% and Epiduo® was statistically significantly inferior to its vehicle ($p<0.001$, ITT and PP population).

A statistically significant difference between Epiduo® and CD5789 Gel vehicle was observed from Day15 onwards (all $p<0.05$, PP population).

At Day27 the percent reduction from Baseline was statistically significant in favor of active, with both CD5789 concentrations as well as with Epiduo® ($p<0.001$, ITT and PP population).

The treatment effect in term of percent reduction from Baseline in total lesion count was 47.9 % with CD5789 0.01%, 29.6% with CD5789 0.005% and 28.7% with Epiduo® in the PP population at Day27.

- Inflammatory lesion count at all visits and percent reduction over time

Inflammatory lesion count with CD5789 0.005% Gel was statistically significantly inferior to its Vehicle from Day15. This was also observed for Epiduo® versus the vehicle. A statistically significant difference in favor of active between CD5789 0.01% Gel and its vehicle was observed on Day 08 and at Day27.

The percent reduction of CD5789 0.01% Gel at Day 08 and Day27 and CD5789 0.005% Gel from Day22 onwards was statistically superior to the vehicle. Percent reduction in inflammatory lesions with Epiduo® was statistically superior to the vehicle at Day15 and Day27.

Results at Endpoint/ITT LOCF confirmed the outcome.

- Non-inflammatory lesion count at all visits and percent reduction over time

Non-inflammatory lesion count with CD5789 Gel at 0.01% and 0.005%, as well as with Epiduo®, was statistically significantly inferior to that of its vehicle from Day 08.

The percent reduction from baseline confirmed these results (except for Epiduo® at Day 08).

Results at Endpoint/ITT LOCF confirmed the outcome.

- Efficacy preference at Day27

Statistically significantly more Investigators and subjects in the ITT and PP population considered that sides treated with CD5789 0.01% Gel, CD5789 0.005% Gel or Epiduo® had better improved than those treated with the Vehicle.

- Safety

Overall, 18 (72%) subjects in the CD5789 0.01% Gel/Vehicle group, 12 (48%) in the CD5789 0.005% Gel/vehicle group and 6 (23%) in the Epiduo®/Vehicle group had their dosage regimen modified due to skin irritation.

A total of 18 (72%) subjects in the CD5789 0.01% Gel/Vehicle group experienced 28 adverse events. Thirteen (13) of these adverse events in 10 subjects were related to the active treatment, with 12 events of dermatologic nature and considered as related. Two (2) of the related adverse events were severe. There was no serious adverse event and no adverse event leading to subject discontinuation in this group.

Table 4 Overview of adverse events: CD5789 0.01%/Vehicle

	CD5789 0.01% Gel (N= 25)			Vehicle (N= 25)			Total (N= 25)		
	n events	n subj.*	% subj.	n events	n subj.*	% subj.	n events	n subj.*	% subj.
All AEs	28	18	72.0	15	12	48.0	28	18	72.0
Related AEs	13	10	40.0	0	0	0.0	13	10	40.0
All dermatologic AEs	12	10	40.0	0	0	0.0	12	10	40.0
Related dermatologic AEs	12	10	40.0	0	0	0.0	12	10	40.0
All severe AEs	2	2	8.0	0	0	0.0	2	2	8.0
Related severe AEs	2	2	8.0	0	0	0.0	2	2	8.0
All serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
Related serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
All AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
Related AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
Deaths	0	0	0.0	0	0	0.0	0	0	0.0

Adverse events are summarized only for events occurred after the first use of study product.
If an AE is not zone specific it will be summarized in each study treatment.
Note: The numbers in the columns cannot be added because a given subject may have reported more than one AE.

In the CD5789 0.005% Gel/Vehicle group 13 (52%) subjects reported 22 adverse events. Four (4) of these events were considered treatment related. From the 5 dermatologic adverse events, 4 were related to treatment with CD5789 Gel at 0.005%. One adverse event was severe but not treatment related. There was one serious adverse event, not related (idopathic thrombocytopenic purpura) leading to the discontinuation of that subject as well as one other not related adverse events (migraine) leading to the discontinuation reported. There were no deaths.

