20. Efficacy outcomes	Not applicable
21. Safety outcomes	A total of 108 AEs were reported during the study in 36.7% (88) of subjects. The most common AEs were in the Nervous System Disorders System Organ Class (SOC). Of the 108 reported AEs, 18 (in 16 subjects) were assessed as related to study drugs by the Investigator: 17 were cutaneous in nature (skin irritation and skin burning sensation) and 1 was a headache. Most of the related AEs occurred in subjects in the CD5789 100 µg/g + BPO 5% group (7 AEs in 6 subjects) and the remaining 11 related AEs occurred in 10 subjects: 3 subjects in the CD5789 50 µg/g + BPO 2.5% group (3 AEs), 2 subjects in the Zorac 0.1% and Differin 0.1% + BPO 2.5% groups (2 AEs each) and in 1 subject in the CD5789 25 µg/g + BPO 2.5%, CD5789 25 µg/g + BPO 5% and Epiduo groups (1, 1, and 2 AEs, respectively). No related AEs occurred in the CD5789 50 µg/g + BPO 5% treatment group. Of the 16 subjects with related AEs, a total of 11 subjects (4.6%) were reported to have related AESIs (11) of skin irritation. There were 2 types of AESI skin irritation reported: - Six (6) subjects presented with skin irritation typical of irritative reactions expected with topical retinoids and 4 out of these 6 subjects were part of the treatment group CD5789 100 µg/g + BPO 5%. - Five (5) subjects presented with immediate skin type irritancy. Subjects were distributed equally in 5 different treatment groups and the treatment of 4 of these 5 treatment groups was an association of CD 5789 and BPO. These immediate skin type irritancy reactions were not typical of irritative reactions described with retinoids due to the chronology (they started in the first days after application and shortly after the application and they were intermittent and totally reversible in the following hours) and the semiology (the investigator considered that they looked like non immunological urticaria reactions). Overall, 12 subjects (5.0%) experienced 12 AEs that led to discontinuation. All of these AEs were cutaneous and related to the study drug except for 1 case of seborrhoeic dermatitis which occurred in the Epiduo treatment group. Discontinuations due to AEs were due either to typical retinoid-induced skin irritation or immediate skin type irritancy. Typical retinoid-induced skin irritation was more frequently observed in the CD5789 100µg/g + BPO 5% group (4 out of 6 subjects) than in the other treatment groups. Five (5) other study discontinuations were due to immediate skin type irritancy and distributed in different groups 1 (3.3%) subject in CD5789 100 µg/g + BPO 5% group, CD5789 25 µg/g + BPO 5%, CD5789 50 µg/g + BPO 2.5%, Differin 0.1% + BPO 2.5% and CD5789 25 µg/g + BPO 2.5%, and none of the subjects in the Zorac, Epiduo and CD5789 50 µg/g + BPO 5% groups. No deaths or SAEs occurred during the study.
22. Summary (conclusion)	In conclusion, CD5789 100 µg/g + BPO 5% and Zorac 0.1% were the most irritating products. Epiduo was the best tolerated study drug. All the other study drugs CD5789 (25 µg/g or 50 µg/g) + BPO (2.5% or 5%) presented a tolerance profile between Epiduo and Zorac 0.1%.

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-18231 - Pharmacokinetics study of CD5789 50 and 100 µg/g cream in Japanese and non-Japanese healthy subjects under maximal use conditions
6. Clinical study phase	Phase 1 human pharmacology study
7. Clinical study period	Date of first screened: 17 Jan 2013 Date of last subject completed: 16 Apr 2013
8. Countries where clinical study was conducted	United States
9. Number of subjects	A total of 39 subjects (13 in each group) were enrolled in the study.
10. Aim and secondary	- The objective of this study was to assess and compare the systemic exposure of CD5789 after repeated once-daily topical application of CD5789 50 µg/g and 100

purposes of clinical study	µg/g cream in healthy subjects of Japanese and non-Japanese origin for 29 days. - This assessment was done through determination of the pharmacokinetic (PK) parameters in healthy volunteers under maximized conditions of use (subjects treated with 2 g of cream on a 1000 cm2 body surface area corresponding to zones potentially affected by acne lesions: face, shoulders, upper back, and upper chest) (Guidance for Industry: Acne Vulgaris: Developing Drugs for Treatment). - The study also assessed safety and local tolerability of CD5789 50 µg/g and 100 µg/g cream.
11. Clinical study design	This was a single-center, randomized study in 3 parallel groups. Groups 1 and 2 were double-blind and Group 3 was unblinded: - Group 1: CD5789 50 µg/g cream, subjects of Japanese origin - Group 2: CD5789 100 µg/g cream, subjects of Japanese origin - Group 3: CD5789 100 µg/g cream, subjects of non-Japanese origin Japanese origin is defined as all four grandparents were born in Japan. Subjects having 1 to 3 grandparents born in Japan could not be enrolled in the study.
12. Main inclusion criteria	Key inclusion criteria: - Adult male or female healthy subjects aged 18 to 65 years old; - Body weight between 45 and 100 kg at the Screening visit; - Body mass index (BMI) between 18 and 30 kg/m^2 at the Screening visit; - If female of childbearing potential, the subject agreed to use a highly effective double-barrier contraception method for the duration of the study and at least 1 month after the last product application; - If male, the subject agreed to shave the facial treatment area the evening prior to the Day 1, Day 8, Day 15, Day 22, and Day 29/Early Termination visits (when local tolerability was assessed) and agreed to maintain his routine shaving regimen for the duration of the study.
13. Investigational medicinal product, method of administration, strength	CD5789, topical administration, strength: 50 µg/g and 100 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	Adverse events were to be reported throughout the study. Adverse events with an onset date on or after the date of the administration of the first treatment were classified as treatment emergent.

	- Systemic safety
	  ○ Vital signs (blood pressure, pulse rate) at the Screening, Day 1/Baseline, Day 15, and Day 29/Early Termination visits
	  ○ Physical examination at Screening, Baseline, and end of treatment
	  ○ Routine laboratory parameters (hematology, blood chemistry, urinalysis) at the Screening and Day 29/Early Termination visits
	- Cutaneous safety
	  ○ Local tolerability assessments (erythema, scaling, dryness, pruritus, and stinging/burning on the face only) on a 4-point scale (0 = none to 3 = severe) at the Day 1/Baseline, Day 8, Day 15, Day 22, and Day 29/Early Termination visits.

18. Statistical methods	The following variables were summarized by descriptive statistics: - Demographics and baseline characteristics; - PK parameters (if quantifiable data); - Physical examination, vital signs (blood pressure and pulse rate); - Routine laboratory parameters (hematology, blood chemistry, urinalysis); - Cutaneous safety (local tolerability assessments); - Adverse events (AEs). If quantifiable, plasma concentration parameters were to be submitted, after logarithmic transformation (Ln), to an analysis of variance, in order to evaluate time and group factors separately. A statistical analysis was performed separately for each treatment group to investigate the time effect. Another analysis was performed separately for each day to investigate the group effect (dose and ethnicity). For both analyses, the Ln of AUC(0-24hr) and Cmax was submitted to an analysis of variance. The model included time, subject, and group as factors. The residual error variance was used to compute 90% confidence intervals of the pairwise differences between time points (Day 1, Day 15, and Day 29) on the Ln scale. The limits of the intervals were back transformed into an exponential to obtain 90% confidence intervals of the ratios of geometric means between time points, on the original scale.
19. Demographic indicators of the study population (gender, age, race, etc.)	Of the 73 subjects screened, 39 were included in the Full Analysis (pharmacokinetic) and Safety populations. Reasons for screen failure were inclusion/exclusion criteria not met (17 of 34 screen failures) and "other" (17 of 34 screen failures). A summary of demographic data is provided in Table 1. The mean age of subjects was 41.5 years, ranging from 37.2 to 46.4 across treatment groups. The majority of subjects (71.8%) were male. An equal number of Black/African American subjects and white subjects comprised the non-Japanese group, along with 1 Asian subject. Mean BMI was 24.0 kg/m2, ranging from 23.4 to 24.7 kg/m2 across treatment groups.

