Table 6 **Percent reduction in total lesion counts at the end of treatment (Short contact)**

		CD5789 100 µg/g /Vehicle Short contact 5 minutes			CD5789 100 µg/g /Vehicle Short contact 30 minutes			Tazarotene 0.1% gel / vehicle gel Short contact 5 minutes		
		Active	Vehicle	A - V	Active	Vehicle	A - V	Active	Vehicle	A - V
Endpoint (ITT)	N	22	22	22	18	18	18	20	20	20
	Mean	54.3	29.8	24.5	50.1	22.2	27.9	39.1	30.5	8.6
	SD	22.2	24.4	19.1	13.7	30.1	27.5	30.4	26.7	27.8
	Median	55.8	32.5	**21.4**	48.6	34.8	**25.4**	46.1	29.3	15.6
	(Min,Max)	(0.0,77.6)	(-20.0,70.0)	(-12.0,59.3)	(22.9,80.0)	(-50.0,52.5)	(-12.3,85.7)	(-22.6,81.4)	(-20.7,76.7)	(-50.3,46.7)
	P-value*			**<0.001**			**<0.001**			0.165
Day 29 (PP)	N	22	22	22	17	17	17	18	18	18
	Mean	54.3	29.8	24.5	51.7	21.4	30.2	42.9	36.0	7.0
	SD	22.2	24.4	19.1	12.3	30.8	26.4	29.0	22.0	28.4
	Median	55.8	32.5	**21.4**	48.6	34.5	**27.8**	49.3	30.8	15.6
	(Min,Max)	(0.0,77.6)	(-20.0,70.0)	(-12.0,59.3)	(29.5,80.0)	(-50.0,52.5)	(-3.4,85.7)	(-22.6,81.4)	(10.0,76.7)	(-50.3,46.7)
	P-value*			**<0.001**			**<0.001**			0.284

* p-value by two-sided Wilcoxon rank signed test

A - V is Active – Vehicle

Secondary efficacy criteria:

- Inflammatory lesions

A significant difference between the active and the vehicle in terms of inflammatory lesion counts and percent reduction from baseline was observed in the CD5789 100 µg/g / vehicle gel leave on 5x/week group at Endpoint (ITT population) and at Day 29 (PP population).

For the CD5789 100µg/g / vehicle leave on 2x/week group, at Day 29 (PP population), there were significantly less inflammatory lesions on the active-treated side than on the vehicle-treated side and this difference was almost significant for percent reduction at Day 29 (PP population). In the ITT population, differences were not significant.

For the Tazarotene 0.1% gel /Vehicle Leave on 5x/week group, at Day 29 (PP population) and at Endpoint (ITT population), difference in inflammatory lesions between the active-treated side and the vehicle-treated side was not statistically significant.

For the CD5789 100µg/g / vehicle short contact 5 minutes 5x/week group and the CD5789 100µg/g / vehicle short contact 30 minutes 5x/week group, at Day 29 (PP population) and at endpoint (ITT population), there were statistically less inflammatory lesions on the active-treated side than on the vehicle-treated side. The difference between the active and the vehicle was also statistically significant in both populations for percent reduction.

For the Tazarotene 0.1% gel / vehicle short contact 5 minutes 5x/week group, at Day 29 (PP population) and at Endpoint (ITT population), there were no differences between active-treated side and vehicle-treated side in inflammatory lesion count and in percent reduction.

- Non-inflammatory lesions

A significant difference between the active and the vehicle in terms of non-inflammatory lesion counts and percent reduction was found in the CD5789 100 µg/g / vehicle gel leave on 5x/week group at endpoint (ITT population) and at Day 29 (PP population).

For the CD5789 100µg/g / vehicle Leave on 2x/week group, at endpoint (ITT population) and at Day 29 (PP population), there were statistically less non inflammatory lesions on the active-treated side than on the vehicle-treated side. However, this difference was not statistically significant for percent reduction in both populations.

	In the Tazarotene 0.1% gel / vehicle Leave on 5x/week group, at Day 29 (PP population) and at Endpoint (ITT population), the difference in non-inflammatory lesions between the active-treated side and the vehicle-treated side was not statistically significant. For the CD5789 100µg/g / vehicle short contact 5 minutes 5x/week group and the CD5789 100µg/g / vehicle short contact 30 minutes 5x/week group, at Day 29 (PP population) and at Endpoint (ITT population), there were statistically less non inflammatory lesions on the active-treated side than on the vehicle-treated side. The difference between active and vehicle was also statistically significant in both populations for percent reduction in non-inflammatory lesion count. In the Tazarotene 0.1% gel / vehicle short contact 5 minutes 5x/week group, at Day 29 (PP population) and at Endpoint (ITT population), there were no difference between active-treated side and vehicle-treated side in non-inflammatory lesions and in percent reduction. - Total lesions Significant differences between the active and the vehicle in terms of total lesion count were observed for the group CD5789 100 µg/g / vehicle gel leave on 5x/week from Day 08 on sustaining until Day 36 (all $p \leq 0.044$). Differences in percent reduction were significant starting Day 15 and sustaining until Day 36 (all $p \leq 0.026$). Significant differences between the active and the vehicle in terms of total lesion count were observed for the group CD5789 100 µg/g / vehicle gel leave on 2x/week at Day 22 and Day 29 ($p=0.002$ and 0.014, respectively). The difference in percent reduction was significant at Day 22, only ($p=0.003$). The difference in lesion count for Tazarotene 0.1% gel / vehicle leave on 5x/week was significantly at Day 22 ($p=0.018$), only. Significant differences in percent reduction were observed at Day 08 ($p=0.021$) and Day 22 ($p=0.003$). Significant differences between the active and the vehicle in terms of lesion count were observed in the CD5789 100 µg/g / vehicle short contact 5 and 30 minutes group starting Day 08 and sustaining until Day 36. Percent reduction was significantly superior (all $p \leq 0.012$) with the active over the vehicle in the CD5789 100 µg/g / vehicle short contact 5 and 30 minutes groups from Day 08 on, sustaining until Day 36. There was no difference in the Tazarotene 0.1% gel / vehicle short contact 5 minutes group, at any visit. - Efficacy preference Investigators significantly preferred the side treated with CD5789 100 µg/g gel leave on 5x/week from the side treated with vehicle at Day 29 and Day 36 in both populations. They further preferred the side treated with CD5789 100 µg/g gel leave on 2x/week from the side treated with vehicle but it was not significant. No statistical difference in terms of investigator preference was observed for Tazarotene 0.1% gel leave on 5x/week. Investigators significantly preferred the side treated with CD5789 100 µg/g gel short contact 5 minutes 5x/week from the side treated with vehicle at Day 29 and at Day 36 in both populations. They significantly preferred the side treated with CD5789 100 µg/g gel short contact 30 minutes 5x/week from the side treated with vehicle at Day 29 and at Day 36 in both populations. No statistical difference in term of investigator preference was found for Tazarotene 0.1% gel short contact 5 minutes 5x/week.
21. Safety outcomes	- Adverse events Four (4) subjects in the CD5789 100 µg/g / vehicle leave on 5x/week group missed at least one application due to irritation in the active side and one in the vehicle side. The

first occurrence was at day 3. One subject (at Day 19) in Tazarotene 0.1%gel / vehicle leave on 5x/week missed its application due to irritation in the active side. No subject missed any application due to irritation in the CD5789 100 µg/g / vehicle leave on 2x/week.

Five (5) subjects in CD5789 100 µg/g / vehicle short contact 5 minutes on 5x/week group missed at least one application due to irritation in the active side and one in the vehicle side. The first occurrence was at day 4. Two (2) subjects in CD5789 100µg/g / vehicle short contact 30 minutes 5x/week missed their application due to irritation in the active side. No subject missed any application due to irritation in the Tazarotene 0.1%gel / vehicle short contact 5 minutes 5x/week.

Among the 4 subjects in the CD5789 100 µg/g gel /vehicle gel leave on 5x/week who missed application due to irritation, one missed 1 application in the active side, 2 missed 2 applications in the active side and 1 missed 3 applications in both sides during their study stay. In the Tazarotene 0.1% gel /vehicle leave on 5x/week, the subject missed one application due to irritation in the active side.

Among the 5 subjects in the CD5789 100µg/g gel / vehicle gel short contact 5 minutes 5x/week who missed application due to irritation, three missed 1 application, 1 missed 2 applications and 1 missed 7 applications during their study stay. In CD5789 100µg/g gel / vehicle gel short contact 30 minutes 5x/week, one subject missed one application and the other one, 2 applications.

Table 7 Overview of adverse events: CD5789 100 µg/g gel /Vehicle Leave on 5x/week

	CD5789 100 µg/g Leave on 5x/week (N= 19)			Vehicle Leave on 5x/week (N= 19)			Total (N= 19)		
	n events	n subj.	% subj.	n events	n subj.	% subj.	n events	n subj.	% subj.
All AEs	21	8	42.1	16	7	36.8	22	8	42.1
Related AEs	7	5	26.3	2	2	10.5	8	5	26.3
All dermatologic AEs	6	4	21.1	1	1	5.3	7	4	21.1
Related dermatologic AEs	6	4	21.1	1	1	5.3	7	4	21.1
AESI	6	4	21.1	1	1	5.3	7	4	21.1
All severe AEs	2	2	10.5	1	1	5.3	3	2	10.5
Related severe AEs	2	2	10.5	1	1	5.3	3	2	10.5
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 medication.

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 100µg/g gel / vehicle gel leave on 5x/week group, 22 AEs were reported by 8 subjects (42.1%). None led to discontinuation or was serious. Four (4) of the 19 subjects (21.1%) presented dermatologic related adverse events and one subject presented a related eye irritation (Table 7).

Two (2) subjects presented related severe dermatologic AEs (skin irritation, subject n°5424-009 on both sides and subject n° 5424-046 on CD5789 treated side).

Table 8 Overview of adverse events: CD5789 100 µg gel /g /Vehicle Leave on 2x/week

	CD5789 100 µg/g Leave on 2x/week (N= 20)			Vehicle Leave on 2x/week (N= 20)			Total (N= 20)		
	n events	n subj.	% subj.	N events	n subj.	% subj.	n events	n subj.	% subj.
All AEs	11	8	40.0	11	8	40.0	11	8	40.0
Related AEs	0	0	0.0	0	0	0.0	0	0	0.0
All dermatologic AEs	0	0	0.0	0	0	0.0	0	0	0.0
Related dermatologic AEs	0	0	0.0	0	0	0.0	0	0	0.0
AESI	0	0	0.0	0	0	0.0	0	0	0.0
All severe AEs	0	0	0.0	0	0	0.0	0	0	0.0
Related severe AEs	0	0	0.0	0	0	0.0	0	0	0.0
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

In the CD5789 100µg/g gel / vehicle gel leave on 2x/week, 11 AEs were reported by 8 subjects (40.0%). None were related to the study drug and none led to discontinuation.

Table 9 Overview of adverse events: Tazarotene 0.1% gel / vehicle gel Leave on 5x/week

	Tazarotene 0.1% gel Leave on 5x/week (N= 18)			Vehicle gel Leave on 5x/week (N= 18)			Total (N= 18)		
	n events	n subj.	% subj.	n events	n subj.	% subj.	n events	n subj.	% subj.
All AEs	11	5	27.8	10	5	27.8	11	5	27.8
Related AEs	1	1	5.6	0	0	0.0	1	1	5.6
All dermatologic AEs	2	2	11.1	1	1	5.6	2	2	11.1
Related dermatologic AEs	1	1	5.6	0	0	0.0	1	1	5.6
AESI	1	1	5.6	0	0	0.0	1	1	5.6
All severe AEs	0	0	0.0	0	0	0.0	0	0	0.0
Related severe AEs	0	0	0.0	0	0	0.0	0	0	0.0
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

In the Tazarotene 0.1% gel / vehicle leave on 5x/week group, 11 AEs were reported by 5 subjects (27.8%). None led to discontinuation. One of the 18 subjects (5.6%) presented dermatologic related adverse event on the active side (Table 9).

Table 10 **Overview of adverse events: CD5789 100 µg/g gel / Vehicle Short contact 5 minutes**

	CD5789 100 µg/g Short contact 5 minutes (N= 22)			Vehicle Short contact 5 minutes (N= 22)			Total (N= 22)		
	n events	n subj.	% subj.	n events	n subj.	% subj.	n events	n subj.	% subj.
All AEs	17	7	31.8	10	5	22.7	19	7	31.8
Related AEs	9	5	22.7	2	1	4.5	11	5	22.7
All dermatologic AEs	9	5	22.7	2	1	4.5	11	5	22.7
Related dermatologic AEs	9	5	22.7	2	1	4.5	11	5	22.7
AESI	9	5	22.7	2	1	4.5	11	5	22.7
All severe AEs	3	2	9.1	0	0	0.0	3	2	9.1
Related severe AEs	3	2	9.1	0	0	0.0	3	2	9.1
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

In the CD5789 100µg/g gel / vehicle gel short contact 5 minutes 5x/week group, 19 AEs were reported by 7 subjects (31.8%). None led to discontinuation or was serious. Five (5) of the 22 subjects (22.7%) presented dermatologic related adverse events (Table 10).

Two (2) subjects presented related severe dermatologic AEs (skin irritation: subject n°5424-006 and 5604-007) on the active side.

Table 11 **Overview of adverse events: CD5789 100 µg/g gel /Vehicle Short contact 30 minutes**

	CD5789 100 µg/g Short contact 30 minutes (N= 18)			Vehicle Short contact 30 minutes (N= 18)			Total (N= 18)		
	n events	n subj.	% subj.	n events	n subj.	% subj.	n events	n subj.	% subj.
All AEs	17	9	50.0	15	8	44.4	18	9	50.0
Related AEs	3	3	16.7	1	1	5.6	4	3	16.7
All dermatologic AEs	4	4	22.2	2	2	11.1	5	4	22.2
Related dermatologic AEs	3	3	16.7	1	1	5.6	4	3	16.7
AESI	2	2	11.1	1	1	5.6	3	2	11.1
All severe AEs	0	0	0.0	0	0	0.0	0	0	0.0
Related severe AEs	0	0	0.0	0	0	0.0	0	0	0.0
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	1	1	5.6	1	1	5.6	2	1	5.6
Related AEs leading to discontinuation	1	1	5.6	1	1	5.6	2	1	5.6
Deaths	0	0	0.0	0	0	0.0	0	0	0.0

In the CD5789 100µg/g gel /Vehicle gel short contact 30 minutes 5x/week group, 18 AEs were reported by 9 subjects (50.0%). One related AE on both side led to discontinuation (skin irritation, subject n° 5074-012). None was serious or severe. Three (3) of the 18 subjects (16.7%) presented dermatologic related adverse events (Table 11).

Table 12 Overview of adverse events: Tazarotene 0.1% gel / vehicle gel Short contact 5 minutes

	Tazarotene 0.1% gel Short contact 5 minutes (N= 20)			Vehicle gel Short contact 5 minutes (N= 20)			Total (N= 20)		
	n events	n subj.	% subj.	n events	n subj.	% subj.	n events	n subj.	% subj.
All AEs	11	6	30.0	11	6	30.0	11	6	30.0
Related AEs	0	0	0.0	0	0	0.0	0	0	0.0
All dermatologic AEs	0	0	0.0	0	0	0.0	0	0	0.0
Related dermatologic AEs	0	0	0.0	0	0	0.0	0	0	0.0
AESI	0	0	0.0	0	0	0.0	0	0	0.0
All severe AEs	0	0	0.0	0	0	0.0	0	0	0.0
Related severe AEs	0	0	0.0	0	0	0.0	0	0	0.0
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	1	1	5.0	1	1	5.0	1	1	5.0
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

In the Tazarotene 0.1% gel /Vehicle short contact 5 minutes 5x/week group (Table 12) 11 AEs were reported by 6 subjects (30.0%). None were related, serious or severe. One AE not related to the study drug led to discontinuation (increase in transaminases in subject n°5424-043).

- Local tolerance

Erythema, scaling, dryness, stinging/burning were assessed on each half face before treatment application at every visit from Baseline (Day 1) to Day 29/early termination visit and Day 36. A global tolerance score was also assessed on each half face before treatment application at every visit from Day 2 to Day 29/early termination visit and Day 36.

In all 3 leave on groups, occurrence of erythema, scaling, dryness and stinging/burning was higher on the active-treated than on the vehicle-treated side. CD5789 100 µg/g gel /vehicle leave on 2x/week was better tolerated compared to the 2 other Leave on 5x/week groups.

One subject in the CD5789 100µg/g gel leave on 5x/week experienced a very severe global tolerance score on the active side.

Occurrence of erythema, scaling, dryness and stinging/burning were higher on the active-treated side than on the vehicle-treated side for all 3 short contact groups. Tazarotene 0.1% gel / vehicle gel short contact 5 minutes 5x/week was the best tolerated compared the 2 short contact treatments with CD5789 / Vehicle.

One subject in the CD5789 100 µg/g gel short contact 5 minutes 5x/week experienced a very severe global tolerance score on the active side

- Vital signs, physical findings and laboratory parameters

Vital signs and physical findings assessed at the end of the study did not raise safety concerns.

Except for one subject in the Tazarotene 0.1% gel /Vehicle short contact 5 minutes 5x/week group, standard laboratory values had not changes from screening values.

22. Summary (conclusion)	CD5789 100µg/g gel leave on 5x/week, CD5789 100µg/g gel short contact 5 minutes 5x/week and CD5789 100µg/g gel short contact 30 minutes 5x/week compared to their

	vehicle gel showed significant differences in terms of total, inflammatory, non-inflammatory lesion counts and their corresponding percent reductions (from baseline). Less significant efficacy was observed with CD5789 100µg/g gel leave on 2x/week. Tazarotene 0.1% gel Leave on 5x/week and Tazarotene 0.1% gel short contact 5 minutes 5x/week did not show significant efficacy compared to the CD5789 vehicle in terms of total, inflammatory and non-inflammatory lesion counts and respective percent reductions (from baseline). No serious adverse event was observed. Four (4) related AEs were rated severe: 2 each in the CD5789 100µg/g gel leave on 5x/week and in the CD5789 100µg/g gel short contact 5 minutes 5x/week. Skin intolerance was observed and led to discontinuation from the study in one case and to missing applications in others. The twice a week application dose regimen with CD5789 is less efficacious but better tolerated than the daily regimens. Short contact therapy does not appear to provide a significant tolerability advantage.

