	- The success rate (clearing score at Day 25) was very low with all tested concentrations of CD5789 and its placebo and varied between 27.6% and 37.9% for combination treatment. Dovobet® had the highest success rate of 85.8%, confirming previous findings on TSS. **Other efficacy variables** PK evaluation showed that CD5789 penetrated the total skin in a dose proportional manner. Dose proportionality was only observed in the SC. There was a high variability in the deep skin layers of epidermis and dermis. PD evaluation showed that CD5789 had no effect on total SC protein levels and PD markers, at any of the tested concentrations.
21. Safety outcomes	Tolerance assessment revealed that the majority of subjects showed no signs of irritation during the study. No subjects reported severe signs of irritation. A total of 27 AEs were reported in 17 subjects (53.1%) throughout the study. There were 4 dermatologic AEs of 'skin irritation' (3 subjects, 9.4%), of which 3 were related (2 subjects, 6.3%) and accounted for all related AEs. One subject experienced a serious AE of pneumonia which was not treatment-related. This event was severe and led to study discontinuation. There were no deaths or AEs of special interest. No clinically significant changes in blood chemistry, hematology or vital signs were observed during the course of this study.
22. Summary (conclusion)	In conclusion, treatment of psoriasis over 25 days with the new HE1 concept cream formulation of CD5789 applied alone did not show improved efficacy over its placebo at any of the tested concentrations. Likewise, the association of the new CD5789 cream formulation with CD1680 did not lead to any clinically significant improvement in psoriatic plaques compared to treatment with CD1680 alone, regardless of the CD5789 concentration. The product was well tolerated and there was no clear difference in terms of local tolerance and AE reporting between study treatments or CD5789 concentrations.

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 multicenter, randomized, double-blind, parallel-group vehicle-controlled study to compare the efficacy and safety of CD5789 50µg/g cream versus vehicle cream in subjects with acne vulgaris, rd-03-sre-18251
6. Clinical study phase	Phase 3
7. Clinical study period	From **30 November 2015** until **17 November 2017** Study Initiation Date (first Subject enrolled) - Study Completion/Termination Date (last Subject completed)
8. Countries where clinical study was conducted	United States – Canada – Puerto Rico – Hungary – Germany
9. Number of subjects	A total of 1208 subjects were randomly assigned to either CD5789 50 µg/g cream (612 subjects) or Vehicle Cream (596 subjects). All randomized subjects received at least 1 dose of study medication.

10. Aim and secondary purposes of clinical study	The objective of the study was to assess the efficacy and safety of CD5789 50 µg/g cream applied once daily for 12 weeks in subjects with moderate acne vulgaris.
11. Clinical study design	Multicenter, randomized, double-blind, parallel-group, vehicle-controlled study comparing CD5789 50 µg/g cream applied once daily in the evening versus its Vehicle Cream.
12. Main inclusion criteria	Male or female subjects, 9 years or older at Screening. Subjects were to have moderate acne vulgaris on the face with Investigator's Global Assessment (IGA) severity score of 3 (moderate) and at least 20 inflammatory lesions and 25 non-inflammatory lesions on the face at Screening and Baseline. Subjects also were to have moderate acne vulgaris on the trunk with Physician Global Assessment (PGA) severity score of 3 (moderate) on the trunk at Screening and Baseline and at least 20 inflammatory lesions and 20 non-inflammatory lesions but not more than 100 non-inflammatory lesions on the trunk (shoulders, upper back, and upper anterior chest) reachable to self-application of the study drug. The criteria regarding moderate truncal acne were optional for subjects between 9 and 11 years of age.
13. Investigational medicinal product, method of administration, strength	CD5789 (trifarotene), cream, topical administration, strength: 50 µg/g
14. Reference medicinal product, method of administration, strength	Vehicle cream, topical administration, strength: not applicable
15. Concomitant therapy	Not Applicable
16. Efficacy evaluation criteria	**Primary efficacy endpoints** The primary efficacy endpoint consisted of the following 3 co-primary endpoints: - Success rate, defined as the percentage of subjects who achieved an IGA score of 1 (Almost Clear) or 0 (Clear) and at least a 2-grade improvement from Baseline to Week 12. - Absolute change in facial non-inflammatory lesion count from Baseline to Week 12. - Absolute change in facial inflammatory lesion count from Baseline to Week 12. **Secondary efficacy endpoints** The secondary efficacy endpoint consisted of the following 3 co-secondary endpoints: - Percentage of subjects who achieved a PGA score of 1 (Almost Clear) or 0 (Clear) and at least a 2-grade improvement from Baseline to Week 12. - Absolute change in truncal non-inflammatory lesion count from Baseline to Week 12. - Absolute change in truncal inflammatory lesion count from Baseline to Week 12. **Supportive endpoints** - Percent change in facial non-inflammatory lesion counts from Baseline to Week

	12. - Percent change in facial inflammatory lesion counts from Baseline to Week 12. - Percent change in truncal non-inflammatory lesion counts from Baseline to Week 12. - Percent change in truncal inflammatory lesion counts from Baseline to Week 12. - Subject's assessment of facial acne improvement. **Efficacy assessments** - IGA and PGA assessments were conducted at Screening, Baseline, and at Weeks 1, 2, 4, 8, and 12/End of Treatment (ET) visits. Efficacy was assessed on the facial region by IGA and on the upper truncal region (shoulders, upper back, and upper anterior chest) by PGA. Both IGA and PGA assessments were based on a 5-point scale from 0 (clear) to 4 (severe). - Lesion counts (inflammatory and non-inflammatory) were performed separately on the face and on the trunk at all visits by Investigators or qualified study personnel, who used both visual observations and palpation strictly, after assessing the IGA and the PGA. Inflammatory lesions included papules and pustules, and non-inflammatory lesions included open and closed comedones. - Subject's self-assessment of facial acne improvement was conducted at Week 12/ET based on a 6-point scale (ranging from 0 [complete improvement] to 5 [worse]), and was to occur before any Investigator assessment.
17. Safety evaluation criteria	Safety assessments of adverse events and local tolerability were conducted for all subjects at Screening and all subsequent visits until the Week 12/ET Visit. Laboratory tests were performed at Screening and the Week 12/ET visit, and physical examination and vital signs were assessed at Screening, Baseline, and Week 12/ET.
18. Statistical methods	**Primary efficacy endpoints:** IGA success rate was analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center based on the ITT population. The p-value for the treatment comparison was generated from the general association statistic of the stratified CMH test. Difference in success rate between treatment groups (CD5789 50 µg/g cream – Vehicle Cream) and the 95% confidence interval (CI) of the difference were based on the large sample approximation method for binary data. Changes from Baseline in facial lesion counts was analyzed separately by lesion type (inflammatory and non-inflammatory) using an analysis of covariance (ANCOVA) model that included baseline lesion count, analysis center, and treatment as factors. The p-value for the treatment comparison, estimate of the treatment difference (CD5789 50 µg/g cream – Vehicle Cream), and the 95% CI of the difference was generated from the ANCOVA model. The superiority of CD5789 50 µg/g cream to Vehicle Cream was declared only if the statistical significance of all 3 co-primary efficacy endpoints were met. That is, the 2-sided p-values for the difference between the 2 treatment groups in all 3 co-primary efficacy endpoints had to be <0.05. The primary analyses were performed using the ITT population based on the MI methodology assuming the data were missing at random (MAR) as the imputation method for missing values. In addition to the planned analyses, post-hoc analyses of the success rate of IGA at each visit and of change in lesion counts from baseline at each visit were conducted using both MI and observed data. **Analysis of secondary efficacy endpoints:** The 3 co-secondary efficacy endpoints were analyzed with the same statistical methods as those used for the co-primary efficacy endpoints, using the intent-to-treat on the trunk (ITTT) population (ie, all subjects in the ITT population who had moderate acne on the

	trunk at Baseline), with MI as the primary imputation method for missing values. The testing of the secondary efficacy endpoints was conditional on the success of the 3 co-primary endpoints. Therefore, no adjustment for multiplicity was required in this study. To claim the superiority of CD5789 50 μg/g cream to Vehicle Cream on the trunk, a pre-specified order of hypotheses was tested: - First, superiority of CD5789 50 μg/g to Vehicle Cream on the face was tested ($p<0.05$) for all 3 co-primary efficacy endpoints. If successful then, - All 3 co-secondary efficacy endpoints were tested ($p<0.05$) for superiority. The analyses for the secondary efficacy endpoints were repeated using the per protocol (PPT) population (ie, all subjects in the ITTT population with no major protocol deviations). In addition, post-hoc analysis of PGA success rate at each visit and change in truncal lesion counts from baseline at each visit were conducted for both MI and observed data using ITTT population.
19. Demographic indicators of the study population (gender, age, race, etc.)	The demographic and baseline characteristics were similar between CD5789 50 μg/g cream and Vehicle Cream as shown in Table 1.The overall mean age of the ITT population was 19.4 (SD = 6.41) years, ranging from 9 to 58 years (median = 18 years). There were 592 (49.0%) subjects who were <18 years old, including 573 (47.4%) subjects age 12 to 17 years, and 19 subjects (1.6%) age 9 to 11 years. There were 616 (51.0%) adult subjects (≥18 years), including 418 (34.6%) subjects aged 18 to 24 years. As expected, considering the studied indication, there were no subjects aged ≥65 years. There were more females (629 [52.1%] subjects) than males (579 [47.9%] subjects), and the majority of subjects were white (992 [82.1%] subjects), Not Hispanic or Latino (925 [76.6%] subjects), and had skin phototype I to III (904 [74.8%] subjects).

Table 1 Summary of subject demographic characteristics – Intent-to-treat population

	CD5789 50 µg/g cream (N = 612)	Vehicle Cream (N = 596)	Total (N = 1208)
Age (years)			
Mean (SD)	19.6 (6.88)	19.3 (5.89)	19.4 (6.41)
Median	17.0	18.0	18.0
Min, Max	9, 58	10, 50	9, 58
Age Group 1 (%)			
<18 Years	314 (51.3)	278 (46.6)	592 (49.0)
9 to 11 Years	10 (1.6)	9 (1.5)	19 (1.6)
12 to 17 Years	304 (49.7)	269 (45.1)	573 (47.4)
≥18 Years	298 (48.7)	318 (53.4)	616 (51.0)
Age Group 2 (%)			
Pediatric	314 (51.3)	278 (46.6)	592 (49.0)
9 to 13 Years	72 (11.8)	47 (7.9)	119 (9.9)
14 to 17 Years	242 (39.5)	231 (38.8)	473 (39.2)
Adult	298 (48.7)	318 (53.4)	616 (51.0)
18 to 24 Years	189 (30.9)	229 (38.4)	418 (34.6)
25 to 64 Years	109 (17.8)	89 (14.9)	198 (16.4)
≥65 Years	0	0	0
Gender (%)			
Female	305 (49.8)	324 (54.4)	629 (52.1)
Male	307 (50.2)	272 (45.6)	579 (47.9)
Race (%)			
White	508 (83.0)	484 (81.2)	992 (82.1)
Black or African American	47 (7.7)	49 (8.2)	96 (7.9)
Asian	23 (3.8)	32 (5.4)	55 (4.6)
American Indian or Alaska Native	11 (1.8)	5 (0.8)	16 (1.3)
Native Hawaiian or Other Pacific Islander	1 (0.2)	1 (0.2)	2 (0.2)
Multiple	8 (1.3)	10 (1.7)	18 (1.5)
Other	14 (2.3)	15 (2.5)	29 (2.4)
Ethnicity (%)			
Hispanic or Latino	135 (22.1)	148 (24.8)	283 (23.4)
Not Hispanic or Latino	477 (77.9)	448 (75.2)	925 (76.6)
Skin Phototype (%)			
Type I	31 (5.1)	34 (5.7)	65 (5.4)
Type II	197 (32.2)	182 (30.5)	379 (31.4)
Type III	233 (38.1)	227 (38.1)	460 (38.1)
Type IV	97 (15.8)	91 (15.3)	188 (15.6)
Type V	43 (7.0)	48 (8.1)	91 (7.5)
Type VI	11 (1.8)	14 (2.3)	25 (2.1)

Max=maximum; Min=minimum; N=number of subjects; SD=standard deviation.
Note: Baseline was defined as the last measurement prior to the first application of study drug.

The acne baseline characteristics for face and trunk were similar between CD5789 50 µg/g cream and Vehicle Cream (Table 2). As per protocol, at Baseline visit, all subjects in the ITT population had moderate facial acne (IGA grade = 3), and 1185 (98.1%) subjects had moderate truncal acne (PGA grade = 3). At Baseline, there were 17 subjects who had a PGA score of 0, 3 subjects who had a PGA score of 1, and 3 subjects who had a PGA score of 2.

Twenty-three (23) subjects with a PGA score of 0, 1, or 2 at Baseline were excluded in the ITTT population and the per protocol on the trunk (PPT) population (ie, all subjects in the PP population with moderate truncal acne at Baseline and no protocol deviations that would affect the evaluability of truncal acne).

At Baseline, mean counts of inflammatory and non-inflammatory lesions were:

- On the face, 34.7 (SD = 13.02) and 53.0 (SD = 28.55), respectively

- On the trunk, 36.9 (SD = 17.89) and 46.4 (SD = 21.57), respectively

Inflammatory lesions on the face and trunk were mostly papules (mean counts: 24.6 [SD = 10.4] and 26.6 [SD = 14.00], respectively). The number of open comedones compared with closed comedones was slightly lower both on the trunk (mean counts were 18.4 and 28.5, respectively) and on the face (mean counts were 22.3 and 31.1, respectively). The majority of subjects had no nodules on the face (1129 subjects, 93.5%) or the trunk (1135 subjects, 94.0%). Forty-two of 612 subjects (6.9%) in the CD5789 group and 37 of 596 subjects (6.2%) had at least 1 nodule on the face, and 37 subjects (6.0%) in the CD5789 group and 36 subjects (5.9%) in the Vehicle group had at least 1 nodule on the trunk.

Table 2 Summary of subject baseline characteristics – Intent-to-treat population

	CD5789 50 µg/g cream (N = 602)	Vehicle Cream (N = 610)	Total (N = 1212)
Baseline IGA Grade, n (%)			
Clear (0)	0	0	0
Almost Clear (1)	0	0	0
Mild (2)	0	0	0
Moderate (3)	612 (100)	596 (100)	1208 (100)
Severe (4)	0	0	0
Baseline PGA Grade, n (%)			
Clear (0)	9 (1.5)	8 (1.3)	17 (1.4)
Almost Clear (1)	1 (0.2)	2 (0.3)	3 (0.2)
Mild (2)	2 (0.3)	1 (0.2)	3 (0.2)
Moderate (3)	600 (98.0)	585 (98.2)	1185 (98.1)
Severe (4)	0	0	0
Baseline Inflammatory Facial Lesion Count, n (%)			
Mean (SD)	34.7 (13.02)	34.8 (13.61)	34.8 (13.31)
Median	31.0	31.0	31.0
Min, Max	20, 131	20, 113	20, 131
Baseline Facial Nodules Count, n (%)			
0	570 (93.1)	559 (93.8)	1129 (93.5)
1	41 (6.7)	36 (6.0)	77 (6.4)
≥2	1 (0.2)	1 (0.2)	2 (0.2)
Baseline Non-Inflammatory Facial Lesion Count, n (%)			
Mean (SD)	54.0 (28.55)	52.8 (26.08)	53.4 (27.35)
Median	46.0	45.0	46.0
Min, Max	22, 225	21, 191	21, 225
Baseline Inflammatory Truncal Lesion Count, n (%)			
Mean (SD)	36.9 (17.89)	35.6 (16.70)	36.3 (17.32)
Median	32.0	31.0	32.0
Min, Max	0, 140	0, 115	0, 140
Baseline Truncal Nodules Count, n (%)			
0	575 (94.0)	560 (94.0)	1135 (94.0)
1	34 (5.6)	35 (5.9)	69 (5.7)
≥2	2 (0.3)	0	2 (0.2)
Missing	1 (0.2)	1 (0.2)	2 (0.2)
Baseline Non-Inflammatory Truncal Lesion Count, n (%)			
Mean (SD)	46.4 (21.57)	47.5 (21.94)	46.9 (21.75)
Median	42.0	43.0	42.0
Min, Max	0, 125	0, 107	0, 125

IGA=Investigator's Global Assessment; Max=maximum; Min=minimum; N=number of subjects; PGA=Physician's Global Assessment; SD=standard deviation.

Note: Baseline was defined as the last measurement prior to the first application of study drug. Baseline PGA summary included all subjects with or without truncal acne at baseline. Baseline truncal lesion counts summary included all subjects with or without truncal acne at baseline.