Table 1 Demographics and baseline characteristics (safety analysis population)

	Japanese			Non-Japanese	Total (N=39)
	CD5789		Subtotal (N=26)	CD5789	
	50 µg/g (N=13)	100 µg/g (N=13)		100 µg/g (N=13)	
Age (years)					
Mean (SD)	41.0 (13.38)	46.4 (12.17)	43.7 (12.83)	37.2 (13.06)	41.5 (13.10)
Median	40.0	50.0	48.0	36.0	40.0
Minimum, maximum	23.0, 63.0	23.0, 62.0	23.0, 63.0	18.0, 58.0	18.0, 63.0
Age group (years), n (%)					
≤40	8 (61.5)	3 (23.1)	11 (42.3)	9 (69.2)	20 (51.3)
>40	5 (38.5)	10 (76.9)	15 (57.7)	4 (30.8)	19 (48.7)
BMI (kg/m^2)					
Mean (SD)	23.8 (2.78)	23.4 (2.19)	23.6 (2.46)	24.7 (3.31)	24.0 (2.78)
Median	23.3	23.1	23.2	25.3.	23.4
Minimum, maximum	20.1, 29.9	19.6, 28.6	19.6, 29.9	19.3, 29.8	19.3, 29.9
Sex, n (%)					
Male	8 (61.5)	8 (61.5)	16 (61.5)	12 (92.3)	28 (71.8)
Female	5 (38.5)	5 (38.5)	10 (38.5)	1 (7.7)	11 (28.2)
Smoker, n (%)					
Yes	0 (0.0)	1 (7.7)	1 (3.8)	0 (0.0)	1 (2.6)
No	13 (100)	12 (84.6)	25 (96.2)	13 (100)	38 (97.4)
Ethnicity, n (%)					
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)	2 (15.4)	2 (5.1)
Not Hispanic or Latino	13 (100)	13 (100)	26 (100)	11 (84.6)	37 (94.9)
Race, n (%)					
Asian	13 (100)	13 (100)	26 (100)	1 (7.7)	27 (69.2)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)	6 (46.2)	6 (15.4)
White	0 (0.0)	0 (0.0)	0 (0.0)	6 (46.2)	6 (15.4)

BMI=body mass index; SD=standard deviation

20. Efficacy outcomes	Not Applicable
21. Safety outcomes	The safety parameters assessed included AEs, local tolerability assessments, physical examinations, vital signs, laboratory tests, and electrocardiograms (ECGs). **- Adverse events** All 39 subjects in the study experienced at least 1 treatment-emergent AE (TEAE) and at least 1 TEAE considered by the investigator to be related to study drug (Table 3). No subject experienced a TEAE considered by the investigator to be severe in intensity, an SAE, an AE of special interest (AESI), or prematurely discontinued study drug due to a TEAE.

Table 3 **Overview of treatment-emergent adverse events (safety analysis population)**

Type of adverse event	Number (%) of subjects			
	Japanese			Non-Japanese
	CD5789		Subtotal (N=26)	CD5789
	50 µg/g (N=13)	100 µg/g (N=13)		100 µg/g (N=13)
Any TEAE	13 (100)	13 (100)	26 (100)	13 (100)
Any related TEAE	13 (100)	13 (100)	26 (100)	13 (100)
Any serious AE	0	0	0	0
Any AESI	0	0	0	0
Any moderate TEAE	6 (46.2)	8 (61.5)	14 (53.8)	7 (53.8)
Any moderate related TEAE	5 (38.5)	8 (61.5)	13 (50.0)	6 (46.2)
Any severe TEAE	0	0	0	0
Any TEAE leading to discontinuation of study drug	0	0	0	0

Treatment-related skin irritation was experienced by all 39 subjects (Table 4). Other common treatment-related TEAEs were isolated cases of pruritus or erythema.

Table 4 **Treatment-emergent adverse events with a reasonable possibility of relationship to treatment (safety analysis population)**

System Organ Class Preferred term	Number (%) of subjects			
	Japanese			Non-Japanese
	CD5789		Subtotal (N=26)	CD5789
	50 µg/g (N=13)	100 µg/g (N=13)		100 µg/g (N=13)
Any related TEAE	13 (100)	13 (100)	26 (100)	13 (100)
Injury, Poisoning and Procedural Complications	0	1 (7.7)	1 (3.8)	0
Scratch	0	1 (7.7)	1 (3.8)	0
Skin and Subcutaneous Tissue Disorders	13 (100)	13 (100)	26 (100)	13 (100)
Erythema	2 (15.4)	1 (7.7)	3 (11.5)	1 (7.7)
Pruritus	2 (15.4)	4 (30.8)	6 (23.1)	0
Skin burning sensation	1 (7.7)	0	1 (3.8)	0
Skin irritation	13 (100)	13 (100)	26 (100)	13 (100)

The TEAE profile of the 2 Japanese treatment groups was generally similar, with the exception that there was a 2-fold greater incidence of treatment-related pruritus at the higher CD5789 dose compared with the lower CD5789 dose and a 2-fold greater incidence of treatment-related erythema at the lower dose compared with the higher dose. In addition, treatment-related TEAEs considered by the investigator to be moderate in severity (mostly skin irritation) were experienced by a greater percentage of subjects in the CD5789 100 µg/g cream group than in the CD5789 50 µg/g cream group.

The TEAE profile of the Japanese CD5789 100 µg/g cream and non-Japanese CD5789 100 µg/g cream subjects was generally similar, with the exception that 4 (30.8%) Japanese subjects experienced treatment-related pruritus compared with no non-Japanese subjects. In addition, treatment-related TEAEs considered by the investigator to be moderate in severity (mostly skin irritation) were experienced by a greater percentage of subjects in the Japanese 100 µg/g cream group than in the non-Japanese 100 µg/g cream group.

- Local tolerability

Local tolerability (erythema, scaling, dryness, pruritus, and stinging/burning on the face) was assessed on a 4-point scale before the study drug application at baseline and Days 8,

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

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD-06-SRE-40187E - Exploratory study to investigate the effect of CD5789 on the physiopathology of acne scarring in scar prone and non scar prone acne patients
6. Clinical study phase	Phase 1
7. Clinical study period	Date of first subject screened: 19 November 2012 Date of last subject completed: 22 July 2013
8. Countries where clinical study was conducted	France
9. Number of subjects	28 subjects were eligible (20 acne subjects and 8 healthy subjects with no history of acne). Out of the 28 subjects, 1 acne subject failed screening due to inclusion/exclusion criteria not met. A total of 27 subjects were included in the intent-to-treat (ITT) and Safety populations. Due to a major protocol deviation, 1 scar prone subject was excluded from the per protocol (PP) population.
10. Aim and secondary purposes of clinical study	Primary objective: to investigate the involvement at the transcriptomic and proteomic levels of markers implicated in signaling pathways of immunity in acne scaring. Secondary objectives: - To evaluate the modulations induced by a new therapeutic agent (CD5789) on the pathway and markers previously selected;

	- To determine the correlation between the sub-types of P. acnes and the development of scars or not.
11. Clinical study design	This was an exploratory, controlled, non-randomized, open, prospective, monocentric study involving 19 subjects with moderate inflammatory acne on the back (10 scar prone [i.e. with ≥ 20 scars of ≥ 1.5 mm] and 9 non scar prone [i.e. with ≤ 3 scars of ≥ 1.5 mm]) and 8 healthy subjects who never suffered from acne as control. This study comprised the following periods: - For acne subjects: screening period (Day -15 to Day -1), pre-treatment period (Day -3 to Day -1), treatment period (Day 0 to Day 27) and follow-up visit (10 days [± 3 days] after the last product application, Day 37) for acne subjects; - For healthy subjects: screening period (Day -15 to Day -1), Day 0 and follow-up visit (Day 11) for healthy subjects. During the screening period, 2 different areas were defined on the back of both acne and healthy subjects. In addition, during the screening period, the Investigator: - Conducted physical examination and checked vital signs; - Took blood samples for virology, hematology and blood chemistry; - Performed a urinary pregnancy test; - Performed a urinalysis. **Visits for healthy subjects** On Day 0, 2 biopsies of normal skin were performed on each side of the subject's back. Suture was performed to close the wounds. The biopsies (explants) were immediately immersed in formol (for histology and immunohistochemistry analyses) and in ribonucleic acid (RNA) later buffer for 16 hours at 4°C before freezing them at -80°C (for transcriptomic analyses). On Day 11 (follow-up visit), suture of biopsy areas were removed and the safety assessments were performed. The Investigator: - Removed the sutures of biopsies; - Questioned subjects about the occurrence of adverse events (AEs) and any change on concomitant therapies; - Conduced physical examinations and checked vital signs. **Visits for acne subjects** During the pre-treatment period (Day -3 to Day -1) at least 2 papules (1 on each area of the back) were identified to ensure that two 48-hour old papules could be selected on Day 0. During a 4-week treatment period the treatment was applied (avoiding the biopsy areas) at the study center, once daily, 5 days per week (every day except Saturday and Sunday) except