Applicant (Marketing Authorization Holder)	(signature) Régis Schulz (full name)	**GALDERMA SA** Zählerweg 10 CH-6300 Zug 058 455 85 00

Annex 30
to the Procedure for expertise of registration materials for medicinal products submitted for state registration (renewal), as well as expertise of the materials on variations to the registration materials during the marketing authorization validity period
(clause 4 of Section IV)

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD-03-SRE-40129 - Exploratory study to assess facial tolerability after daily application of several concentrations and formulations containing CD5789 in acne subjects
6. Clinical study phase	Phase 2a: therapeutic exploratory
7. Clinical study period	Date of first subject screened: 4 April 2011 Date of last subject completed:27 July 2011
8. Countries where clinical study was conducted	Hungary, France, Belgium
9. Number of subjects	A sample size of 42 evaluable subjects was planned for Cohort 1 and 28 evaluable subjects for Cohort 2, for a total of 70 evaluable subjects. The sample size was an

	approximation, as no formal hypothesis testing was planned in this study. A total of 68 subjects were randomized.
10. Aim and secondary purposes of clinical study	To evaluate the facial tolerability and subject's adherence to treatment of different formulations of CD5789 when applied once daily (QD) over 4 weeks by acne subjects, in comparison with Tazarotene 0.1%.

11. Clinical study design	This was a multicenter, randomized, evaluator-blind, parallel-group exploratory study to investigate the facial tolerability and subject adherence to treatment for different formulations of CD5789 in subjects with acne vulgaris. Tazarotene 0.1% Gel was selected as an active comparator.
	Two cohorts were defined. Within each cohort, the corresponding treatments and number of subjects to be allocated to each treatment group were as follows:
	- Cohort 1
	  ○ A: CD5789 50 µg/g Cream A, n=14
	  ○ B: CD5789 25 µg/g Cream A, n=14
	  ○ C: CD5789 50µg/g Gel, n=7
	  ○ D: Tazarotene 0.1% Gel, n=7
	- Cohort 2
	  ○ E: CD5789 50 µg/g Cream B, n=14
	  ○ C: CD5789 50µg/g Gel, n=7
	  ○ D: Tazarotene 0.1% Gel, n=7

12. Main inclusion criteria	Key inclusion criteria - Male or female subjects 18-35 years old; - Moderate to severe facial acne vulgaris; - At least 20 inflammatory lesions and 30 non-inflammatory lesions; - If female of childbearing potential, she agrees to use a highly effective double-barrier contraception method for the duration of the study and one month after the last study drug application.
13. Investigational medicinal product, method of administration, strength	Cream A: CD5789, cream, topical administration, strength : 25µg/g (0.0025%) & 50 µg/g CD8789, gel, tropical administration, strength: 50 µg/g Cream B: CD5789, cream, topical administration, strength: 50 µg/g
14. Reference medicinal product, method of administration, strength	Tazarotene, gel, topical administration, strength: 0.1%
15. Concomitant therapy	Not Applicable
16. Efficacy evaluation criteria	- Lesion counts: inflammatory (papules, pustules), non-inflammatory (open and closed comedones), other acne lesion count (nodules); total lesion count was calculated as the sum of inflammatory lesions, non-inflammatory lesions, and nodules;

	- Efficacy criteria ○ Not applicable, as this study was not designed to show the efficacy of CD5789. However, lesion count data were obtained (total, inflammatory, and non-inflammatory) to prepare data summaries on the numbers of lesions and also the percent reductions in lesions over time by treatment group.
17. Safety evaluation criteria	- Adverse events - Physical examinations and vital signs - Laboratory safety testing - Local tolerance
18. Statistical methods	No inferential analyses were conducted for this study. Subject disposition, demographics, baseline characteristics, previous therapies, and concomitant therapies were summarized by treatment group using descriptive statistics. Efficacy data were analyzed at each visit for the Safety Population. Lesion counts (inflammatory, non-inflammatory and total) as well as changes and percent reduction in lesion counts from baseline were descriptively summarized by visit and by treatment. Adverse events, general physical examination, vital signs, laboratory parameters and cosmetic acceptability questionnaires were summarized by descriptive statistics. Local tolerability assessments were summarized by treatment using means over time, frequency by severity over time, and worst response (from Day 1 to Day 29) over time. Sample size: For Cohort 1, screening of 50 subjects was planned in order to enroll 42 evaluable subjects. For Cohort 2, screening of 33 subjects was planned in order to enroll 28 evaluable subjects, with allocation to treatment groups as follows: 7 subjects in the CD5789 Gel and Tazarotene 0.1% Gel groups and 14 subjects in the CD5789 50 µg/g Cream B group in order to have the same numbers of subjects in the corresponding groups across the 2 cohorts. No formal hypothesis testing was planned in this study.
19. Demographic indicators of the study population (gender, age, race, etc.)	- For randomized subjects, no apparent imbalances in demographic characteristics were observed among the treatment groups (Table 1). All (100%) of randomized subjects were Caucasian, and the randomized subjects were predominantly males (57.4%). The mean age of randomized subjects overall was 21.6 years, ranging from 18 to 33 years. - Subjects were required to have at least 20 inflammatory lesions and 30 non-inflammatory lesions on the face to be eligible for this study. In each treatment group, mean non-inflammatory lesion counts were higher than mean inflammatory lesion counts (Table 2). No obvious differences were observed among the treatment groups for any lesion count category.

Table 1 **Demographic characteristics, Safety Population**

	SCREENED	RANDOMIZED					
	Total	CD5789 50µg/g CREAM B	CD5789 25µg/g CREAM A	CD5789 50µg/g CREAM A	CD5789 50µg/g GEL	TAZAROTENE 0.1% GEL	Total
Age (years)							
n	70	12	14	16	12	14	68
Mean	21.6	20.8	21.6	21.4	22.9	21.4	21.6
Median	21.0	19.0	20.5	21.0	21.5	20.0	21.0
SD	3.6	2.9	4.3	2.8	4.4	3.7	3.6
(Min,Max)	(18,33)	(18,26)	(18,31)	(18,27)	(18,33)	(18,31)	(18,33)
Race (n, %)							
Caucasian	69 (98.6%)	12 (100.0%)	14 (100.0%)	16 (100.0%)	12 (100.0%)	14 (100.0%)	68 (100.0%)
Hispanic	1 (1.4%)	0	0	0	0	0	0
Total	70 (100.0%)	12 (100.0%)	14 (100.0%)	16 (100.0%)	12 (100.0%)	14 (100.0%)	68 (100.0%)
Sex (n, %)							
Female	31 (44.3%)	4 (33.3%)	5 (35.7%)	8 (50.0%)	5 (41.7%)	7 (50.0%)	29 (42.6%)
Male	39 (55.7%)	8 (66.7%)	9 (64.3%)	8 (50.0%)	7 (58.3%)	7 (50.0%)	39 (57.4%)
Total	70 (100.0%)	12 (100.0%)	14 (100.0%)	16 (100.0%)	12 (100.0%)	14 (100.0%)	68 (100.0%)

In this study, the Safety Population included all randomized subjects
Max=maximum; Min=Minimum; SD=standard deviation

Table 2 **Baseline disease characteristics, Safety Population**

	CD5789 50µg/g CREAM B	CD5789 25µg/g CREAM A	CD5789 50µg/g CREAM A	CD5789 50µg/g GEL	TAZAROTENE 0.1% GEL
Total lesion counts					
n	12	14	16	12	14
Mean	63.2	67.1	65.3	62.2	67.1
SD	6.0	11.9	15.1	8.5	10.1
Median	62.5	66.0	60.0	60.5	64.5
(Min,Max)	(53.0,72.0)	(53.0,90.0)	(55.0,111.0)	(53.0,78.0)	(51.0,90.0)
Inflammatory lesion counts					
n	12	14	16	12	14
Mean	25.8	23.6	25.7	25.3	28.6
SD	4.5	2.8	4.9	5.6	7.4
Median	24.5	22.0	25.0	23.0	27.0
(Min,Max)	(21.0,37.0)	(20.0,29.0)	(20.0,40.0)	(21.0,40.0)	(21.0,50.0)
Non-inflammatory lesion counts					
n	12	14	16	12	14
Mean	37.3	43.1	39.6	36.7	38.4
SD	3.9	10.7	14.7	4.4	7.5
Median	36.5	39.5	34.5	36.5	37.5
(Min,Max)	(31.0,45.0)	(31.0,67.0)	(31.0,91.0)	(31.0,46.0)	(30.0,62.0)

Max=maximum; Min=Minimum; SD=standard deviation

20. Efficacy outcomes

- For total lesions, at the end of the 4-week treatment period, the mean numbers of total lesions were lower than Day 1 in all treatment groups, ranging from 21.0 lesions in the CD5789 50 µg/g Cream B group to 28.9 lesions in the CD5789 50 µg/g Cream A group (Table 3). Total lesions on Day 29 were reduced in all treatment groups relative to baseline, ranging from 55.4% in the CD5789 50 µg/g Cream A group to 68.2% in the CD5789 50 µg/g Gel group (Table 4). The largest early effect was observed in the CD5789 50 µg/g Cream B group, for which a 40.6% mean percent reduction in total lesions was observed at Day 8.
- For inflammatory lesions, mean numbers of lesions on Day 29 were lower than Day 1 in all treatment groups, ranging from 8.4 lesions in the CD5789 50 µg/g

Gel group to 13.1 lesions in the CD5789 50 µg/g Cream A group. Inflammatory lesions on Day 29 were reduced in all treatment groups, ranging from 51.0% in the CD5789 50 µg/g Cream A group to 66.2% in the CD5789 50 µg/g Gel group. In general, a cumulative effect was observed over the treatment period in each treatment group with respect to mean percent reduction in inflammatory lesions.

- For non-inflammatory lesions, mean numbers of lesions were lower than Day 1 in all treatment groups, ranging from 10.5 lesions in the CD5789 50 µg/g Cream B group to 16.2 lesions in the CD5789 25 µg/g Cream A group. Non-inflammatory lesions on Day 29 were reduced in all treatment groups, ranging from 58.7% in the CD5789 50 µg/g Cream A group to 71.5% in the CD5789 50 µg/g Cream B group. A cumulative effect was observed over the treatment period in each treatment group with respect to mean percent reduction in non-inflammatory lesions.

Table 3 **Total lesion counts, Safety Population**

		CD5789 50µg/g CREAM B	CD5789 25µg/g CREAM A	CD5789 50µg/g CREAM A	CD5789 50µg/ g GEL	TAZAROTENE 0.1% GEL
Day 01	n	12	14	16	12	14
	Mean	63.2	67.1	65.3	62.2	67.1
	SD	6.0	11.9	15.1	8.5	10.1
	Median	62.5	66.0	60.0	60.5	64.5
	(Min,Max)	(53.0,72.0)	(53.0,90.0)	(55.0,111.0)	(53.0,78.0)	(51.0,90.0)
Day 08	n	11	14	16	12	14
	Mean	37.5	46.9	50.8	40.6	48.4
	SD	12.0	9.3	21.4	17.3	14.5
	Median	35.0	47.5	44.0	36.5	43.5
	(Min,Max)	(25.0,64.0)	(35.0,64.0)	(28.0,108.0)	(18.0,70.0)	(28.0,73.0)
Day 29	n	11	13	16	12	14
	Mean	21.0	25.2	28.9	20.2	23.2
	SD	15.9	12.6	13.0	13.2	11.9
	Median	15.0	24.0	28.5	18.5	22.5
	(Min,Max)	(3.0,54.0)	(13.0,47.0)	(5.0,53.0)	(4.0,52.0)	(5.0,46.0)
Day 35	n	11	13	16	12	13
	Mean	22.3	25.3	26.9	20.3	21.7
	SD	17.8	13.2	11.7	12.2	9.6
	Median	19.0	25.0	27.5	20.0	19.0
	(Min,Max)	(3.0,59.0)	(7.0,53.0)	(5.0,52.0)	(3.0,44.0)	(8.0,44.0)

Max=maximum; Min=Minimum; SD=standard deviation

Table 4 **Percent reduction in total lesion counts from Day 1, Safety Population**

		CD5789 50µg/g CREAM B	CD5789 25µg/g CREAM A	CD5789 50µg/g CREAM A	CD5789 50µg/ g GEL	TAZAROTENE 0.1% GEL
Day 08	n	11	14	16	12	14
	Mean	40.6	28.2	23.9	35.9	26.5
	SD	18.6	18.6	19.8	21.8	23.1
	Median	45.0	31.1	28.7	37.3	24.5
	(Min,Max)	(0.0,63.9)	(0.0,53.2)	(-20.0,49.1)	(1.4,66.0)	(-11.9,63.1)
Day 29	n	11	13	16	12	14
	Mean	66.1	61.3	55.4	68.2	65.5
	SD	27.4	20.7	19.1	18.1	16.8
	Median	79.2	67.9	56.6	68.4	66.6
	(Min,Max)	(5.3,95.0)	(32.8,85.6)	(23.2,91.5)	(26.8,93.9)	(30.0,91.7)
Day 35	n	11	13	16	12	13
	Mean	63.9	60.8	58.3	67.8	67.5
	SD	31.1	22.6	17.6	17.4	13.2
	Median	72.2	61.8	56.7	66.9	68.6
	(Min,Max)	(-3.5,95.0)	(10.2,89.9)	(24.6,91.5)	(38.0,95.5)	(41.7,86.7)

Max=maximum; Min=Minimum; SD=standard deviation

21. Safety outcomes	A total of 34 AEs were reported for 17 subjects (Table 5). The overall incidence of AEs did not appear to increase with dose, as the numbers of subjects with AEs in the CD5789 50 µg/g groups (Cream A, Cream B, and Gel) was not notably higher than in the CD5789 25 µg/g Cream A group. However, the CD5789 25 µg/g Cream A group was the only treatment group in which no dermatologic AEs were reported. Likewise, no apparent dose-dependent trends were observed for individual AEs. The most common AE overall was headache, which was reported in 5 subjects: 1 subject each in the CD5789 50 µg/g Cream B, CD5789 25 µg/g Cream A, and CD5789 50 µg/g Cream A groups, and 2 subjects in the Tazarotene 0.1% Gel group. The only severe AE in this study was reported in the CD5789 50 µg/g Cream B group: an SAE of facial palsy reported for Subject 5715-031, which was assessed by the Investigator as not related to the study drug. All AEs that were assessed by the Investigators as related to study drug were in the skin and subcutaneous tissue disorders System Organ Class (Table 6). Dry skin and skin irritation were the most common related AEs overall, reported for 3 subjects each overall. No related AEs were reported in the CD5789 25 µg/g Cream A group. No more than 1 subject in any treatment group reported any particular related AE. All AEs that were assessed as related to study drug were of mild or moderate severity. The largest number of moderate AEs was reported in the Tazarotene 0.1% Gel group (3 subjects) and included skin burning sensation, skin irritation, herpes zoster, and increased blood bilirubin in 1 subject each. No deaths occurred in this study. An unrelated SAE of facial palsy was reported for 1 subject in the CD5789 50 µg/g Cream B group, and resulted in the subject's discontinuation from the study. No AESIs were observed in this study. Local tolerance for CD5789 50µg/g Cream B appeared to be slightly better relative to CD5789 50µg/g Gel and Tazarotene 0.1% Gel for the moderate and severe parameters in the erythema and stinging/burning categories (Figure 1). However, mean scores over time did not always reflect this for all local tolerability parameters. Furthermore, CD5789 50µg/g Cream B did not appear to be highly dissimilar from CD5789 50µg/g Gel when comparing mean scores over time. The mean scores in the CD5789 treatment groups peaked after 1 week of treatment, followed by a progressive diminishing over time that was more rapid for stinging/burning. No clinically meaningful abnormal trends were observed in laboratory parameters, vital signs, or physical examinations for any treatment groups.

Table 5 Overview of adverse events, Safety Population

	CD5789 50µg/g CREAM B		CD5789 25µg/g CREAM A		CD5789 50µg/g CREAM A		CD5789 50µg/g GEL		TAZAROTENE 0.1% GEL		Total	
	AEs	n (%)[a]	AEs	n (%)[a]	AEs	n (%)[a]	AEs	n (%)[a]	AEs	n (%)[a]	AEs	n (%)[a]
All AEs	8	4 (33.3)	3	3 (21.4)	6	3 (18.8)	5	3 (25.0)	12	4 (28.6)	34	17 (25.0)
Related AEs	4	2 (16.7)	0	0	3	2 (12.5)	2	1 (8.3)	4	3 (21.4)	13	8 (11.8)
All dermatologic[b] AEs	4	2 (16.7)	0	0	3	2 (12.5)	2	1 (8.3)	5	3 (21.4)	14	8 (11.8)
Related dermatologic[b] AEs	4	2 (16.7)	0	0	3	2 (12.5)	2	1 (8.3)	4	3 (21.4)	13	8 (11.8)
Severe AEs	1	1 (8.3)	0	0	0	0	0	0	0	0	1	1 (1.5)
Severe related AEs	0	0	0	0	0	0	0	0	0	0	0	0
AEs of special interest	0	0	0	0	0	0	0	0	0	0	0	0
All SAEs	1	1 (8.3)	0	0	0	0	0	0	0	0	1	1 (1.5)
Related SAEs	0	0	0	0	0	0	0	0	0	0	0	0
All AEs leading to discontinuation	1	1 (8.3)	0	0	0	0	0	0	0	0	1	1 (1.5)
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 defined as events that occurred on the day of, or after, the first use of study drug.

[a] n=Number of subjects with at least one event.