20. Efficacy outcomes	The summary for the primary, secondary, and supportive efficacy endpoints is provided in Table 3.

	Results from this double-blind, randomized, vehicle-controlled study showed that treatment with CD5789 50 µg/g cream once daily for 12 weeks had superior efficacy in treating moderate facial and truncal acne vulgaris compared with Vehicle Cream in subjects 9 years or older. This was observed in IGA success rate, PGA success rate, and change from Baseline in inflammatory and non-inflammatory lesion counts on the face and trunk. Compared with Vehicle Cream, treatment with CD5789 50 µg/g cream resulted in statistically significantly higher IGA and PGA success rates ($p<0.001$) as well as statistically significantly greater reductions in facial and truncal inflammatory ($p<0.001$) and non-inflammatory lesion counts ($p \leq 0.001$) from Baseline at Week 12. These results were consistent with the PP and PPT populations for the primary and secondary efficacy endpoints as well as with the sensitivity analyses. Results of the percent change in facial and truncal inflammatory and non-inflammatory lesion counts from Baseline to Week 12 also showed statistically significant improvement in facial and truncal acne with CD5789 50 µg/g cream compared with Vehicle Cream ($p<0.001$). The proportions of subjects who reported facial acne improvement from Baseline to Week 12 were higher in the CD5789 50 µg/g cream group compared with the Vehicle Cream group. Subjects were considered to have had overall success if they had an IGA score of "clear" (0) or "almost clear" (1) at Week 12, and at least a 2-grade improvement from Baseline to Week 12, as well as a PGA score of "clear" (0) or "almost clear" (1) at Week 12, and at least a 2-grade improvement from Baseline to Week 12. The overall success rate was higher in subjects who received CD5789 50 µg/g cream compared with subjects who received Vehicle Cream.

Table 3 Summary of analyses for face at Week 12, ITT population

	CD5789 50 µg/g cream	Vehicle Cream	Treatment Difference (95% CI)[c]	P value	Multiple Imputation	Observed Data
Primary Efficacy (ITT Population), MI						
IGA Success Rate at Week 12 (%)[a, b]	29.4	19.5	9.8 (4.8, 14.8)	<0.001[d]	<0.001[d]	<0.001[d]
Absolute change from Baseline in facial inflammatory lesion counts at Week 12	-19.0 (0.50)	-15.4 (0.51)	-3.6 (-4.9, -2.2)	<0.001[e]	<0.001[e] (LS means)	<0.001[e]
Absolute change from Baseline in facial non-inflammatory lesion counts at Week 12	-25.0 (0.87)	-17.9 (0.87)	-7.1 (-9.4, -4.8)	<0.001[e]	<0.001[e] (LS means)	<0.001[e]
Secondary Efficacy (ITTT Population), MI						
PGA Success Rate at Week 12 (%)[a, b]	35.7	25.0	10.7 (5.4, 16.1)	<0.001[d]	<0.001[d]	<0.001[d]
Absolute change from Baseline in truncal inflammatory lesion counts at Week 12	-21.4 (0.54)	-18.8 (0.55)	-2.5 (-4.0, -1.1)	<0.001[e]	<0.001[e] (LS means)	<0.001[e]
Absolute change from Baseline in truncal non-inflammatory lesion counts at Week 12	-21.9 (0.93)	-17.8 (0.94)	-4.1 (-6.6, -1.7)	0.001[e]	0.001[e] (LS means)	<0.001[e]
Supportive Efficacy (ITT Population), MI						
Mean percent change from Baseline in facial inflammatory lesion counts at Week 12	-54.4	-44.8	-	<0.001[g]	<0.001[g]	<0.001[g]
Mean percent change from Baseline in facial non-inflammatory lesion counts at Week 12	-49.7	-35.7	-	<0.001[g]	<0.001[g]	<0.001[g]
Mean percent change from Baseline in truncal inflammatory lesion counts at Week 12	-57.4	-50.0	-	<0.001	<0.001[e] (LS means)	<0.001[g]
Mean percent change from Baseline in truncal non-inflammatory lesion counts at Week 12	-49.1	-40.3	-	<0.001	0.001[e] (LS means)	<0.001[g]
Subject assessment of facial acne improvement from Baseline to Week 12 as complete improvement, n (%)	30 (5.5)	14 (2.6)	-	-		
Subject assessment of facial acne improvement from Baseline to Week 12 as marked improvement, n (%)	191 (35.2)	122 (22.7)	-	-		
Subject assessment of facial acne improvement from Baseline to Week 12 as moderate improvement, n (%)	185 (34.1)	203 (37.8)	-	-		
Subject assessment of facial acne improvement from Baseline to Week 12 as minimal improvement, n (%)	99 (18.3)	132 (24.6)	-	-		

	CD5789 50 µg/g cream	Vehicle Cream	Treatment Difference (95% CI)[c]	P value	Multiple Imputation	Observed Data
Subject assessment of facial acne improvement from Baseline to Week 12 as no change, n (%)	32 (5.9)	55 (10.2)	-	-		
Subject assessment of facial acne improvement from Baseline to Week 12 as worse, n (%)	5 (0.9)	11 (2.0)	-	-		
Other Supportive Efficacy (ITTT Population), MI						
Overall success rate at Week 12, (%)[f]	21.0	14.0	-	-		

ANCOVA=analysis of covariance; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; IGA=Investigator's Global Assessment; ITT=intent-to-treat; ITTT=intent-to-treat Trunk; LS=least squares; MI=multiple imputation; N=number of subjects; PGA=Physician's Global Assessment.

[a] Success was defined as IGA or PGA score of "clear (0)" or "almost clear (1)" at Week 12 and at least 2-grade improvement from Baseline to Week 12.

[b] Success rate was calculated as the number of subjects achieving success divided by the number of subjects with IGA or PGA data at Week 12.

[c] Confidence intervals were based on the large-sample approximation method for binary data without the use of a continuity correction.

[d] P-values were based on the general association statistic from a CMH test stratified by analysis center.

[e] P-values and CIs were based on an ANCOVA model with baseline lesion count, analysis center, and treatment as factors.

[f] Additional analyses were conducted to evaluate the overall success rate at Week 12 in the ITTT population using the MI dataset. These analyses were performed in subjects with presence of both facial and truncal acne lesions. Subjects were considered to have had overall success if they had an IGA score of "clear" (0) or "almost clear" (1) at Week 12 and at least a 2-grade improvement from Baseline to Week 12 as well as a PGA score of "clear" (0) or "almost clear" (1) at Week 12 and at least a 2-grade improvement from Baseline to Week 12. The overall success rate was calculated as the number of subjects who achieved overall treatment success at that visit divided by the number of subjects with both IGA and PGA data at that visit.

[g] P-values were based on the row mean difference statistic from a Cochran-Mantel-Haenszel test stratified by analysis center using ridit scoring.

After database lock had occurred, it was decided to perform a post-hoc analysis of time to onset of effect. To determine the time of efficacy onset, analyses of each co-primary and co-secondary endpoint were repeated post-hoc at each visit prior to Week 12. Onset of a statistically significant effect on inflammatory lesions was observed at Week 2 and Week 4 (face and trunk, respectively) and on non-inflammatory lesions at Week 2 and Week 4 (face and trunk, respectively), progressing to a statistically significant difference in IGA as early as Week 4 and in PGA at Week 8.

21. Safety outcomes

A total of 1208 subjects were included in the safety population; 617 subjects in the CD5789 50 µg/g cream group and 591 subjects in the Vehicle Cream group. The mean treatment duration for face and trunk was similar between treatment groups (approximately 78 days for CD5789 50 µg/g cream and approximately 79 days for Vehicle Cream). The mean daily study drug usage was similar between CD5789 50 µg/g cream and Vehicle Cream (1.3g/day and 1.4g/day, respectively).

Treatment-emergent adverse events were reported by 209 (33.9%) subjects in the CD5789 50 µg/g cream group and 123 (20.8%) subjects in the Vehicle Cream group. A higher proportion of subjects who received CD5789 50 µg/g cream compared with Vehicle Cream reported TEAEs in the General disorders and administration site conditions SOC, mainly due to application site irritation (66 [10.7%] subjects in CD5789 50 µg/g cream and 4 [0.7%] subjects in Vehicle Cream), in the Injury, poisoning and procedural complications mainly due to sunburn (27 [4.4%] subjects in CD5789 50 µg/g cream and 5 [0.8%] subjects in Vehicle Cream), and in Skin and subcutaneous tissue disorders mainly due to skin irritation (8 [1.3%] subjects in CD5789 50 µg/g cream and 0 subjects in Vehicle Cream).

Treatment-emergent adverse events with incidence ≥1% (at the preferred term level) of subjects in the CD5789 50 µg/g cream group were (by decreasing frequency): application site irritation (10.7%), sunburn (4.4%), application site pruritus (3.9%), nasopharyngitis (3.9%), upper respiratory tract infection (1.6%), skin irritation (1.3%), influenza (1.0%),

	sinusitis (1.0%), and headache (1.0%). Treatment-emergent adverse events with incidence ≥1% (at the preferred term level) of subjects in the Vehicle Cream group were (by decreasing frequency): nasopharyngitis (4.6%), headache (2.0%), influenza (1.5%), upper respiratory tract infection (1.4%), and application site pruritus (1.4%). Most of the TEAEs reported in both treatment groups were mild or moderate in severity. Few TEAEs were severe (10 TEAEs in 8 [1.3%] subjects in the CD5789 50 µg/g cream group; 1 TEAE in 1 [0.2%] subject in the Vehicle Cream group). Severe related TEAEs were reported in 6 (1.0%) subjects in the CD5789 50 µg/g cream group and 1 (0.2%) subject in the Vehicle Cream group. Among subjects who received CD5789 50 µg/g cream, the most common (i.e. reported in ≥1% of subjects) TEAEs assessed as related to the study drug were, by decreasing frequency: application site irritation (10.4%), application site pruritus (3.7%), sunburn (2.1%), and skin irritation (1.0%). No deaths were reported during the study. Four serious TEAEs were reported by 4 (0.6%) subjects in the CD5789 50 µg/g cream group and 3 serious TEAEs were reported by 2 (0.3%) subjects in the Vehicle Cream group. None of the serious TEAEs was cutaneous in nature or assessed as related to study drug. The serious TEAEs reported in the CD5789 50 µg/g cream subjects were infectious mononucleosis, procedural dizziness, facial bones fracture, and cellulitis (each in 1 subject); serious TEAEs in the Vehicle Cream group were atypical pneumonia and urinary tract infection in 1 subject; and hereditary angioedema in 1 subject. Adverse Events of Special Interest were reported by 16 (2.6%) subjects in the CD5789 50 µg/g cream group; they were all cutaneous in nature (application site irritation in 9 subjects [1.5%], dermatitis allergic in 3 subjects [0.5%], acne in 2 subjects [0.3%], and skin irritation in 2 subjects [0.3%]). In the Vehicle Cream group, 5 AESIs were reported in 2 (0.3%) subjects: blood creatinine increased, hyperuricemia, and liver function test abnormal in 1 subject and blood creatinine increased and liver function test abnormal in another subject. Treatment-emergent adverse events that led to discontinuation were reported by 14 (2.3%) subjects in the CD5789 50 µg/g cream group and 1 (0.2%) subject in the Vehicle Cream group. Of the 14 subjects in the CD5789 50 µg/g cream group, 13 subjects had 13 TEAEs that were cutaneous in nature and related to study drug. One subject in the Vehicle Cream group had a TEAE that led to study drug discontinuation, which was not cutaneous and not related to study drug. There were no clinically significant mean changes from Baseline to Week 12 in hematology or blood chemistry in either treatment group. There were no clinically significant mean changes from Baseline to Week 12 in vital signs (systolic and diastolic blood pressure, and pulse rate). Four subjects in the CD5789 50 µg/g cream group had treatment-emergent abnormal and clinically significant physical exam findings on the skin that were reported as TEAEs. These were erythematous maculae with severe excoriations on the trunk and face, dermatitis on the skin of chest, erythema, oozing of nostrils on the upper lip, and red itchy rash on the treatment area. Signs/symptoms of local tolerability (erythema, dryness, scaling, and stinging/burning) on the face and the trunk occurred in a greater proportion of subjects in the CD5789 50 µg/g cream group compared with the Vehicle Cream group. A better local tolerability profile was observed on the trunk compared with the face. These signs/symptoms increased and decreased (crescendo – decrescendo pattern) over the course of the study. On the face, peak irritation was observed at Week 1, except for erythema, which peaked at Weeks 1 to 2, while on the trunk a peak was observed at Weeks 1 or 2, followed by a plateau and then a gradual decrease after Week 4 (truncal erythema or dryness) or Week 8 (truncal scaling

	or stinging/burning). In the CD5789 50 µg/g cream group, the highest local tolerability scores that worsened from Baseline on the face were graded as mild (34.6% [erythema] to 44.0% [dryness]), moderate (16.3% [stinging/burning] to 23.7% [erythema]), or severe (2.5% [erythema and dryness] to 4.2% [stinging/burning]). On the trunk, the highest local tolerability scores that worsened from Baseline were graded as mild (23.7% [scaling and stinging/burning] to 30.3% [dryness]), moderate (9.0% [stinging/burning] to 14.6% [erythema]), or severe (0.3% [scaling] to 3.3% [erythema]) in the CD5789 50 µg/g cream group. The percentage of subjects who reported at least 1 TEAE was comparable across most of the subgroup categories. The sign/symptoms of local tolerability worsened from Baseline on the face and trunk at the final visit and also at the worst post-baseline visits were consistent across most of the subgroup categories. The data need to be interpreted with caution given the small number of subjects in some of the subgroup categories. Dermatitis allergic was diagnosed or could not be ruled out in 3 subjects in CD5789 50 µg/g cream group. All 3 cases of dermatitis allergic were assessed as related to the study drug. There were 2 pregnancies reported during the study period. One was an uneventful full-term pregnancy with a healthy infant delivered at 41 weeks (Vehicle Cream group); the other subject had an elective abortion (Vehicle Cream group).
22. Summary (conclusion)	All objectives of this pivotal study were met: robust efficacy of CD5789 50 µg/g cream in the treatment of moderate facial and truncal acne vulgaris was demonstrated. Subjects treated with CD5789 50 µg/g cream experienced clinically meaningful and statistically significant improvement in the primary and secondary efficacy endpoints: IGA and PGA success rates (Clear and Almost Clear with at least a 2-grade improvement) at Week 12 and facial and truncal inflammatory and non-inflammatory lesions change from Baseline to Week 12 when compared with corresponding vehicle. CD5789 50 µg/g cream was safe in all safety assessments performed throughout the study. Most of the TEAEs occurred at the application site. Most of the cutaneous TEAEs and the recorded signs and symptoms of skin irritation followed the well-known pattern of retinoid dermatitis with acceptable and manageable tolerability when CD5789 50 µg/g cream was applied to large body surface areas of face and trunk.

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-SPR-103813 - Twenty nine days multiple dose pharmacokinetic and safety study of CD5789 cream HE1 in healthy subjects from Japanese and non-Japanese origins
6. Clinical study phase	Phase 1
7. Clinical study period	Date of first screened: 22 December 2014 Date of last subject completed: 29 November 2015
8. Countries where clinical study was conducted	United Kingdom
9. Number of subjects	Number of subjects planned: 36. Number of subjects analyzed: 36 (12 subjects in Cohort 1 and 6 subjects/group in Cohorts 5 and 6).