	the last day (Day 27) when no drug was applied. A total of 19 applications were performed. On Day 0, 4 biopsies were performed on the 2 areas defined on the subject's back before study drug application: 2 biopsies of inflammatory papules (i.e. involved skin) and 2 of apparently normal skin without acne (i.e. non-involved skin). Suture was performed to close the wounds. Healing of biopsies was monitored every day during site visits until suture removal on Day 11. On Day 0, bacteriological samplings before study drug application was taken for P. acnes strains determination on 4 different inflammatory papulo-pustular lesions. From Day 4 to Day 6, at least 4 papules were identified in order to select on Day 7 or Day 8, four 48-hour old papules (2 on each area of the back). On Day 11, the suture of the biopsies done on Day 0 was removed. On Day 27, 4 biopsies were performed from 4 resolved inflammatory papules already identified on Day 7 or Day 8: 2 biopsies of "resolved papules" treated with CD5789 0.005% cream and 2 of "resolved papules" treated with CD5789 vehicle cream. Suture was performed to close the wounds. All biopsies (explants on Days 0 and 27) were immediately immersed in formol (for histology and immunohistochemistry analyses) and in RNA later buffer for 16 hours at 4°C before freezing them at -80°C (for transcriptomic analyses). In total, 8 biopsies (3 mm diameter punch) were performed per acne subject. In acne subjects, standardized digital photographs were taken: - Of the whole back on Days -3, -2, -1, 0, 4, 5, 6, 7, 8, 15, 22 and 27; - Of the targeted papules on Days 0, 7, 8, 15, 22 and 27.
12. Main inclusion criteria	The study population comprised female or male subjects with moderate inflammatory acne (i.e. with "Echelle de cotation des lésions d'acné" [ECLA] score between 2 and 4 for the whole back, with at least one area scored at 2 and with a maximum of 3 nodules). Acne subjects werescar prone (i.e. with ≥ 20 scars of ≥ 1.5mm on the back) or non scar prone (i.e. with ≤ 3 scars of ≥ 1.5mm on the back) and had to exhibit at least two 48-hour old papules at Baseline (Day 0). Healthy female or male subjects, with no acne history, were included as control.
13. Investigational medicinal product, method of administration, strength	CD5789, cream, topical administration, strength: 0.005%
14. Reference medicinal product, method of administration, strength	Comparator: cream, topical administration, strength: Not Applicable
15. Concomitant therapy	Not Applicable

16. Efficacy evaluation criteria	**Primary and secondary endpoints** Difference in the expression of biomarkers of cutaneous immunity evaluated at the transcriptomic and proteomic levels between scar prone and non-scar prone subjects. Large-scale and focused transcriptomic analyses were performed to compare expression of messenger RNA (mRNA) in scar prone subjects versus non scar prone subjects. Large-scale analyses were conducted using Affymetrix technology. Focused analyses were conducted to study the gene expression of markers used in the proteomic analysis (see below) using quantitative reverse transcription polymerase chain reaction (qRT-PCR). At proteomic level, an immunohistochemistry analysis was performed to assess the expression of the following markers: interleukin (IL)-1, IL-2, IL-6, IL-8, IL-10, tumor necrosis factor alpha (TNFα), matrix metalloproteinase (MMP)-1, -9, -3, -13, tissue inhibitors of metalloproteinases (TIMP)-1, -2, toll-like receptor (TLR)2, TLR4, peroxisome proliferator-activated receptor (PPAR), fibroblast growth factor (FGF), transforming growth factor beta (TGFβ), insulin-like growth factor 1 (IGF1), human beta-defensin-2 (hBD2), Smad 3/4, SKI proto-oncogene (cSKI), activator protein 1 (AP1; cJUN subunit). Modulations induced by a new therapeutic agent (CD5789 0.005% cream) on these same markers both at the transcriptomic and proteomic levels after 27 days of topical application on inflammatory papules in scar prone and non-scar prone subjects.
17. Safety evaluation criteria	- AEs, recorded at each visit; - Local tolerance for acne subjects, recorded at each visit during the treatment period and 10 days ± (3 days) after the last product application (i.e. follow-up visit, Day 37); - Physical examination and vital signs, recorded at Screening, Day 0 for all subjects, Day 11 for healthy subjects only, and Day 27 and 10 days (± 3 days) after the last product application (i.e. follow-up visit, Day 37) for acne subjects only; - Laboratory safety tests, recorded at Screening for all subjects and Day 27 for acne subjects only.
18. Statistical methods	Transcriptomic analyses included the following type of biopsy samples: - Healthy skin; And from scar and non-scar prone subjects: - Non-involved skin; - Papule less than 48 hours of age; - "resolved papules" with CD5789 vehicle cream treatment on Day 27; - "resolved papules" with CD5789 0.005% cream on Day 27.

	The following were the main comparison for transcriptomic analyses: - Non-involved skin in non-scar prone subjects and scar prone subjects versus normal skin in healthy subjects; - Papule less than 48 hours of age versus non-involved skin in scar prone and non-scar prone subjects; - Comparison of papules less than 48 hours of age between scar- and non-scar-prone subjects; - Papule from area of the back treated with CD5789 vehicle cream on Day 27 versus papule less than 48 hours of age in scar prone and non-scar prone subjects; - Papule from area of the back treated with CD5789 vehicle cream on Day 27 versus non-involved skin in scar prone subjects; - Papule from area of the back treated with CD5789 0.005% cream on Day 27 versus papule from area of the back treated with CD5789 vehicle cream on Day 27 in scar prone and non-scar prone subjects. For intergroup analyses, an analysis of variance (ANOVA) model was used, then the Tukey multiple comparison test was done to assess the significance of the comparison for all probe sets. The resulting p values were adjusted to test multiplicity by controlling the false discovery rate (FDR), using the Benjamini-Hochberg correction. The subject effect was included in the ANOVA model as random effect for the comparison within subjects. A non-supervised analysis was performed independently to assess the significance of contrasts and identify most discriminated markers on global basis. This analysis (non-negative matrix factorization [NMF]) was done, but due to lack of informative results, data are not shown in this report. Demographics and Baseline data, and safety data were descriptively summarized. AEs were tabulated by study treatment in frequency tables by system organ class (SOC) and preferred term (PT).
19. Demographic indicators of the study population (gender, age, race, etc.)	All subjects were White with a mean ± standard deviation (SD) age of 26.48±4.55 years. Overall, the majority of subjects were males (17 [62.96%]), in particular all scars prone subjects were males. At Screening, mean ± SD height and weight were 174.0±7.73 cm and 69.68±14.06 kg, respectively, with no major differences across acne and healthy subjects. Family history of scarring, ECLA score (overall ranging from 1 to 2) and number of nodules (overall ranging from 0 to 2) were similar in scar prone and non-scar prone subjects.
20. Efficacy outcomes	<u>Large-scale transcriptomic analyses</u> Transcriptomic analyses conducted to investigate the molecular mechanisms leading to scar formation showed that: - In non involved skin of scar prone and non scar prone subjects compared to normal skin of healthy subjects there was a sub-clinical inflammation,

	hyperproliferative changes in epidermis and high sebaceous gland activity. This was more pronounced in scar prone subjects than in non scar prone subjects; - In 48-hour old papules of scar prone and non scar prone subjects compared to non involved skin there was induction of both innate and adaptive immune responses. An analysis of specific markers revealed that macrophages tended to be more numerous and/or activated in non scar prone subjects, while T cells seemed to be more elevated in scar prone subjects; - In non scar prone subjects, the gene expression profiles of "resolved papules" and non-involved skin were similar, indicating a resolution of inflammation. Conversely, in scar prone subjects, the gene expression profile of "resolved papules" compared to that of non-involved skin indicated an inflammatory response. This suggests that the inflammatory process lasts longer in scar prone subjects than in non scar prone subjects; In scar prone subjects, the gene expression profile of "resolved papules" compared to that of non-involved skin indicated a decrease in lipids metabolism markers (specific of the sebaceous gland) as well as a strong signature of dermal remodeling that could correspond to the destruction (at least partial) of the pilosebaceous unit and dermal damage. Overall, these results indicate that in scar prone subjects, scarring might be a consequence of damage caused by a persistent inflammation occurring in the sebaceous follicle, leading to its destruction. Presumably, the repair of the destroyed area with remodeling of granulation tissue is not able to restore the initial tissue volume, leading to atrophic scars. Transcriptomic analyses conducted to investigate the potential therapeutic impact of CD5789 on the molecular mechanisms leading to scar formation showed that: - Based on hierarchical clustering, CD5789 0.005% cream did not affect inflammatory lesions, which were still observed in scar prone acne subjects; - Analysis of the gene set specifically modulated by CD5789 0.005% cream demonstrated a common biological response between the two populations of acne subjects, although CD5789 0.005% cream had a more pronounced effect on the non scar prone population (higher number of modulated genes and stronger modulation level); - The analysis of altered processes identified expected retinoid effects, namely anti keratinizing and proliferative effect, leading to an accelerated turnover of epidermal cells and modification of epidermal permeability barrier in both populations of acne subjects. On the other hand, an activation of melanogenesis was only noted in the non scar prone population;