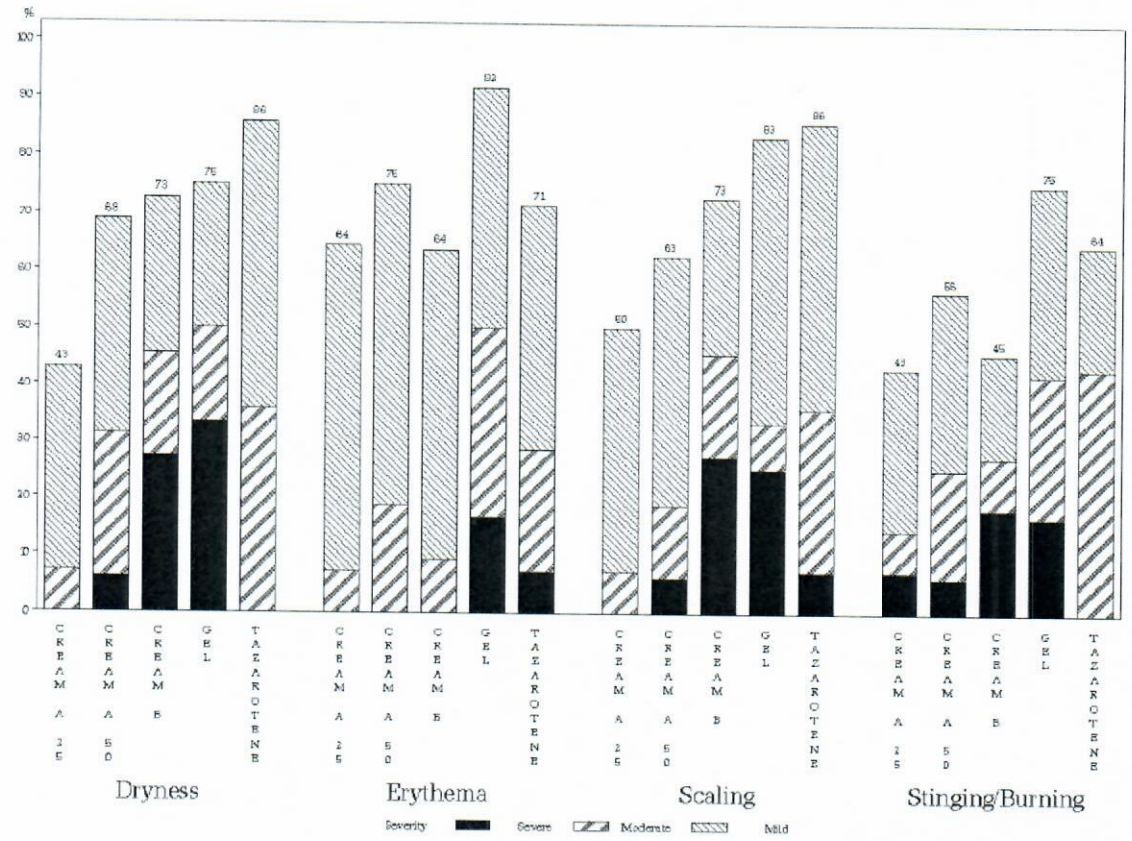
[b] Dermatologic AEs = All AEs related to System Organ Class = Skin and Subcutaneous Disorders.

Table 6 Frequency of related adverse events by System Organ Class and Preferred Term, Safety Population

System Organ Class/ Preferred Term	CD5789 50µg/g CREAM B		CD5789 25µg/g CREAM A		CD5789 50µg/g CREAM A		CD5789 50µg/g GEL		TAZAROTENE 0.1% GEL		Total	
	AEs	n (%)[a]	AEs	n (%)[a]	AEs	n (%)[a]	AEs	n (%)[a]	AEs	n (%)[a]	AEs	n (%)[a]
Skin and Subcutaneous Tissue Disorders	4	2 (16.7)	0	0	3	2 (12.5)	2	1 (8.3)	4	3 (21.4)	13	8 (11.8)
Dry skin	1	1 (8.3)	0	0	0	0	1	1 (8.3)	1	1 (7.1)	3	3 (4.4)
Skin irritation	0	0	0	0	1	1 (6.3)	1	1 (8.3)	1	1 (7.1)	3	3 (4.4)
Pain of skin	1	1 (8.3)	0	0	0	0	0	0	1	1 (7.1)	2	2 (2.9)
Skin burning sensation	1	1 (8.3)	0	0	1	1 (6.3)	0	0	0	0	2	2 (2.9)
Skin exfoliation	0	0	0	0	1	1 (6.3)	0	0	1	1 (7.1)	2	2 (2.9)
Pruritus	1	1 (8.3)	0	0	0	0	0	0	0	0	1	1 (1.5)
Total	4	2 (16.7)	0	0	3	2 (12.5)	2	1 (8.3)	4	3 (21.4)	13	8 (11.8)

Adverse events are defined as events that occurred on the day of, or after, the first use of study drug.

[a] n=Number of subjects with at least one event.

	Figure 1 **Incidence of worst score for each sign/symptom, Safety Population** 
22. Summary (conclusion)	For local tolerability (erythema, dryness, scaling, and stinging/burning), mean scores in the CD5789 treatment groups peaked after 1 week of treatment, followed by a progressive diminishing over time, as seen with other topical retinoids. This reduction in local tolerability symptoms was more rapid for stinging/burning. A noticeable reduction of both inflammatory and non-inflammatory lesions was observed with all CD5789 products tested in this study. All evaluated concentrations of CD5789 products were well-tolerated and safe. No clinically meaningful abnormal trends were observed in laboratory parameters, vital signs, or physical examinations for any treatment groups for the duration of the study.

Applicant (Marketing Authorization Holder)	(signature) Régis Schulz (full name) **GALDERMA SA** Zählerweg 10 CH-6300 Zug 058 455 85 00

Annex 30
to the Procedure for expertise of registration materials for medicinal products submitted for state registration (renewal), as well as expertise of the materials on variations to the registration materials during the marketing authorization validity period
(clause 4 of Section IV)

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD-03-SRE-40149E - EXPLORATORY STUDY TO EVALUATE THE SAFETY AND EFFICACY OF CD5789 IN SUBJECTS WITH HEREDITARY PALMOPLANTAR KERATODERMAS
6. Clinical study phase	Phase 1
7. Clinical study period	Date of first subject screened: 23 December 2011. Date of last subject completed: 31 August 2012.
8. Countries where clinical study was conducted	France – United States of America – Mauritius – Dominican Republic

<table>
<tr><td>9. Number of subjects</td><td>

▪ **Number of subjects (planned and analyzed)**

Table 1 Disposition of Subjects

	Subjects, N (%)
Enrolled	28 (100.0%)
Completed the Study	27 (96.4%)
Assessable for efficacy (PP)	27 (96.4%)
Assessable for safety	28 (100.0%)
Discontinued *(specify reasons)* *Medical reason* *Non-medical reason* *Lost to follow-up*	One (3.6%) subject has been discontinued following a SAE not related to the products

PP = Per-Protocol.

</td></tr>
<tr><td>10. Aim and secondary purposes of clinical study</td><td>

Primary objective

The primary objective of this study was to evaluate the local tolerability and systemic safety of CD5789 100 µg/g cream B (Simulgel) compared to its vehicle, after six weeks of once daily 5 days a week (from Monday to Friday) non-occlusive applications on soles in subjects with hereditary PPK.

Secondary objectives

The secondary objective of this study was to conduct an exploratory assessment of the efficacy of CD5789 100 µg/g cream B compared to its vehicle.

</td></tr>
<tr><td>11. Clinical study design</td><td>This was an exploratory, multicenter, randomized, controlled, double-blind, intra-individual (left versus right comparison) study, involving approximately 20 subjects with hereditary palmoplantar keratoderma, meeting specific inclusion/exclusion criteria.</td></tr>
<tr><td>12. Main inclusion criteria</td><td>The subject was a female of non-childbearing potential or a male between 18 and 65 years old and presenting a clinical diagnosis of diffuse, focal or punctate form of hereditary PPK at screening visit. Eligible subjects must have at Screening visit, a minimum severity of 2 (i.e. moderate) on the Investigator's Global Assessment (I.G.A.) scale of disease severity and a bilateral involvement of soles with similar severity of left and right lesions at screening and baseline.</td></tr>
<tr><td>13. Investigational medicinal product, method of administration, strength</td><td>CD5789 100 µg/g cream B, tropical administration</td></tr>
<tr><td>14. Reference medicinal product, method of administration, strength</td><td>None</td></tr>
<tr><td>15. Concomitant therapy</td><td>Not Applicable</td></tr>
<tr><td>16. Efficacy evaluation criteria</td><td>Clinical evaluations (Hyperkeratosis, pain, scaling and fissures) performed on the soles at Screening visit, Run in visit(s), Day 1 , Day 8± 2, Day 15 ± 2, Day 22 ± 2, Day 29 ±</td></tr>
</table>

	2, Day 36 ± 2 and Day 40/42 / Early Termination visits using 4-point scales (0: none to 3: severe). Investigator's global assessment (I.G.A.) scale of disease severity performed on a 4-point scale (0: no evidence of disease to 3: severe disease) at Screening visit, Run in visit, Day 1, Day ±8 2, Day 15 ± 2, Day 22 ± 2, Day 29 ± 2, Day 36 ± 2 and Day 40/42 / Early Termination visits. Patient comparative evaluation of left versus right foot performed by the investigator and by the patient at the end of the treatment period (Day 40/42), on a 5-point scale (-2: left foot much better than right foot to +2: right foot much better than left foot). Functional impairment assessed by the patient at Baseline visit and at the end of the treatment period (Day 40/42) for the left and right sides on a 5-point scale (0: no difficulty to 5: totally unable).
17. Safety evaluation criteria	Local tolerance assessed by the investigator before study products application using a 4-point scale (from 0: none to 3: severe) for scoring of erythema, pruritus and stinging/burning for each sole at the following visits: at Day -14, Day -7 (if there is a run-in phase), Day 1, Day 8 ± 2, Day 15 ± 2, Day 22 ± 2, Day 29 ± 2, Day 36 ± 2 and Day 40/42 / Early Termination visits. Laboratory parameters assessed at Screening visit and Day 40/42 / Early Termination visits for routine clinical laboratory safety profile (hematology, biochemistry). Physical examination assessed at Screening visit and Day 40/42 / Early Termination visits. Vital signs assessed at Screening visit and Day 40/42 / Early Termination visits. ECG assessed at Screening visit and Day 40/42 / Early Termination visit. Adverse Events (AEs) collected from the screening visit and at every following visit.
18. Statistical methods	Preferences were analyzed by Wilcoxon Signed Rank test. Individual clinical scores and Investigator's Global Assessment of disease severity will be analyzed by Wilcoxon signed rank test for paired data. All tests will be two-sided and the 0.10 probability level will be chosen to declare significance.

19. Demographic indicators of the study population (gender, age, race, etc.)

Table 2 Demographic data and baseline characteristics

Demographic Data	
	Subjects, N (%)
Screened (ICF signed)	29
Enrolled	28 (100.0%)
Males/Females *Females* *Males*	 11 (39.3%) 17 (60.7%)
Age (mean/range)	41.8±13.3 years old
Race *(to precise)* *Caucasian* *Black* *Asian* *Hispanic*	 12 (42.9%) 2 (7.1%) 4 (14.3%) 10 (35.7%)
Clinical Pattern *Diffuse form* *Punctate form* *Focal form*	 18 (64.3%) 2 (7.1%) 8 (28.6%)

Baseline Characteristics of the Disease (PP population, Mean (SD))		
	CD5789 100 µg/g cream B (n=27)	CD5789 cream B vehicle (n=27)
IGA	2.3 (0.5)	2.3 (0.5)
Hyperkeratosis	2.4 (0.5)	2.4 (0.5)
Pain	0.8 (1.0)	0.8 (1.0)
Scaling	1.3 (0.9)	1.3 (0.9)
Fissures	1.0 (0.9)	0.9 (0.9)

ICF = informed consent form; SD = standard deviation.

20. Efficacy outcomes

CD5789 100 µg/g cream B was not significantly different from its vehicle ($p>0.1$) whatever the criterion, IGA, hyperkeratosis, pain, scaling or fissure, after 6 weeks of treatment.

Table 3 Primary and secondary efficacy criteria at endpoint (PP population)

		CD5789 100 µg/g cream B	CD5789 cream B vehicle	P-value*
IGA	N	27	27	0.375
	Mean ±SD	2.0±0.7	2.1±0.7	
	Median	2.0	2.0	
	(Min, Max)	(1,3)	(0,3)	
Hyperkeratosis	N	27	27	>0.999
	Mean ±SD	1.9±0.8	2.0±0.8	
	Median	2.0	2.0	
	(Min, Max)	(0,3)	(0,3)	
Pain	N	27	27	>0.999
	Mean ±SD	0.4±1.0	0.4±1.0	
	Median	0.0	0.0	
	(Min, Max)	(0,3)	(0,3)	
Scaling	N	27	27	0.375
	Mean ±SD	0.9±0.8	1.0±0.9	
	Median	1.0	1.0	
	(Min, Max)	(0,2)	(0,3)	
Fissures	N	27	27	>0.999
	Mean ±SD	0.6±0.9	0.5±0.8	
	Median	0.0	0.0	
	(Min, Max)	(0,3)	(0,3)	

Neither the investigator nor the subjects showed any preference for the foot treated with CD5789 100 µg/g cream B at the end of the treatment period, on the basis of the comparative evaluation scale.

Table 4 Investigator and Subject comparative evaluation (PP population, N(%))

		CD5789 / vehicle	p*
Investigator	N	27	0.581
	Active much better or better than Vehicle	8(29.6%)	
	No clinical difference between Active and Vehicle	14(51.9%)	
	Vehicle much better or better than Active	5(18.5%)	
Subject	N	27	0.791
	Active much better or better than Vehicle	6(22.2%)	
	No clinical difference between Active and Vehicle	13(48.1%)	
	Vehicle much better or better than Active	8(29.6%)	

No differences have been showed into evidence as regard the functional impairment at the end of study, as compared with before the treatment.

Table 5 Functional impairment in term of frequency distribution (PP population, N (%))

		Active	Vehicle	A - V	p*
Socks/stockings on/off					
Baseline /PP	N	27	27	27	N/A
	0			27 (100.0%)	
	1: No difficulty	23 (85.2%)	23 (85.2%)		
	2: Mild difficulty	1 (3.7%)	1 (3.7%)		
	3: Moderate difficulty	2 (7.4%)	2 (7.4%)		
	4: Severe difficulty	1 (3.7%)	1 (3.7%)		
Day 40-42 /PP	N	27	27	27	>0.999
	0			26 (96.3%)	
	1			1 (3.7%)	
	1: No difficulty	25 (92.6%)	25 (92.6%)		
	2: Mild difficulty		1 (3.7%)		
	3: Moderate difficulty	2 (7.4%)	1 (3.7%)		
Standing barefoot					
Baseline /PP	N	27	27	27	>0.999
	-3			1 (3.7%)	
	0			25 (92.6%)	
	1			1 (3.7%)	
	1: No difficulty	18 (66.7%)	18 (66.7%)		
	2: Mild difficulty	5 (18.5%)	5 (18.5%)		
	3: Moderate difficulty	2 (7.4%)	1 (3.7%)		
	4: Severe difficulty	2 (7.4%)	2 (7.4%)		
	5: Totally unable		1 (3.7%)		
Day 40-42 /PP	N	27	27	27	>0.999
	-3			1 (3.7%)	
	0			26 (96.3%)	
	1: No difficulty	19 (70.4%)	19 (70.4%)		
	2: Mild difficulty	5 (18.5%)	4 (14.8%)		
	3: Moderate difficulty	1 (3.7%)	1 (3.7%)		
	4: Severe difficulty	2 (7.4%)	2 (7.4%)		
	5: Totally unable		1 (3.7%)		

		Active	Vehicle	A - V	p*
Standing wearing shoes					
Baseline /PP	N	27	27	27	>0.999
	-3			1 (3.7%)	
	0			25 (92.6%)	
	1			1 (3.7%)	
	1: No difficulty	17 (63.0%)	17 (63.0%)		
	2: Mild difficulty	4 (14.8%)	4 (14.8%)		
	3: Moderate difficulty	4 (14.8%)	3 (11.1%)		
	4: Severe difficulty	2 (7.4%)	2 (7.4%)		
	5: Totally unable		1 (3.7%)		
Day 40-42 /PP	N	27	27	27	>0.999
	-2			1 (3.7%)	
	0			26 (96.3%)	
	1: No difficulty	20 (74.1%)	20 (74.1%)		
	2: Mild difficulty	4 (14.8%)	3 (11.1%)		
	3: Moderate difficulty	2 (7.4%)	2 (7.4%)		
	4: Severe difficulty	1 (3.7%)	2 (7.4%)		

21. Safety outcomes

A majority of subjects had local tolerance score of 0 (no irritation) regarding erythema, pruritus and Stinging/Burning.

Table 6 **Local tolerance: worst score after investigational product application in term of frequency distribution**

		CD5789	Vehicle
Erythema	N	28	28
	0: None	22 (78.6%)	23 (82.1%)
	1: Mild	5 (17.9%)	4 (14.3%)
	2: Moderate	1 (3.6%)	1 (3.6%)
Pruritus			
	0: None	22 (78.6%)	22 (78.6%)
	1: Mild	4 (14.3%)	5 (17.9%)
	2: Moderate	2 (7.1%)	
	3: Severe		1 (3.6%)
Stinging/Burning			
	0: None	21 (75.0%)	22 (78.6%)
	1: Mild	6 (21.4%)	5 (17.9%)
	2: Moderate	1 (3.6%)	1 (3.6%)

Table 7 Overview of treatment-emergent adverse events (Safety population)

	CD5789 (N= 28)			Vehicle (N= 28)			Overall (N= 28)		
	n events	n subj.	% subj.	n events	n subj.	% subj.	n events	n subj.	% subj.
All AEs	26	14	50.0	25	15	53.6	30	16	57.1
Related AEs	2	2	7.1	3	2	7.1	5	4	14.3
All dermatologic AEs	3	2	7.1	4	4	14.3	5	4	14.3
Related dermatologic AEs	1	1	3.6	2	2	7.1	3	3	10.7
Non dermatologic AEs	23	12	42.9	21	12	42.9	25	13	46.4
Related non dermatologic AEs	1	1	3.6	1	1	3.6	2	2	7.1
All serious AEs	1	1	3.6	1	1	3.6	1	1	3.6
Related serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
All AEs leading to discontinuation	1	1	3.6	1	1	3.6	1	1	3.6
Related AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
AESIs	1	1	3.6	0	0	0.0	1	1	3.6
Related AESIs	1	1	3.6	0	0	0.0	1	1	3.6
Deaths	0	0	0.0	0	0	0.0	0	0	0.0

AE = adverse event.

A total of 30 Adverse Events (AE) occurred in 16 subjects (57.1%) over the treatment period of this study. One (1) of this AE (Subclavian artery thrombosis) occurring in 1 (3.6%) subject has been classified as an unrelated Serious Adverse Event (SAE) and led to the discontinuation of this subject. Another unrelated SAE (Otitis media acute) occurred in another subject before the first dosing and was not accounted in the above table. After SAE resolution, the subject was rescreened and included in the study.