10. Aim and secondary purposes of clinical study	- Cohort 1: To assess the systemic exposure of CD5789 after repeated once daily topical applications of CD5789 200µg/g cream HE1 for 29 days in healthy adult subjects of non-Japanese origin. - Cohorts 5 and 6: To assess and compare the systemic exposure of CD5789 after twice weekly topical application of CD5789 100 µg/g and 200 µg/g cream HE1 for 29 days in healthy adult subjects of non-Japanese and Japanese origins. - All cohorts: To assess the local tolerability and systemic safety of once daily CD5789 200 µg/g cream HE1 and twice weekly topical application of CD5789 100 and 200 µg/g cream HE1.
11. Clinical study design	This study was originally planned as an open-label, dose-escalation (200 µg/g and 400 µg/g), multi-cohort study to assess the systemic exposure and safety of CD5789 cream HE1 after repeated once daily applications over a period of 29 days in subjects of non-Japanese and Japanese origins. Four cohorts were planned to be included in the study (Cohorts 1 to 4). Due to a strong irritation level observed with daily application of CD5789 200 µg/g cream HE1 in Cohort 1, which included subjects of non–Japanese origin, the original study design was amended. Dose escalation to 400 µg/g in subjects of non-Japanese origin was not performed (i.e., Cohort 2), and it was decided to not treat subjects of Japanese origin with the daily regimen used in Cohort 1 (i.e., Cohort 3 and consequently Cohort 4 were cancelled). A new regimen with decreased frequency of application (i.e., treatment applied twice weekly over 29 days) was introduced, and a lower concentration of CD5789 cream HE1 (i.e., 100 µg/g) using the twice weekly regimen was evaluated. Two new cohorts, each comprising 2 randomized treatment groups, were introduced: - Group 1/Cohort 5: subjects of non-Japanese origin treated twice weekly with CD5789 100 µg/g cream HE1. - Group 2/Cohort 5: subjects of non-Japanese origin treated twice weekly with CD5789 200 µg/g cream HE1. - Group 3/Cohort 6: subjects of Japanese origin treated twice weekly with CD5789 100 µg/g cream HE1. - Group 4/Cohort 6: subjects of Japanese origin treated twice weekly with CD5789 200 µg/g cream HE1.
12. Main inclusion criteria	Male or female healthy subjects of non-Japanese and Japanese origins aged from 18 (or 20 if of Japanese origin) to 65 years were to be enrolled in the study. Subjects of non-Japanese origin had to be Caucasian, while subjects of Japanese origin had to have all 4 grandparents born in Japan.
13. Investigational medicinal product, method of administration, strength	CD5789, cream, topical administration, strength: 100 µg/g & 200 µg/g
14. Reference medicinal product, method of administration, strength	None

15. Concomitant therapy	Not Applicable
16. Efficacy evaluation criteria	Not Applicable
17. Safety evaluation criteria	- Local Tolerability - erythema, scaling, dryness, stinging/burning (assessed using specific 4-point scales) - Adverse Events (AEs) reported before Baseline and treatment-emergent adverse events (TEAEs) - Laboratory tests: hematology, blood chemistry, and urinalysis - Vital signs and physical examination - Electrocardiograms (ECGs).
18. Statistical methods	**PK variables:** - Cohort 1: o Evaluation of time effect An analysis of variance was performed for Ctrough, AUC0-24h and Cmax after logarithmic (Ln) transformation. The model included time and subject as factors. The residual error variance was used to compute 90% confidence intervals (CIs) of the pairwise differences between the last time point and each preceding time point (Day 29 vs. Day 1, Day 5 and Day 15 for AUC0-24h and Cmax; Day 29 vs. Day 2, Day 5, Day 6, Day 10, Day 15, Day 16 and Day 22 for Ctrough) on the Ln scale. The limits of the intervals were back-transformed into exponential to obtain 90% CIs of the ratios of geometric means between time points, on the original scale. - Cohorts 5 and 6: o Evaluation of time effect by cohort and group An analysis of variance was performed for Ctrough, AUC0-24h and Cmax after Ln transformation. The model included time and subject as factors. The residual error variance was used to compute 90% CIs of the pairwise differences between Day 29 and each preceding time point (Day 29 vs. Day 1, Day 5 and Day 15 for AUC0-24h and Cmax; Day 30 vs. Day 2, Day 6, and Day 16 for Ctrough) on the Ln scale. The limits of the intervals were back-transformed into exponential to obtain 90% CIs of the ratios of geometric means between time points, on the original scale. The same analysis was performed for the cumulated concentration in SC, concentration in skin biopsy (dermis and epidermis) and cumulated concentration in total skin (Day 30 vs. Day 6). - Evaluation of group effect by study day An analysis of variance was performed for Ctrough, AUC0-24h and Cmax after Ln transformation. The model included cohort/group as factor; 90% CIs of the pairwise differences between treatment groups on the Ln scale was calculated. The limits of the intervals were back-transformed into exponential to obtain 90% CIs of the ratios of geometric means between treatment groups, on the original scale. Four pairwise ratios were provided: Japanese origin/Non-Japanese origin per dose (200 µg/g or 100 µg/g), and 200µg/g / 100µg/g per origin (Japanese or non-Japanese). The same analysis was performed for the cumulated concentration in SC, concentration in skin biopsy (dermis and epidermis) and cumulated concentration in total skin (Day 30 vs. Day 6). Calculation of descriptive statistics of PK parameters was not performed when less than 50% of the data were quantifiable. Otherwise, below limit of quantitation Cmax and

	Ctrough values (<5 pg/mL) were replaced by the limit of quantitation (i.e., 5 pg/mL) and AUC0-t and AUC0-24h by the lowest AUC value by treatment determined in the study. Missing skin concentrations and skin to plasma ratios were imputed with the lowest observed value by treatment. All safety data were analyzed by descriptive statistics.
19. Demographic indicators of the study population (gender, age, race, etc.)	**Table 1 Demographic data – Cohort 1, Safety analysis set**

	Cohort 1 200 µg/g N = 12
Gender, n (%)	
Female	3 (25.00%)
Male	9 (75.00%)
Age (years)	
Mean (SD)	33.3 (13.3)
Median (Min - Max)	31.5 (18.0 - 63.0)
Race, n (%)	
Asian	0
White	12 (100%)
Origin, n (%)	
Caucasian	12 (100%)
Japanese	0
BSA (m^2)	
Mean (SD)	1.9 (0.2)
Median (Min - Max)	1.8 (1.6 - 2.1)
BMI (kg/m^2)	
Mean (SD)	23.2 (1.0)
Median (Min - Max)	23.4 (21.3 - 24.7)
Height (cm)	
Mean (SD)	175.5 (9.4)
Median (Min - Max)	177.5 (157.0 -190.0)
Weight (kg)	
Mean (SD)	71.6 (7.8)
Median (Min - Max)	72.8 (58.0 - 87.0)

BMI = body mass index; Max = maximum; Min = minimum; SD = standard deviation

Table 2 Demographic data – Cohorts 5 and 6, Safety analysis set

	Cohort 5		Cohort 6	
	Group 1 100 µg/g N = 6	Group 2 200 µg/g N = 6	Group 3 100 µg/g N = 6	Group 4 200 µg/g N = 6
Gender, n (%)				
Female	0	3 (50.00%)	0	1 (16.67%)
Male	6 (100%)	3 (50.00%)	6 (100%)	5 (83.33%)
Age (years)				
Mean (SD)	28.3 (12.3)	27.5 (4.8)	32.5 (7.6)	27.3 (7.3)
Median (Min - Max)	25.0 (19.0 - 52.0)	28.0 (19.0 - 32.0)	31.5 (23.0 - 46.0)	24.0 (22.0 - 41.0)
Race, n (%)				
Asian	0	0	6 (100%)	6 (100%)
White	6 (100%)	6 (100%)	0	0
Origin, n (%)				
Caucasian	6 (100%)	6 (100%)	0	0
Japanese	0	0	6 (100%)	6 (100%)
BSA (m^2)				
Mean (SD)	1.9 (0.1)	1.8 (0.2)	1.7 (0.1)	1.7 (0.1)
Median (Min - Max)	1.8 (1.8 - 2.0)	1.8 (1.4 - 2.1)	1.7 (1.4 - 1.8)	1.6 (1.4 - 1.7)
BMI (kg/m^2)				
Mean (SD)	22.2 (2.2)	22.6 (2.4)	20.7 (2.3)	20.9 (1.6)
Median (Min - Max)	22.3 (19.8 - 24.5)	23.9 (19.0 - 24.5)	19.7 (18.9 - 24.6)	21.7 (18.7 - 22.2)
Height (cm)				
Mean (SD)	179.3 (3.4)	171.8 (12.4)	170.3 (7.4)	167.0 (9.3)
Median (Min - Max)	180.0 (173.0 - 183.0)	175.0 (155.0 - 189.0)	169.0 (161.0 - 181.0)	168.0 (151.0 - 177.0)
Weight (kg)				
Mean (SD)	71.4 (6.7)	67.5 (14.1)	60.2 (8.1)	58.2 (6.5)
Median (Min - Max)	70.3 (64.6 - 79.9)	67.5 (48.7 - 86.6)	60.0 (49.0 - 69.5)	59.3 (49.8 - 65.7)

20. Efficacy outcomes

Not Applicable

21. Safety outcomes

Cohort 1

- A total of 10 subjects completed the study, while 2 subjects discontinued due to adverse events of special interest (AESIs). The mean (SD) study duration was 28.00 (2.66) days and the mean (SD) number of applications was 27.75 (2.70). Overall, mean amount of study drug used at each visit and the mean percentage of applied BSA decreased with time due to cutaneous irritation. Specifically, mean (SD) amount of study drug used ranged from 35.75 (0.20) g on Day 1 to 9.42 (8.75) g on Day 29. Applied BSA decreased from 100% on Day 1 to 0% on Day 29 for neck; and from 100% on Day 1 to 10%-35% on Day 29 for the other body areas.
- Strong cutaneous irritation (measured with 4-point scales on the applied BSA) was observed in all the subjects, with mean scores of erythema, scaling, dryness and stinging/burning increasing with time. Highest scores were observed for erythema; indeed, during the study the majority of subjects experienced severe erythema in at least one body area. Body areas mostly affected by cutaneous irritation were face, neck and anterior trunk. Post-dose stinging/burning was observed in a few subjects, and it was mostly of mild intensity.
- All subjects in Cohort 1 experienced at least 1 AE (69 events in total) and 1 treatment-related AE (37 events in total). The majority of AEs (53/69 events) and treatment-related AEs (35/37 events) were of cutaneous nature.
- The most frequently reported AEs and treatment-related AEs (observed in all subjects) were skin irritation (on both applied BSA, and non-applied BSA due to

study drug contamination from applied BSA) and pruritus (generalized in 10 subjects).

- Other cutaneous AEs reported in >subject were: papule (on applied BSA), 3 events in 3 (25.00%) subjects and post-inflammatory pigmentation change, 2 events in 2 (16.67%) subjects. All of these events were considered as related to the study drug. In addition, 4 events of laceration were reported in 4 (33.33%) subjects and were considered as unrelated to the study drug.
- The worst AEs intensity experienced was moderate for the majority of subjects (11 [91.67%] subjects). Moderate AEs reported in >1 subject were: skin irritation (in 9 [75.00%] subjects) and 'pruritus' (pruritus generalised in 10 [83.33%] subjects; pruritus in 2 [16.67%] subjects), all of which were considered as related to the study drug. There was only 1 severe AE, which was considered as related to the study drug, reported in 1 (8.33%) subject (skin irritation).
- Of a total of 3 (25.00%) subjects experiencing 4 AESIs (musculoskeletal pain, dermatitis allergic, dermatitis and arthralgia), 2 (16.67%) subjects discontinued the study due to those events (i.e., cutaneous AESIs of dermatitis allergic and dermatitis). All AESIs were mild or moderate and resolved.
- No serious adverse events (SAEs) or deaths were reported during the study.
- There were no clinically significant (CS) findings in terms of hematology, blood chemistry and urinalysis parameters.
- Overall, systolic and diastolic blood pressure (SBP and DBP, respectively) and heart rate (HR) were stable through time.
- Most body systems were found to be normal and the majority of subjects had normal ECG at each timepoint. All abnormalities were considered as non-clinically significant (NCS).

<u>Cohorts 5 and 6</u>

Apart from 1 subject in Group 1/Cohort 5 who discontinued the study on Day 3 (per subject's request), all subjects in all groups/cohorts completed the study. Mean (SD) treatment duration was 29.00 (0.00) days for Group 2/Cohort 5, Group 3/Cohort 6 and Group 4/Cohort 6, and mean (SD) number of applications was 9.00 (0.00). Due to the discontinuation of 1 subject on Day 3 (last treatment on Day 1), in Group 1/Cohort 5, mean (SD) treatment duration for was 24.33 (11.43) days, and mean (SD) number of application was 7.67 (3.27). Overall, the amount of study drug applied at each visit approximately corresponded to the expected dose of 32 g/application in all groups/cohorts.

For the majority of body areas the mean percentage of applied BSA were ≥80%; exceptions were face, neck and anterior trunk, for which by Day 29 the mean percentage of BSA ranged from 15% to 65%. Greater reduction in applied BSA was observed in subjects treated with CD5789 200 µg/g cream HE1. Reduction in applied BSA was due to cutaneous irritation.

Mean scores of erythema, scaling, dryness and stinging/burning were generally ≤1. Moderate irritation occurred sporadically. Highest scores were observed for erythema, followed by scaling and dryness. Stinging/burning was rarely observed. Body areas mostly affected by cutaneous irritation were face, neck and anterior trunk. Overall, cutaneous irritation was slightly more severe in subjects treated with CD5789 200 µg/g cream HE1 than in subjects treated with CD5789 100 µg/g cream HE1. Although neck seemed slightly more sensitive in Japanese subject, no significant differences were observed between subjects of Japanese and non-Japanese origins in terms of cutaneous tolerability.

The large majority of subjects in each group experienced at least 1 AE (≥83.33% of subjects) and 1 treatment-related AE (≥66.67% of subjects). Overall, the number (%) of subjects experiencing AEs was similar across groups. However, the number of AEs and

treatment-related AEs reported in Cohort 5 was higher in subjects treated with CD5789 200 µg/g cream HE1 than in subjects treated with CD5789 100 µg/g cream HE1 (28 vs. 11 AEs; 19 vs. 6 treatment-related AEs, respectively). The majority of AEs reported during the studies were cutaneous and considered as related to the study drug. Overall, no major differences were observed between subjects of Japanese and non-Japanese origins in terms of AEs.

The most frequently reported AEs and treatment-related AEs were pruritus, skin irritation and papule:

'Pruritus' (pruritus generalised and pruritus), all considered as related to the study drug:

- 1 AE of pruritus generalised in 1 (16.67%) subject in Group 2/Cohort 5
- 14 AEs of pruritus (mostly on the areas where skin irritation was observed): 2 events in 2 (33.33%) subjects in Group 1/Cohort 5, 4 events in 3 (50.0%) subjects in Group 2/Cohort 5 and 4 events in 4 (66.7%) subjects in Groups 3 and 4/Cohort 6.

Skin irritation – on both applied BSA and non-applied BSA due to study drug contamination from applied BSA:

- 1 AE in 1 (16.67%) subject in Group 1/Cohort 5, considered as related to the study drug and study procedure
- 5 AEs in 3 (50.00%) subjects in Group 2/Cohort 5; of these events, 3 in 2 (33.33%) subjects were considered as related to the study drug and study procedure
- 3 AEs in 3 (50.00%) subjects in Group 3 /Cohort 6; of these events, 2 in 2 (33.33%) subjects were considered as related to the study drug and study procedure
- 9 AEs in 5 (83.33%) subjects in Group 4/Cohort 6; of these events, 6 in 5 (83.33%) subjects were considered as related to the study drug and study procedure.

Another treatment-related AE due to study drug contamination from applied BSA to non-applied BSA was eyelid irritation, reported in 1 (16.67%) subject in Group 1/Cohort 5 and in 2 (33.33%) subjects in Group 2/Cohort 5.

Papule:

- 1 AE 1 (16.67%) subject in Group 1/Cohort 5
- 4 AEs in 4 (66.67%) subjects in Group 2/Cohort 5
- 4 AEs in 3 (50.00%) subjects in Group 3 /Cohort 6
- 2 AEs in 2 (33.33%) subjects in Group 4/Cohort 6.

All the AEs of papules were considered as related to the study drug.

Overall, cutaneous treatment-related AEs were more common and slightly more severe in subjects treated with CD5789 200 µg/g cream HE1 than in subjects in treated with CD5789 100 µg/g cream HE1. No major differences were observed between subjects of Japanese and non-Japanese origins in terms of AEs.

Overall, the majority of AEs were mild in intensity, and the proportion of subjects with worst AE/treatment-related AE intensity of mild was ≥50.00% in all groups, except Group 4/Cohort 6 (in which 50.00% of subjects had worst AE intensity of moderate). There were 2 severe AEs, which were considered as related to the study drug, reported in 1 (16.67%) subject in Group 2/Cohort 5 (eyelid irritation) and in 1 (16.67%) subject in Group 4/Cohort 6 (skin irritation).

There was only 1 AESI (eye pain) reported in 1 (16.67%) subject in Group 2/Cohort 5. This event was due to study drug contamination of the eye and was therefore considered as related to the study drug.

	No SAEs, AEs leading to discontinuation or deaths were reported in any groups. There were no CS findings in terms of hematology, blood chemistry and urinalysis parameters in the majority of subjects. Transient CS white blood count abnormalities were observed in 1 subject in Group 1/Cohort 5. The Investigator considered these abnormalities as unrelated to the study drug but related to a concomitant AE of viral gastroenteritis experienced by the subject. Overall, SBP, DBP and HR were stable through time. Most body systems were found to be normal and the majority of subjects had normal ECG at each timepoint. All abnormalities were considered as NCS.
22. Summary (conclusion)	Results from Cohort 1 showed that CD5789 200 µg/g cream HE1 led to strong cutaneous irritation when applied once daily over a period of 29 days in healthy subjects of non-Japanese origin. Conversely, good local tolerability profiles were observed in Cohorts 5 and 6, when subjects of Japanese or non-Japanese origins were treated with CD5789 100 µg/g or 200 µg/g cream HE1 twice weekly over a period of 29 days. In addition, in Cohorts 5 and 6 no relevant difference was observed in the safety profile across dose or ethnic (Japanese or non-Japanese) groups. Plasma PK assessment demonstrated that repeated topical applications of CD5789 cream HE1 resulted in low and similar CD5789 systemic levels in all the cohorts. The systemic exposure parameters (C_{max} and $AUC_{0\text{-}24h}$) were in the same range whatever the treatment condition and ethnicity. There was no dose proportionality between CD5789 100 and 200 µg/g cream HE1. In Cohorts 5 and 6 there was no systemic accumulation during the 4 weeks of treatment and steady state was achieved after 2 weeks. Skin PK assessment demonstrated a preferential retention of CD5789 in the skin compartment in comparison to systemic compartment, with mean skin concentration at least 218-fold higher than the corresponding plasma concentration. At the skin level, a dose proportionality trend was observed between CD5789 100 and 200 µg/g cream HE1.