	- This large-scale gene expression profiling did not allow us to observe an effect of CD5789 0.005% cream on acne scarring processes. Proteomic and focused transcriptomic analyses These analyses were conducted by Fiona Jasson as part of her PhD dissertation, under the supervision of Prof. Brigitte Dréno (CHU, Nantes, France). Clinical assessment of papule healing At the end of the treatment period, no specific effects of CD5789 were noted in terms of papule healing compared to its vehicle.
21. Safety outcomes	Acne subjects: In the area of the back treated with CD5789 0.005% cream, erythema and pruritus were reported with similar frequency in scar prone (in 6 [60%] and 7 [70%] subjects, respectively) and non scar prone subjects (in 8 [88.9%] and 7 [77.8%] subjects, respectively). All acne subjects in the area of the back treated with CD5789 0.005% cream, had none or at most moderate signs of erythema and pruritus, except for 1 (5.26%) non scar prone subject who exhibited a severe erythema on Days 22, 25 and 26. Signs of erythema and pruritus were observed starting within the first 11 days of treatment. Overall, in all acne subjects, erythema and pruritus signs worsened during the study reaching a plateau and disappearing 10 days (± 3 days) after the last product application (with the exception of signs of pruritus that persisted in 1 non scar prone subject). Of note, mean scores of erythema and pruritus appeared overall lower in scar prone subjects (ranging from 0.10 to 1.10 and from 0.10 to 0.60, respectively) than in non scar prone subjects (ranging from 0.11 to 1.56 and from 0.11 to 1.0, respectively). Signs of burning/stinging were at most mild, were experienced sporadically (by 2 [20%] scar prone and 1 [11.1%] non scar prone subject) and were absent in all subjects 10 days (± 3 days) after the last product application. In the area of the back treated with CD5789 vehicle cream, signs of erythema and pruritus were at most mild and were experienced sporadically (erythema: by 2 [20%] scar prone subjects and 2 [22.2%] non scar prone subject; pruritus: by 3 [30%] scar prone subjects and 2 [22.2%] non scar prone subjects). In both scar prone and non scar prone subjects, no signs of stinging/burning were noted with CD5789 vehicle cream and no signs of edema were noted either with CD5789 0.005% cream or CD5789 vehicle cream at any time points. Overall, 16 AEs were reported in 11 (57.89%) acne subjects during the treatment period. During the course of this study, no serious AEs (SAEs), AEs leading to discontinuation or AEs of special interest were reported. All AEs were mild (14 [87.5%]) or moderate (2 [12.5%]) and resolved by the end of the study, with the exception of 1

	(6.25%) event of nasopharyngitis in 1 (5.26%) scar prone subject that did not resolve. Of the 16 AEs, 8 (50%) were dermatologic and were reported in 7 (36.84%) acne subjects: 1/8 (12.5%) event of skin hyperpigmentation and 7/8 (87.5%) events of pruritus (in 7 [36.84%] subjects). Pruritus was the most frequently reported dermatologic AE. All AEs of pruritus were related to the study drug and to protocol procedure (i.e. biopsy), resolved by the end of the study and were mild, except 1/8 (12.5%) event that was moderate in 1 (5.26%) non scar prone subject. The AE of skin hyperpigmentation was not related to the study treatment. All non-dermatologic AEs reported during the study were not related to the study treatment. Overall, frequency of dermatologic AEs was the following: 3/8 (37.5%) AEs in 3 (30%) scar prone subjects versus 5/8 (62.5%) AEs in 4 (44.44%) non scar prone subjects. Non-dermatologic AEs were reported with similar frequency in scar prone (4/8 [50%] AEs in 4 [40%] subjects) and non scar prone subjects (4/8 [50%] AEs in 3 [33.33%] subjects). Prior to the treatment period, a total of 5 AEs were reported in 3 (15.79%) acne subjects (4 [80%] AEs in 2 [22.22%] non scar prone subjects and 1 AE [20%] in 1 [10%] scar prone subject). Prior to the treatment period, headache was the most frequently reported AE (1 event in 1 [10%] scar prone subject and 3 events in 2 [22.22%] non scar prone subjects). <u>Healthy subjects:</u> A total of 8 AEs were reported in 5 (62.5%) healthy subjects. Headache and nasopharyngitis were the AEs reported most frequently in healthy subjects (both in 2 [25%] subjects). Overall, there were no clinically significantly abnormal values in terms of urine, hematology and blood chemistry parameters.
22. Summary (conclusion)	In conclusion, scar prone subjects tended to present a long-lasting inflammatory gene profile. The prolonged and severe inflammation observed in scar prone subjects might lead to destruction of sebaceous gland structure, likely followed by inefficient remodeling of granulation tissue and ultimately by atrophic scar formation. There were no remarkable specific effects of CD5789 0.005% cream versus CD5789 vehicle cream in terms of modulation of gene expression and quality of healing. Overall, 16 AEs were reported in 11 (57.89%) acne subjects during the treatment period. During the course of this study, no SAEs or AEs leading to discontinuation were reported. Out of the 16 AEs, 8 (50%) were dermatologic and 8 (50%) were non-dermatologic. Pruritus was the most frequently reported dermatologic AE. All AEs of pruritus were treatment-related, resolved by the end of the study and were mild, except 1 event that was moderate. All non-dermatologic AEs reported during

	the study were not related to the study treatment.

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-18250 - A long-term safety and efficacy study of CD5789 50 µg/g cream in subjects with acne vulgaris
6. Clinical study phase	Phase 3
7. Clinical study period	Date of first screened: 23 February 2015 Date of last subject completed: 23 February 2017
8. Countries where clinical study was conducted	United States – Germany – Hungary – Czech Republic
9. Number of subjects	A total of 455 subjects were enrolled in the study, of whom 453 were treated with CD5789 50 µg/g.
10. Aim and secondary	The primary objective of the study was to determine the safety of CD5789 50 µg/g cream in the long-term treatment (up to 52 weeks) of subjects with acne vulgaris. Efficacy was

purposes of clinical study	evaluated as secondary objective.
11. Clinical study design	Multi-center, open-label, non-comparative, long-term safety study.
12. Main inclusion criteria	Male or female subjects aged ≥9 years at Screening visit. Subjects were to have moderate facial acne (Investigator's global assessment [IGA] = 3, and a minimum of 20 inflammatory lesions and 25 non inflammatory lesions on the face at Screening and Baseline visits. Subjects were to have moderate truncal acne (Physician global assessment [PGA] = 3), and a minimum of 20 inflammatory lesions and 20 non inflammatory lesions on the shoulders, upper back and anterior chest at Screening and Baseline visits. The criteria regarding truncal acne were optional for subjects aged 9-11 years.
13. Investigational medicinal product, method of administration, strength	CD5789, cream, topical administration, strength: 50 μg/g
14. Reference medicinal product, method of administration, strength	None
15. Concomitant therapy	Not Applicable
16. Efficacy evaluation criteria	- **IGA** and **PGA** assessments were conducted at Screening, Baseline, and at Weeks 12, 20, 26, 38 and 52/early termination (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 (ranging from 0 [clear] to 4 [severe]). - **Subject's self-assessment of facial acne improvement** was conducted at Weeks 12, 26 and 52/ET visits – Subjects were to evaluate their facial acne improvement by comparing what they recalled on their disease at the start of the study based on a 6-point scale (ranging from 0 [complete improvement] to 5 [worse]).
17. Safety evaluation criteria	- **Local tolerability** (erythema, scaling, dryness, stinging/burning) assessments were conducted at each planned visit. Local tolerability was assessed separately on the face and the trunk, using specific 4-point scales, ranging from 0 (none) to 3 (severe). - **Adverse Event** assessment was conducted at each planned and unscheduled visit as appropriate. - **Laboratory tests:** hematology, blood chemistry and urinalysis assessments were conducted at Screening, Week 26 and Week 52/ET visits. - **Vital signs** and **physical examination** assessments were conducted at Screening, Baseline, Week 12, Week 26, Week 52/ET visits, and any unscheduled visit as appropriate.
18. Statistical methods	This study was an open-label, non-comparative study. Hence, all efficacy and safety data were summarized descriptively. **Efficacy endpoints:**