Four (4) subjects experienced with 5 related AEs of which 3 were dermatologic (skin irritation, skin exfoliation and pruritus) of which the severity was mild or moderate. None of those adverse events led to study permanent discontinuation. One of these AE (skin irritation) has been classified as an AESI as the subject stopped the product application during 4 days in the course of the study and then resumes applications.

No other clinically significant changes in laboratory measurements, vital signs, physical examination occurred during the study.

22. Summary (conclusion)	This study assessed the effect of CD5789 100 µg/g cream B in subjects presenting a hereditary Palmoplantar Keratosis over a six weeks treatment period. CD5789 100 µg/g cream B did not show any efficacy under the conditions of the study. Applications of CD5789 100 µg/g cream B during 6 weeks of once a day (5 days a week) were well tolerated by the subjects.

Applicant (Marketing Authorization Holder)	(signature) Régis Schulz (full name) GALDERMA SA Zählerweg 10 CH-6300 Zug 058 455 85 00

Annex 30
to the Procedure for expertise of registration materials for medicinal products submitted for state registration (renewal), as well as expertise of the materials on variations to the registration materials during the marketing authorization validity period
(clause 4 of Section IV)

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD-03-SRE-40153E - Plaque test study to evaluate the efficacy and safety of CD5789 in two different formulations in subjects with Psoriasis
6. Clinical study phase	Phase 2a
7. Clinical study period	Date of first enrolment: 15 March 2011 Date of last subject completed: 11 July 2011
8. Countries where clinical study was conducted	France
9. Number of subjects	It was planned to screen about 90 subjects to randomize approximately 43. Finally, 41 subjects were randomized and included in the intent-to-treat (ITT) analysis. Two subjects were excluded from the per-protocol (PP) analysis (N=39).

10. Aim and secondary purposes of clinical study	To evaluate the efficacy, in subjects with psoriasis vulgaris, of two concentrations of CD5789 (50 and 100 µg/g) in two different formulations (Gel and Cream A) compared to their respective vehicles (Vehicle Gel and Vehicle Cream A) after a four-week treatment period of once daily applications. To position the two formulations and concentrations of CD5789 efficacy relatively to each other. To assess the global cutaneous tolerance of both formulations of CD5789.
11. Clinical study design	This was an exploratory, multi-centre, randomized, controlled, Investigator-blinded, intra-individual-incomplete block design study. In this study, 7 study products were tested: - CD5789 Gel 50 µg/g (0.005%); - CD5789 Gel 100 µg/g (0.01%); - Vehicle Gel (negative control); - CD5789 Cream A 50 µg/g (0.005%); - CD5789 Cream A 100 µg/g (0.01%); - Vehicle Cream A (negative control); - Daivobet® ointment (calcipotriol 50 µg/g / betamethasone dipropionate 500 µg/g) (positive control). Each subject received 4 of the 7 study products, which were randomized to be applied to 4 psoriatic plaques of similar severity (identical baseline Total Sum Score [TSS] or variation of ± 1 grade) located either on the knees and elbows, or all 4 on the limbs or trunk (face, scalp, hands, feet and folds excluded). Each study drug was applied once daily for 4 weeks (5 days per week). The study comprised a Screening visit (within 4 weeks prior to the start of treatment), a 4-week treatment (with site visits for study drug application and study assessments 5 days per week, Day 1-Day 26) and a Final visit (Day 29) comprised within the 4 weeks of treatment. Efficacy was assessed twice weekly using individual clinical scores and clearing scores. Safety was assessed by cutaneous tolerance (every visit from Day 2 to Day 29), adverse events (AEs, at every visit from Day 1 to Day 29), physical examinations, vital signs, pregnancy tests (Screening, Day 1 and Day 29), and laboratory tests (Screening and Day 29). Photographs were taken at Day 1 and Day 29.
12. Main inclusion criteria	Male or female, aged 18 to 70 years, with a clinical diagnosis of stable plaque psoriasis, defined as no flare in the month before the Screening visit and Baseline visit. At Baseline (Day 1), the subject presented 4 target plaques which: - were either all located on the knees and elbows, or were all located on the limbs and trunk (excluding plaques on the groin, axillae and other intertriginous areas); - were of a similar size between 20 and 200 cm^2 (i.e. surface of each plaque no more than twice the surface of the smallest plaque); - had erythema, scaling and plaque elevation/induration scores, each item separately superior or equal to 2 (at least moderate); - presented similar severity among each other (i.e.: identical baseline TSS or variation of ±1 grade between each other).
13. Investigational medicinal	- CD5789 Gel 50 µg/g; - CD5789 Gel 100 µg/g ;

product, method of administration, strength	- CD5789 Cream A 50 µg/g; - CD5789 Cream A 100 µg/g. Route of administration: topical
14. Reference medicinal product, method of administration, strength	**Vehicle Therapy (negative control)** - Vehicle Gel; - Vehicle Cream A. Route of administration: topical Strength: Not Applicable **Sensitivity comparator** -Daivobet® ointment (calcipotriol 50 µg/g / betamethasone dipropionate 500 µg/g) Route of administration: topical
15. Concomitant therapy	Not Applicable
16. Efficacy evaluation criteria	**Primary variable:** Area Under the Curve (AUC) of TSS (sum of individual clinical scores for erythema, scaling and plaque elevation/induration) from Day 1 (Baseline) to Day 29. **Secondary efficacy variables:** TSS over time and the TSS change from Baseline; AUC of individual clinical scores (erythema, scaling and plaque elevation/induration) from Day 1 (Baseline) to Day 29; Erythema, scaling and induration/elevation plaque over time and their change from Baseline; Success (i.e. clearing score of 0 or 1) at each visit from Day 4, and time to success.
17. Safety evaluation criteria	- Global cutaneous tolerance (at every visit from Day 2); - AE recording (at Baseline and every following visit); - General physical examination, vital signs and urine pregnancy tests (at Screening, Baseline and Day 29); - Laboratory safety tests (at Screening and Day 29).
18. Statistical methods	**Efficacy variables:** The AUC of TSS as well as AUCs of each individual clinical score were calculated from Day 1 (before application) up to Day 29 by subject and by study treatment, using the trapezoidal rule. The AUCs were submitted to analyses of variance including subject and study treatment as factors in the model. Due to the incomplete block design, only the least square means (LSmeans) were used to make inferences. The Tukey-Kramer multiple comparison test was used to classify all study treatments based on the LSmeans (with a 2-sided 5% level of significance). **Safety variables:** The global cutaneous tolerance score was summarized descriptively by visit and study treatment. The worst score was also summarized.

	Incidence and multiplicity of AEs, as well as safety lab results were described.
19. Demographic indicators of the study population (gender, age, race, etc.)	In total, 41 subjects from 4 centers in France were randomized. All subjects were Caucasians, with a mean age (±standard deviation [SD]) of 45.32±12.05 years. Most were males (N=32, 78.0%). All the 41 randomized subjects were included in the Safety population and in the ITT population. Two subjects discontinued the study prematurely (due to pregnancy in 1 case and at the subject's request in the other case) and were therefore excluded from the PP population (N=39).
20. Efficacy outcomes	**Primary efficacy variable** The AUC of TSS from Day 1 (Baseline) to Day 29 in the PP population is presented below:

		CREAM A 50 µg/g	CREAM A 100 µg/g	DAIVOBET OINTMENT	GEL 50 µg/g	GEL 100 µg/g	VEHICLE CREAM A	VEHICLE GEL
PP	N	20	24	18	24	24	24	22
	Mean	174.0	177.4	112.6	170.9	177.2	176.7	170.5
	SD	29.90	32.60	40.27	38.27	41.31	31.45	37.65
	Median	169.5	176.5	107.5	180.8	171.3	172.0	169.5
	Min~Max	127.0~ 238.0	100.5~ 245.0	60.0~ 216.5	71.0~ 231.0	105.5~ 263.5	108.0~ 260.5	100.5~ 238.0
ITT	N	22	26	19	24	25	25	23
	Mean	167.4	172.0	111.7	170.9	174.2	173.8	166.9
	SD	35.67	36.64	39.34	38.27	43.15	33.91	40.74
	Median	169.3	176.3	106.0	180.8	166.0	171.0	168.0
	Min~Max	93.5~ 238.0	100.5~ 245.0	60.0~ 216.5	71.0~ 231.0	102.0~ 263.5	105.5~ 260.5	86.5~ 238.0

For both formulations (Gel and Cream A), there were no statistically significant differences in AUC of TSS ($p>0.8$) between any CD5789 concentrations (50 or 100 µg/g) and the corresponding vehicle.

There were no significant differences in AUC of TSS between CD5789 concentrations (50 or 100 µg/g), both within each formulation ($p>0.6$) and between formulations ($p>0.5$).

Improvement in TSS score was greater with Daivobet® than with any other study treatment ($p<0.001$).

These results were confirmed in the ITT population.

Statistical comparisons between study treatments for the AUC of TSS from Day 1 (Baseline) to Day 29 in the PP population are presented below:

	LSmean	Difference	Adjusted p-value
CREAM A 50 µg/g - CREAM A 100 µg/g	170.3 - 172.4	-2.14	1.000
CREAM A 50 µg/g - DAIVOBET OINTMENT	170.3 - 103.4	66.85	<.001
CREAM A 50 µg/g - GEL 50 µg/g	170.3 - 172.5	-2.29	1.000
CREAM A 50 µg/g - GEL 100 µg/g	170.3 - 182.7	-12.5	0.540
CREAM A 50 µg/g - VEHICLE CREAM A	170.3 - 175.1	-4.86	0.991
CREAM A 50 µg/g - VEHICLE GEL	170.3 - 180.7	-10.5	0.758
CREAM A 100 µg/g - DAIVOBET OINTMENT	172.4 - 103.4	68.99	<.001
CREAM A 100 µg/g - GEL 50 µg/g	172.4 - 172.5	-0.14	1.000
CREAM A 100 µg/g - GEL 100 µg/g	172.4 - 182.7	-10.3	0.684
CREAM A 100 µg/g - VEHICLE CREAM A	172.4 - 175.1	-2.71	1.000
CREAM A 100 µg/g - VEHICLE GEL	172.4 - 180.7	-8.31	0.871
DAIVOBET OINTMENT - GEL 50 µg/g	103.4 - 172.5	-69.1	<.001
DAIVOBET OINTMENT - GEL 100 µg/g	103.4 - 182.7	-79.3	<.001
DAIVOBET OINTMENT - VEHICLE CREAM A	103.4 - 175.1	-71.7	<.001
DAIVOBET OINTMENT - VEHICLE GEL	103.4 - 180.7	-77.3	<.001
GEL 50 µg/g - GEL 100 µg/g	172.5 - 182.7	-10.2	0.698
GEL 50 µg/g - VEHICLE CREAM A	172.5 - 175.1	-2.57	1.000
GEL 50 µg/g - VEHICLE GEL	172.5 - 180.7	-8.17	0.877
GEL 100 µg/g - VEHICLE CREAM A	182.7 - 175.1	7.62	0.901
GEL 100 µg/g - VEHICLE GEL	182.7 - 180.7	2.02	1.000
VEHICLE CREAM A - VEHICLE GEL	175.1 - 180.7	-5.60	0.980

Secondary efficacy variables

Change from Baseline in TSS:

The mean percent changes of TSS from Baseline to Day 29 in the PP population were -27.0% and -20.5% with D5789 Cream A at concentrations of 50 µg/g and 100 µg/g, respectively, and -20.9% with Vehicle Cream A. Corresponding values for the Gel were -22.6% and -16.5% at concentrations of 50 and 100 µg/g, respectively, and -20.8% with Vehicle Gel. The improvement of TSS under Daivobet® was -71.9%.

AUC of individual scores for erythema, scaling and plaque elevation/induration:

For both formulations (Gel and Cream A), there were no statistically significant differences ($p>0.7$) between any CD5789 concentrations (50 or 100 µg/g) and the corresponding vehicle (PP population).

There were no significant differences between CD5789 concentrations (50 or 100 µg/g) for any clinical score, both within each formulation ($p>0.8$) and between formulations ($p>0.3$). Improvements in all 3 clinical scores were greater with Daivobet® than with any other study treatment ($p< 0.001$).

Success rate based on clearing score at Day 29:

The number of subjects with a target plaque clearing considered to be a success was 4 (20.0%) and 5 (20.8%) for CD5789 Cream A 50 µg/g and 100 µg/g, respectively, compared with 4 (16.7%) for their vehicle. Corresponding values for the Gel were 6 (25.0%) and 4 (16.7%) for the 50 µg/g and 100 µg/g concentrations, respectively, compared with 6 (27.3%) for their vehicle. The observed success rate was the highest for Daivobet® (77.8%).

The results regarding secondary efficacy variables were confirmed in the ITT population.

21. Safety outcomes	Local cutaneous tolerance:

- Severe irritation was reported as the worst tolerance score by 1 subject on a plaque treated with Vehicle Cream A. This irritation, which was reported at Day 8, decreased progressively in intensity to reach 0 at Day 29.
- Moderate irritation was reported as the worst tolerance score for 1 subject each with CD5789 Cream A 50 µg/g, Cream A 100 µg/g and their vehicle, 2 subjects each with CD5789 Gel 50 µg/g, Gel 100 µg/g and 3 subjects with Vehicle Gel.
- Slight irritation was reported as the worst tolerance score for 5 subjects each with CD5789 Cream A 50 µg/g, Cream A 100 µg/g and their vehicle, 4 subjects each with CD5789 Gel 50 µg/g, Gel 100 µg/g and 2 subjects with Vehicle Gel.
- Only slight irritation was reported with Daivobet® for 3 subjects.

AEs:

A total of 20 subjects (48.8%) experienced 46 AEs. Twelve subjects (29.3%) reported 25 related AEs, all in the system order class (SOC) Skin and Subcutaneous Disorders. There was approximately twice the proportion of subjects reporting related AEs with the higher dose (100 µg/g) than with the lower dose (50 µg/g) of CD5789, for both formulations. Five (19.2%) versus 2 (9.1%) subjects reported related AEs with CD5789 Cream A 100 µg/g and 50 µg/g, respectively, while 5 (20.0%) versus 3 (12.5%) subjects reported related AEs with CD5789 Gel 100 µg/g and 50 µg/g, respectively.

Summary of AEs

	CREAM A 50 µg/g (N=22)	CREAM A 100 µg/g (N=26)	DAIVOBET OINTMENT (N=19)	GEL 50 µg/g (N=24)	GEL 100 µg/g (N=25)	VEHICLE CREAM A (N=25)	VEHICLE GEL (N=23)	TOTAL (N=41)
All AEs	9 (40.9%)	11 (42.3%)	8 (42.1%)	12 (50.0%)	11 (44.0%)	9 (36.0%)	7 (30.4%)	20 (48.8%)
Related AEs	2 (9.1%)	5 (19.2%)	2 (10.5%)	3 (12.5%)	5 (20.0%)	1 (4.0%)	2 (8.7%)	12 (29.3%)
All dermatologic AEs	2 (9.1%)	5 (19.2%)	2 (10.5%)	3 (12.5%)	6 (24.0%)	1 (4.0%)	2 (8.7%)	13 (31.7%)
Related dermatologic AEs	2 (9.1%)	5 (19.2%)	2 (10.5%)	3 (12.5%)	5 (20.0%)	1 (4.0%)	2 (8.7%)	12 (29.3%)
All serious AEs	1 (4.5%)	1 (3.8%)	1 (5.3%)	0	0	0	1 (4.3%)	1 (2.4%)
AEs of Special Interest	0	1 (3.8%)	0	0	0	0	0	1 (2.4%)
Related AEs of Special Interest	0	1 (3.8%)	0	0	0	0	0	1 (2.4%)

The most common related AE was pruritus (N=9, 22.0%), which was observed with all study treatments except Vehicle Cream A, and was mainly experienced with CD5789 Cream A 100 µg/g (N=4, 15.4%) and CD5789 Gel 100 µg/g (N=3, 12.0%). Skin burning sensation was reported by 4 subjects in total (9.8%), on plaques treated with CD5789 Cream A 100 µg/g, Daivobet®, and Vehicle Cream A (1 subject each) and CD5789 Gel 100 µg/g (2 subjects).

Skin discomfort and skin erosion were both observed in 1 subject. Skin erosion, which was observed on 3 plaques, led to treatment discontinuation on the plaque with CD5789 Cream A 100 µg/g and was therefore considered as an AE of special interest (AESI).

There were no other permanent discontinuations of treatment due to AEs.

One subject became pregnant. She was treated with CD5789 Cream A 50 µg/g, Vehicle Gel, Daivobet® and CD5789 Cream A 100 µg/g. Pregnancy was confirmed on 2 May 2011 (after 14 days of treatment and 9 product applications) and study drugs were

	immediately discontinued. The same subject experienced a serious AE (SAE) of miscarriage on 15 May 2011, which was not considered by the Investigator to be treatment-related. There were no severe AEs and no deaths in this study. <u>General physical examination and vital signs:</u> No clinically significant changes in weight, vital signs, biochemistry, hematology, urinalysis or physical examination were observed.
22. Summary (conclusion)	This was an exploratory, multi-centre (4 sites in France), randomized, controlled, Investigator-blinded, intra-individual-incomplete block design study to assess the efficacy and tolerance of 4 weeks of treatment with 2 concentrations of CD5789 (50 and 100 µg/g) in 2 different formulations (Gel and Cream A) compared to their respective vehicles (Vehicle Gel and Vehicle Cream A) in subjects with *Psoriasis vulgaris*. The primary efficacy variable, the AUC of TSS from Day 1 to Day 29, did not improve with CD5789, regardless of its concentration (50 or 100 µg/g) and formulation (Cream A or Gel), when compared to the corresponding vehicle. Similar findings were reported for the mean percent changes of TSS from Baseline to Day 29 for each individual clinical score. The plaques treated with Daivobet® had significantly improved TSS and individual scores for erythema, scaling and plaque elevation/induration compared to any other study treatment. The success rate based on clearing score at Day 29 was similar with all study treatments (range: 16.7-27.3%) except Daivobet® (77.8%). Severe irritation, which resolved by the end of treatment, was reported as the worst tolerance score by 1 subject (plaque treated with Vehicle Cream A). Moderate irritation was reported in all the study treatments except Daivobet® (1 to 3 subjects, depending on study treatment). All but 1 subject treated with CD5789 Gel 100 µg/g had no sign of irritation at follow-up. In the Safety population (N=41), 12 subjects (29.3%) reported 25 related AEs, all of which were dermatological. There was approximately twice the proportion of subjects reporting related AEs with the higher dose (100 µg/g) than with the lower dose (50 µg/g) of CD5789 for both formulations. The most common related AE was pruritus (N=9, 22.0%), which was mainly experienced with CD5789 Cream A 100 µg/g (N=4, 15.4%) and CD5789 Gel 100 µg/g (N=3, 12.0%). Other related AEs were skin burning sensation, skin discomfort and skin erosion. Skin erosion led to treatment discontinuation with CD5789 Cream A 100 µg/g on 1 psoriasis plaque and was therefore considered an AESI. There were no other permanent discontinuations of treatment due to AEs. One subject became pregnant 14 days after the treatment started (9 product applications). The same subject experienced an SAE of miscarriage, which was not considered to be treatment-related by the Investigator. There were no severe AEs and no deaths. No safety concerns were highlighted by assessment of weight, vital signs, laboratory safety tests or physical examination. In conclusion, treatment with topical CD5789 over 4 weeks (in the form of Gel or Cream A at 2 different concentrations) did not demonstrate superior efficacy to the corresponding vehicle in subjects with psoriasis. Tolerance assessment revealed a severe but temporary irritation with Vehicle Cream A, and moderate irritation with all study treatments except Daivobet®. Approximately twice the proportion of subjects reported related dermatological AEs with the higher dose than the lower dose of CD5789. There

	was 1 SAE of miscarriage (not considered treatment-related by the Investigator) and 1 AESI (skin erosion). There were no other safety concerns.