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-40040-EUS - Pharmacokinetics study after single application of microdose of CD5789 in Human
6. Clinical study phase	Pre-Phase 1
7. Clinical study period	Date of first enrollment: 30 July 2007 Date of last subject completed: 06 March 2007
8. Countries where clinical study was conducted	The Netherlands
9. Number of subjects	6 subjects were planned, enrolled and analyzed
10. Aim and secondary	To investigate the plasma pharmacokinetics of the metabolic pool of CD5789 using human microdosing approach, after a single topical application of [^{14}C]-CD5789

<table>
<tr><td>purposes of clinical study</td><td>formulated at 0.01 % in healthy male subjects.</td></tr>
<tr><td>11. Clinical study design</td><td>This study was a single center open-label pharmacokinetic study, in 6 healthy Caucasian male subjects aged 18 to 24 years.</td></tr>
<tr><td>12. Main inclusion criteria</td><td>Key inclusion criteria:
- Healthy males, 18 to 40 years of age</td></tr>
<tr><td>13. Investigational medicinal product, method of administration, strength</td><td>CD5789, topical administration, strength: 0.01% solution</td></tr>
<tr><td>14. Reference medicinal product, method of administration, strength</td><td>Not Applicable</td></tr>
<tr><td>15. Concomitant therapy</td><td>Not Applicable</td></tr>
<tr><td>16. Efficacy evaluation criteria</td><td>Not Applicable</td></tr>
<tr><td>17. Safety evaluation criteria</td><td>- Clinical laboratory (hematology, blood chemistry, coagulation and urinalysis); Vital signs (blood pressure and heart rate) and electrocardiogram (ECG)
- Adverse events (AEs)</td></tr>
<tr><td>18. Statistical methods</td><td>
<table>
<tr><td>Criteria for evaluation and statistical method(s):</td><td></td></tr>
<tr><td>Pharmacokinetics:</td><td>• CD5789 and total ^{14}C radioactivity plasma concentrations (AMS method)
• Pharmacokinetic parameters (Kinetica software): C_{max}, T_{max}, $AUC_{(0-24h)}$, $AUC_{(last)}$ and $AUC_{(0-inf)}$
• Total ^{14}C-radioactivity measurements in skin strip samples and samples with application contact material (Liquid Scintillation Counting method)</td></tr>
<tr><td>Safety:</td><td>• Clinical laboratory (hematology, blood chemistry, coagulation and urinalysis); Vital signs (blood pressure and heart rate) and electrocardiogram (ECG)
• Adverse events (AEs)</td></tr>
</table>
</td></tr>
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19. Demographic indicators of the study population (gender, age, race, etc.)	**Demographics and other subject's baseline characteristics**

	Investigational Product: CD5789
Enrolled:	6
Males	6
Age (mean/range):	20.7 ± 2.2 (range 18-24)
Race:	Caucasian
Discontinued	0
Completed the Study	
Evaluable for pharmacokinetics:	6
Evaluable for safety:	6

20. Efficacy outcomes	Not Applicable
21. Safety outcomes	Adverse Events : - Deaths (related to study drug) : 0 - Other serious AEs events (related to study drug): 0 - Subject discontinuations due to AE (related to study drug): 0 - AEs related to study drug: 2 - Number (%) of subjects with AE related to study drug: 1 (17%) A single topical application of 0.01% CD5789 was safe and well tolerated by 6 healthy male subjects. There were no serious AEs and no AEs leading to discontinuation of the study. All TEAEs were mild in intensity and recovered without sequelae. Two TEAEs of irritant dermatitis for one subject, one starting 10 days and one starting 11 days post-dose were considered to be related to the study treatment. They had spontaneously resolved by 21 days post-dose. There were no clinically significant changes in clinical laboratory, vital signs, ECG and physical examination.
22. Summary (conclusion)	A single topical application of 0.01 % CD5789 was safe and well tolerated by 6 healthy male subjects. A mean of 52.2 ± 16.1 percent was absorbed from the drug product by 24 h after application to the skin, this being measured as the difference in ^{14}C between the applied dose and that recovered in stripped skin and surface excess. The mean area under the plasma concentration-time curve over a 24-hour dosing Interval (mean $AUC_{(0\rightarrow 24h)}$ for total ^{14}C was 0.00221 ± 0.0016 ng eq.h/ml for the six subjects. For the most exposed subject, the estimated peak concentration of 0.00051 ng eq/ml was measured at 16 h after application. The total $AUC_{(0\rightarrow inf)}$ was estimated to be 0.0211 ng eq.h/ml.

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 multicenter, randomized, double-blind, parallel-group vehicle-controlled study to compare the efficacy and safety of CD5789 50 µg/g cream versus vehicle cream in subjects with acne vulgaris, RD.03.SRE.18252
6. Clinical study phase	Phase 3
7. Clinical study period	Date of first subject screened: 23 Nov 2015 Date of last subject completed: 12 May 2017
8. Countries where clinical study was conducted	United States – Hungary – Spain – Czech Republic – Romania – Poland – Ukraine – Russia
9. Number of subjects	A total of 1212 subjects were randomly assigned to either CD5789 50 µg/g cream (602 subjects) or Vehicle Cream (610 subjects). All randomized subjects received at least 1 dose of study medication.
10. Aim and	The objective of the study was to assess the efficacy and safety of CD5789 50 µg/g cream

secondary purposes of clinical study	applied once daily for 12 weeks in subjects with moderate acne vulgaris.
11. Clinical study design	Multicenter, randomized, double-blind, parallel-group, vehicle-controlled study comparing CD5789 50 µg/g cream applied once daily in the evening versus its Vehicle Cream.
12. Main inclusion criteria	Male or female subjects, 9 years or older at Screening. Subjects were to have moderate acne vulgaris on the face with Investigator's Global Assessment (IGA) severity score of 3 (moderate) and at least 20 inflammatory lesions and 25 non-inflammatory lesions on the face at Screening and Baseline. Subjects also were to have moderate acne vulgaris on the trunk with Physician Global Assessment (PGA) severity score of 3 (moderate) on the trunk at Screening and Baseline and at least 20 inflammatory lesions and 20 non-inflammatory lesions but not more than 100 non-inflammatory lesions on the trunk (shoulders, upper back and upper anterior chest) reachable to self-application of the study drug. The criteria regarding moderate truncal acne were optional for subjects between 9 and 11 years of age.
13. Investigational medicinal product, method of administration, strength	CD5789 (trifarotene), cream, topical administration, strength: 50 µg/g
14. Reference medicinal product, method of administration, strength	Vehicle, cream, topical administration, strength: not applicable
15. Concomitant therapy	Not Applicable
16. Efficacy evaluation criteria	**Primary efficacy endpoints** The primary efficacy endpoint consisted of the following 3 co-primary endpoints: - Success rate, defined as the percentage of subjects who achieved an IGA score of 1 (Almost Clear) or 0 (Clear) and at least a 2-grade improvement from Baseline to Week 12 - Absolute change in facial non-inflammatory lesion count from Baseline to Week 12 - Absolute change in facial inflammatory lesion count from Baseline to Week 12 **Secondary efficacy endpoints** The secondary efficacy endpoint consisted of the following 3 co-secondary endpoints: - Percentage of subjects who achieved a PGA score of 1 (Almost Clear) or 0 (Clear) and at least a 2-grade improvement from Baseline to Week 12 - Absolute change in truncal non-inflammatory lesion count from Baseline to Week 12 - Absolute change in truncal inflammatory lesion count from Baseline to Week 12 **Supportive endpoints**

	- Percent change in facial non-inflammatory lesion counts from Baseline to Week 12 - Percent change in facial inflammatory lesion counts from Baseline to Week 12 - Percent change in truncal non-inflammatory lesion counts from Baseline to Week 12 - Percent change in truncal inflammatory lesion counts from Baseline to Week 12 - Subject's assessment of facial acne improvement **Efficacy assessments** - IGA and PGA assessments were conducted at Screening, Baseline, and at Weeks 1, 2, 4, 8, and 12/End of Treatment (ET) visits. Efficacy was assessed on the facial region by IGA and on the upper truncal region by PGA. Both IGA and PGA assessments were based on a 5-point scale from 0 (clear) to 4 (severe). - Lesion counts (inflammatory and non-inflammatory) were performed separately on the face and on the trunk at all visits by Investigators or qualified study personnel, who used both visual observations and palpation strictly, after assessing the IGA and the PGA. Inflammatory lesions included papules and pustules, and non-inflammatory lesions included open and closed comedones. - Subject's self-assessment of facial acne improvement was conducted at Week 12/ET based on a 6-point scale (ranging from 0 [complete improvement] to 5 [worse]), and was to occur before any Investigator assessment.
17. Safety evaluation criteria	Safety assessments of adverse events and local tolerability were conducted for all subjects at Screening and all subsequent visits until the Week 12/ET Visit. Laboratory tests were performed at Screening and the Week 12/ET visit, and physical examination and vital signs were assessed at Screening, Baseline, and Week 12/ET.
18. Statistical methods	**Primary efficacy endpoints:** IGA success rate was analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center based on the Intent-to-treat (ITT) population, which included all randomized subjects. The p-value for the treatment comparison was generated from the general association statistic of the stratified CMH test. Difference in success rate between treatment groups (CD5789 50 µg/g – Vehicle) and the 95% confidence interval (CI) of the difference were based on the large sample approximation method for binary data. Changes from Baseline in facial lesion counts was analyzed separately by lesion type (inflammatory and non-inflammatory) using an analysis of covariance (ANCOVA) model that included baseline lesion count, analysis center, and treatment as factors. The p-value for the treatment comparison, estimate of the treatment difference (CD5789 50 µg/g – Vehicle), and the 95% CI of the difference was generated from the ANCOVA model. The superiority of CD5789 50 µg/g cream to Vehicle Cream was declared only if the statistical significance of all 3 co-primary efficacy endpoints were met. That is, the 2-sided p-values for the difference between the 2 treatment groups in all 3 co-primary efficacy endpoints had to be <0.05. The primary analyses were performed using the ITT population based on the multiple imputation (MI) methodology assuming the data were missing at random (MAR) as the imputation method for missing values. In addition to the planned analyses, post-hoc analyses of the success rate of IGA at each visit and of change in lesion counts from baseline at each visit were conducted using both MI and observed data. **Analysis of secondary efficacy endpoints:** The 3 co-secondary efficacy endpoints were analyzed with the same statistical methods as those used for the co-primary efficacy endpoints, using the intent-to-treat on the trunk (ITTT) population (ie, all subjects in the ITT population who had moderate acne on the trunk at Baseline), with MI as the primary imputation method for missing values.

	The testing of the secondary efficacy endpoints was conditional on the success of the 3 co-primary endpoints. Therefore, no adjustment for multiplicity was required in this study. To claim the superiority of CD5789 50μg/g cream to Vehicle Cream on the trunk, a pre-specified order of hypotheses was tested: - First, superiority of CD5789 50μg/g to Vehicle Cream on the face was tested ($p<0.05$) for all 3 co-primary efficacy endpoints. If successful then, - All 3 co-secondary efficacy endpoints were tested ($p<0.05$) for superiority. The analyses for the secondary efficacy endpoints were repeated using the per protocol (PP) population (ie, all subjects in the ITT population with no major protocol deviations). In addition, post-hoc analysis of PGA success rate at each visit and change in truncal lesion counts from baseline at each visit were conducted for both MI and observed data using ITTT population.
19. Demographic indicators of the study population (gender, age, race, etc.)	The demographic and baseline characteristics were similar between CD5789 50 μg/g cream and Vehicle Cream as shown in Table 1. The overall mean age of the ITT population was 19.7 (SD [standard deviation] = 6.29) years, ranging from 11 to 49 years (median = 18 years). There were 570 (47.0%) subjects who were <18 years old, including 555 (45.8%) subjects aged 12 to 17 years and 15 (1.2%) subjects aged 9 to 11 years. There were 642 (53.0%) adult subjects (≥18 years), including 419 (34.6%) subjects aged 18 to 24 years. As expected considering the studied indication, there were no subjects aged ≥65 years. There were more females (695 [57.3%] subjects) than males (517 [42.7%] subjects). The majority of subjects were White (1119 [92.3%] subjects), Not Hispanic or Latino (1090 [89.9%] subjects), and had skin phototype I to III (1077 [88.8%] subjects).

Table 1 Summary of subject demographic characteristics – Intent-to-treat population

	CD5789 50 µg/g Cream (N = 602)	Vehicle Cream (N = 610)	Total (N = 1212)
Age (years)			
Mean (SD)	19.6 (6.20)	19.9 (6.38)	19.7 (6.29)
Median	18.0	18.0	18.0
Min, Max	11, 49	11, 46	11, 49
Age Group 1, n (%)			
<18 years	276 (45.8)	294 (48.2)	570 (47.0)
9 to 11 years	9 (1.5)	6 (1.0)	15 (1.2)
12 to 17 years	267 (44.4)	288 (47.2)	555 (45.8)
≥18 years	326 (54.2)	316 (51.8)	642 (53.0)
Age Group 2, n (%)			
Pediatric	276 (45.8)	294 (48.2)	570 (47.0)
9 to 13 years	57 (9.5)	50 (8.2)	107 (8.8)
14 to 17 years	219 (36.4)	244 (40.0)	463 (38.2)
Adult	326 (54.2)	316 (51.8)	642 (53.0)
18 to 24 years	226 (37.5)	193 (31.6)	419 (34.6)
25 to 64 years	100 (16.6)	123 (20.2)	223 (18.4)
≥65 years	0	0	0
Gender, n (%)			
Female	357 (59.3)	338 (55.4)	695 (57.3)
Male	245 (40.7)	272 (44.6)	517 (42.7)
Race, n (%)			
White	565 (93.9)	554 (90.8)	1119 (92.3)
Black or African American	27 (4.5)	42 (6.9)	69 (5.7)
Asian	2 (0.3)	6 (1.0)	8 (0.7)
American Indian or Alaska Native	1 (0.2)	2 (0.3)	3 (0.2)
Native Hawaiian or Other Pacific Islander	0	1 (0.2)	1 (0.1)
Multiple	2 (0.3)	2 (0.3)	4 (0.3)
Other	5 (0.8)	3 (0.5)	8 (0.7)
Ethnicity, n (%)			
Hispanic or Latino	60 (10.0)	62 (10.2)	122 (10.1)
Not Hispanic or Latino	542 (90.0)	548 (89.8)	1090 (89.9)
Skin Phototype, n (%)			
Type I	36 (6.0)	37 (6.1)	73 (6.0)
Type II	274 (45.5)	249 (40.8)	523 (43.2)
Type III	233 (38.7)	248 (40.7)	481 (39.7)
Type IV	33 (5.5)	38 (6.2)	71 (5.9)
Type V	14 (2.3)	19 (3.1)	33 (2.7)
Type VI	12 (2.0)	19 (3.1)	31 (2.6)

Max=maximum; Min=minimum; N=number of subjects; SD=standard deviation.
Note: Baseline was defined as the last measurement prior to the first application of study drug.

The acne baseline characteristics for face and trunk were similar between CD5789 50 µg/g cream and Vehicle Cream (Table 2). As per protocol, at Baseline visit, all subjects in the ITT population had moderate facial acne (IGA grade = 3) and 1207 (99.6%) subjects had moderate truncal acne (PGA grade = 3).

There were 4 (0.3%) subjects who had PGA score of 0 at Baseline; all were aged 11 years, and 3 of the 4 subjects were randomized to CD5789 50 µg/g cream and 1 subject to Vehicle Cream). There was 1 subject aged 11 years who had a PGA score of 1 at Baseline. These 4 subjects with a PGA score of 0 or 1 at Baseline were excluded in the ITTT population.

At Baseline, mean counts of inflammatory and non-inflammatory lesions were:

On the face, 36.6 (SD = 13.84) and 50.9 (SD = 25.83), respectively

On the trunk, 39.1 (SD = 16.80) and 45.9 (SD = 19.87), respectively.

Inflammatory lesions on the face and trunk were mostly papules (mean counts:

22.9 [SD = 9.72] and 24.8 [SD = 11.45], respectively). The number of open and closed comedones was comparable on the face (mean counts were 21.5 and 21.0, respectively) and the trunk (mean counts were 20.0 and 22.0, respectively). The majority of subjects had no nodule on the face (1145 subjects, 94.5%) or the trunk (1160 subjects, 95.7%). Thirty-two (32) of 602 subjects (5.3%) in the CD5789 50 µg/g cream group and 35 of 610 subjects (5.7%) in the Vehicle Cream group had 1 or more nodules on the face, and 30 subjects (5.0%) in the CD5789 50 µg/g cream group and 21 subjects (3.4%) in the Vehicle Cream group had 1 or more nodules on the trunk.