	- IGA and PGA success rate at Weeks 12, 20, 26, 38 and 52 visits. The IGA/PGA success rate was calculated as the number of subjects considered a success (i.e., subjects who had an IGA/ PGA score of "clear" [0] or "almost clear" [1] at that visit and had a grade change [improvement] of at least 2 from Baseline visit) at that visit divided by the number of subjects with IGA/PGA data at that visit. - Grade change from Baseline visit of IGA and PGA Weeks 12, 20, 26, 38 and 52 visits. - Subject's assessment of facial acne improvement at Weeks 12, 26 and 52/ET visits. **Change from Baseline in DLQI and C-DLQI total and dimensional scores at Weeks 12, 26 and 52/ET visits.** **Safety endpoints:** see safety evaluation criteria **Analysis populations:** - The Safety Analysis Population (SAF) was defined as all subjects who applied the study drug at least once. The SAF population was used for the analyses of IGA and all safety endpoints, except for the local tolerability parameters on the trunk. - The Safety Population for the Trunk (SAFT) was defined as all subjects in the SAF population who also applied the study drug to the trunk region (i.e., upper trunk, middle and/or lower back areas) at least once. The SAFT population was used for the analysis of the local tolerability parameters on the trunk. - Safety population for the analysis of PGA (SAFP) was defined as all subjects in the SAFT population with moderate truncal acne at Baseline visit. The SAFP population was used for the analyses of PGA.
19. Demographic indicators of the study population (gender, age, race, etc.)	Demographic and baseline disease characteristics are presented in Table 1 for the SAF and SAFP populations. Demographics and baseline disease characteristics were similar in the 2 populations. As per protocol definition, the SAFP population included subjects with moderate truncal acne (PGA grade = 3) at Baseline; thus, 9 subjects with PGA grade <3 who were included in the SAF population were excluded from the SAFP population.

Table 1 Demographics and baseline characteristics – SAF population

	SAF population (N = 453)	SAFP population (N = 444)
Age (years)		
Mean (SD)	18.3 (6.6)	18.4 (6.5)
Median	16.0	16.0
(Min, Max)	(9.0, 54.0)	(9.0, 54.0)
Gender, n (%)		
Female	226 (49.9)	217 (48.9)
Male	227 (50.1)	227 (51.1)
Race, n (%)		
White	432 (95.4)	424 (95.5)
Black or African American	12 (2.6)	11 (2.5)
Asian	3 (0.7)	3 (0.7)
American Indian or Alaska Native	1 (0.2)	1 (0.2)
Native Hawaiian or Other Pacific Islander	3 (0.7)	3 (0.7)
Multiple	2 (0.4)	2 (0.5)
Ethnicity, n (%)		
Hispanic or Latino	47 (10.4)	44 (9.9)
Not Hispanic or Latino	406 (89.6)	400 (90.1)
Skin Phototype, n (%)		
Type I	13 (2.9)	13 (2.9)
Type II	188 (41.5)	182 (41.0)
Type III	184 (40.6)	183 (41.2)
Type IV	53 (11.7)	52 (11.7)
Type V	7 (1.5)	7 (1.6)
Type VI	2 (0.4)	1 (0.2)
Missing	6 (1.3)	6 (1.4)
Baseline IGA Grade, n (%)		
Clear (0)	0	0
Almost Clear (1)	0	0
Mild (2)	0	0
Moderate (3)	453 (100)	444 (100)
Severe (4)	0	0
Baseline PGA Grade, n (%)		
Clear (0)	4 (0.9)	0
Almost Clear (1)	4 (0.9)	0
Mild (2)	1 (0.2)	0

	SAF population (N = 453)	SAFP population (N = 444)
Moderate (3)	444 (98.0)	444 (100)
Severe (4)	0	0
Baseline Inflammatory Facial Lesion Count		
n	453	444
Mean (SD)	36.9 (15.0)	37.0 (15.1)
Median	32	32
Min, Max	20, 123	20, 123
Baseline Non-Inflammatory Facial Lesion Count		
n	453	444
Mean (SD)	58.2 (36.7)	58.5 (37.0)
Median	48	48
(Min, Max)	(22, 363)	(22, 363)
Baseline Inflammatory Truncal Lesion Count		
n	446	444
Mean (SD)	43.4 (28.6)	43.5 (28.5)
Median	34	34
Min, Max	0, 202	0, 202
Baseline Non-Inflammatory Truncal Lesion Count		
n	446	444
Mean (SD)	56.1 (39.5)	56.3 (39.4)
Median	45	45
Min, Max	0, 350	0, 350

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

20. Efficacy outcomes	The IGA success rates at Week 12, 20, 26, 32 and 52 were 26.6%, 43.3%, 50.1%, 57.6% and 65.1% respectively. The PGA success rates at Week 12, 20, 26, 32 and 52 were 38.6%, 54.1%, 58.4%, 62.5% and 66.9% respectively. Overall, the success rate for both IGA and PGA increased over time and the trunk had a higher success rate compared to the face. The overall success rate (defined as having both IGA and PGA success in the same subject) was 22.0%, 36.8%, 43.3%, 49.9% and 57.9% at Week 12, Week 20, Week 26, Week 38 and Week 52, respectively. Mean IGA and PGA scores improved (i.e., decreased) over time during the study period, from 3 at Baseline visit to 1.3 (SD = 0.75) for IGA and 1.3 (SD =0.84) for PGA at Week 52 visit. Subjects who self-reported having a marked or complete improvement of facial acne increased over time, from 166/401 (41.4%) subjects at Week 12 visit to 233/350 (66.6%) subjects at Week 52 visit.
21. Safety outcomes	<u>Local tolerability</u> At Baseline visit, >80% of the subjects did not exhibit any local tolerability signs/symptoms on the face and >88% on the trunk. During the study period, up to 88.3% of subjects had any worst post-Baseline signs/symptoms on the face (dryness [88.3%] followed by erythema [85.2%], scaling [83.0%] and stinging/burning [69.3%]) and up to 59.2% of subjects had any worst post-Baseline signs/symptoms on the trunk (erythema [59.2%] followed by dryness [57.0%], scaling [48.4%] and stinging/burning [41.9%]). Among subjects with assessments of local tolerability signs/symptoms, the following subjects had highest scores worsened from Baseline graded for face: - Erythema – 210 (46.8%) subjects were mild, 111 (24.7%) moderate, 10 (2.2%) subjects were severe - Scaling – 210 (46.8%) subjects were mild, 131 (29.2%) moderate, 10 (2.2%) subjects were severe

- Dryness – 195 (43.4%) subjects were mild, 140 (31.2%) moderate, 26 (5.8%) subjects were severe
- Stinging/burning – 169 (37.6%) subjects were mild, 95 (21.2%) moderate and 32 (7.1%) subjects were severe.

Mean local tolerability scores were higher for the face than for the trunk for all parameters assessed:

- Face – a peak irritation was observed at Week 1 visit, across the local tolerability signs/symptoms, which gradually improved over time.
- Trunk – Except for erythema, a peak in irritation was observed at Week 2 for most of the local tolerability signs/symptoms, which were either maintained or improved during the course of the study. For erythema, the peak irritation occurred at Week 4.

Treatment-emergent adverse events (TEAEs)

A total of 218 (48.1%) subjects reported 468 TEAEs. The majority of TEAEs occurred during the first quarter of the study: 249 events in 154 (34.0%) subjects and decreased thereafter (91 events in 68 [17.7%] subjects during the second quarter; 85 events in 62 [16.8%] subjects during the third quarter; 43 events in 36 [10.3%] subjects in the fourth quarter).