Applicant (Marketing Authorization Holder)	(signature) Régis Schulz (full name) **GALDERMA SA** Zählerweg 10 CH-6300 Zug 058 455 85 00

Annex 30

to the Procedure for expertise of registration materials for medicinal products submitted for state registration (renewal), as well as expertise of the materials on variations to the registration materials during the marketing authorization validity period

(clause 4 of Section IV)

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD-03-SRE-40189 - Evaluation of the Photosensitization Potential of CD5789 Cream and Corresponding Vehicle Following Repeated Applications to the Skin of Healthy Subjects
6. Clinical study phase	Phase 1, Human Pharmacology
7. Clinical study period	Date of first screened: 28 Aug 2012 Date of last subject completed: 08 Nov 2012
8. Countries where clinical study was conducted	France
9. Number of subjects	55 subjects randomized
10. Aim and secondary	To determine the photosensitization potential of CD5789 Cream at various concentration

Table 5 Overview of Adverse Events (Safety population)

MedDRA v14.0	CD5789 100ug/g (N=55)		CD5789 25ug/g (N=55)		CD5789 Vehicle (N=55)		Untreated (N=55)		White petrolatum (N=55)		TOTAL (N=55)	
	N	N(%)	N	N(%)	N	N(%)	N	N(%)	N	N(%)	N	N(%)
All AEs	29	23 (41.8%)	29	23 (41.8%)	29	23 (41.8%)	29	23 (41.8%)	29	23 (41.8%)	29	23 (41.8%)
Related AEs	0	0	0	0	0	0	0	0	0	0	0	0
All dermatologic AEs	3	2 (3.6%)	3	2 (3.6%)	3	2 (3.6%)	3	2 (3.6%)	3	2 (3.6%)	3	2 (3.6%)
Related dermatologic AEs	0	0	0	0	0	0	0	0	0	0	0	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
Severe AEs	0	0	0	0	0	0	0	0	0	0	0	0
Related severe AEs	0	0	0	0	0	0	0	0	0	0	0	0
AEs of Special Interest	0	0	0	0	0	0	0	0	0	0	0	0
Related AEs of Special Interest	0	0	0	0	0	0	0	0	0	0	0	0
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 defined as events occurring the day or after of the first use of medication.

Numbers in columns cannot be added because a given subject may have reported more than one AE. Source: Table 14.3.2.1

Table 6 Related adverse events (Safety population)

No related AEs

22. Summary (conclusion)

Fifty-nine (59) subjects were screened, among them, 55 were randomized and completed the study normally. The mean age was around 38 years (from 19 to 63 years). Twenty-eight (50.9%) of the subjects were males. All subjects were Caucasians.

During the study, twenty-three subjects (41.8%) experienced 29 adverse events. None of them were related to any of the treatments, none of them were serious, and none of them led to discontinuation. No major deviations to the protocol were observed.

During the Induction Phase, the worst score did not exceed 2 "Erythema with slight to moderate oedema" for any treatment area during the Induction Phase. Majority of higher scores were observed on both CD5789 100µg/g and CD5789 25µg/g treated areas. There was a dose - dependent effect of the CD5789 cream on induced Skin Reactions and the mean Skin Reactions Score of CD5789 cream at both concentrations was more elevated than those observed for the three other treatments. This was explained by the well-known irritating effect of retinoids which was superimposed to the UV erythema effect.

Results of the Challenge Phase indicated that no reaction of photosensitization was observed on all of the tested areas.

Therefore, in the conditions of this study, CD5789 was found to be non-photosensitizing.

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Annex 30
to the Procedure for expertise of registration materials for medicinal products submitted for state registration (renewal), as well as expertise of the materials on variations to the registration materials during the marketing authorization validity period
(clause 4 of Section IV)

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD.03.SRE.40190 - Evaluation of the Sensitization Potential of CD5789 Cream and Corresponding Vehicle Following Repeated Applications to the Skin of Healthy Subjects (Human Repeated Insult Patch Test Clinical or HRIPT)
6. Clinical study phase	Phase 1, Human Pharmacology
7. Clinical study period	Date of first screened: 28 Aug 2012 Date of last subject completed: 21 Dec 2012
8. Countries where clinical study was conducted	France
9. Number of subjects	Approximately 260 subjects were to be screened to randomize 240 subjects in order to obtain at least 200 evaluable subjects at the end of the clinical trial.
10. Aim and	To determine the sensitization potential of CD5789 Cream at 25 µg/g and 100 µg/g and

secondary purposes of clinical study	corresponding vehicle following repeated applications to the skin of healthy subjects.
11. Clinical study design	Single-center, randomized, vehicle- and negative-controlled, evaluator-blinded, intra-individual design clinical trial enrolling healthy male and female subjects. The Study drug was CD5789 cream at various concentrations (25 and 100 µg/g), its corresponding cream vehicle and a negative control (white petrolatum). Healthy male or female subjects (18 to 65 years of age), with skin phototype I to IV on Fitzpatrick's scale and meeting all inclusion/exclusion criteria. **Screening** A Screening visit was to take place within 21 days but for females of childbearing potential at least 10 days prior to the start of the Induction Phase (Day 1). **Induction Phase** During the Induction Phase, each study drug was to be applied under semi occlusive patches to a designated skin site on the subject's mid part of the back three times a week (Monday, Wednesday, and Friday or Tuesday, Thursday and Saturday) for three consecutive weeks. A Skin Reaction Assessment (6 point scale) on the designated skin sites was to be performed on Days 3, 5, 8, 10, 12, 15, 17, 19, and 22, at least 30 minutes after patch removal. **Rest Period** A two-week Rest Phase with no study drug applications or clinical evaluations was to follow the Induction Phase. **Challenge Phase** One application was to be made under semi occlusive patches to naive designated skin sites on a part of the subject's back different from the Induction Phase area designated skin sites for 48 hours. A Skin Reaction Assessment of these designated skin sites was to be performed at least 30 minutes and approximately 48 hours after patch removal. A Sensitization Reaction Evaluation (negative, equivocal, positive) of the designated skin sites was to be performed approximately 48 hours after patch removal. If the Sensitization Reaction Evaluation was equivocal, a facultative reading was to be performed at the Investigator's discretion approximately 96 to 120 hours after patch removal. **Re-challenge Phase** A Re-challenge Phase was to be completed for subjects who developed an equivocal sensitization reaction to a specific study drug during the Challenge Phase. Re-challenge was to be also conducted with individual ingredients for subjects who developed a positive sensitization reaction to the study drug or its vehicle. Re-challenge phase design was to be the same as the challenge phase. Re-challenge was to be performed on naïve areas, no sooner than 2 weeks after challenge.
12. Main inclusion criteria	Key inclusion criteria: - Healthy male or female 18 to 65 years of age inclusive at screening visit - The subject is, in the opinion of the Investigator, in good general health. - Skin phototype of I to IV (Wolff and Fitzpatrick 2007) - Female of childbearing potential with a negative urine pregnancy test at screening and Day 1 visits.

<table>
<tr><td></td><td>- Female of Childbearing potential agrees to use a double-barrier contraception method during all the study participation, until the last study drug application, and for at least one month after the last study drug application, consisting of use of condom and a highly effective and approved method of contraception</td></tr>
<tr><td>13. Investigational medicinal product, method of administration, strength</td><td>CD5789 cream, dermal administration, strength: 25 µg/g and 100 µg/g
Test product dosage form
<table>
<tr><th></th><th>Investigational product</th><th>Investigational product</th><th>Comparator Product</th><th>Comparator Product (negative control)</th></tr>
<tr><td>Trade Name or Equivalent</td><td>N/A</td><td>N/A</td><td>N/A</td><td>Vaseline</td></tr>
<tr><td>Name of Drug Substance</td><td>N/A</td><td>N/A</td><td>N/A</td><td>White petrolatum</td></tr>
<tr><td>Internal Code</td><td>CD5789</td><td>CD5789</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Pharmaceutical Form</td><td>cream</td><td>cream</td><td>cream</td><td>ointment</td></tr>
<tr><td>Strength OR Concentration</td><td>25 µg/g</td><td>100 µg/g</td><td>Placebo</td><td>N/A</td></tr>
<tr><td>Packaging (type and size)</td><td>Megaplast Bottle 50 ml</td><td>Megaplast Bottle 50 ml</td><td>Megaplast Bottle 50 ml</td><td>Aluminum Tube 45 g</td></tr>
<tr><td>Storage Conditions</td><td>Store below 25°C – Do not Freeze or refrigerate</td><td>Store below 25°C – Do not Freeze or refrigerate</td><td>Store below 25°C – Do not Freeze or refrigerate</td><td>Store below 30°C</td></tr>
<tr><td>Route</td><td>Dermal</td><td>Dermal</td><td>Dermal</td><td>Dermal</td></tr>
<tr><td>Location of Treated Area</td><td>Defined test sites on the subject's back</td><td>Defined test sites on the subject's back</td><td>Defined test sites on the subject's back</td><td>Defined test sites on the subject's back</td></tr>
</table></td></tr>
<tr><td>14. Reference medicinal product, method of administration, strength</td><td>Comparator cream: CD5789, dermal administration, strength: placebo
Comparator (negative control) ointment: white petrolatum (Vaseline), dermal administration, strength: Not Applicable
Test product dosage form
<table>
<tr><th></th><th>Investigational product</th><th>Investigational product</th><th>Comparator Product</th><th>Comparator Product (negative control)</th></tr>
<tr><td>Trade Name or Equivalent</td><td>N/A</td><td>N/A</td><td>N/A</td><td>Vaseline</td></tr>
<tr><td>Name of Drug Substance</td><td>N/A</td><td>N/A</td><td>N/A</td><td>White petrolatum</td></tr>
<tr><td>Internal Code</td><td>CD5789</td><td>CD5789</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Pharmaceutical Form</td><td>cream</td><td>cream</td><td>cream</td><td>ointment</td></tr>
<tr><td>Strength OR Concentration</td><td>25 µg/g</td><td>100 µg/g</td><td>Placebo</td><td>N/A</td></tr>
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<tr><td>Route</td><td>Dermal</td><td>Dermal</td><td>Dermal</td><td>Dermal</td></tr>
<tr><td>Location of Treated Area</td><td>Defined test sites on the subject's back</td><td>Defined test sites on the subject's back</td><td>Defined test sites on the subject's back</td><td>Defined test sites on the subject's back</td></tr>
</table></td></tr>
<tr><td>15. Concomitant therapy</td><td>Not Applicable</td></tr>
<tr><td>16. Efficacy evaluation criteria</td><td>Not Applicable - Efficacy was not assessed in this study.</td></tr>
</table>

<table>
<tr><td>17. Safety evaluation criteria</td><td>- Skin Reaction Assessment
- Sensitization Reaction Evaluation
- Adverse Events
- Vital signs / Physical Examination</td></tr>
<tr><td>18. Statistical methods</td><td>No statistical tests were performed. All data were summarized by descriptive statistics.
<u>Induction Phase:</u>
1. Skin Reaction Assessment score was summarized using frequency and percentage by visit by study drug.
2. The worst score post baseline for each subject during the induction phase was also summarized using frequency and percentage by study drug.
<u>Challenge Phase:</u>
A frequency table summarizing sensitization reaction evaluation by category (negative, equivocal, positive) was performed for each study drug.
The categorical variables (skin reaction assessment scores) were summarized using frequency and percentage by visit and study drug (N, %).
<u>Adverse Events (AEs):</u>
Incidence of AEs was summarized by study drug. AEs that were not associated with any specific zone were summarized under all study drugs.</td></tr>
<tr><td>19. Demographic indicators of the study population (gender, age, race, etc.)</td><td>▪ Demographics and baseline disease characteristics
Table 1 Demographic data
<table>
<tr><th></th><th></th><th>TOTAL</th></tr>
<tr><td>Age in Years</td><td>N
Mean
SD
Median
Min~Max
Q1~Q3</td><td>240
42.6
12.18
42
19~65
32~53</td></tr>
<tr><td>Gender</td><td>N
Female
Male</td><td>240 (100%)
171 (71.3%)
69 (28.8%)</td></tr>
<tr><td>Race</td><td>N
WHITE</td><td>240 (100%)
240 (100.0%)</td></tr>
<tr><td>Skin Phototype</td><td>N
TYPE II
TYPE III
TYPE IV</td><td>240 (100%)
31 (12.9%)
204 (85.0%)
5 (2.1%)</td></tr>
</table></td></tr>
<tr><td>20. Efficacy outcomes</td><td>Not Applicable</td></tr>
<tr><td>21. Safety outcomes</td><td>- Adverse Events
One hundred and twenty-nine subjects experienced 205 AEs. Two subjects discontinued the study due to non-related AEs. One of these 2 AEs was considered as serious.</td></tr>
</table>

Table 2 Overview of adverse events (Safety population)

MedDRA v14.0	CD5789 100 µg/g (N=240)		CD5789 25 µg/g (N=240)		CD5789 Vehicle (N=240)		White petrolatum (N=240)		TOTAL (N=240)	
	N events	N(%) subjects	N events	N(%) subjects	N events	N(%) subjects	N events	N(%) subjects	N events	N(%) subjects
All AEs	198	128 (53.3%)	197	125 (52.1%)	196	126 (52.5%)	193	125 (52.1%)	205	129 (53.8%)
Related AEs	5	4 (1.7%)	4	2 (0.8%)	3	2 (0.8%)	0	0	12	6 (2.5%)
All dermatologic AEs	8	7 (2.9%)	7	5 (2.1%)	6	5 (2.1%)	3	3 (1.3%)	15	9 (3.8%)
Related dermatologic AEs	5	4 (1.7%)	4	2 (0.8%)	3	2 (0.8%)	0	0	12	6 (2.5%)
All serious AEs	1	1 (0.4%)	1	1 (0.4%)	1	1 (0.4%)	1	1 (0.4%)	1	1 (0.4%)
Related serious AEs	0	0	0	0	0	0	0	0	0	0
Severe AEs	0	0	0	0	0	0	0	0	0	0
Related severe AEs	0	0	0	0	0	0	0	0	0	0
AEs of Special Interest	2	1 (0.4%)	2	1 (0.4%)	1	1 (0.4%)	0	0	5	1 (0.4%)
Related AEs of Special Interest	2	1 (0.4%)	2	1 (0.4%)	1	1 (0.4%)	0	0	5	1 (0.4%)
AEs leading to discontinuation	2	2 (0.8%)	2	2 (0.8%)	2	2 (0.8%)	2	2 (0.8%)	2	2 (0.8%)
Related AEs leading to discontinuation	0	0	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0	0	0

Adverse events are defined as events occurred after the first use of medication

Note: Numbers in columns cannot be added because a given subject may have reported more than one AE.

Six subjects experienced 12 related AEs as follows:

- 4/240 subjects (1.7%) experienced 5 related AEs on the CD5789 100 µg/g treated site (three subjects with 1 episode of Pruritus each, and 1 subject with 2 episodes of Skin sensitization);
- 2/240 subjects (0.8%) experienced 4 related AEs on the CD5789 25 µg/g treated site (one subject with 1 episode of Pruritus, and 1 subject with 2 episodes of Skin sensitization and 1 episode of Allergic Dermatitis);
- 2/240 subjects (0.8%) experienced 3 related AEs on the CD5789 vehicle treated site (one subject with 1 episode of Pruritus and 1 subject with 1 episode of Skin sensitization and 1 episode of Urticaria).
- There were no related AEs on the White petrolatum treated site.

Among these 6 subjects, 5 subjects presented with one episode of pruritus and one subject (5074-8114) presented with several episodes on several treated areas the reactions of skin sensitization, allergic dermatitis and urticaria finally assessed as allergic to propylene glycol after patch test investigations.

None of these AEs led to the discontinuation of the study.

Table 3 Related adverse events (Safety population)

MedDRA v14.0		CD5789 100 µg/g (n=240)	CD5789 25 µg/g (n=240)	CD5789 Vehicle (n=240)	White petrolatum (n=240)	TOTAL (n=240)
TOTAL NUMBER OF AEs		5	4	3	0	12
TOTAL NUMBER OF SUBJECTS WITH AEs		4 (1.7%)	2 (0.8%)	2 (0.8%)	-	6 (2.5%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		4 (1.7%)	2 (0.8%)	2 (0.8%)	-	6 (2.5%)
	Dermatitis allergic	-	1 (0.4%)	-	-	1 (0.4%)
	Pruritus	3 (1.3%)	1 (0.4%)	1 (0.4%)	-	5 (2.1%)
	Skin sensitization	1 (0.4%)	1 (0.4%)	1 (0.4%)	-	1 (0.4%)
	Urticaria	-	-	1 (0.4%)	-	1 (0.4%)

Adverse events are defined as events occurring the day or after of the first use of medication

Numbers in columns cannot be added because a given subject may have reported more than one AE

A subject was counted once per preferred term even if more than one occurrence of the event was experienced

A subject was counted once per SOC even if more than one event was experienced within the SOC

There were no relevant changes in vital signs or physical examination findings during the study.