Table 2 Summary of subject baseline characteristics – Intent-to-treat population

	CD5789 50 µg/g cream (N = 602)	Vehicle Cream (N = 610)	Total (N = 1212)
Baseline IGA Grade (%)			
Clear (0)	0	0	0
Almost Clear (1)	0	0	0
Mild (2)	0	0	0
Moderate (3)	602 (100)	610 (100)	1212 (100)
Severe (4)	0	0	0
Baseline PGA Grade (%)			
Clear (0)	3 (0.5)	1 (0.2)	4 (0.3)
Almost Clear (1)	1 (0.2)	0	1 (0.1)
Mild (2)	0	0	0
Moderate (3)	598 (99.3)	609 (99.8)	1207 (99.6)
Severe (4)	0	0	0
Baseline Inflammatory Facial Lesion Count			
Mean (SD)	36.1 (12.47)	37.1 (15.06)	36.6 (13.84)
Median	33.0	34.0	33.0
Min, Max	10, 110	7, 200	7, 200
Baseline Facial Nodules Count (%)			
0	570 (94.7)	575 (94.3)	1145 (94.5)
1	32 (5.3)	35 (5.7)	67 (5.5)
≥2	0	0	0
Baseline Non-Inflammatory Facial Lesion Count			
Mean (SD)	50.6 (25.93)	51.2 (25.75)	50.9 (25.83)
Median	43.0	44.0	43.0
Min, Max	25, 232	25, 305	25, 305
Baseline Inflammatory Truncal Lesion Count			
Mean (SD)	39.0 (16.16)	39.1 (17.41)	39.1 (16.80)
Median	35.0	34.0	35.0
Min, Max	0, 100	0, 220	0, 220
Baseline Truncal Nodules Count (%)			
0	571 (94.9)	589 (96.6)	1160 (95.7)
1	30 (5.0)	21 (3.4)	51 (4.2)
≥2	1 (0.2)	0	1 (0.1)
Baseline Non-Inflammatory Truncal Lesion Count			
Mean (SD)	46.1 (20.17)	45.7 (19.58)	45.9 (19.87)
Median	42.0	42.5	42.0
Min, Max	0, 180	0, 260	0, 260

IGA=Investigator's Global Assessment; Max=maximum; Min=minimum; N=number of subjects; PGA=Physician's Global Assessment; SD=standard deviation.
Note: Baseline was defined as the last measurement prior to the first application of study drug. Baseline PGA summary included all subjects with or without truncal acne at baseline. Baseline truncal lesion counts summary included all subjects with or without truncal acne at baseline.

20. Efficacy	The summary for the primary, secondary, and supportive efficacy endpoints is provided in

outcomes	Table 3. Results from this double-blind, randomized, vehicle-controlled study showed that treatment with CD5789 50μg/g cream once daily for 12 weeks had superior efficacy in treating moderate facial and truncal acne vulgaris compared with Vehicle Cream in subjects 9 years or older. This was observed in IGA success rate, PGA success rate, and change from Baseline in inflammatory and non-inflammatory lesion counts on the face and trunk. Compared with Vehicle Cream, treatment with CD5789 50 μg/g cream resulted in statistically significantly higher IGA and PGA success rates ($p<0.001$) as well as statistically significantly greater reductions in facial and truncal inflammatory ($p<0.001$) and non-inflammatory lesion counts ($p\leq0.001$) from Baseline at Week 12. These results were consistent with the PP and PPT populations for the primary and secondary efficacy endpoints as well as with the sensitivity analyses. Results of the percent change in facial and truncal inflammatory and non-inflammatory lesion counts from Baseline to Week 12 also showed statistically significant improvement in facial and truncal acne with CD5789 50 μg/g cream compared with Vehicle Cream ($p<0.001$). The proportions of subjects who reported facial acne improvement from Baseline to Week 12 were higher in the CD5789 50 μg/g cream group compared with the Vehicle Cream group. Subjects were considered to have had overall success if they had an IGA score of "clear" (0) or "almost clear" (1) at Week 12, and at least a 2-grade improvement from Baseline to Week 12, as well as a PGA score of "clear" (0) or "almost clear" (1) at Week 12, and at least a 2-grade improvement from Baseline to Week 12. The overall success rate was higher in subjects who received CD5789 50 μg/g cream compared with subjects who received Vehicle Cream.

Table 3 Summary of efficacy analyses at Week 12

	CD5789 50 µg/g cream	Vehicle Cream	Treatment Difference (95% CI)[c]	P value	Multiple Imputation	Observed Data
Primary Efficacy (ITT Population), MI						
IGA Success Rate at Week 12 (%)[a, b]	42.3	25.7	16.6 (11.3, 22.0)	<0.001[d]	<0.001[d]	<0.001[d]
Absolute change from baseline in facial inflammatory lesion counts at Week 12	-24.2, (0.51)	-18.7, (0.51)	-5.6 (-6.9, -4.3)	<0.001[e]	<0.001[e] (LS means)	<0.001[e]
Absolute change from baseline in facial non-inflammatory lesion counts at Week 12	-30.1 (0.71)	-21.6 (0.71)	-8.5 (-10.3, -6.6)	<0.001[e]	<0.001[e] (LS means)	<0.001[e]
Secondary Efficacy (ITTT Population), MI						
PGA Success Rate at Week 12 (%)[a, b]	42.6	29.9	12.7 (7.2, 18.2)	<0.001[d]	<0.001[d]	<0.001[d]
Absolute change from baseline in truncal inflammatory lesion counts at Week 12	-25.5 (0.59)	-19.8 (0.58)	-5.7 (-7.2, -4.2)	<0.001[e]	<0.001[e] (LS means)	<0.001[e]
Absolute change from baseline in truncal non-inflammatory lesion counts at Week 12	-25.9 (0.67)	-20.8 (0.66)	-5.0 (-6.8, -3.3)	<0.001[e]	0.001[e] (LS means)	<0.001[e]
Supportive Efficacy (ITT Population), MI						
Mean percent change from baseline in facial inflammatory lesion counts at Week 12	-66.2	-51.2	-	<0.001	<0.001[g]	<0.001[g]
Mean percent change from baseline in facial non-inflammatory lesion counts at Week 12	-57.7	-43.9	-	<0.001	<0.001[g]	<0.001[g]
Mean percent change from baseline in truncal inflammatory lesion counts at Week 12	-65.4	-45.1	-	<0.001	<0.001[e] (LS means)	<0.001[g]
Mean percent change from baseline in truncal non-inflammatory lesion counts at Week 12	-55.2	-45.1	-	<0.001	0.001[e] (LS means)	<0.001[g]
Subject assessment of facial acne improvement from Baseline to Week 12 as complete improvement, n (%)	29 (5.2)	13 (2.3)	-	-		
Subject assessment of facial acne improvement from Baseline to Week 12 as marked improvement, n (%)	224 (39.9)	154 (26.8)	-	-		
Subject assessment of facial acne improvement from Baseline to Week 12 as moderate improvement, n (%)	202 (35.9)	191 (33.3)	-	-		
Subject assessment of facial acne improvement from Baseline to Week 12 as minimal improvement, n (%)	71 (12.6)	128 (22.3)	-	-		
Subject assessment of facial acne improvement from Baseline to Week 12 as no change, n (%)	28 (5.0)	74 (12.9)	-	-		

	CD5789 50 µg/g cream	Vehicle Cream	Treatment Difference (95% CI)[c]	P value	Multiple Imputation	Observed Data
Subject assessment of facial acne improvement from Baseline to Week 12 as worse, n (%)	8 (1.4)	14 (2.4)	-	-		
Other Supportive Efficacy (ITTT Population), MI						
Overall success rate at Week 12, (%)[f]		34.7	21.2	-	-	

ANCOVA=analysis of covariance; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; IGA=Investigator's Global Assessment; ITT=intent-to-treat; ITTT=intent-to-treat Trunk; LS=least squares; MI=multiple imputation; N=number of subjects; PGA=Physician's Global Assessment; SE=standard error.

[a] Success was defined as IGA or PGA score of "clear (0)" or "almost clear (1)" at Week 12 and at least 2-grade improvement from Baseline to Week 12.

[b] Success rate was calculated as the number of subjects achieving success divided by the number of subjects with IGA or PGA data at Week 12.

[c] Confidence intervals were based on the large-sample approximation method for binary data without the use of a continuity correction.

[d] P-values were based on the general association statistic from a CMH test stratified by analysis center.

[e] P-values and CIs were based on an ANCOVA model with baseline lesion count, analysis center, and treatment as factors.

[f] Additional analyses were conducted to evaluate the overall success rate at Week 12 in the ITTT population using the MI dataset. These analyses were performed in subjects with presence of both facial and truncal acne lesions. Subjects were considered to have had overall success if they had an IGA score of "clear" (0) or "almost clear" (1) at Week 12 and at least a 2-grade improvement from Baseline to Week 12 as well as a PGA score of "clear" (0) or "almost clear" (1) at Week 12 and at least a 2-grade improvement from Baseline to Week 12. The overall success rate was calculated as the number of subjects who achieved overall treatment success at that visit divided by the number of subjects with both IGA and PGA data at that visit.

After database lock had occurred, it was decided to perform a post-hoc analysis of time to onset of effect. To determine the time of efficacy onset, analyses of each co-primary and cosecondary endpoint were repeated post-hoc at each visit prior to Week 12. Onset of a statistically significant effect on inflammatory and non-inflammatory lesions was observed at Week 1 and Week 2 for face and trunk, respectively, progressing to a statistically significant difference in IGA and PGA as early as Week 8.

21. Safety outcomes

A total of 1212 subjects were included in the safety population; 603 subjects in the CD5789 50 µg/g cream group and 609 subjects in the Vehicle Cream group. The mean treatment duration for face and trunk was similar between treatment groups (approximately 81 days for CD5789 50 µg/g cream and approximately 82 days for Vehicle Cream. The mean daily study drug usage was similar between CD5789 50µg/g cream and Vehicle Cream (1.8 g/day for both CD5789 50 µg/g cream and Vehicle Cream).

Treatment-emergent adverse events were reported by 122 (20.2%) subjects in the CD5789 50 µg/g cream group and 117 (19.2%) subjects in the Vehicle Cream group. The most commonly reported TEAEs were in the Infection and Infestations SOC (CD5789 50 µg/g cream group, 56 [9.3%] subjects; Vehicle Cream group, 73 [12.0%] subjects). In this SOC, the most common TEAE was nasopharyngitis (CD5789 50 µg/g cream, 26 [4.3%] subjects; Vehicle Cream, 29 [4.8%] subjects).

A higher proportion of subjects who received CD5789 50 µg/g cream compared with Vehicle Cream reported TEAEs in the General disorders and administration site conditions SOC, mainly due to application site irritation (CD5789 50 µg/g cream, 18 [3.0%] subjects; Vehicle Cream, 0 subjects), and in the Injury, poisoning and procedural complications SOC, mainly due to sunburn (CD5789 50 µg/g cream, 6 [1.0%] subjects; Vehicle Cream 1 [0.2%] subject).

Treatment-emergent adverse events with incidence ≥1% (at the preferred term level) in the CD5789 50 µg/g cream group were (by decreasing frequency): nasopharyngitis, application site irritation, headache, upper respiratory tract infection, sunburn, and dysmenorrhea.

Treatment-emergent adverse events related to the study drug were reported by 33 (5.5%) subjects in the CD5789 50 µg/g cream group and 5 (0.8%) subjects in the Vehicle Cream group. The most commonly reported TEAEs related to the study drug were in the General disorder and administration site conditions SOC (CD5789 50 µg/g cream, 24 [4.0] subjects; Vehicle Cream, 2 [0.3] subjects).

	Most of the TEAEs reported in both treatment groups were mild or moderate in severity. Few TEAEs were severe (6 TEAEs in 4 [0.7%] subjects in the CD5789 50 µg/g cream group; 7 TEAEs in 7 [0.7%] subjects in the Vehicle Cream group). Severe related TEAEs were reported in 3 (1.6%) subjects in the CD5789 50 µg/g cream group and no subject in the Vehicle Cream group. Among subjects who received CD5789 50 µg/g cream, the most common TEAEs assessed as related to the study drug were, by decreasing frequency: application site irritation (2.5%), application site pruritus (0.8%), application site pain (0.7%), and application site dryness (0.5%). No deaths were reported during the study. Three (3) serious TEAEs were reported by 2 (0.3%) subjects in the CD5789 50 µg/g cream group (suicide attempt and major depression in 1 subject; ligament sprain in 1 subject), and 4 serious TEAEs were reported by 4 (0.7%) subjects in the Vehicle Cream group (suicide attempt, appendicitis, sinusitis and asthma, each in 1 subject). None of the serious TEAEs was cutaneous in nature or assessed as related to study drug. Adverse Events of Special Interest were reported by 9 (1.5%) subjects in the CD5789 50 µg/g cream group, which were all cutaneous in nature and related to the study drug. In this treatment group, the most common AESI was application site irritation (5 [0.8%] subjects). In the Vehicle Cream group, AESIs were reported by 2 (0.3%) subjects (blood bilirubin increase and blood creatinine increase). Treatment-emergent adverse events that led to discontinuation were reported by 10 (1.7%) subjects in the CD5789 50 µg/g cream group and 1 (0.2%) subject in the Vehicle Cream group. Of the 10 subjects in the CD5789 50 µg/g cream group, 7 subjects had 8 TEAEs that were cutaneous in nature and related to study drug. One (1) subject in the Vehicle Cream group had a TEAE that led to study drug discontinuation, which was not cutaneous and not related to study drug. There were no clinically significant mean changes from Baseline to Week 12 in hematology or blood chemistry in either treatment group. There were no clinically significant mean changes from Baseline to Week 12 in vital signs (systolic and diastolic blood pressure, and pulse rate). Three (3) subjects in the CD5789 50 µg/g cream group had treatment-emergent abnormal and clinically significant physical exam findings reported as TEAEs. These were dermatitis on the chest and back, erythematous patches on the chest, and irritant dermatitis. Signs/symptoms of local tolerability (erythema, dryness, scaling, and stinging/burning) on the face and the trunk occurred in a greater proportion of subjects in the CD5789 50 µg/g cream group compared with the Vehicle Cream group. A better local tolerability profile was observed on the trunk compared with the face. These signs/symptoms increased and decreased (crescendo – decrescendo pattern) over the course of the study. On the face, peak irritation was observed at Week 1, while on the trunk a gradual increase was observed up to Week 4 and then signs/symptoms decreased until the end of the study. In the CD5789 50 µg/g cream group, the highest local tolerability scores that worsened from Baseline on the face were graded as mild (26.4% [erythema] to 36.5% [scaling]), moderate (24.9% [stinging/burning] to 36.4% [dryness]), or severe (6.8% [scaling] to 10.0% [erythema]). On the trunk, the highest local tolerability scores that worsened from Baseline were graded as mild (27.0% [erythema] to 35.7% [scaling]), moderate (12.9% [stinging/burning] to 23.2% [erythema]), or severe (2.5% [dryness] to 7.2% [erythema]). The TEAEs in the subgroups were consistent with the SAF population. The percentage of subjects who reported at least 1 TEAE was comparable in both treatment groups for most subgroups. The signs/symptoms of local tolerability on the face and trunk were comparable in the majority of the subgroups and consistent with the SAF population. Few subgroups, such as ages 9 to 11 years old, race (Black, Asian, and Other), ethnicity (Hispanic or Latino), and skin phototype (IV-VI) provided variability compared with the

	SAF population. However, this should be interpreted with caution given the small sample size of these subgroups. A better local tolerability profile was observed on the trunk compared with the face in each demographic subgroup. Suspected skin sensitization was reported for 1 subject in the CD5789 50 µg/g cream group. Results for the rechallenge skin patch test reached a negative conclusion for contact skin sensitization. Final diagnosis was concluded to be irritant dermatitis on the 4th and 5th digits of both hands; i.e., on non-treated areas. The skin response was considered to be irritant in nature and not indicative of allergic contact skin sensitization. There were 2 pregnancies reported during the study period. One (1) was an uneventful full-term pregnancy with a healthy infant delivered at 40 weeks and 6 days (Vehicle Cream group); the other subject was lost to follow-up and no further information is available (CD5789 50 µg/g cream group).
22. Summary (conclusion)	All objectives of this pivotal study were met: Compelling and robust efficacy of CD5789 50 µg/g cream in the treatment of moderate facial and truncal acne vulgaris was demonstrated. Subjects treated with CD5789 50 µg/g cream experienced clinically meaningful and statistically significant improvement in the primary and secondary efficacy endpoints of the study: IGA and PGA success rates (Clear and Almost Clear with at least a 2-grade improvement) at Week 12 and facial and truncal inflammatory and non-inflammatory lesions change from Baseline to Week 12 when compared with corresponding vehicle. CD5789 50 µg/g cream was safe in all safety assessments performed throughout the study. Most of the TEAEs occurred at the application site. Most of the cutaneous TEAEs and the recorded signs and symptoms of skin irritation followed the well-known pattern of retinoid dermatitis with acceptable and manageable tolerability when CD5789 50 µg/g cream was applied to large body surface areas of face and trunk.