The most frequently reported TEAE was nasopharyngitis (in 48 [10.6%] subjects), followed by sunburn (in 27 [6.0%] subjects), application site pruritus (in 23 [5.1%] subjects) and application site irritation (in 22 [4.9%] subjects). Cutaneous TEAEs represented the most common TEAEs (in 107 [23.6%] subjects) and were mostly reported during the first quarter of the study (in 81 [17.9%] subjects). The majority of TEAEs were mild or moderate in intensity (286 events in 111 [24.5%] subjects and 170 events in 98 [21.6%] subjects, respectively). Severe TEAEs were reported in 9 (2%) subjects.

A total of 103 treatment-related TEAEs reported in 57(12.6%) subjects. The majority of treatment-related TEAEs occurred during the first quarter of the study: 80 events in 46 (10.2%) subjects. The most common treatment-related cutaneous TEAEs were application site pruritus (in 21 [4.6%] subjects), application site irritation (in 19 [4.2%] subjects) and sunburn (in 8 [1.8%] subjects), which were mostly observed on treated areas. The majority of treatment related TEAEs were mild (n = 63/103 [61.2%]) or moderate (n = 37/103 [36.0%]); 3/103 (3.0%) events were severe (1 application site irritation, 1 application site pruritus and 1 application site erythema). All of these events resolved during the study.

A total of 16 subjects discontinued the study due to TEAEs. Of these, 13 TEAEs in 13 subjects were related to the study drug and were considered adverse events of special interest (AESIs; 10 events of skin irritation and 3 events of worsening of acne). The remaining three subjects discontinued due to TEAE not related to study drug (1 event of polycystic ovaries and 2 events worsening of acne). Eleven out of 13 AESIs were of moderate intensity, and they all resolved during the study.

A total of 12 serious TEAEs were reported by 10 (2.2%) subjects. None of the serious TEAEs were related to the study drug, none led to permanent discontinuation. There was one pregnancy reported during the study. The pregnancy ended with spontaneous abortion; the outcome was considered as not related to study treatment.

Clinically relevant TEAEs for CD5789 were:

- Skin irritation at application site. Of the cutaneous TEAEs related to the use of CD5789 generally described as skin irritation (in 1 [0.2%]), application site pruritus (in 21 [4.6%] subjects) and application site irritation (in 19 [4.2%] subjects) were the most frequently reported. These events predominantly occurred during the first quarter of the study.
- Skin sensitization, which was reported by 3 subjects as dermatitis allergic (preferred term [PT]). All events occurred on non-treated areas, were assessed as

	not treatment related, and the etiology remained unknown. - Skin pigmentation disorders, which was reported by 2 subjects as application site discolouration (PT) (hyperpigmentation). These events were assessed as not related to study drug, but rather attributed to the inflammation of acne itself (for one event), or due to sequelae from sunburn (for the other event). - Sunburn: 36 TEAEs of sunburn were reported by 27 (6.0%) subjects. A total of 28 events were of mild and 8 were moderate intensity, none was severe. Sunscreen was used before sun exposure in 20 cases and not used in 12 cases (for 4 cases the use of the sunscreen was unknown). A total of 9 TEAEs of sunburn in 8 (1.8%) subjects were considered as related to the study drug. Clinical laboratory evaluations In general, no clinically meaningful changes in mean values from Baseline to Week 26 and Week 52 for all hematology and blood chemistry parameters were observed. The laboratory parameters remained stable over time. There were no remarkable shifts in the hematology or biochemistry parameters from Baseline visit to the last post-Baseline visit, except for mean cell volume and direct bilirubin. These changes were not associated with any clinical sign or symptom and/or changes in associated laboratory parameters, and were considered as non-clinically significant. Vital signs Mean changes from Baseline in systolic blood pressure, diastolic blood pressure and pulse rate values were not clinically meaningful and mean values of all vital signs parameters remained stable over time Physical examination Abnormal clinical significant findings were observed in few subjects (n = 14) and most of them were reported as TEAEs.
22. Summary (conclusion)	CD5789 is a potent topical retinoid with a high specificity to Retinoic Acid Receptor γ agonist receptors. This was a non-controlled, open-label long-term safety study in subjects with facial and truncal acne vulgaris; efficacy was evaluated as a secondary objective. CD5789 50 µg/g cream was safe and well tolerated over the course of the 1-year study. The tolerability and safety profile was consistent with the known profile of topical retinoids. The local tolerability profile was better for the trunk than for the face. Most of the TEAEs reported during the study were mild to moderate skin irritation, occurred in the first quarter of the study and resolved during the course of the study. The most frequently reported non-cutaneous TEAE was nasopharyngitis (in 10.6% of subjects). None of the non-cutaneous TEAEs were considered as related to the study drug and most of the events were mild or moderate in intensity. No clinically meaningful changes were observed in laboratory parameters, vital signs, or physical examinations. Systemic exposure after topical application to face and trunk was minimal in the study. Over the course of the 1-year treatment, there was clinically meaningful improvement of acne vulgaris on the face and trunk, with IGA and PGA success rates (clear and almost clear) increasing from 26.6% at Week 12 visit to 65.1% at Week 52 visit and from 38.6% at Week 12 visit to 66.9% at Week 52 visit), respectively. Success in the same subject (having both IGA and PGA success in the same subject) increased from 22.0% at Week 12 visit to 57.9% at Week 52 visit. Acne improvement was greater on the trunk than on the face.

	_____ (signature) _____Régis Schulz_____ (full name)	**GALDERMA SA** Zählerweg 10 CH-6300 Zug 058 455 85 00

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

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD-06-SRE-18214 - Exploratory study to evaluate the safety and efficacy of different formulations and concentrations of CD5789 in subjects with acne vulgaris
6. Clinical study phase	Phase 1 Human Pharmacology study
7. Clinical study period	Date of first screened: 11Apr2011 Date of last subject completed: 20Jun2011
8. Countries where clinical study was conducted	United States of America
9. Number of subjects	Approximately 60 subjects were to be randomized to ensure that per protocol data of 17 subjects per group were available for evaluation at the end of the study.

10. Aim and secondary purposes of clinical study	To evaluate the safety and efficacy of CD5789 in different formulations and concentrations (50 µg/g gel versus cream B at 25 µg/g or 50 µg/g) in subjects with moderate to severe acne vulgaris after 4 weeks of once daily application, 5 days per week.
11. Clinical study design	Exploratory, multi-centre, randomized, investigator blinded, vehicle-controlled study using intra-individual comparison (right versus left) in 3 parallel groups: • Group 1: CD5789 25µg/g cream B versus vehicle: subjects were to be treated, with 500 µL of CD5789 25µg/g cream B on one half face and other half face received 500 µL of the vehicle cream. • Group 2: CD5789 50µg/g cream B versus vehicle: subjects were to be treated with 500 µL of CD5789 50µg/g cream B on one half face and other half face received 500 µL of the vehicle cream. • Group 3: CD5789 50µg/g gel versus vehicle: subjects were to be treated, with 500 µL of CD5789 50 µg/g gel on one half face and other half face received 500 µL of the vehicle gel.
12. Main inclusion criteria	Key inclusion criteria - Male or female subjects aged 18-35 years old, with: ○ Moderate to severe facial acne vulgaris (at least 20 inflammatory lesions and 30 noninflammatory lesions, excluding nose) (Screening and baseline); ○ Investigators' global assessment (IGA) severity grade 3 or 4 (Screening and baseline); ○ Fitzpatrick skin phototype I to IV (Screening).
13. Investigational medicinal product, method of administration, strength	Cream B: - CD5789, cream, topical administration, strength: 50µg/g - CD5789, cream, topical administration, strength: 25µg/g Gel: - CD5789, gel, topical administration, strength: 50µg/g
14. Reference medicinal product, method of administration, strength	- Vehicle product for Cream B, topical administration, strength: Not Applicable - Vehicle product for CD5789 gel, topical administration, strength: Not Applicable
15. Concomitant therapy	Not Applicable
16. Efficacy evaluation criteria	**Efficacy measurements** - Lesion counts: inflammatory lesion count (papules, pustules), non-inflammatory lesion count (open and closed comedones), other acne lesion count (nodules); total lesion count will be calculated as the sum of inflammatory lesions, non-inflammatory lesions and nodules; - Investigator and subject efficacy preference at the Final visit (Day 29). - Photographic evaluation **Efficacy criteria**

	- Primary efficacy criteria
	  ○ Total acne lesion count and percent reduction at the end of treatment (evaluated clinically).
	- Secondary efficacy criteria
	  ○ Clinical evaluation
	  ▪ Inflammatory, non-inflammatory and total acne lesion count as well as percent reduction at each visit per half face;
	  ▪ Subject and investigator efficacy preference at the end of treatment.
	  - Photographic evaluation:
	  - Inflammatory lesions count at each visit;
	  - Inflammatory lesions reduction at the end of treatment;
	  - Comedones lesions count at each visit;
	  - Comedones lesions reduction at the end of treatment;
	  - Quantification of Propionibacterium acnes by fluorescence reflectance photograph analysis.
	Other
	- Cosmetic acceptability.