- **Cutaneous Tolerance**

During the Induction Phase, both concentrations of CD5789, 25 µg/g and 100 µg/g, were safe. There was a dose dependent skin irritation at the treated sites in line with this class of drugs (topical retinoids).

Table 4 Worse irritancy score

		CD5789 100 µg/g	CD5789 25 µg/g	CD5789 Vehicle	White petrolatum
Worst Score during Induction	N	240	240	240	240
	0	-	-	101 (42.1%)	202 (84.2%)
	0.5	-	8 (3.3%)	113 (47.1%)	36 (15.0%)
	1	61 (25.4%)	137 (57.1%)	21 (8.8%)	2 (0.8%)
	2	148 (61.7%)	93 (38.8%)	5 (2.1%)	-
	3	28 (11.7%)	1 (0.4%)	-	-
	4	3 (1.3%)	1 (0.4%)	-	-

0 No response

0.5 Questionable or faint, indistinct erythema

1 Well-defined erythema

2 Erythema with slight to moderate oedema

3 Vesicles (small blisters) or papules (small, circumscribed elevations)

4 Bullous (large blister), spreading, or other severe reaction

During the Challenge Phase, one subject experienced a positive sensitization reaction on the CD5789 treated sites and an equivocal reaction on the Vehicle treated site. This subject was assessed after patch tests as allergic to the propylene glycol.

Table 5 Sensitization Reaction Evaluation for the Challenge Phase

		CD5789 100 µg/g	CD5789 25 µg/g	CD5789 Vehicle	White petrolatum
Week 6 - Day 40	N(%)	237	237	237	237
	0	234 (98.7%)	235 (99.2%)	236 (99.6%)	237 (100.0%)
	1	2 (0.8%)	1 (0.4%)	1 (0.4%)	-
	2	1 (0.4%)	1 (0.4%)	-	-
96 To 120 Hours After Day 38	N(%)	2	1	1	1
	0	1 (50.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)
	1	1 (50.0%)	-	-	-

0Negative; 1Equivocal; 2Positive

22. Summary (conclusion)

This study was conducted to evaluate the Sensitization Potential of CD5789 cream and corresponding Vehicle following repeated applications to the skin of healthy subjects. It was a single center, randomized, vehicle- and negative –controlled, evaluator-blinded, intra-individual design clinical trial enrolling healthy male and female subjects carried out in a specialized phase 1 unit (CPCAD, Nice in France).

The methodology used was standard for this type of Dermal Safety Study. The subjects were exposed to the CD5789 cream at 25 µg/g and 100 µg/g, its corresponding Vehicle and a negative control the White petrolatum under semi-occlusive conditions for 3 weeks (Induction Phase). Following a 2-week Rest Period, subjects were exposed to the same drugs on naïve sites for 48 hours (Challenge Phase) and skin responses were evaluated.

The 2 concentrations tested cover the range of CD5789 Cream concentrations being evaluated in phase 2 in acne. In particular, the lower concentration allows for discriminating from any primary skin irritation which is more likely to be seen with the highest concentration.

Two hundred and forty subjects were randomized and 237 completed the study. Three subjects discontinued the study, 1 for pregnancy and 2 for non-related AEs (1 SAE miscarriage and 1 chicken-pox like rash). Two-thirds of the subjects were females and all were Caucasian. Subjects had mainly a skin phototype III. At Screening visit, the mean

	age was 42.6 years at screening (range 19 to 65 years). This Dermal Safety study, focusing on the potential for eliciting sensitization, clearly shows that the product is a mild irritant with a confirmed dose effect when applied under semi occlusive conditions, in line with this class of drugs (topical retinoids). CD5789 was found to be non-sensitizing in the study.

Applicant (Marketing Authorization Holder)	(signature) Régis Schulz (full name) GALDERMA SA Zählerweg 10 CH-6300 Zug 058 455 85 00

Annex 30
to the Procedure for expertise of registration materials for medicinal products submitted for state registration (renewal), as well as expertise of the materials on variations to the registration materials during the marketing authorization validity period
(clause 4 of Section IV)

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	A randomised, double-blind vehicle controlled, parallel group thorough QTc study of CD5789 in healthy subjects, with moxifloxacin used as a positive control, preceded by an open pilot phase to determine the feasibility of achieving a supra-therapeutic exposure by the topical route, rd-03-sre-40196
6. Clinical study phase	Phase I
7. Clinical study period	**Period 1 :** Date of first screened: 10 September 2012 Date of last subject completed: 08 October 2012 **Period 2 :** Date of first screened: 20 March 2013 Date of last subject completed: 30 August 2013
8. Countries where clinical study was conducted	France

9. Number of subjects	**Period 1:** Planned: 5, Enrolled: 5, Completed: 5 **Period 2:** Planned: 180, Enrolled: 180, Completed: 173

10. Aim and secondary purposes of clinical study	**Primary objectives:**
	- Period 1: Pilot assessment:
	  ○ To assess the optimal treatment duration to be used in Period 2 based on systemic exposure and the associated local tolerance of CD5789 after repeated once daily topical application over 2 weeks in healthy subjects treated by 12 g/day of CD5789 topical gel at 100 µg/g on 6000 cm² body surface area.
	- Period 2: Thorough QT (TQT)/QTc evaluation:
	  ○ To evaluate the effect of CD5789 at supra-therapeutic dose after repeated topical applications, on ventricular repolarization compared to its vehicle, specifically on the Fridericia's corrected QT interval (QTcF) from the surface electrocardiogram (ECG), in healthy subjects.
	Secondary objectives:
	- Period 1: pilot assessment:
	  ○ To assess the safety (adverse events [AEs] assessment, physical examination, vital signs and laboratory safety tests) of CD5789 topical gel at 100 µg/g.
	- Period 2: TQT/QTc evaluation:
	  ○ To determine if there is a pharmacodynamic relationship between the duration of the QT/QT corrected (QTc) intervals and the plasma concentration of CD5789.
	  ○ Other safety parameters (laboratory safety tests, physical examination, vital signs, local tolerance, AEs) were to be followed.

11. Clinical study design	**Period 1: pilot assessment:** Single-centre, open study in 5 healthy subjects treated with CD5789 topical gel at 100 µg/g. Twelve (12) g of formulation/day will be applied on 6000 cm² over 14 days. **Period 2: TQT/QTc evaluation:** Single-centre, randomized, double-blind, vehicle and positive control (investigator-blind moxifloxacin) thorough QT/QTc period study in three parallel groups: The treatments received by each group are summarized in the table below. Each application of CD5789 gel or its vehicle was of 12 g applied on 6000 cm3. The total treatment duration was 15 days. Pharmacokinetic (PK) data from the healthy subjects showed unquantifiable data with the cream formulation which has been chosen for clinical development, and quantifiable data obtained when using the gel formulation. Therefore, in order to achieve supra-therapeutic systemic exposure, the gel formulation at the dose of 12 g/day on 6000 cm² (6-fold higher than maximal dose used in PK studies) was considered appropriate.

Group	N[a]	CD5789 100µg/g gel	Topical Gel Vehicle	Moxifloxacin 400 mg	Moxifloxacin Placebo
1	60	15 days of topical applications[b] (12 g/application) on 6000 cm²	NA	NA	1 Capsule on Day 15
2	60	NA	15 days of topical applications[b] (12 g/application) on 6000 cm²	1 Tablet on Day 15	NA
3	60	NA	15 days of topical applications[b] (12 g/application) on 6000 cm²	NA	1 Capsule on Day 15

NA=Not applicable

[a] N=number of enrolled subjects. Then, 57 subjects completed the study in group 1 and 58 subjects completed the study in groups 2 and 3

[b] Topical treatment with CD5789 100 µg/g Gel or its vehicle was as follow: once daily applications from days 1 to 13, twice daily at day 14 then, once daily at day 15

12. Main inclusion criteria	Male or female healthy subjects aged 18 to 65 years with a Body Mass Index (BMI) between 18 and 30 kg/m² and with a normal 12-lead ECG (QTcF interval ≤450 ms for males and females; no clinically significant conduction disorders or significant arrhythmias; pulse rate (PR) interval between 120 and 220 ms (inclusive); heart rate (HR) ≤100 bpm and ≥50 bpm, QRS interval ≤110 ms; QT intervals that can be consistently analysed).
13. Investigational medicinal product, method of administration, strength	**Period 1 :** CD5789, topical administration, strength: 100 µg/g **Period 2 :** CD5789, topical administration, strength: 100 µg/g

14. Reference medicinal product, method of administration, strength	**Period 1 :** None
	Period 2 :
	- Comparator:
	  ○ CD5789 gel vehicle, topical administration, strength: Not Applicable
	- Positive control:
	  ○ Moxifloxacin, oral administration, strength: 400 mg
	- Oral comparator (placebo): the oral comparator product is used as a placebo for moxifloxacin (oral non-matching placebo)
	  ○ Placebo, oral administration, strength: Not Applicable

15. Concomitant therapy	Not Applicable
16. Efficacy evaluation criteria	Not Applicable
17. Safety evaluation criteria	Physical examination, vital signs, local tolerability, 12-lead ECG, AEs. Analysis of safety was carried out on the safety population. The number of subjects exposed, the duration of exposure and the dose (weight) to which they were exposed were reported. Local tolerability scores were summarized by visit and by treatment group on the initial treated zone using means over time, frequency by severity over time, and for worst response across visit. Treatment emergent AEs were summarized by Primary System Organ Class, Preferred Term and treatment group for the safety set. Laboratory values were individually listed and flagged for values outside laboratory ranges, quantitative parameters were summarized by descriptive statistics, and the change between the last pre-treatment value and last post-baseline scheduled day value were described for each parameter. Physical examination, vital signs and ECG parameters were individually listed and quantitative parameters were summarized using descriptive statistics. Values, clinically potentially significant abnormalities and changes from study-baseline were described at study-baseline, during the treatment phase and at the end of the study.
18. Statistical methods	**Primary endpoint:** The largest time-matched, baseline-adjusted, mean difference between CD5789 and vehicle: $QTcF_{max}$= max[mean QTcF(CD5789, time=t) – mean QTcF(Placebo,time=t), over all time points]. The primary hypothesis was H0: $QTcF_{max}$ >10 ms vs. H1: $QTcF_{max}$ <10 ms

	The time-matched changes from baseline in QTcF were analysed separately at each scheduled time point (-0h30min, 1h, 1h30min, 2h, 3h, 4h, 5h, 6h, 8h, 12h and 24h) using a one-way analysis of variance (ANOVA) including the treatment group as main effect and 90% confidence intervals (CIs) of the means were calculated. The upper bound of the 90% Cis had to be below 10 ms at all time points to claim no effect **Secondary endpoints:** Time-matched changes in QTcB were analysed in the same manner described for the primary endpoint. The differences between males and females were assessed for the primary endpoint. The following categorical evaluation of QTcF according to pre-defined thresholds was investigated: Actual values: QTcF interval >450 ms (male)/ 470 ms (female), QTcF interval >480 ms, QTcF interval >500 ms. Changes from baseline: QTcF interval increase >30 ms, QTcF interval increase >60 ms. Incidence and percentage of subjects presenting QTcF values per time point as well as maximum values over the day above thresholds previously defined were presented by treatment group. Assay sensitivity: the same model as that used in the primary analysis compared moxifloxacin to vehicle on QTcF at each time point, and 90% CIs of the means were calculated. To adjust for multiplicity, four time points had been pre-specified with at least one showing that the lower bound of the 97.5 CI exceeded 5 ms.
19. Demographic indicators of the study population (gender, age, race, etc.)	**Period 1 :**

Table 1 Demographic data

		CD5789
Age in Years	N	5
	Mean	35.0
	SD	11.68
	Median	38.0
	Min~Max	23.0~51.0
	Q1~Q3	24.0~39.0
Gender	N	5
	Male	5 (100.0%)
Race	N	5
	ASIAN	1 (20.0%)
	WHITE	4 (80.0%)
Body Mass Index (kg/m²)	N	5
	Mean	24.2
	SD	2.50
	Median	23.5
	Min~Max	21.3~28.0
	Q1~Q3	23.4~24.8
Height (cm)	N	5
	Mean	178.8
	SD	6.83
	Median	178.0
	Min~Max	170.0~187.0
	Q1~Q3	175.0~184.0
Weight (kg)	N	5
	Mean	77.0
	SD	4.36
	Median	76.0
	Min~Max	72.0~82.0
	Q1~Q3	74.0~81.0

Max=maximum, Min=minimum

All 5 subjects completed the study and were included in all analyses.

Period 2 :

A total of 180 subjects were equally randomized between the CD5789 Vehicle+Moxifloxacin, CD5789 Vehicle+Placebo and the CD5789+Placebo treatment groups. Five subjects were not included in the safety population set as they never received the treatment. One subject, randomized to the CD5789 Vehicle+Placebo group, was excluded from the analysis of QT, as he was positive for opiates (protocol violation). Two subjects terminated the study after the start of treatment: 1 (1.7%) subject in the CD5789+Placebo group withdrew due to treatment emergent AEs (3 incidences of erythema) and 1 subject in the CD5789 Vehicle+Placebo group was withdrawn due to a protocol violation.

Treatment groups were comparable with respect to the demographic and baseline characteristics and were as expected for a healthy, population.

Table 4 Demographic data - Period 2

		CD5789 Vehicle +Moxifloxacin	CD5789 Vehicle +Placebo	CD5789+Placebo	Total
Age in years	N	60	60	60	180
	Mean	38.72	37.43	37.00	37.72
	SD	14.05	13.59	13.83	13.77
	Median	37.00	35.00	33.50	36.00
	Min~Max	19~65	19~65	19~64	19~65
	Q1~Q3	25~51	25~49	25~47	25~49
	18 to 64 Yrs	59 (98.3%)	59 (98.3%)	60 (100.0%)	178 (98.9%)
	≥65 Yrs	1 (1.7%)	1 (1.7%)	-	2 (1.1%)
Gender	N	60	60	60	180
	F	28 (46.7%)	29 (48.3%)	27 (45.0%)	84 (46.7%)
	M	32 (53.3%)	31 (51.7%)	33 (55.0%)	96 (53.3%)
Race	N	60	60	60	180
	American Indian or Alaska Native	1 (1.7%)	-	1 (1.7%)	2 (1.1%)
	Asian	2 (3.3%)	1 (1.7%)	-	3 (1.7%)
	Black or African American	1 (1.7%)	1 (1.7%)	2 (3.3%)	4 (2.2%)
	White	56 (93.3%)	58 (96.7%)	57 (95.0%)	171 (95.0%)

20. Efficacy outcomes

Not Applicable

21. Safety outcomes

Period 1 :

There were no deaths, serious adverse events (SAEs), AEs leading to study discontinuation or severe AEs in Period 1. All 5 subjects experienced a total of 32 AEs, all of which all were dermatological and considered as related to the study drug.

Table 3 Overview of adverse events (Safety population) - Period 1

MedDRA v13.0	CD5789 (N=5)	
	N events	N(%) subjects
All AEs	32	5 (100%)
Related AEs	32	5 (100%)
All dermatologic AEs	32	5 (100%)
Related dermatologic AEs	32	5 (100%)
All serious AEs	0	0
Related serious AEs	0	0
Severe AEs	0	0
Related severe AEs	0	0
AEs of Special Interest	0	0
Related AEs of Special Interest	0	0
AEs leading to discontinuation	0	0
Related AEs leading to discontinuation	0	0
Deaths	0	0

Adverse events are defined as events occurred after the first use of medication

Numbers in columns cannot be added because a given subject may have reported more than one AE.

All 32 AEs were in the System Organ Class (SOC) Skin and Subcutaneous Tissue Disorders and were of moderate severity. All 5 subjects experienced erythema, one subject experienced skin stinging/burning sensations and one experienced scaling coded as skin exfoliation.

- **Local tolerability and laboratory values**

No subjects reported stinging/burning and there were no reports of severe cutaneous

irritation. Moderate was reported as the worst score for erythema in 4 subjects on abdomen; 4 subjects on back; 3 subjects on the legs, and for scaling in 1, 2 and 2 subjects on the abdomen, back and legs respectively. The worst score for dryness was mild.

No clinically significant changes were observed in hematology or biochemistry over the course of Period 1.

Period 2 :

There were no deaths or SAEs during the study. Two subjects had AEs of special interest: 1 subject in the CD5789+Placebo group had 3 related AEs (erythema) leading to discontinuation and 1 subject in the CD5789 Vehicle+Placebo group had ventricular extrasystoles (the only non-cutaneous, related AE reported during the study).

Table 7 Overview of adverse events (Safety population) - Period 2

	CD5789 Vehicle+Moxifloxacin		CD5789 Vehicle+Placebo		CD5789+Placebo	
	N=58		N=58		N=59	
	N events	N (%) subjects	N events	N (%) subjects	N events	N (%) subjects
All AEs	23	16 (27.6%)	13	11 (19.0%)	320	52 (88.1%)
Related AEs	0	0	1	1 (1.7%)	300	51 (86.4%)
All dermatologic AEs	5	4 (6.9%)	1	1 (1.7%)	308	51 (86.4%)
Related dermatologic AEs	0	0	0	0	299	51 (86.4%)
All serious AEs	0	0	0	0	0	0
Related serious AEs	0	0	0	0	0	0
Severe AEs	0	0	0	0	5	2 (3.4%)
Related severe AEs	0	0	0	0	5	2 (3.4%)
AEs of Special Interest	0	0	1	1 (1.7%)	3	1 (1.7%)
Related AEs of Special Interest	0	0	1	1 (1.7%)	3	1 (1.7%)
AEs leading to discontinuation	0	0	0	0	3	1 (1.7%)
Related AEs leading to discontinuation	0	0	0	0	3	1 (1.7%)
Deaths	0	0	0	0	0	0

Adverse events are defined as events occurred the day of the first use of medication or after. Numbers in columns cannot be added because a given subject may have reported more than one AE.

Related AEs were application site reactions, one case of asymptomatic ventricular extrasystoles in the CD5789 Vehicle+Placebo group and AEs related to blood draws (vasovagal reactions and catheter site pain) and ECG patches (erythema and pruritus). There were no other cardiovascular AEs.

The percentage of subjects reporting any AE was notably higher in the CD5789+Placebo groups (88.1%) compared to the CD5789 Vehicle+Moxifloxacin group (27.6%) and the CD5789 Vehicle+Placebo group (19.0%). In the CD5789+Placebo group the majority of subjects reported AEs that were considered to be related, dermatological AEs (86.4%). No related dermatological AEs were reported in the Vehicle+Moxifloxacin or CD5789 Vehicle+Placebo groups. Most AEs were of moderate severity in all 3 treatment groups. Severe AEs (both erythema) were reported by 2 (3.4%) subjects in the CD5789+Placebo group.