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-40055E-EUS - Evaluation of the irritation potential of CD5789 gel in healthy subjects
6. Clinical study phase	Phase 1
7. Clinical study period	Study Initiation Date (date of first informed consent form signed): 30 Oct 2008 Study Completion/terminated Date (last subject completed): 17 Dec 2008
8. Countries where clinical study was conducted	France
9. Number of subjects	Approximately 30 healthy male subjects were planned A total of 37 subjects were screened at one investigational site, and 31 of them were randomized, treated and analysed.

<table>
<tr><td>10. Aim and secondary purposes of clinical study</td><td>The primary objective of this study was to assess the cumulative irritancy potential of CD5789 in a gel vehicle at five concentrations 0.01%, 0.005%, 0.003%, 0.002% and 0.001% as compared to Tazarotene 0.1% gel, Tazarotene 0.05% gel, Adapalene 0.1% gel or the gel vehicle of CD5789, on the upper back of healthy male subjects and under non-occlusive conditions.

These local tolerance data were generated to allow dose selection for further development of CD5789.

Another objective was to evaluate the systemic drug safety by adverse event reporting, vital signs, electrocardiogram (ECG) and laboratory safety tests follow-up.</td></tr>
<tr><td>11. Clinical study design</td><td>Single-centre, controlled, investigator blinded, intra-individual comparison with randomized applications.</td></tr>
<tr><td>12. Main inclusion criteria</td><td>Key inclusion criteria:
- Healthy male subject, 18 to 50 years old inclusive;
- The subject had a skin phototype of I to IV on Fitzpatrick's scale.</td></tr>
<tr><td>13. Investigational medicinal product, method of administration, strength</td><td>Table 1 Investigational Product Identities
<table>
<tr><td></td><td colspan="5">INVESTIGATIONAL PRODUCT</td><td colspan="4">Comparators</td></tr>
<tr><td>Trade Name or equivalent</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td><td>Zorac®</td><td>Zorac®</td><td>Differine®</td><td>NA</td></tr>
<tr><td>Name of Drug Substance (INN)</td><td colspan="5">CD5789</td><td colspan="2">Tazarotene</td><td>Adapalene</td><td>Vehicle</td></tr>
<tr><td>Pharmaceutical Form</td><td colspan="9">Gel</td></tr>
<tr><td>Concentration</td><td>0.01%</td><td>0.005%</td><td>0.003%</td><td>0.002%</td><td>0.001%</td><td>0.1%</td><td>0.05%</td><td>0.1%</td><td>NA</td></tr>
<tr><td>Packaging (type and size)</td><td colspan="5">30 mL glass vial</td><td colspan="2">Tubes 60g</td><td>Tubes 30g</td><td>30 mL glass vial</td></tr>
<tr><td>Storage Conditions</td><td colspan="5">Store below 25°C, do not freeze</td><td colspan="2">Store below 30°C</td><td colspan="2">Store below 25°C, do not freeze</td></tr>
<tr><td>Dosage (total daily dose)</td><td colspan="9">10 µL (approximately 2 mg/cm²)</td></tr>
<tr><td>Dose regimen</td><td colspan="9"></td></tr>
<tr><td>Route</td><td colspan="9">Topically under non occlusive conditions</td></tr>
<tr><td>Frequency</td><td colspan="9">Once daily</td></tr>
<tr><td>Duration of administration</td><td colspan="9">21 days (15 applications)</td></tr>
<tr><td>Treatment area</td><td colspan="9">Upper back</td></tr>
</table></td></tr>
</table>

14. Reference medicinal product, method of administration, strength

Table 1 Investigational Product Identities

	INVESTIGATIONAL PRODUCT					Comparators			
Trade Name or equivalent	NA	NA	NA	NA	NA	Zorac®	Zorac®	Differine®	NA
Name of Drug Substance (INN)	CD5789					Tazarotene		Adapalene	Vehicle
Pharmaceutical Form	Gel								
Concentration	0.01%	0.005%	0.003%	0.002%	0.001%	0.1%	0.05%	0.1%	NA
Packaging (type and size)	30 mL glass vial					Tubes 60g		Tubes 30g	30 mL glass vial
Storage Conditions	Store below 25°C, do not freeze					Store below 30°C		Store below 25°C, do not freeze	
Dosage (total daily dose)	10 µL (approximately 2 mg/cm^2)								
Dose regimen									
Route	Topically under non occlusive conditions								
Frequency	Once daily								
Duration of administration	21 days (15 applications)								
Treatment area	Upper back								

15. Concomitant therapy

TABLE 6 Concomitant therapies by ATC code

	Randomized (n=31)		
	n therapies	n subj.	% subj.
Subjects with at least one concomitant therapy	9	6	19.4
Anilides	5	4	12.9
Imidazole and triazole derivatives	1	1	3.2
Magnesium	1	1	3.2
Multivitamins, other combinations	1	1	3.2
Selective beta-2-adrenoreceptor agonists	1	1	3.2

Note: The numbers in the columns cannot be added because a given subject could report more than one concomitant therapy.

Six (6; 19.4%) of the randomized subjects reported at least one concomitant therapy. Four (4; 12.9%) reported the use of 5 anilides to treat 5 adverse events (3 cases of headache, one case of flu syndrom and one rhinopharyngitis). The following therapies were reported for one subject each (3.2%): imidazole and triazole derivates, magnesium, multivitamins, other combinations and selective beta-2-adrenoreceptor agonists (Source: Table 6).

16. Efficacy evaluation criteria

Not Applicable

17. Safety evaluation criteria

- Safety assessments included treatment site evaluation at every visit from Day1 to Day21, for each zone of the subject's upper back, using a 5-point skin reaction scale ranging from "No reaction (0)" to "Erythema with vesicles or erosion or bullae (4)".
- Other safety assessments included adverse event recording at each visit, laboratory data (hematology, chemistry, and urinalysis), vital signs, electrocardiogram and changes in physical examination.

18. Statistical methods

Not Applicable

19. Demographic indicators of the study population (gender, age, race, etc.)	**14.3.1 Subjects characteristics** SPR 40055 - February 12, 2009 / 16:24 TABLE 3 Demographic data 1 			Screened		Randomized	
---	---	---	---	---	---
		n	%	n	%
GENDER	Total	37		31	
	Male	37	100.0	31	100.0
RACE	Total	37		31	
	Caucasian	37	100.0	31	100.0
PHOTYPE	Total	37		31	
	II	7	18.9	6	19.4
	III	29	78.4	24	77.4
	IV	1	2.7	1	3.2 | SPR 40055 - February 12, 2009 / 16:24 TABLE 3bis Demographic data 2 |		Screened	Randomized
---	---	---	---
AGE	n	37	31
	Mean	31.8	31.9
	Median	31.0	31.0
	Sd	7.1	7.3
	(Min,Max)	(22.0,48.0)	(22.0,48.0)	 All subjects randomized were males and Caucasians. The majority of randomized subjects (77.4%) had a Phototype III; their mean age was 31.9 years at baseline (Source: Table 3 and 3bis)
20. Efficacy outcomes	Not Applicable
21. Safety outcomes	A total of 31 subjects received study products and were analyzed in the safety population. Two (2) subjects did not have all applications (in one subject, applications were stopped at Day 18 due to a non-related skin irritation; another subject prematurely discontinued the study at Day 18 due to a non-related adverse event). After Day15, the mean daily irritation index increased notably with Tazarotene at 0.1% and 0.05% as well as for CD5789 0.01%. Indices for CD5789 at doses up to 0.005% and for the vehicle remained low throughout the study. Adapalene 0.1% was not irritating. The mean cumulative irritation index (MCII) reached 0.19 (on an index scale ranging from 0 to 4) with Tazarotene 0.1%. The MCII with the highest dose of CD5789 (0.01%) was 0.04, identical to that of Tazarotene 0.05%. For the worst score skin reaction, only one subject reported a score of "4" for CD5789 0.01% gel treatment. Of the 31 subjects included in the safety population, 5 subjects (16.1%) experienced at least one AE. All AEs were considered by the Investigator as not related to the study products. One discontinuation from the study due to AE was reported for a subject who experienced a rash on the whole test side area, and withdrew from the study at Day 18. There were no serious adverse events (SAEs) and no deaths reported in this study. One subject was withdrawn at Day 18 from the study due a rash (see above). No abnormal findings were reported for vital signs and physical examination. ECG and laboratory testing did not identify any cause for concern. Abnormal laboratory tests (increased ASAT, ALAT and gamma GT), not-related to the study products, were observed in one subject.
22. Summary (conclusion)	The Sponsor conducted this 21-day cumulative irritation potential study to assess, on the upper back of healthy subjects and under non-occlusive conditions, the cumulative irritancy potential of CD5789 gel at 5 concentrations (0.01%, 0.005%, 0.003%, 0.002% and 0.001%) as compared to Tazarotene 0.1% gel, Tazarotene 0.05% gel, Adapalene 0.1% gel and to CD5789 gel vehicle. Results from this study demonstrated that the tolerance of CD5789 at doses of up to

	0.01% formulated in a gel and compared to Tazarotene 0.05 and 0.1% gel was acceptable and did not raise systemic safety concerns. No irritation was reported with Adapalene 0.1% and only one subject reported mild irritation with the vehicle.

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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-40124E - STUDY TO EVALUATE THE EFFICACY AND SAFETY OF CD5789 GEL IN SUBJECTS WITH PSORIASIS
6. Clinical study phase	Phase 2a
7. Clinical study period	Date of first enrolment: 25 October 2010 Date of last subject completed: 20 December 2010
8. Countries where clinical study was conducted	France
9. Number of subjects	It was planned to enroll approximately 50 subjects in order to randomize approximately 24. Finally, 32 subjects were randomized and all subjects completed the study.

10. Aim and secondary purposes of clinical study	- To evaluate the efficacy in subjects with psoriasis of three concentrations of CD5789 gel (0.01%, 0.005%, and 0.0025%) compared to its vehicle gel after a four-week treatment period of once daily application to a mini-zone. - To assess the local tolerance of CD5789 compared to its vehicle gel and Zorac® gel. - An additional exploratory objective was to gather preliminary data on proteins and mRNA as potential markers of the effect of CD5789 on psoriatic lesions.
11. Clinical study design	This was an exploratory, multi-center, randomized, controlled, investigator-blinded, intraindividual study. Subjects received each of the following treatments which were randomized to be applied to 6 different mini-zones on one or more psoriatic plaques of identical severity (similar baseline Total Sum Score (TSS) or variation of ± 1 grade) located on the upper and lower extremities (elbows, knees and shin area excluded) and/or trunk: - CD5789 gel 0.0025%; - CD5789 gel 0.005%; - CD5789 gel 0.01%; - CD5789 vehicle gel (negative control); - Daivobet® ointment (calcipotriol 50µg/g / betamethasone dipropionate 500µg/g) (used for sensitivity analysis); - Zorac® gel 0.05% (Tazarotene 0.05%) (Safety comparator). Treatment was applied once daily for 4 weeks (5 days per week). Individual clinical scores and clearing scores were assessed twice weekly. AEs and concomitant therapies were recorded and cutaneous tolerance was assessed at each application visit. Photographs were taken at Day 1 (Baseline) and Day 29 (Final visit/ early termination). Tape stripping (optional assessment) was performed at Day 29 (Final visit).
12. Main inclusion criteria	Male or female, aged 18 to 70, with a clinical diagnosis of stable plaque psoriasis, defined as no flare in the month before the Screening visit or Baseline visit. At baseline visit, the subject presented six target sites on one or more psoriasis plaques which: - were located on the upper and lower extremities and/or trunk (elbow, knees and shin area excluded). Plaques on the face, scalp, hands, feet and folds were not be eligible as test areas. - had a Total Sum Score (TSS) (sum of erythema, induration/plaque elevation and scaling) superior or equal to 6 and each item separately being ≥ 2 - had similar severity, i.e.: identical baseline TSS or variation of ± 1 grade - were approximately 2 cm in diameter - were at least 2 cm apart from each other
13. Investigational medicinal product, method of administration, strength	- CD5789 gel 0.0025%; - CD5789 gel 0.005%; - CD5789 gel 0.01%. Route of administration: Topical
14. Reference medicinal	**Vehicle Therapy (negative control)** - CD5789 vehicle gel, strength : Not Applicable

product, method of administration, strength	Route of administration: Topical **Sensitivity comparator** -Daivobet® ointment (calcipotriol 50µg/g / betamethasone dipropionate 500µg/g) Route of administration: Topical **Safety comparator** Zorac® gel 0.05% (Tazarotene 0.05%) Route of administration: Topical
15. Concomitant therapy	Not Applicable
16. Efficacy evaluation criteria	Primary variable: Area Under the Curve (AUC) from Day 1 to Day 29 of TSS (sum of individual clinical scores erythema, plaque elevation/induration and scaling). Secondary efficacy variables: - TSS and percent change from Baseline at each visit; - The AUC of individual clinical scores (erythema, scaling and induration/plaque elevation) from Day 1 to Day 29; - Erythema, Scaling and Induration/Plaque Elevation score and their change from Baseline at each visit; - Success (defined as a clearing score of 0 or 1) at each evaluation visit and the time to success.
17. Safety evaluation criteria	- Global cutaneous tolerance (at every visit from Day 2); - Adverse event (AE) recording (at Baseline and every following visit); - General physical examination and vital signs (at Screening, Baseline and Day 29); - Laboratory safety tests (at Screening).
18. Statistical methods	The AUC of the TSS, as well as AUC of each individual clinical score was calculated from Day 1 (before application) up to Day 29 by subject and by treatment, using the trapezoidal rule. The AUCs were submitted to analyses of variance including subject and treatment as factors in the model. The Tukey multiple comparison test was used to classify all products. Significance was declared at the 5% two-sided level. The global cutaneous tolerance score was summarized descriptively by visit and study product. The worst score was also summarized. Incidence and multiplicity of AEs were also described.
19. Demographic indicators of the study population (gender, age, race, etc.)	In total, 39 subjects were screened and 32 subjects were randomized from 3 centers in France. Thirty-one subjects (96.9%) were Caucasians; 17 were males (53.1%) with a mean age (±standard deviation) of 44.2±14.0 years. All the 32 randomized subjects were included in the Safety population and in the intent-to-treat (ITT) population, and 24 subjects were included in the per-protocol (PP) population.
20. Efficacy outcomes	**Primary efficacy variable**

The AUC from Day 1 (Baseline) to Day 29 of the TSS is presented below:

		CD5789 0.0025%	CD5789 0.005%	CD5789 0.01%	CD5789 VEHICLE	Daivobet®	Zorac® 0.05%
Intent to Treat	N	32	32	32	32	32	32
	Mean	184.1	175.5	179.5	186.6	72.00	152.1
	SD	51.24	51.17	45.19	54.44	25.63	52.88
	Median	178.0	166.0	171.0	192.5	64.50	153.0
	Min~Max	102.5~ 308.0	89.5~ 287.5	100.5~ 277.0	72.5~ 292.0	30.0~ 141.0	51.0~ 248.5

There were no statistically significant differences ($p>0.6$) between any of the CD5789 concentrations versus vehicle. Neither were there any statistically significant differences (all $p>0.8$) between any of the three CD5789 concentrations.

The Daivobet® treated mini-zone had statistically significantly improved TSS scores ($p<0.001$) compared to each other treated mini-zone. The Zorac® treated mini-zone had statistically significantly improved TSS scores ($p<0.014$) compared to the CD5789 vehicle treated mini-zone and each CD5789 treatment group. These results were confirmed in the PP population (apart from CD5789 0.005% versus Zorac® where there was no significant difference between TSS scores).

Table 1 **Statistical difference between groups of the AUC from Day 1 (Baseline) to Day 29 of the TSS:**

ITT-LOCF	LSmean	Difference	Adjusted p-value
CD5789 0.0025% - CD5789 0.005%	184.08 - 175.5	8.58	0.826
CD5789 0.0025% - CD5789 0.01%	184.08 - 179.4	4.61	0.986
CD5789 0.0025% - CD5789 VEHICLE	184.08 - 186.5	-2.50	0.999
CD5789 0.0025% - Daivobet®	184.08 - 72.00	112.1	<.001
CD5789 0.0025% - Zorac® 0.05%	184.08 - 152.1	31.95	<.001
CD5789 0.005% - CD5789 0.01%	175.50 - 179.4	-3.97	0.993
CD5789 0.005% - CD5789 VEHICLE	175.50 - 186.5	-11.1	0.614
CD5789 0.005% - Daivobet®	175.50 - 72.00	103.5	<.001
CD5789 0.005% - Zorac® 0.05%	175.50 - 152.1	23.38	0.014
CD5789 0.01% - CD5789 VEHICLE	179.47 - 186.5	-7.11	0.913
CD5789 0.01% - Daivobet®	179.47 - 72.00	107.5	<.001
CD5789 0.01% - Zorac® 0.05%	179.47 - 152.1	27.34	0.002
CD5789 VEHICLE - Daivobet®	186.58 - 72.00	114.6	<.001
CD5789 VEHICLE - Zorac® 0.05%	186.58 - 152.1	34.45	<.001
Daivobet® - Zorac® 0.05%	72.00 - 152.12	-80.1	<.001

Secondary efficacy variables

- Change from Baseline in TSS:

The mean percent change from Baseline with vehicle gel was -24.4%. The largest changes from Baseline in TSS were with Daivobet® (-86.5%) and Zorac® (-40.9%). CD5789 0.01%, CD5789 0.005% and CD5789 0.0025% had similar changes from Baseline (-30.6%, -29.9% and -25.2% respectively).