17. Safety evaluation criteria	- Adverse events recorded at each visit after the Screening visit; - Local tolerance assessed on each half-face using a 4-point skin reaction scale at every visit from Baseline (Day 1) to the Final visit (Day 29); - Physical examination and vital signs at Screening, Baseline (Day 1) and the Final visit (Day 29); - Laboratory safety tests at Screening and the Final visit (Day 29).
18. Statistical methods	Local tolerability scores were summarized using means over time and worst response across visits. Adverse events, general physical examination, vital signs, laboratory parameters and cosmetic acceptability questionnaires were summarized by descriptive statistics. Efficacy data were analyzed at each visit for the per protocol population, and for endpoint response in the ITT population (using the last observation of the treatment period carried forward). Lesion counts (inflammatory, non inflammatory and total) as well as percent reduction 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. P. acnes quantification after Ln transformation and their changes from baseline were analyzed using the paired Student's test. All tests were two-sided and the 5% probability level was chosen to declare significance.
19. Demographic indicators of the study population (gender, age, race, etc.)	Eight (8) US centers screened 89 subjects (ranging from 6 to 25 subjects per center). Among these subjects, 59 were randomized: 18 in CD5789 25µg/g cream B versus vehicle, 21 in CD5789 50µg/g cream B versus vehicle and 20 in CD5789 50µg/g gel versus vehicle. Five (5) subjects (1 in CD5789 25µg/g cream B versus vehicle, 3 in CD5789 50 µg/g cream B versus vehicle and 1 in CD5789 50 µg/g gel versus vehicle) were excluded from the PP population due to protocol deviations. Three (3, one in each group) of the 59 randomized subjects discontinued the study prematurely: one due to subject request's in the group CD5789 25µg/g cream B versus vehicle, one due to subject request's in the group CD5789 50µg/g cream B versus vehicle and one due to not related adverse event in the group CD5789 50µg/g gel versus vehicle.

The majority of randomized subjects were white (93.2%) and 61.0% were female. The mean age was 23.1 years (range 18-35).

Table 1 Demographic

			Randomized			
		Screened	CD5789 25 µg/g cream B versus vehicle	CD5789 50 µg/g cream B versus vehicle	CD5789 50 µg/g gel versus vehicle	All
		N (%)	N (%)	N (%)	N (%)	N (%)
Gender	N	89	18	21	20	59
	Male	30 (33.7%)	10 (55.6%)	5 (23.8%)	8 (40.0%)	23 (39.0%)
	Female	59 (66.3%)	8 (44.4%)	16 (76.2%)	12 (60.0%)	36 (61.0%)
Race	N	89	18	21	20	59
	White	80 (89.9%)	16 (88.9%)	20 (95.2%)	19 (95.0%)	55 (93.2%)
	Black or African American	5 (5.6%)	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (1.7%)
	Asian	2 (2.2%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	2 (3.4%)
	Other	2 (2.2%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (1.7%)
Age (years)	N	89	18	21	20	59
	Mean	23.2	22.1	23.5	23.5	23.1
	SD	4.6	5.4	3.9	4.4	4.5
	Median	22.0	20.0	23.0	24.0	22.0
	(Min,Max)	(18,35)	(18,35)	(18,33)	(18,31)	(18,35)
Phototype	N	75	18	21	20	59
	I	6 (8.0%)	0 (0.0%)	3 (14.3%)	1 (5.0%)	4 (6.8%)
	II	29 (38.7%)	9 (50.0%)	8 (38.1%)	6 (30.0%)	23 (39.0%)
	III	26 (34.7%)	4 (22.2%)	7 (33.3%)	10 (50.0%)	21 (35.6%)
	IV	12 (16.0%)	5 (27.8%)	3 (14.3%)	3 (15.0%)	11 (18.6%)
	V	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	VI	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity	N	89	18	21	20	59
	Hispanic or Latino	10 (11.2%)	2 (11.1%)	2 (9.5%)	2 (10.0%)	6 (10.2%)
	Not Hispanic or Latino	79 (88.8%)	16 (88.9%)	19 (90.5%)	18 (90.0%)	53 (89.8%)

20. Efficacy outcomes

- Primary efficacy criteria

At the end of treatment (D29), a statistically significant difference ($p<0.05$) between the active and vehicle treatment side in favor of the active was observed in all groups for both the total lesion count as well as the percent reduction. The difference between active and vehicle in terms of median percent reduction was 21.1% with CD5789 50 µg/g cream B. Statistically significant differences were confirmed in the ITT population.

Table 3 Total Lesions Count

Total lesion count		CD5789 25 µg/g cream B versus vehicle			CD5789 50 µg/g cream B versus vehicle			CD5789 50 µg/g gel versus vehicle		
		Active	Vehicle	A - V	Active	Vehicle	A - V	Active	Vehicle	A - V
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Day 01 (ITT)	N	18	18	18	21	21	21	20	20	20
	Mean	38.8	36.8	1.9	41.4	41.2	0.2	34.6	35.2	-0.6
	SD	12.2	10.6	7.3	15.1	14.3	8.8	11.6	9.8	5.0
	Median	35.0	34.0	1.0	37.0	36.0	0.0	30.5	32.0	-1.0
	(Min,Max)	(25,63)	(26,61)	(-9,14)	(25,73)	(26,73)	(-12,21)	(25,65)	(24,60)	(-12,9)
	P-value*	-	-	**0.478**	-	-	**0.862**	-	-	**0.650**
Endpoint (ITT)	N	18	18	18	21	21	21	20	20	20
	Mean	15.7	21.6	-5.9	18.6	25.9	-7.2	18.1	21.7	-3.6
	SD	7.6	11.3	8.5	10.0	13.2	8.4	10.7	8.7	6.1
	Median	15.0	22.0	-5.5	18.0	25.0	-7.0	15.0	21.5	-4.5
	(Min,Max)	(6,32)	(6,45)	(-20,14)	(6,51)	(10,65)	(-21,6)	(0,39)	(4,37)	(-17,11)
	P-value*	-	-	**0.010**	-	-	**<0.001**	-	-	**0.014**
Day 01 (PP)	N	17	17	17	18	18	18	19	19	19
	Mean	39.1	37.5	1.6	42.9	42.3	0.6	35.1	35.7	-0.7
	SD	12.5	10.6	7.4	15.7	15.0	9.2	11.7	9.7	5.1
	Median	35.0	37.0	1.0	39.0	37.5	-0.5	31.0	32.0	-1.0
	(Min,Max)	(25,63)	(26,61)	(-9,14)	(25,73)	(26,73)	(-12,21)	(25,65)	(27,60)	(-12,9)
	P-value*	-	-	**0.634**	-	-	**0.991**	-	-	**0.571**
Day 29 (PP)	N	17	17	17	18	18	18	19	19	19
	Mean	16.2	22.2	-6.1	18.5	27.1	-8.6	19.1	22.6	-3.5
	SD	7.5	11.3	8.7	10.7	13.9	8.2	10.1	7.8	6.2
	Median	15.0	22.0	-6.0	17.0	25.0	-8.0	15.0	22.0	-5.0
	(Min,Max)	(6,32)	(6,45)	(-20,14)	(6,51)	(10,65)	(-21,5)	(8,39)	(10,37)	(-17,11)
	P-value*	-	-	**0.013**	-	-	**<0.001**	-	-	**0.021**