Table 8 Related adverse events (Safety population) - Period 2

MedDRA v14.0	CD5789 Vehicle +Moxifloxacin	CD5789 Vehicle +Placebo	CD5789 +Placebo
	(n=58)	(n=58)	(n=59)
Total number of AEs	0	1	300
Total number of subjects with AEs	0 (0.0%)	1 (1.7%)	51 (86.4%)
Cardiac disorders	-	1 (1.7%)	-
Ventricular extrasystoles	-	1 (1.7%)	-
Skin and subcutaneous tissue disorders	-	-	51 (86.4%)
Erythema	-	-	50 (84.7%)
Skin exfoliation	-	-	15 (25.4%)
Pain of skin	-	-	1 (1.7%)
Rash papular	-	-	1 (1.7%)
Vascular disorders	-	-	1 (1.7%)
Haematoma	-	-	1 (1.7%)

Adverse events are defined as events occurred the day of the first use of medication or after

A subject was counted once per preferred term even if more than one occurrence of the event was experienced

A subject was counted once per SOC even if more than one event was experienced within the SOC

- **Local tolerability and laboratory values**

Most subjects in the CD5789 Vehicle+Moxifloxacin and CD5789 Vehicle+Placebo groups experienced no cutaneous irritation on the abdomen, back and legs. Most cutaneous irritation was reported in the CD5789+Placebo group, with the abdomen and back having the worst postbaseline scores compared to the legs. For most of these subjects the worst score was mild, with the exception of erythema. The most frequently occurring scores of moderate severity were erythema (61% of subjects on the abdomen; 78% of subjects on the back) and scaling (37.3% of subjects on the abdomen; 42.4% of subjects on the back). All other cutaneous irritation of moderate severity were reported for <35% of subjects. Worst scores of severe were reported by 7 subjects in the CD5789+Placebo group (erythema in 4 subjects, scaling in 1 subject and dryness in 2 subjects).

No clinically significant changes in hematology or biochemistry were observed over the course of Period 2.

22. Summary (conclusion)

Period 1:

After 14 days of once daily topical applications, all subjects had quantifiable CD5789 plasma levels, and the highest systemic exposures were observed on Day 14 with a mean C_{max} value of 30.6±22.9 pg/mL. (range 14.3-69.5 pg.mL) and a mean $AUC_{0\text{-}24hr}$ of 446±289 pg.hr/mL (range 212±933 pg/mL). A 14-day period was therefore considered to be the most appropriate treatment duration to achieve a supra therapeutic systemic exposure. The T_{max} values ranged from 4 to 12 hours with a median value of 4 hours, so the chosen PK/ECG time-points for Period 2 (i.e. pre-dose, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours post-dose) were considered adequate.

The recommendations for Period 2 from this pilot phase of the study were to apply the product once daily for 15 days, with twice daily application on Day 14 in order to ensure that the highest systemic exposure was achieved.

The product is safe to apply under these conditions. However, in order to prevent or reduce irritation and help subjects complete the study, subjects were instructed to systematically apply the moisturizer several times daily from the first to the last day of application including during the follow-up period if needed.

	Period 2: Based on the QTcF double-delta data available (baseline adjusted, placebo subtracted), there was no statistical indication of drug induced QT/QTc prolongation with CD5789 100 µg/g (supra-therapeutic dose). For QTcF, the upper bounds of the 90% CI were less than 10 ms for all the post-dose time points. The lower bound of the 97.5% CI for the QTcF double-delta between moxifloxacin and placebo was greater than 5 ms for the post-dose time points between Hour 3 and Hour 5, demonstrating assay sensitivity. The findings were similar for QTcB, an alternative methodology for analyzing ventricular repolarization data. The combination of a negative effect of a supra-therapeutic dose of CD5789 on the QT interval duration coupled with an adequate response of the active (moxifloxacin) control confirming assay sensitivity, constitutes the criteria for a negative thorough QT study (in accordance with the International Conference on Harmonization (ICH) E-14 Guidance for Industry, October 2005). Repeated topical applications of CD5789 Gel resulted in quantifiable levels in 95% of subjects, with a mean C_{max} of 33±34 pg/mL (range from <5 pg/mL to 187 pg/mL) and a median T_{max} of 4.2 h (range from 0 to 24 h). There was no correlation between QTcF changes from baseline, adjusted for the mean placebo value at the corresponding time-point and CD5789 concentrations (raw and logarithmically transformed values). The safety assessment of CD5789 100 µg/g gel in this study confirmed the retinoid type of skin irritation seen with this class of topical agents and showed no new safety signals.

Applicant (Marketing Authorization Holder)	(signature) Régis Schulz (full name) GALDERMA SA Zählerweg 10 CH-6300 Zug 058 455 85 00

Annex 30
to the Procedure for expertise of registration materials for medicinal products submitted for state registration (renewal), as well as expertise of the materials on variations to the registration materials during the marketing authorization validity period
(clause 4 of Section IV)

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD-03-SRE-40205E - Exploratory study to evaluate the safety and efficacy of the association of CD5789 with a topical steroid in subjects with severe acne vulgaris.
6. Clinical study phase	Phase I
7. Clinical study period	Date of first subject screened: 28 December 2012 Date of last subject completed: 8 July 2013
8. Countries where clinical study was conducted	Canada
9. Number of subjects	A total of 40 subjects were screened, 21 subjects were randomized and included in the intent to treat (ITT), per protocol (PP) and safety populations. All subjects completed the study and there were no major protocol deviations.

10. Aim and secondary purposes of clinical study	**Primary objective** The primary objective of this study was to evaluate the safety of CD5789 100 µg/g associated with a topical corticosteroid over a 2-week combination therapy period followed by a 2-week monotherapy period with CD5789 100 µg/g, applied once daily, 5 days a week, in subjects with severe *acne vulgaris*. **Secondary objectives** The secondary objective of this study was to evaluate if CD5789 100 µg/g associated with a topical corticosteroid over 2 weeks provided a better efficacy in severe acne vulgaris than CD5789 100 µg/g alone.
11. Clinical study design	This was an exploratory, multi-center (4 sites in Canada), randomized, investigator blinded, controlled study using intra-individual comparison (right versus left) which involved 21 subjects with severe acne vulgaris meeting specific inclusion and exclusion criteria. The study consisted of a screening period of up to 4 weeks followed by a treatment period of 4 weeks during which subjects were treated with a once daily application of investigational medical products, 5 days per week. During the first 2 weeks, CD5789 100 µg/g cream and the topical steroid cream (Clobetasol propionate 0.05%) were applied on one half-face versus CD5789 100 µg/g cream and Vehicle applied on the other half-face. Half of the subjects were first treated by Clobetasol propionate 0.05% or its Vehicle followed by CD5789 100 µg/g cream (Group 1), and the order of application was reversed in the other half of subjects (Group 2). There was a 1-hour interval between each treatment. During the following 2 weeks, only CD5789 100 µg/g cream was applied on the full face. Each application was performed at the investigational site by trained study staff other than the investigator.
12. Main inclusion criteria	Eligible subjects were male or female, aged 18 to 40 years, with a clinical diagnosis of severe acne vulgaris defined by a severity grade of 4 (severe) on the Investigator's Global Assessment (IGA) scale, with at least 40 inflammatory lesions and 3 acne nodules At Baseline, a maximum difference of 2 nodules was allowed between each half-face and the number of inflammatory lesions on one half-face was not to be any greater than twice the number on the other half-face.
13. Investigational medicinal product, method of administration, strength	- CD5789, cream, topical administration, strength: 100 µg/g - DERMOVATE®, cream, topical administration, strength: 0.05%
14. Reference medicinal product, method of administration, strength	Vehicle: DERMABASE® Marcelle Inc, cream, topical administration, strength: Not Applicable
15. Concomitant therapy	Not Applicable

16. Efficacy evaluation criteria	Efficacy was assessed once a week during clinic visits, on Days 1, 8, 15, 22, and at the final visit (Day 29)/early termination (ET) visit. Lesion counts were performed along with the measurement of the size of nodules pre-existing at Baseline. **Primary efficacy variable** - Inflammatory lesion count at Week 2 and its percent change from Baseline **Secondary efficacy variables** - Total lesion count (sum of inflammatory, non-inflammatory and nodules counts) at Weeks 2 and 4 and percent change from Baseline - Nodule count at Weeks 2 and 4 - Inflammatory lesion count at Week 4 and percent change from Baseline - Non-Inflammatory lesion count at Weeks 2 and 4 and percent change from Baseline - Nodule size reduction (percent and absolute variation) of pre-existing nodules at Weeks 2 and 4 - Subject and investigator efficacy preference at the end of treatment
17. Safety evaluation criteria	- Local tolerability (irritation: erythema, scaling, dryness, stinging/burning) - Adverse events: Local reaction potentially due to topical steroid (skin atrophy, telangiectasia, striae, purpura, hyper- or hypopigmentation, perioral dermatitis and hypertrichosis) - Physical examination and vital signs - Laboratory safety tests - Electrocardiogram (ECG)
18. Statistical methods	Lesion counts (inflammatory, non-inflammatory and total) and percent reductions in lesions counts were descriptively summarized by visit and by arm and treatment received. The bilateral differences between treatments within each arm were analyzed by visit using a Wilcoxon rank signed test. Nodule counts and percent reductions in size of pre-existing nodules were analyzed using the same method. 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. Safety was descriptively summarized.
19. Demographic indicators of the study population (gender, age, race, etc.)	In total, 21 subjects (18 white and 3 Asian) from 4 centers in Canada were randomized. The mean age±SD was 22.4±5.6 years and the majority of the subjects were males (N=16, 76.2%). In the ITT population, the mean inflammatory lesion count at Baseline was 23.4±3.5 on the half-face treated with CD5789 100 µg/g cream and Clobetasol propionate 0.05% versus 22.8±3.6 on the half-face treated with CD5789100 µg/g cream and Vehicle. The mean acne lesion counts at Baseline were also similar between half-faces for both non-inflammatory and total lesions. Nodules were of a similar number and size on each half-face.
20. Efficacy outcomes	**Primary efficacy variable** There were no statistically significant differences in the mean counts of inflammatory lesions between the two combination treatments at Day 15, for both orders of product application combined (p=0.275). **Secondary efficacy variable** There were no statistically significant differences in the mean counts of inflammatory lesions between the two combination treatments, at Day 29 (p=0.978). Inflammatory lesion count decreased with time on both sides of the face.

At Day 15 and Day 29, there were no statistically significant differences in the total and noninflammatory lesion counts between the 2 combination treatments. Regarding the percent change from Baseline, a significant difference was found at Day 29, between the 2 treatments for the non-inflammatory lesion count with a greater reduction observed in the half-face cotreated with CD5789 100 µg/g cream and Clobetasol propionate 0.05% (p=0.044). In terms of nodule count and nodule size reduction, there were no statistically significant differences between the 2 combination treatments.

The order of product application only had a statistically significant effect on the non-inflammatory lesion count at Day 29, in subjects who were first treated with CD5789 100 µg/g cream followed by Clobetasol propionate 0.05%/Vehicle, with a greater improvement observed on the half-face treated with the active ingredient (p=0.016). The percent reduction from Baseline was also statistically significant for these subjects (p=0.004).

Bilateral comparison of the half-faces by the Investigator and by subjects on Day 29 showed that there was no efficacy preference between the 2 combination treatments. The order of product application had an effect on the efficacy preference of subjects treated with Clobetasol proprionate 0.05%/Vehicle before CD5789 100 µg/g cream, who considered the half-face treated with the active ingredient to be better than the other half-face (p=0.031). The same trend was seen on the Investigator's efficacy preference.

21. Safety outcomes

Local cutaneous tolerance

Local tolerance assessment revealed that the majority of subjects had a worst score of grade 0 or grade 1 for each local tolerance component during the first part of the study, and grade 1 or grade 2 during the second part of the study.

- **Adverse events**

MedDRA v15.0	All Subjects (both orders of product application)					
	CD5789 + Clobetasol propionate (N=21)		CD5789 + Vehicle (N=21)		TOTAL (N=21)	
	N events	N(%) subjects	N events	N(%) subjects	N events	N(%) subjects
All AEs	16	10 (47.6%)	15	9 (42.9%)	19	10 (47.6%)
Related AEs	5	4 (19.0%)	5	4 (19.0%)	8	4 (19.0%)
All dermatologic AEs	3	3 (14.3%)	3	3 (14.3%)	6	3 (14.3%)
Related dermatologic AEs	3	3 (14.3%)	3	3 (14.3%)	6	3 (14.3%)
All serious AEs	0	0	0	0	0	0
Related serious AEs	0	0	0	0	0	0
Severe AEs	0	0	0	0	0	0
Related severe AEs	0	0	0	0	0	0
AEs of Special Interest	0	0	0	0	0	0
Related AEs of Special Interest	0	0	0	0	0	0
AEs leading to discontinuation	0	0	0	0	0	0
Related AEs leading to discontinuation	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

Adverse events (AEs) are summarized only for events occurred after the first use of medication.
If an AE is not zone specific: Non cutaneous AE or Cutaneous AE on Non-Treated area(s), it will be summarized in each study treatment.
Related AE is an AE with "Reasonable possibility of a Relationship of Event to Study Drug".
Note: The numbers in the columns cannot be added because a given subject may have reported more than one AE.

A total of 10 subjects (47.6%) experienced 19 AEs throughout the study. There were a similar number of AEs in each half-face in both groups. There were a total of 8 related AEs reported in 4 subjects (19%), and 6 dermatologic AEs reported in 3 subjects (14.3%), all of which were related. All related and dermatologic AEs occurred in Group 1. The incidence of AEs was greater in Group 1 (14 AEs in 7 subjects) compared to Group 2 (5 AEs in 3 subjects).

	There were no serious AEs (SAEs), no severe AEs, no AEs of special interest (AESIs), no AEs leading to discontinuation and no deaths in this study. There were no events of skin atrophy throughout the entire study. Only one subject (8060-001) had telangiectasia on both half-faces with a worst score of grade 1 during Part 1 of the study. **General physical examination and vital signs:** No clinically significant changes in weight, vital signs, biochemistry, hematology, urinalysis or physical examination were observed.
22. Summary (conclusion)	In conclusion, treatment of severe acne for 2 weeks with CD5789 100 µg/g cream combined with the topical corticosteroid Clobetasol proprionate 0.05%, followed by a 2-week treatment with CD5789 100 µg/g cream alone did not lead to any additional efficacy over CD5789 100 µg/g cream combined with Vehicle. Local tolerability was good. Overall, the combination of CD5789 100 µg/g cream with Clobetasol proprionate 0.05% was safe and well tolerated under the conditions of this clinical trial.

Applicant (Marketing Authorization Holder)	(signature) Régis Schulz (full name)	**GALDERMA SA** Zählerweg 10 CH-6300 Zug 058 455 85 00

Annex 30
to the Procedure for expertise of registration materials for medicinal products submitted for state registration (renewal), as well as expertise of the materials on variations to the registration materials during the marketing authorization validity period
(clause 4 of Section IV)

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD-03-SRE-40208 - Evaluation of the phototoxic potential of CD5789 cream and corresponding vehicle following single application to the skin of healthy subjects.
6. Clinical study phase	Phase 1, Human Pharmacology
7. Clinical study period	Date of first screened: 4-June-2013 Date of last subject completed: 28-June-2013
8. Countries where clinical study was conducted	France
9. Number of subjects	Thirty-five randomized subjects
10. Aim and secondary	To determine the potential of CD5789 cream at 50 µg/g and 100 µg/g to induce phototoxic (photo-irritation) reaction in healthy subjects

<table>
<tr><td>purposes of clinical study</td><td></td></tr>
<tr><td>11. Clinical study design</td><td>Single-center, randomized, vehicle- and negative-controlled, evaluator-blinded, intra-individual comparison clinical trial enrolling healthy male and female subjects</td></tr>
<tr><td>12. Main inclusion criteria</td><td>Key inclusion criteria:
- Male or female 18 to 65 years of age inclusive at screening visit.
- The subject was, in the opinion of the Investigator, in good general health.
- Skin phototype of I to IV (Wolff 2007)
- Female of non-childbearing potential (postmenopausal [absence of menstrual bleeding for 1 year prior to screening, without any other medical reason], hysterectomy or bilateral oophorectomy).
- Female of childbearing potential with a negative UPT at screening and baseline visits
- Female of childbearing potential who agreed to use a double-barrier contraception method during all the study participation until the last study drug application/last study drug administration and for at least one month after the last study drug application/last study drug administration, consisting of use of condom and a highly effective and approved method of contraception.</td></tr>
<tr><td>13. Investigational medicinal product, method of administration, strength</td><td>CD5789 cream, topical (dermal) administration, strength: 50 µg/g and 100 µg/g
Test product dosage form
<table>
<tr><th></th><th>Investigational product</th><th>Investigational product</th><th>Comparator Product (Vehicle)</th><th>Comparator Product (negative control)</th></tr>
<tr><td>Trade Name or Equivalent</td><td>NA</td><td>NA</td><td>NA</td><td>Vaseline</td></tr>
<tr><td>Name of Drug Substance</td><td>NA</td><td>NA</td><td>NA</td><td>White petrolatum</td></tr>
<tr><td>Internal Code</td><td>CD5789</td><td>CD5789</td><td>NA</td><td>NA</td></tr>
<tr><td>Pharmaceutical Form</td><td>Cream</td><td>Cream</td><td>Cream</td><td>Ointment</td></tr>
<tr><td>Strength</td><td>50 µg/g</td><td>100 µg/g</td><td>Vehicle</td><td>NA</td></tr>
<tr><td>Packaging (type and size)</td><td>Bottle* 50mL</td><td>Bottle* 50 mL</td><td>Bottle* 50 mL</td><td>Aluminum Tube 80 g</td></tr>
<tr><td>Storage Conditions</td><td>Store below 25°C – Do not freeze or refrigerate</td><td>Store below 25°C – Do not freeze or refrigerate</td><td>Store below 25°C – Do not freeze or refrigerate</td><td>Store below 30°C</td></tr>
<tr><td>Dosage (per patch application)</td><td>50 µL</td><td>50 µL</td><td>50 µL</td><td>50 µL</td></tr>
<tr><td>Dose Regimen</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Route</td><td>Topical (Dermal)</td><td>Topical (Dermal)</td><td>Topical (Dermal)</td><td>Topical (Dermal)</td></tr>
<tr><td>Frequency</td><td>Single application</td><td>Single application</td><td>Single application</td><td>Single application</td></tr>
<tr><td>Duration of administration</td><td>Patch test is applied for approximately 24 hours</td><td>Patch test is applied for approximately 24 hours</td><td>Patch test is applied for approximately 24 hours</td><td>Patch test is applied for approximately 24 hours</td></tr>
<tr><td>Location of Treated Area</td><td>Back (two sets of test sites symmetrically distributed to the left and right)</td><td>Back (two sets of test sites symmetrically distributed to the left and right)</td><td>Back (two sets of test sites symmetrically distributed to the left and right)</td><td>Back (two sets of test sites symmetrically distributed to the left and right)</td></tr>
</table>
* 50 mL polypropylene (PP)/high density polyethylene (PEHD) white airless bottle closed with a PP white pump and a PP overcap.</td></tr>
<tr><td>14. Reference medicinal product, method of administration, strength</td><td>Comparator cream (vehicle) : topical (dermal) administration, strength: vehicle
Comparator (negative control) ointment: white petrolatum (vaseline), topical (dermal) administration, strength: Not Applicable</td></tr>
</table>