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

None of the three CD5789 concentrations were statistically significantly different from the CD5789 vehicle in any clinical score, nor were any of the CD5789 concentrations significantly different from each other. Each clinical score improved with Daivobet® compared to all CD5789 concentrations and the CD5789 vehicle ($p< 0.001$).

Zorac® was found to be statistically superior to the vehicle ($p<0.05$) and also statistically superior to all CD5789 concentrations for both scaling and plaque elevation ($p<0.033$).

- Success rate based on clearing score at Day 29:

	The number of subjects with a target lesion considered to be a success was 2 (6.3%) or 3 (9.4%) for the three CD5789 concentrations compared to 5 subjects (15.6%) for the vehicle. The observed success rate was the highest for Daivobet® (96.9%) and was 28.1% for Zorac®.
21. Safety outcomes	**Adverse events:** **Table 2 Summary of adverse events** In the safety population (n=32), 12 subjects (37.5%) experienced treatment-related AEs, all in the system order class (SOC) Skin and Subcutaneous Disorders. Pruritus was the most common treatment-related AE. All AEs were of mild or moderate severity. There were no withdrawals or discontinuations of treatment due to AEs. No serious adverse events (SAEs) or deaths occurred in this study. Zorac® was the safety comparator in this study. The overall incidence of AEs was similar between all concentrations of CD5789 and Zorac®. The most common AE, pruritus occurred with similar frequency across treatments, whereas skin irritation was much more common with the highest concentration of CD5789 0.01% (n=7) compared to Zorac® (n=2). The overall distribution of treatment-related AEs between treatments was not noteworthy. However skin burning and skin discomfort occurred with CD5789 0.0025% (n=1 [3.1%] each AE) and CD5789 0.01% (n=1 [3.1%] each AE) and not at all with Zorac®. **Local cutaneous Tolerance:** All treatments were well tolerated. Slight irritation was reported as the worst tolerance score for 5 subjects with Zorac® and only 3 subjects across the range of CD5789 concentrations. Moderate irritation however was not reported at all with Zorac® but was the worst reported score for 3 subjects with CD5789 (1 subject each with CD5789 0.0025% and CD5789 0.01% and 1 subject had moderate irritation with both CD5789 0.01% and vehicle). **General physical examination and vital signs;** No clinically significant changes in weight, vital signs or physical examination were observed. In conclusion, the safety assessment raised no cause for concern and all concentrations of CD5789 were well tolerated.
22. Summary (conclusion)	This was an exploratory, multi-center, randomized, controlled, investigator blinded, intra individual study to evaluate the efficacy and tolerance of 4 weeks of treatment with CD5789 gel (0.0025%, 0.005%, 0.01%) in subjects with Psoriasis vulgaris. The primary efficacy variable, the AUC from Day 1 to Day 29 of the TSS did not improve with any concentration of CD5789 compared to vehicle. Pairwise comparisons based on Tukey Kramer test showed that mini-zones treated with Daivobet® had significantly improved scores than each other treatment. Zorac® was superior to CD5789 and its vehicle. Daivobet® also had significantly improved scores compared to CD5789 for each individual clinical score; erythema, scaling and plaque elevation. Zorac® had

	CD5789 0.0025% (N=32)	CD5789 0.005% (N=32)	CD5789 0.01% (N=32)	CD5789 VEHICLE (N=32)	Daivobet® (N=32)	Zorac® 0.05% (N=32)	TOTAL (N=32)
All AEs	26 (81.3%)	23 (71.9%)	27 (84.4%)	23 (71.9%)	22 (68.8%)	24 (75.0%)	28 (87.5%)
Related AEs	7 (21.9%)	3 (9.4%)	5 (15.6%)	4 (12.5%)	3 (9.4%)	4 (12.5%)	12 (37.5%)
All dermatologic AEs	16 (50.0%)	15 (46.9%)	18 (56.3%)	11 (34.4%)	9 (28.1%)	15 (46.9%)	25 (78.1%)
Related dermatologic AEs	7 (21.9%)	3 (9.4%)	5 (15.6%)	4 (12.5%)	3 (9.4%)	4 (12.5%)	12 (37.5%)

	significantly improved scores compared to CD5789 for scaling and plaque elevation but not erythema. The results of the safety assessments did not raise any cause for concern. No SAEs or deaths occurred in this study. There were no withdrawals or discontinuations of treatment due to AEs. The overall incidence of AEs was similar between all concentrations of CD5789 and Zorac® (the safety comparator). In the safety population (n=32), 12 subjects (37.5%) experienced treatment-related AEs, all in the SOC Skin and Subcutaneous Tissue Disorders. The overall distribution of treatment related AEs between treatments was not noteworthy. Pruritus was the most common treatment related AE and occurred with similar frequency across treatments, whereas skin irritation was more common with the highest concentration of CD5789 0.01% (n=7) compared to Zorac® (n=2). However skin burning and skin discomfort occurred in 1 subject each with CD5789 0.0025% and CD5789 0.01%, and no subjects with Zorac®. All treatments were well tolerated with only 3 subjects (9.4%) reporting moderate irritation as their worst tolerance score (n=1 subject each with CD5789 0.0025% and CD5789 0.01% and n=1 subject had moderate irritation with both CD5789 0.01% and vehicle). In conclusion, treatment with topical CD5789 gel over 4 weeks did not demonstrate superior efficacy to its vehicle or to the comparators Daivobet® and Zorac® in subjects with psoriasis. No clear difference was observed in terms of AE reporting and local tolerance between treatment groups.

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	Exploratory study to evaluate the efficacy and safety of CD5789 in subjects with acne, RD.03.SRE40076E
6. Clinical study phase	Phase 2a
7. Clinical study period	Date of first subject screened: 17Mar2009 Date of last subject completed:03Dec2009
8. Countries where clinical study was conducted	France
9. Number of subjects	Approximately 70 randomized subjects.
10. Aim and secondary	Efficacy Objective:

<table>
<tr><td>purposes of clinical study</td><td>- Evaluation of efficacy on acne lesions
Safety Objectives:
- Evaluation of the local tolerance of the study product.
- Evaluation of the systemic safety by adverse event reporting, physical examination, vital signs and laboratory safety tests follow-up.</td></tr>
<tr><td>11. Clinical study design</td><td>Multi-center study, controlled, randomized, investigator-blinded, intra-individual comparison (right versus left).</td></tr>
<tr><td>12. Main inclusion criteria</td><td>Key inclusion criteria
- Male or female subjects aged from 18 to 35 years;
- Subject had a medical diagnosis of acne vulgaris on the face;
- Subjects had, on the face, at least 15 inflammatory lesions and 25 non-inflammatory lesions but no more than 2 nodules;
- Subjects had a severity grade 2 through 5 according to the Leeds Revised Acne Grading System.</td></tr>
<tr><td>13. Investigational medicinal product, method of administration, strength</td><td>CD5789, gel, topical administration, strength: 0.01% and 0.005%</td></tr>
<tr><td>14. Reference medicinal product, method of administration, strength</td><td>- Comparator: Epiduo®, gel, topical administration, strength: fixed combination Adapalene 0.1% and Benzoyl peroxide 2.5%
- Vehicle of CD5789, gel, topical administration, strength: Not Applicable</td></tr>
<tr><td>15. Concomitant therapy</td><td>14.2.1.8 Table 9: Concomitant therapies by ATC code
<table>
<tr><th></th><th colspan="2">CD5789 0.01%/Vehicle (N= 25)</th><th colspan="2">CD5789 0.005%/Vehicle (N= 25)</th><th colspan="2">Epiduo/Vehicle (N= 26)</th></tr>
<tr><th></th><th>n therapies</th><th>Subject</th><th>n therapies</th><th>Subject</th><th>n therapies</th><th>Subject</th></tr>
<tr><td>Subjects reporting at least one concomitant therapy</td><td>47</td><td>17(68.0%)</td><td>40</td><td>16(64.0%)</td><td>55</td><td>20(76.9%)</td></tr>
<tr><td>ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES</td><td>0</td><td></td><td>0</td><td></td><td>1</td><td>1(3.8%)</td></tr>
<tr><td>ANALGESICS AND ANESTHETICS</td><td>1</td><td>1(4.0%)</td><td>0</td><td></td><td>0</td><td></td></tr>
<tr><td>ANESTHETICS, LOCAL</td><td>0</td><td></td><td>0</td><td></td><td>1</td><td>1(3.8%)</td></tr>
<tr><td>ANILIDES</td><td>8</td><td>6(24.0%)</td><td>11</td><td>9(36.0%)</td><td>15</td><td>12(46.2%)</td></tr>
<tr><td>ANTIANDROGENS AND ESTROGENS</td><td>1</td><td>1(4.0%)</td><td>0</td><td></td><td>0</td><td></td></tr>
<tr><td>ANTIBIOTICS</td><td>1</td><td>1(4.0%)</td><td>0</td><td></td><td>0</td><td></td></tr>
<tr><td>ANTIINFECT. AND ANTISEPT. FOR LOCAL ORAL TREAT</td><td>0</td><td></td><td>1</td><td>1(4.0%)</td><td>0</td><td></td></tr>
<tr><td>ANTIINFL. PREP., NON-STEROIDS FOR TOPICAL USE</td><td>0</td><td></td><td>0</td><td></td><td>1</td><td>1(3.8%)</td></tr>
<tr><td>ANTISEPTICS</td><td>2</td><td>2(8.0%)</td><td>1</td><td>1(4.0%)</td><td>3</td><td>2(7.7%)</td></tr>
<tr><td>BENZODIAZEPINE DERIVATIVES</td><td>0</td><td></td><td>1</td><td>1(4.0%)</td><td>1</td><td>1(3.8%)</td></tr>
</table>
The numbers in the columns cannot be added because a given subject could report more than one previous therapy.</td></tr>
<tr><td>16. Efficacy evaluation criteria</td><td>Efficacy measurements
- Inflammatory lesions count (papules, pustules and nodules);
- Non inflammatory lesions count (whiteheads and blackheads);
- Total lesions count (including inflammatory and non inflammatory lesions);
- Efficacy preference at the end of treatment by the Investigator and by the Subject
Efficacy criteria
- Primary efficacy criteria:</td></tr>
</table>

	○ Total acne lesion count and percent reduction at end of treatment (D27) evaluated clinically. - Secondary efficacy criteria ○ Clinical inflammatory, non-inflammatory and total lesions count and percent reduction at each visit; ○ Efficacy preference at the end of treatment by Investigator and Subject. - Exploratory criteria ○ Photographic evaluation: ▪ Inflammatory lesions count at each visit; ▪ Inflammatory lesions reduction at end of treatment; ▪ Severity measurement at each visit; ▪ Severity measurement reduction at end of treatment; ○ Evaluation of treatment on Propionibacterium acnes by UVA reflectance photographs analysis.
17. Safety evaluation criteria	- **Adverse Events** Adverse events recording at each visit after the screening visit. - **Local Tolerance** Clinical irritation was assessed, on each treated area, every day from Day 2 to Day 27/End of treatment visit and Day 36/Follow-up visit or before in case of early termination, using a 5-point skin reaction scale. - **General Physical examination** Physical examination and Vital signs were conducted at Screening, Day 1, Day 27/End of treatment visit and Day 36/Follow-up visit or before in case of early termination. - **Laboratory Safety Tests** Laboratory tests were conducted at Screening and Day 27/End of treatment visit or before in case of early termination. - **Systemic exposure measurement** Blood sampling was performed one and 16 hours after the last treatment application.
18. Statistical methods	**Principal statistical methods** Clinical lesion counts (inflammatory, non-inflammatory and total) and percent reductions in lesion counts were descriptively summarized by visit and by treatment received. The bilateral differences between treatments were summarized and analyzed by visit using a Wilcoxon rank signed test. Investigator and subject's preferences were analyzed using a sign test. All tests were two-sided and the 5% probability level was chosen to declare significance. Local tolerance, general physical examination, vital signs and laboratory parameters were summarized by descriptive statistics.
19. Demographic indicators of the study population (gender, age, race, etc.)	Ninety-three (93) subjects were screened at 5 study sites and 3 sites randomized 76 subjects. Among the 76 randomized subjects (ITT population), 2 in CD5789 0.005% Gel/Vehicle group withdrew prematurely due to treatment unrelated adverse events. The PP population comprised 66 subjects, 21 in the CD5789 0.01% Gel/Vehicle as well as in the CD5789 0.005% Gel/Vehicle and 24 subjects in the Epiduo®/Vehicle. The safety population comprised all 76 randomized subjects. A total 40 (5.26%) female and 36 (47.4%) male subjects were randomized into the study. Seventy-five (75, 98.7%) Caucasians and one Hispanic subject were randomized. The mean age was 22.3 years, with a min/max of 18/35 years. The majority (45, 59.2%) had Phototype III. There was no difference for any lesion type between the active and vehicle-controlled treatment side, in any of the groups and between treatment groups. Detailed baseline disease characteristics are presented in Table 1 below.

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

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

20. Efficacy outcomes

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

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

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

Table 2 **Clinical Evaluation: Total Lesions Count at Day 27**

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

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

A - V is Active – Vehicle

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

Table 3 Clinical evaluation: Total lesion percent reduction from Baseline

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

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

A - V is Active – Vehicle

Secondary efficacy criteria:

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

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

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

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

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

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

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

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

Results at Endpoint/ITT LOCF confirmed the outcome.

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

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

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

Results at Endpoint/ITT LOCF confirmed the outcome.

- Efficacy preference at Day27

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

21. Safety outcomes	Overall, 18 (72%) subjects in the CD5789 0.01% Gel/Vehicle group, 12 (48%) in the CD5789 0.005% Gel/vehicle group and 6 (23%) in the Epiduo®/Vehicle group had their dosage regimen modified due to skin irritation. A total of 18 (72%) subjects in the CD5789 0.01% Gel/Vehicle group experienced 28 adverse events. Thirteen (13) of these adverse events in 10 subjects were related to the active treatment, with 12 events of dermatologic nature and considered as related. Two (2) of the related adverse events were severe. There was no serious adverse event and no adverse event leading to subject discontinuation in this group.

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

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

Adverse events are summarized only for events occurred after the first use of study product.

If an AE is not zone specific it will be summarized in each study treatment.

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

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

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

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

Adverse events are summarized only for events occurred after the first use of study product.

If an AE is not zone specific it will be summarized in each study treatment.

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

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

Table 6 Overview of adverse events: Epiduo®/Vehicle

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

Adverse events are summarized only for events occurred after the first use of study product.

If an AE is not zone specific it will be summarized in each study treatment.

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

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

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

	Seven (7, 26.9%) of subjects reported 10 adverse events with Epiduo®. Two subjects reported burning skin sensation or skin irritation and one subject reported erythema, irritation of the eyelid or periorbital edema. There were no deaths reported during the study. No subject discontinued the study due to treatment related adverse events. One subject in the CD5789 0.005%/Vehicle group reported one serious adverse event, not related to the treatment (idopathic thrombocytopenic purpura). Two subjects treated with CD5789 0.01% Gel reported severe adverse events related to the treatment (scab and burning sensation of the skin). At Day27 no notable changes from Screening in vital signs and physical findings in any of the treatment groups was reported. Except for one subject reporting a not related serious adverse event leading to discontinuation of the study, no notable changes at Day27 from Screening in routine laboratory parameters in any of the treatment groups was reported. Systemic exposure to CD5789 in all tested plasma samples the concentration was below the limit of quantification. As expected, all subjects treated with CD5789 reported skin irritation. Worst skin irritation score over time with CD5789 0.01% Gel was severe in 6 (24%) of the subjects compared to 3 (12%) subjects treated with CD5789 0.005% Gel and one with Epiduo®. The incidence of at least moderate irritation showed that a maximum was reached at the end of each 5-day treatment period. After 2 days of no treatment, scores had decreased but re-increased at the end of the following treatment period. Overall, the number of severe cases of skin irritation at the end of each treatment period was low and did not exceed 3 subjects (Day12 with CD5789 0.01% Gel).
22. Summary (conclusion)	The present study demonstrated that CD5789 Gel at doses of 0.01% and 0.005% applied for 20 days was statistically significant superior to its vehicle in decreasing the total, inflammatory and non-inflammatory lesion count in subjects with acne vulgaris and was relatively well tolerated. The local safety profile characterized by irritation of the skin with CD5789 Gel at 0.01% and 0.005% is in line with that of currently available topical RAR agonists. The systemic safety of CD5789 of up to 0.01% was good, the level of exposure was below the limit of quantification in all analyzed samples.

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	Pilot study to explore efficacy and safety of different dose regimens of CD5789 in subjects with acne vulgaris, RD.03.SRE.40126
6. Clinical study phase	Phase 2a study
7. Clinical study period	Date of first screened: 12 November 2010 Date of last subject completed:24 June 2011
8. Countries where clinical study was conducted	France, Hungary, Germany, Belgium
9. Number of subjects	Approximately 150 subjects were to be screened in order to randomize 120 subjects (20 subjects per arm).