Table 5 Overview of adverse events: CD5789 0.005%/Vehicle

	CD5789 0.005% Gel (N= 25)			Vehicle (N= 25)			Total (N= 25)		
	n events	n subj.*	% subj.	n events	n subj.*	% subj.	n events	n subj.*	% subj.
All AEs	22	13	52.0	18	11	44.0	22	13	52.0
Related AEs	4	3	12.0	0	0	0.0	4	3	12.0
All dermatologic AEs	5	3	12.0	1	1	4.0	5	3	12.0
Related dermatologic AEs	4	3	12.0	0	0	0.0	4	3	12.0
All severe AEs	1	1	4.0	1	1	4.0	1	1	4.0
Related severe AEs	0	0	0.0	0	0	0.0	0	0	0.0
All serious AEs	1	1	4.0	1	1	4.0	1	1	4.0
Related serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
All AEs leading to discontinuation	2	2	8.0	2	2	8.0	2	2	8.0
Related AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
Deaths	0	0	0.0	0	0	0.0	0	0	0.0

Adverse events are summarized only for events occurred after the first use of study product.
If an AE is not zone specific it will be summarized in each study treatment.
Note: The numbers in the columns cannot be added because a given subject may have reported more than one AE.

In the Epiduo®/Gel group, 19 (73.1%) subjects reported 24 adverse events. Ten (10) adverse events in 7 subjects were related to Epiduo®, all were of dermatologic nature. From the 3 severe adverse events, 2 were related to Epiduo®. There were no deaths, serious adverse events or related adverse events leading to subject discontinuation.

Table 6 Overview of adverse events: Epiduo®/Vehicle

	Epiduo® (N= 26)			Vehicle (N= 26)			Total (N= 26)		
	n events	n subj.*	% subj.	n events	n subj.*	% subj.	n events	n subj.*	% subj.
All AEs	33	19	73.1	23	17	65.4	34	19	73.1
Related AEs	10	7	26.9	0	0	0.0	10	7	26.9
All dermatologic AEs	10	7	26.9	1	1	3.8	11	8	30.8
Related dermatologic AEs	10	7	26.9	0	0	0.0	10	7	26.9
All severe AEs	3	2	7.7	1	1	3.8	3	2	7.7
Related severe AEs	2	2	7.7	0	0	0.0	2	2	7.7
All serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
Related serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
All AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
Related AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
Deaths	0	0	0.0	0	0	0.0	0	0	0.0

Adverse events are summarized only for events occurred after the first use of study product.
If an AE is not zone specific it will be summarized in each study treatment.
Note: The numbers in the columns cannot be added because a given subject may have reported more than one AE.

A total of 10 (40.0%) subjects reported 13 adverse events related to treatment with CD5789 0.01% Gel. The majority was skin irritation (7 subjects), followed by burning sensation of the skin (2 subjects) and with facial pain or scab (one subject each).

Three (3, 12.0%)) subjects reported 4 related adverse events with CD5789 0.005% Gel. One subject reported burning sensation on the skin, one skin exfoliation and one irritation of the skin.

Seven (7, 26.9%) of subjects reported 10 adverse events with Epiduo®. Two subjects reported burning skin sensation or skin irritation and one subject reported erythema, irritation of the eyelid or periorbital edema.

There were no deaths reported during the study. No subject discontinued the study due to treatment related adverse events. One subject in the CD5789 0.005%/Vehicle group reported one serious adverse event, not related to the treatment (idopathic thrombocytopenic purpura). Two subjects treated with CD5789 0.01% Gel reported severe adverse events related to the treatment (scab and burning sensation of the skin).

At Day27 no notable changes from Screening in vital signs and physical findings in any of the treatment groups was reported.

Except for one subject reporting a not related serious adverse event leading to discontinuation of the study, no notable changes at Day27 from Screening in routine laboratory parameters in any of the treatment groups was reported.

Systemic exposure to CD5789 in all tested plasma samples the concentration was below the limit of quantification.

As expected, all subjects treated with CD5789 reported skin irritation. Worst skin irritation score over time with CD5789 0.01% Gel was severe in 6 (24%) of the subjects compared to 3 (12%) subjects treated with CD5789 0.005% Gel and one with Epiduo®.

The incidence of at least moderate irritation showed that a maximum was reached at the end of each 5-day treatment period. After 2 days of no treatment, scores had decreased but re-increased at the end of the following treatment period.

Overall, the number of severe cases of skin irritation at the end of each treatment period was low and did not exceed 3 subjects (Day12 with CD5789 0.01% Gel).

- **Conclusion**

The present study demonstrated that CD5789 Gel at doses of 0.01% and 0.005% applied for 20 days was statistically significant superior to its vehicle in decreasing the total, inflammatory and non-inflammatory lesion count in subjects with *acne vulgaris* and was relatively well tolerated.

The local safety profile characterized by irritation of the skin with CD5789 Gel at 0.01% and 0.005% is in line with that of currently available topical RAR agonists. The systemic safety of CD5789 of up to 0.01% was good, the level of exposure was below the limit of quantification in all analyzed samples.