Test product dosage form

	Investigational product	Investigational product	Comparator Product (Vehicle)	Comparator Product (negative control)
Trade Name or Equivalent	NA	NA	NA	Vaseline
Name of Drug Substance	NA	NA	NA	White petrolatum
Internal Code	CD5789	CD5789	NA	NA
Pharmaceutical Form	Cream	Cream	Cream	Ointment
Strength	50 µg/g	100 µg/g	Vehicle	NA
Packaging (type and size)	Bottle* 50mL	Bottle* 50 mL	Bottle* 50 mL	Aluminum Tube 80 g
Storage Conditions	Store below 25°C – Do not freeze or refrigerate	Store below 25°C – Do not freeze or refrigerate	Store below 25°C – Do not freeze or refrigerate	Store below 30°C
Dosage (per patch application)	50 µL	50 µL	50 µL	50 µL
Dose Regimen				
Route	Topical (Dermal)	Topical (Dermal)	Topical (Dermal)	Topical (Dermal)
Frequency	Single application	Single application	Single application	Single application
Duration of administration	Patch test is applied for approximately 24 hours	Patch test is applied for approximately 24 hours	Patch test is applied for approximately 24 hours	Patch test is applied for approximately 24 hours
Location of Treated Area	Back (two sets of test sites symmetrically distributed to the left and right)	Back (two sets of test sites symmetrically distributed to the left and right)	Back (two sets of test sites symmetrically distributed to the left and right)	Back (two sets of test sites symmetrically distributed to the left and right)

* 50 mL polypropylene (PP)/high density polyethylene (PEHD) white airless bottle closed with a PP white pump and a PP overcap.

15. Concomitant therapy	A total of 25 concomitant therapies were reported among 19 subjects (54.3%). The most reported concomitant treatments were contraceptives drugs (n=15). None of these therapies were judged to interfere with the evaluations in this study.
16. Efficacy evaluation criteria	Not Applicable - Efficacy was not assessed in this study.
17. Safety evaluation criteria	- Skin Reaction Assessment - Phototoxic reactions - Adverse Events Subject disposition, demographics, baseline characteristics, previous therapies and concomitant therapies were summarized by descriptive statistics. The categorical variables (Skin Reaction Assessment scores) were summarized using frequency and percentage by visit and study drug for the irradiated and non-irradiated sides (N, %). The continuous variables were summarized using means, medians, minimum, maximum, and standard deviations.
18. Statistical methods	No statistical test was performed, the analyses were descriptive. - Primary efficacy endpoint: Not Applicable - Secondary efficacy endpoints: Not Applicable
19. Demographic indicators of the study population (gender, age,	The mean age of subjects was 37.3 years at screening (range 22 to 63 years). Subjects were all Caucasian. Subjects had mainly a skin phototype III (94.3%).

race, etc.)	**Table 1 Demographic data** 			Screened	Randomized
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Gender	N	35	35
	Male	15 (42.9%)	15 (42.9%)
	Female	20 (57.1%)	20 (57.1%)
Race	N	35	35
	White	35 (100.0%)	35 (100.0%)
Age (years)	N	35	35
	Mean±SD	37.3±11.2	37.3±11.2
	Median	36.0	36.0
	(Min,Max)	(22,63)	(22,63)
Phototype	N	35	35
	II	2 (5.7%)	2 (5.7%)
	III	33 (94.3%)	33 (94.3%)	 *Specific criteria for women* All female subjects of childbearing potential (75%) had a negative UPT at Screening, Day 1 and Day 4 visits. *Medical history* A total of 19 (54.3%) subjects reported at least one relevant or major illness before screening visit. *Previous therapies and Procedures* No previous therapies and procedures were reported. *Concomitant therapies* A total of 25 concomitant therapies were reported among 19 subjects (54.3%). The most reported concomitant treatments were contraceptives drugs (n=15). None of these therapies were judged to interfere with the evaluations in this study. *MED determination* The mean MED obtained on the 35 included subjects was 40.5±17.5 mJ/cm² (range 18.2 to 90.1 mJ/cm²), the median value was 33.8 mJ/cm². *Vital signs and physical examination at screening visit* Vital signs assessed at Screening were found "normal" for 31 out of the 35 screened subjects and "abnormal and not clinically significant" for 4 out of the 35 screened subjects. Physical examinations performed at Screening visit were found "normal" for 34 out of the 35 screened subjects and "abnormal and not clinically significant" for 1 subject (Body system: other: thyroid).
20. Efficacy outcomes	Not Applicable
21. Safety outcomes	• **Adverse Events** **Table 2 List of Adverse events before first use of medication** | Subject	Treatment	Location	System Organ Class/ Preferred Term	Serious/ Severity	Action taken/ Outcome	Study drug/ Procedure	AESI
---	---	---	---	---	---	---	---
5074-201	NA	Non cutaneous	Infections and infestations/ Cystitis	No/ Mild	Not applicable/ Recovered	Not related/ Not related	No
5074-220	NA	Non cutaneous	Nervous system disorders/ Migraine	No/ Moderate	Not applicable/ Recovered	Not related/ Not related	No
5074-228	NA	Non cutaneous	Nervous system disorders/ Headache	No/ Mild	Not applicable/ Recovered	Not related/ Not related	No

One Treatment Emergent Adverse Events was observed in the study (see Table 3 below):

Table 3 **List of Treatment Emergent Adverse Events (TEAE)**

Subject	Treatment	Location	System Organ Class/ Preferred Term	Serious/ Severity	Action taken/ Outcome	Study drug/ Procedure	AESI
5074-222	NA	Non cutaneous	Injury, poisoning and procedural complications/ Ligament sprain	No/ Moderate	Not applicable/ Not recovered	Not related/ Not related	No

- **Related adverse events (Safety population)**

No related adverse event.

- **Skin reactions**

Clinical evaluations for skin irritation were performed by the Investigator or qualified Evaluator at least 30 minutes, and approximately 24 and 48 hours after patch site irradiation.

Table 4 below shows the worst skin reaction scores observed for each study drug on irradiated and non-irradiated sides over all visits.

Table 4 Worst skin reaction scores

Worst score	CD5789 100 µg/g		CD5789 50 µg/g		CD5789 Vehicle		White Petrolatum		Untreated	
	Irrad	Non Irrad	Irrad	Non Irrad	Irrad	Non Irrad	Irrad	Non Irrad	Irrad	Non Irrad
N	35	35	35	35	35	35	35	35	35	35
0-No response	0 (0.0%)	15 (42.9%)	0 (0.0%)	15 (42.9%)	1 (2.9%)	11 (31.4%)	0 (0.0%)	14 (40.0%)	0 (0.0%)	12 (34.3%)
0.5-Indistinct erythema	11 (31.4%)	7 (20.0%)	9 (25.7%)	4 (11.4%)	10 (28.6%)	9 (25.7%)	12 (34.3%)	11 (31.4%)	9 (25.7%)	9 (25.7%)
1-Well-defined erythema	24 (68.6%)	13 (37.1%)	26 (74.3%)	16(45.7%)	24 (68.6%)	15 (42.9%)	23 (65.7%)	10 (28.6%)	26 (74.3%)	14 (40.0%)
Mean±SD	0.8±0.2	0.5±0.5	0.9±0.2	0.5±0.5	0.8±0.3	0.6±0.4	0.8±0.2	0.4±0.4	0.9±0.2	0.5±0.4
Median	1.0	0.5	1.0	0.5	1.0	0.5	1.0	0.5	1.0	0.5
(Min,Max)	(1,1)	(0,1)	(1,1)	(0,1)	(0,1)	(0,1)	(1,1)	(0,1)	(1,1)	(0,1)

- **Phototoxic reactions**

All phototoxic responses assessed were negative at Days 3 and 4 for all the study drugs (see Table 5).

Table 5 Phototoxic reaction

		CD5789 100 µg/g	CD5789 50 µg/g	CD5789 Vehicle	White Petrolatum	Untreated
Day 3	N	35	35	35	35	35
	0-Negative	35 (100.0%)	35 (100.0%)	35 (100.0%)	35 (100.0%)	35 (100.0%)
Day 4	N	35	35	35	35	35
	0-Negative	35 (100.0%)	35 (100.0%)	35 (100.0%)	35 (100.0%)	35 (100.0%)

No phototoxic reaction occurred during the study.

22. Summary (conclusion)

The purpose of this study trial was to determine the potential of CD5789 cream at 50 µg/g and 100 µg/g to induce phototoxic (photo-irritation) reaction in healthy subjects. This was a single-center, randomized, vehicle- and negative-controlled, evaluator-blinded, intra-individual comparison clinical trial enrolling healthy male and female subjects. Study drugs were CD5789 cream at 50 µg/g and 100 µg/g, corresponding vehicle and white petrolatum as a negative control.

Study drugs were applied under occlusive conditions for approximately 24 hours to the middle back. Based on the MED obtained, test sites were irradiated with 20 J/cm^2 of Ultraviolet A (UVA), then 0.75 MED of UVA/UVB, immediately after patch removal.

	Skin reactions were assessed at least 30 minutes, and approximately 24 and 48 hours after patch site UV irradiation. The phototoxic response was assessed approximately 48 hours after irradiation. Thirty-five subjects were screened and thirty-five were randomized. The mean age of subjects was 37.3 years at Screening (range 22 to 63 years). Subjects were all Caucasian and had mainly a skin phototype III (94.3%). One moderate AE (ligament sprain) was reported in one subject during the clinical trial and was considered as not related to the study drugs or procedure. Three non-cutaneous AEs mild or moderate (cystitis, migraine and headache) were observed before study drugs application and considered as not related to the study drugs or procedure. There was no SAE and no death. Analysis of the skin reaction scores over the course of the 5-day trial showed that the distributions of scores were globally comparable for all tested products and the untreated area and for irradiated and non-irradiated sides. No score 2 or higher were observed in the study. Whatever the visit of assessment, no phototoxic reaction occurred during the study. In the conditions of this study, CD5789 cream at 50 µg/g and 100 µg/g did not induce any phototoxic reaction.

Applicant (Marketing Authorization Holder)	(signature) Régis Schulz (full name) **GALDERMA SA** Zählerweg 10 CH-6300 Zug 058 455 85 00

Annex 30
to the Procedure for expertise of registration materials for medicinal products submitted for state registration (renewal), as well as expertise of the materials on variations to the registration materials during the marketing authorization validity period
(clause 4 of Section IV)

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD-06-SRE-40229E - Evaluation of cutaneous tolerance of CD5789 when associated with benzoyl peroxide (BPO) in healthy volunteers
6. Clinical study phase	Phase 1
7. Clinical study period	Date of first subject enrolled: 28 May 2014 Date of last subject completed: 13 October 2014
8. Countries where clinical study was conducted	France
9. Number of subjects	A total of 253 subjects were screened and 240 subjects were randomized and enrolled in this study. Of the 240 subjects enrolled into the study, 226 subjects (94.2%) completed the study. The safety population was defined as the subjects who were randomized and were administered the study drug(s) at least once. The safety population included 240 subjects (30 subjects in each treatment group).

10. Aim and secondary purposes of clinical study	The objective was to evaluate the cutaneous tolerance of CD5789 cream associated with benzoyl peroxide (BPO) gel when applied once daily to the face for 3 weeks. Study drugs included 5 associations of 3 different concentrations of CD5789 cream (25, 50, or 100 µg/g) with Cutacnyl gel (benzoyl peroxide (BPO) 2.5% or 5%) and the following 3 comparators: Epiduo gel, Zorac 0.1% gel, and Differin 0.1% gel plus benzoyl peroxide 2.5% gel). The study was designed to: - Select the dose for further development of the combination - Compare safety profiles of each of the associations with Epiduo gel - Compare safety profiles of each of the associations with Zorac 0.1% gel In addition, to address the question of possible dilution effects of associations versus combinations, the combination Epiduo gel was compared to the association of Differin 0.1% gel plus benzoyl peroxide 2.5% gel and to the association of CD5789 100 µg/g cream plus benzoyl peroxide 5% gel.
11. Clinical study design	This was a single-center, randomized, parallel-group, investigator-blinded study that was conducted in France with healthy subjects. The study consisted of a maximum 4-week screening period (one or two visits) and a 3-week application period during which the subject came once daily to the center from Monday to Saturday. On Sundays, the application was performed at home by the subject. Eight (8) groups were randomized to receive one or two study products that were applied to the facial area. Subjects received a total of 500 µL of study medication to be applied equally on each half face (250 µl on each half face). During the 22-day study, applications were performed once daily including weekends and scoring was performed once daily, from Monday to Saturday. For each subject, a total of 21 applications (Day 1 to Day 21) and 18 scorings were done before applications (Day 2 to Day 22).
12. Main inclusion criteria	The healthy subject was a male or a female between 18 and 40 years old inclusive (screening visit). The subject presented a skin phototype between I and III on the Fitzpatrick scale (screening visit). Female of childbearing potential who agreed to use a highly effective and approved contraceptive method(s) for the duration of study. A highly effective method of contraception was defined as: 1. bilateral tubal ligation or section; 2. combined oral contraceptives (estrogens and progesterone), patch, implanted or injectable contraceptives on a stable dose for at least 1 month prior to baseline visit; 3. intra uterine device (IUD) inserted since at least 1 month prior to baseline visit. The female subject of childbearing potential had a negative urinary pregnancy test result at the beginning of the study (screening and baseline visits). Female subject of non-childbearing potential: postmenopausal (e;g.: absence of menstrual bleeding for at least 1 year without any other medical reason), hysterectomy or bilateral ovariectomy (screening visit).

13. Investigational medicinal product, method of administration, strength	**Table 1 Test product dosage form** See table below
14. Reference medicinal product, method of administration, strength	**Table 1 Test product dosage form** See table below
15. Concomitant therapy	Not Applicable
16. Efficacy evaluation criteria	Efficacy measurements – Not applicable. Efficacy endpoints – Not applicable.
17. Safety evaluation criteria	Safety was assessed as follows: - Local tolerability (erythema, scaling, dryness, pruritus and burning sensation), - Adverse events, - Physical examination at the screening visit.
18. Statistical methods	- Primary efficacy endpoint: Not applicable - Secondary efficacy endpoint: Not applicable
19. Demographic indicators of the study population (gender, age, race, etc.)	Two hundred and forty (240) subjects between the ages of 18 and 40 were enrolled into the study. The mean age of subjects was 29.53□6.11 years. Subjects in the study were all White (240 subjects [100%]) and fairly evenly divided with 111 female subjects (46.3%) and 129 male subjects (53.8%). The majority of subjects in the study had skin phototype III (222 subjects [92.5%]).

	Investigational product	Investigational product	Investigational product	Investigational product	Investigational product	Comparator product	Comparator product	Comparator product
Trade Name or Equivalent	NA			Cutacnyl 2.5%	Cutacnyl 5%	Zorac 0.1%	Epiduo	Differin
Name of Drug Substance	Trifarotene			Benzoyl peroxide		Tazarotene	Adapalene + Benzoyl peroxide	Adapalene
Internal Code	CD5789			CD1579	CD1579	N/A	CD0271/CD1579	CD0271
Pharmaceutical Form	Cream			Gel				
Formula number	0219.0118	0219.0102	0219.0073	20	21	NA	324	NA
Concentration	0.0025%	0.0050%	0.01%	2.5%	5%	0.1%	0.1% (Adapalene) 2.5% (BPO)	0.1%
Packaging (type and size)	30 g laminated tube			40 g HDPE Tube		60 g laminated Tube	30 g HDPE Tube	30 g HDPE Tube
Storage Conditions	Store below 25°C – Do not Freeze or refrigerate			Store below 25°C		Store below 30°C	Store below 25°C	Store below 25°C – Do not freeze
Dosage (total daily dose)	500 µl							
Route	Topical							
Dose Regimen	Once daily seven days a week							
Duration of administration	3 weeks							
Location of Treated Area	Face							

	Investigational product	Investigational product	Investigational product	Investigational product	Investigational product	Comparator product	Comparator product	Comparator product
Trade Name or Equivalent	NA			Cutacnyl 2.5%	Cutacnyl 5%	Zorac 0.1%	Epiduo	Differin
Name of Drug Substance	Trifarotene			Benzoyl peroxide		Tazarotene	Adapalene + Benzoyl peroxide	Adapalene
Internal Code	CD5789			CD1579	CD1579	N/A	CD0271/CD1579	CD0271
Pharmaceutical Form	Cream			Gel				
Formula number	0219.0118	0219.0102	0219.0073	20	21	NA	324	NA
Concentration	0.0025%	0.0050%	0.01%	2.5%	5%	0.1%	0.1% (Adapalene) 2.5% (BPO)	0.1%
Packaging (type and size)	30 g laminated tube			40 g HDPE Tube		60 g laminated Tube	30 g HDPE Tube	30 g HDPE Tube
Storage Conditions	Store below 25°C – Do not Freeze or refrigerate			Store below 25°C		Store below 30°C	Store below 25°C	Store below 25°C – Do not freeze
Dosage (total daily dose)	500 µl							
Route	Topical							
Dose Regimen	Once daily seven days a week							
Duration of administration	3 weeks							
Location of Treated Area	Face							