<table>
<tr><td>10. Aim and secondary purposes of clinical study</td><td>Efficacy objectives were:
To evaluate the efficacy of CD5789 on Inflammatory, Non-inflammatory and Total acne lesions counts at the end of treatment and at each visit per half face;
To evaluate the efficacy of CD5789 on the Investigator's Global Assessment, success being defined as a 2 points reduction from baseline per half-face;
To evaluate the efficacy preference by subjects and investigator at the end of treatment.
Safety objectives were:
Adverse Events (AEs) reporting: All adverse events occurring during the study were recorded and classified per MedDRA terms;
Local tolerability assessment: clinical evaluation was made, using a 5-points skin reaction scale, every day from Day 2 to Day 36/ Follow-up visit. Scores for specific signs and symptoms of local tolerability will also be recorded (Erythema, Scaling, Dryness, and Stinging/Burning) from D1 to D36 ;
Clinical laboratory tests evaluation, performed at Screening and Day 29;
Vital signs measurement, at Day 1, Day 29 and Day 36
Other objectives:
Photos of the face to document the efficacy using standardized methods.</td></tr>
<tr><td>11. Clinical study design</td><td>This pilot study was a multicenter, randomized, blinded, vehicle-controlled study using intra individual comparison (right versus left) in 6 parallel groups:<table>
<tr><td>Group 1</td><td>CD5789 100µg/g gel versus vehicle gel</td><td>Leave on 5 times per week</td></tr>
<tr><td>Group 2</td><td>CD5789 100µg/g gel versus vehicle gel</td><td>Leave on twice a week</td></tr>
<tr><td>Group 3</td><td>CD5789 100µg/g gel versus vehicle gel</td><td>Short contact 5 minutes 5 times/week</td></tr>
<tr><td>Group 4</td><td>CD5789 100µg/g gel versus vehicle gel</td><td>Short contact 30 minutes 5 times/week</td></tr>
<tr><td>Group 5</td><td>Tazarotene 0.1% gel versus vehicle gel</td><td>Leave on 5 times/week</td></tr>
<tr><td>Group 6</td><td>Tazarotene 0.1% gel versus vehicle gel</td><td>Short contact 5 minutes 5 times/week</td></tr>
</table></td></tr>
<tr><td>12. Main inclusion criteria</td><td>Key inclusion criteria
The subject is a male or female, 18 to 35 years old;
The subject has a medical diagnosis of moderate to severe facial acne vulgaris;
The subject has, on the face, at least 20 inflammatory lesions and 30 non-inflammatory lesions;
The subject has a severity grade of 3 or 4 on the IGA scale on either side of the face;</td></tr>
<tr><td>13. Investigational medicinal product, method of administration , strength</td><td>CD5789, gel, topical administration, strength: 100 µg/g</td></tr>
<tr><td>14. Reference medicinal product, method of administration , strength</td><td>Comparator product: Tazarotene, gel, topical administration, strength: 0,1%
Vehicle product: vehicle of CD5789, gel, topical administration, strength: Not Applicable</td></tr>
</table>

15. Concomitant therapy	Not Applicable
16. Efficacy evaluation criteria	Primary efficacy criteria: - Total acne lesion count and percent reduction of total lesions at the end of treatment Secondary efficacy criteria - Inflammatory, Non-Inflammatory and Total lesions count and their percent reduction at each visit per half face - IGA dichotomized as success and failure at end of treatment (success is defined as a 2 point reduction) per half face - Efficacy preference at the end of treatment rated by the Investigator and subject
17. Safety evaluation criteria	Adverse events were to be reported throughout the study. Systemic safety: - Vital signs (blood pressure, pulse rate) - Physical examination at Baseline and end of treatment - Routine laboratory parameters (hematology, blood chemistry) Cutaneous safety: - Local tolerability assessments (irritation on the face on a 5-point scale, as well as erythema, scaling, dryness, and stinging/burning sensation separately on the face on a 4-point scale (0 = None to 3 = Severe))
18. Statistical methods	Subject disposition, demographics, baseline characteristics, previous therapies, concomitant therapies and treatment duration were to be summarized by descriptive statistics. Lesion counts (inflammatory, non-inflammatory and total) and percent reductions in lesions counts were to be descriptively summarized by visit and by treatment received. The bilateral differences between treatments were to be summarized and analyzed by visit using a Wilcoxon rank signed test. Investigator and subject's preferences were to be analyzed using a sign test. The effect of center on the difference between the percent reduction from D01 for Active and for Vehicle was to be tested by a CMH test stratified on treatment group (CMH2, score=Ridit). Adverse Events were to be tabulated by group and study treatment and in frequency tables by System Organ Class (SOC) and Preferred Term (PT) based on the MedDRA dictionary. Additional summary tables were to be provided for Adverse Events that were considered serious (SAEs), related to the study drug, Adverse Events of special interest, and Adverse Events leading to discontinuation. All AE summary tables were to be based on the number of subjects who experienced AE(s). For a given AE, a subject was to be counted once even if he or she has experienced multiple episodes for that particular AE. The analysis of adverse events was to be based on treatment emergent signs and symptoms (TESS). Due to the intra-individual study design and whenever possible (known from CRF) AE were to be imputed to the treated area, when not possible then the AE was to be imputed to both treated sides. Global tolerance in term of frequency distribution and the worst score (from Day 2 to Day 26) over time of each individual's signs and global tolerance was to be calculated. General physical examination, vital signs and laboratory parameters were to be

	summarized by descriptive statistics. Shift tables for the laboratory data were to be tabulated for each laboratory parameter.
19. Demographic indicators of the study population (gender, age, race, etc.)	Most of the randomized subjects were Caucasian (97.4%) and 56.4% were female. The mean age was between 21.5 to 23.6 years (range 18-35) and 75.7% had no sensitive or dry skin at screening. Demographic parameters were evenly distributed across groups. **Table 1 Demographic**

			Randomized					
		Screened	CD5789 100 µg/g /Vehicle Leave on 5x/week	CD5789 100 µg/g /Vehicle Leave on 2x/week	Tazarotene 0.1% gel /Vehicle gel Leave on 5x/week	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
Gender	N	144	19	20	18	22	18	20
	Male	60 (41.7%)	6 (31.6%)	8 (40.0%)	7 (38.9%)	11 (50.0%)	8 (44.4%)	11 (55.0%)
	Female	84 (58.3%)	13 (68.4%)	12 (60.0%)	11 (61.1%)	11 (50.0%)	10 (55.6%)	9 (45.0%)
Race	N	144	19	20	18	22	18	20
	Caucasian	139 (96.5%)	17 (89.5%)	20 (100.0%)	18 (100.0%)	21 (95.5%)	18 (100.0%)	20 (100.0%)
	Black	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)
	Asian	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Hispanic	3 (2.1%)	2 (10.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Age (years)	N	144	19	20	18	22	18	20
	Mean	22.8	23.6	23.4	21.8	21.7	22.6	21.5
	SD	4.5	4.8	4.8	4.7	4.3	3.3	3.9
	Median	22.0	24.0	22.0	20.0	19.5	22.5	20.0
	(Min,Max)	(18,35)	(18,35)	(18,31)	(18,35)	(18,32)	(18,28)	(18,32)
Sensitive or dry skin	N	140	19	20	18	22	18	20
	No	106 (75.7%)	13 (68.4%)	15 (75.0%)	11 (61.1%)	17 (77.3%)	14 (77.8%)	15 (75.0%)
	Yes	34 (24.3%)	6 (31.6%)	5 (25.0%)	7 (38.9%)	5 (22.7%)	4 (22.2%)	5 (25.0%)

20. Efficacy outcomes	**Primary efficacy criterion:** - Leave on population For the CD5789 100 µg/g / vehicle Leave on 5x/week group, at Day 29 (PP) and at Endpoint (ITT), there were statistically less total lesions on the active-treated side than on the vehicle-treated side (-11.5 lesions with SD of 10.9 – effect size of 1.06). The clinical expectation was an effect size of 0.8 for all groups. Differences between active and vehicle were also statistically significant for percent reduction in total lesions count (median = 26.3%). For the CD5789 100 µg/g / vehicle Leave on 2x/week group, at Day 29 (PP population) and at Endpoint (ITT population), there were statistically less total lesions on the active-treated side than on the vehicle-treated side (for ITT population, -5.2 lesions with SD of 8.0 – effect size of 0.65). Differences between active and vehicle were not statistically significant for percent reduction in total lesion count at Endpoint (ITT population, median= 10.6%) and not significant at Day 29 (PP population, median = 11.8%). For the leave on reference group Tazarotene 0.1% gel / vehicle Leave on 5x/week, at Day 29 (PP population) and at Endpoint (ITT population), there were less total lesions on the active-treated side than on the vehicle-treated side but it is not statistically significant (-2.2 lesions with SD of 10.3 – effect size of 0.21). For percent reduction in total lesion, it was also not significant (median=14.3%). Details are provided in Table 3 and Table 4.

Table 3 Total lesion count (Leave on)

		CD5789 100 µg/g /Vehicle Leave on 5x/week			CD5789 100 µg/g /Vehicle Leave on 2x/week			Tazarotene 0.1% gel /Vehicle gel Leave on 5x/week		
		Active	Vehicle	A - V	Active	Vehicle	A - V	Active	Vehicle	A - V
Day 01 (ITT)	N	19	19	19	20	20	20	18	18	18
	Mean	39.5	42.5	-2.9	39.5	41.2	-1.8	41.7	39.2	2.5
	SD	14.2	19.7	8.3	10.2	11.9	7.3	11.1	9.9	5.6
	Median	36.0	35.0	-2.0	38.5	39.0	-0.5	38.0	37.5	1.5
	(Min, Max)	(26,86)	(26,107)	(-21,12)	(25,70)	(26,66)	(-21,8)	(29,63)	(27,59)	(-8,11)
	P-value*			0.108			0.555			0.101
Endpoint (ITT)	N	19	19	19	20	20	20	18	18	18
	Mean	15.8	27.4	-11.5	26.9	32.1	-5.2	24.5	26.7	-2.2
	SD	7.8	14.4	10.9	13.9	16.6	8.0	11.5	11.8	10.3
	Median	12.0	23.0	-10.0	23.5	30.5	-5.0	21.0	25.0	-4.5
	(Min, Max)	(7,31)	(6,67)	(-39,5)	(5,53)	(7,67)	(-19,12)	(10,45)	(10,59)	(-18,15)
	P-value*			**<0.001**			**0.010**			0.423
Day 01 (PP)	N	19	19	19	18	18	18	18	18	18
	Mean	39.5	42.5	-2.9	39.3	40.3	-1.0	41.7	39.2	2.5
	SD	14.2	19.7	8.3	10.5	11.0	6.7	11.1	9.9	5.6
	Median	36.0	35.0	-2.0	38.5	39.0	-0.5	38.0	37.5	1.5
	(Min, Max)	(26,86)	(26,107)	(-21,12)	(25,70)	(26,66)	(-21,8)	(29,63)	(27,59)	(-8,11)
	P-value*			0.108			0.824			0.101
Day 29 (PP)	N	19	19	19	18	18	18	18	18	18
	Mean	15.8	27.4	-11.5	25.1	30.4	-5.3	24.5	26.7	-2.2
	SD	7.8	14.4	10.9	13.0	16.1	8.4	11.5	11.8	10.3
	Median	12.0	23.0	-10.0	22.5	28.5	-5.0	21.0	25.0	-4.5
	(Min, Max)	(7,31)	(6,67)	(-39,5)	(5,50)	(7,67)	(-19,12)	(10,45)	(10,59)	(-18,15)
	P-value*			**<0.001**			**0.014**			0.423

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

Table 4 Percent reduction in total lesion counts (Leave on)

		CD5789 100 µg/g /Vehicle Leave on 5x/week			CD5789 100 µg/g /Vehicle Leave on 2x/week			Tazarotene 0.1% gel /Vehicle gel Leave on 5x/week		
		Active	Vehicle	A - V	Active	Vehicle	A - V	Active	Vehicle	A - V
Endpoint (ITT)	N	19	19	19	20	20	20	18	18	18
	Mean	58.7	32.4	26.2	33.5	23.0	10.5	41.5	32.3	9.2
	SD	18.2	29.0	23.4	29.3	33.6	27.0	24.0	23.2	20.9
	Median	57.1	41.9	26.3	39.1	17.8	10.6	45.8	29.4	14.3
	(Min,Max)	(22.5,86.0)	(-129,81.3)	(-26.5,63.6)	(-19.0,80.0)	(-63.4,74.1)	(-37.5,64.4)	(-216,74.4)	(-113,66.7)	(-327,45.2)
	P-value*			**<0.001**			0.169			0.090
Day 29 (PP)	N	19	19	19	18	18	18	18	18	18
	Mean	58.7	32.4	26.2	37.8	25.1	12.7	41.5	32.3	9.2
	SD	18.2	29.0	23.4	27.5	34.9	27.5	24.0	23.2	20.9
	Median	57.1	41.9	26.3	42.3	25.2	11.8	45.8	29.4	14.3
	(Min,Max)	(22.5,86.0)	(-129,81.3)	(-26.5,63.6)	(-19.0,80.0)	(-63.4,74.1)	(-37.5,64.4)	(-216,74.4)	(-113,66.7)	(-327,45.2)
	P-value*			**<0.001**			0.099			0.090

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

- Short contact population

For the CD5789 100 µg/g /vehicle short contact 5 minutes 5x/week group, at Day 29 (PP population) and at Endpoint (ITT population), there were significantly less total lesions on the active-treated side than on the vehicle-treated side (-9.3 lesions with SD of 7.4 – effect size of 1.26). The difference between active and vehicle was also significant in both populations for the percent reduction (median= 21.4%).

For the CD5789 100 µg/g / vehicle short contact 30 minutes 5x/week group, at Day 29 (PP population) and at Endpoint (ITT population), there were significantly less total

lesions on the active-treated side than on the vehicle-treated side (for ITT population, -10.8 lesions with SD of 12.2 – effect size of 0.89). Difference between active and vehicle was also significant in both populations for percent reduction in total lesion count (median= 25.4% for ITT population).

For the short contact reference group Tazarotene 0.1% gel / vehicle short contact 5 minutes 5x/week, at Day 29 (PP) and at Endpoint (ITT population), there were no difference between active-treated side and vehicle-treated side in total lesions and in percent reduction (for the ITT population, -0.9 lesions with SD of 10.4 – effect size of 0.09).

Details are provided in Table 5 and Table 6.

Table 5 Total lesion count (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		
Total lesion count		Active	Vehicle	A - V	Active	Vehicle	A - V	Active	Vehicle	A - V
Day 01 (ITT)	N	22	22	22	18	18	18	20	20	20
	Mean	38.9	39.5	-0.6	40.3	39.9	0.4	40.9	38.1	2.8
	SD	12.1	18.4	10.7	10.1	9.4	6.6	14.4	9.6	7.9
	Median	33.5	35.0	1.5	36.0	37.5	-0.5	38.0	34.0	2.0
	(Min,Max)	(28,76)	(25,93)	(-39,12)	(28,59)	(27,59)	(-12,13)	(27,84)	(26,58)	(-7,28)
	P-value*			0.741			0.635			0.161
Endpoint (ITT)	N	22	22	22	18	18	18	20	20	20
	Mean	17.8	27.1	-9.3	20.4	31.2	-10.8	25.5	26.4	-0.9
	SD	10.8	13.9	7.4	8.0	15.2	12.2	16.6	12.8	10.4
	Median	14.0	21.5	-9.0	18.0	26.0	-7.0	19.0	24.0	-1.0
	(Min,Max)	(7,44)	(9,65)	(-25,6)	(6,34)	(16,70)	(-42,3)	(8,66)	(7,65)	(-22,24)
	P-value*			**<0.001**			**<0.001**			0.627
Day 01 (PP)	N	22	22	22	17	17	17	18	18	18
	Mean	38.9	39.5	-0.6	40.6	40.1	0.5	38.9	37.6	1.4
	SD	12.1	18.4	10.7	10.3	9.6	6.8	10.7	8.9	5.5
	Median	33.5	35.0	1.5	37.0	38.0	0.0	38.0	34.0	0.0
	(Min,Max)	(28,76)	(25,93)	(-39,12)	(28,59)	(27,59)	(-12,13)	(27,57)	(26,58)	(-7,11)
	P-value*			0.741			0.588			0.340
Day 29 (PP)	N	22	22	22	17	17	17	18	18	18
	Mean	17.8	27.1	-9.3	20.1	31.6	-11.6	22.6	23.7	-1.1
	SD	10.8	13.9	7.4	8.0	15.5	12.1	14.0	9.2	11.0
	Median	14.0	21.5	-9.0	18.0	27.0	-7.0	17.0	22.5	-3.5
	(Min,Max)	(7,44)	(9,65)	(-25,6)	(6,34)	(16,70)	(-42,2)	(8,57)	(7,42)	(-22,24)
	P-value*			**<0.001**			**<0.001**			0.587

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

A - V is Active – Vehicle