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

A - V is Active — Vehicle

Table 4 Percent reduction in total lesion count

Percent reduction in total lesion count		CD5789 25 µg/g cream B versus vehicle			CD5789 50 µg/g cream B versus vehicle			CD5789 50 µg/g gel versus vehicle		
		Active	Vehicle	A - V	Active	Vehicle	A - V	Active	Vehicle	A - V
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Endpoint (ITT)	N	18	18	18	21	21	21	20	20	20
	Mean	58.7	42.1	16.6	53.6	37.4	16.2	49.1	37.2	11.9
	SD	16.5	24.5	24.4	18.1	21.4	21.4	22.8	23.9	15.1
	Median	57.1	37.1	18.3	53.6	38.5	15.5	48.5	38.5	12.4
	(Min,Max)	(28.1,89.3)	(-36,81.0)	(-27.3,51.8)	(14.8,90.2)	(-25.0,64.7)	(-19.8,55.1)	(6.5,100.0)	(-16.1,83.3)	(-16.5,46.1)
	P-value*			**0.012**			**0.003**			**0.002**
Day 29 (PP)	N	17	17	17	18	18	18	19	19	19
	Mean	57.5	41.0	16.6	56.3	36.2	20.1	46.4	34.8	11.6
	SD	16.2	24.7	25.2	16.6	22.7	20.2	20.0	21.9	15.5
	Median	57.1	34.7	18.7	54.4	38.0	21.1	48.1	36.2	12.3
	(Min,Max)	(28.1,89.3)	(-36,81.0)	(-27.3,51.8)	(25.0,90.2)	(-25.0,64.7)	(-10.7,55.1)	(6.5,73.2)	(-16.1,80.0)	(-16.5,46.1)
	P-value*			**0.017**			**0.001**			**0.004**

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

A - V is Active – Vehicle

- Secondary efficacy criteria
  - Inflammatory lesions

A statistically significant difference ($p<0.05$) in favor of CD5789 50 µg/g cream B was demonstrated in the inflammatory lesion count at Day 22 and Day29 and at Day29. No significant difference vs the vehicle was observed.

	The percent reduction was statistically significantly higher with CD5789 50 µg/g in cream B and gel at Day29 compared to vehicle, and reached almost significance for CD5789 50 µg/g cream B at Day22 (p=0.051). ○ Non-inflammatory lesions A statistically significant difference in favor of the active was observed between the active and the vehicle as early as Day08 with CD5789 25 µg/g cream B and as early as Day15 with CD5789 50 µg/g cream B sustaining until Day 29. Results in percent reduction from Day01 paralleled these results. ○ Total lesions A statistically significant difference in favor of CD5789 50 µg/g cream B versus the vehicle was observed as of Day22 with. All treatment groups showed a significant difference at the end of treatment. Results in percent reduction from Day01 paralleled these results with a significant difference as of Day15 and throughout the study duration. ○ - Subject and investigator preference The investigator preferred CD5789 50 µg/g cream B more than the vehicle in 61.1% subjects ($p<0.05$; PP population). This correlated with the subject's preference (77.8%; $p<0.05$; PP population). ○ Cosmetic acceptability A total of 52.4% of subjects preferred CD5789 50 µg/g cream B over the vehicle (28.6%); however, this difference was not statistically significant. This results contrast with results for the question "Which product felt best on your skin?"; a statistically significant difference in favor of the vehicle ($p<0.05$) was observed for CD5789 50 µg/g cream B and 25 µg/g cream B. No other statistically significant difference between any of the actives and the vehicle was observed.
21. Safety outcomes	Two subjects in each group missed their application due to irritation on the active side. The first occurrence was at Day12 and at Day19 for the CD5789 25µg/g cream B group, at Day9 and at Day25 for the CD5789 50 µg/g cream B group and at Day11 and at Day12 for the CD5789 50 µg/g gel group. The 2 subjects in the CD5789 25 µg/g cream B missed one application among 20 due to irritation. In the CD5789 50 µg/g cream B group, one subject missed 2 applications and the other one, 4 and in the CD5789 50 µg/g gel, one subjects missed one application and the other missed 2 applications. The mean number of applications received ranged from 17.9 (CD5789 50 µg/g cream B group) to 18.9 (CD5789 25 µg/g cream B group). The theoretical number of applications to be received was 20. - CD5789 25 µg/g cream B versus vehicle A total of 7 subjects reported 9 AEs. Among these, 6 AEs were related to the treatment (4 with the active: pruritus, skin burning sensation, skin hypopigmentation and skin irritation and 2 with the vehicle: pruritus); all were dermatologic AEs and none was severe. There were neither AESI nor severe or serious AEs reported and none led to treatment discontinuation.

Table 5 Overview of adverse events: CD5789 25 µg/g cream B versus vehicle

	CD5789 25µg/g cream B (N= 18)			Vehicle (N= 18)			Total (N= 18)		
	n events	n subj.	% subj.	n events	n subj.	% subj.	n events	n subj.	% subj.
All AEs	7	6	33.3	5	4	22.2	9	7	38.9
Related AEs	4	3	16.7	2	1	5.6	6	4	22.2
All dermatologic AEs	4	3	16.7	2	1	5.6	6	4	22.2
Related dermatologic AEs	4	3	16.7	2	1	5.6	6	4	22.2
AESI	0	0	0.0	0	0	0.0	0	0	0.0
All severe AEs	0	0	0.0	0	0	0.0	0	0	0.0
Related severe AEs	0	0	0.0	0	0	0.0	0	0	0.0
All serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
Related serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
All AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
Related AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
Deaths	0	0	0.0	0	0	0.0	0	0	0.0

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

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

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

- CD5789 50 µg/g cream B versus vehicle

A total of 11 subjects reported 17 AEs. Among these 11 subjects, all reported 16 AEs with the active and 10 reported 12 AEs with the vehicle. Five subjects reported 7 related AEs.

Five subjects reported 6 related events (flushing, headache, skin burning sensation, skin irritation, sunburn) with CD5789 50 µg/g cream B, 5 were dermatologic and none of those was severe. Two subjects reported one event of headache and one event of pain of the skin with the vehicle.

One subject reported one AESI of headache (non-dermatological treatment-related AEs). There was no serious AE and none led to treatment discontinuation.

One subject treated with CD5789 50 µg/g cream B got pregnant during the study. The subject gave normal birth to a girl, one week earlier than planned. No malformation or safety issues were reported except a two- day non related respiratory distress at birth with signs consistent with a possible clear fluid inhalation. The baby's follow-up doctor visit at 10 days confirmed that the baby gained weight and had no safety issue including no breath disorder.

Table 6 Overview of adverse events: CD5789 50µg/g cream B versus vehicle

	CD5789 50µg/g cream B (N= 21)			Vehicle (N= 21)			Total (N= 21)		
	n events	n subj.	% subj.	n events	n subj.	% subj.	n events	n subj.	% subj.

All AEs	16	11	52.4	12	10	47.6	17	11	52.4
Related AEs	6	5	23.8	2	2	9.5	7	5	23.8
All dermatologic AEs	6	5	23.8	2	2	9.5	7	5	23.8
Related dermatologic AEs	5	4	19.0	1	1	4.8	6	4	19.0
AESI	1	1	4.8	1	1	4.8	1	1	4.8
All severe AEs	1	1	4.8	1	1	4.8	1	1	4.8
Related severe AEs	0	0	0.0	0	0	0.0	0	0	0.0
All serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
Related serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
All AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
Related AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
Deaths	0	0	0.0	0	0	0.0	0	0	0.0

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

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

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

- CD5789 50 µg/g gel versus vehicle

A total of 8 subjects reported 10 AEs. Among these 8 subjects, all reported 10 AEs with the active and 7 reported 7 AEs with the vehicle. Four subjects reported related dermatologic AEs: 4 with the active (dermatitis, skin irritation (2 events) and sunburn) and one event of sunburn with the vehicle, none of the events was severe. There was no AESI reported. One subject reported one serious and severe AE (bacterial mastitis) leading to the discontinuation of that subject.

Table 7 Overview of adverse events: CD5789 50µg/g gel versus vehicle

	CD5789 50µg/g gel (N= 20)			Vehicle (N= 20)			Total (N= 20)		
	n events	n subj.	% subj.	n events	n subj.	% subj.	n events	n subj.	% subj.
All AEs	10	8	40.0	7	7	35.0	10	8	40.0
Related AEs	4	4	20.0	1	1	5.0	4	4	20.0
All dermatologic AEs	4	4	20.0	1	1	5.0	4	4	20.0
Related dermatologic AEs	4	4	20.0	1	1	5.0	4	4	20.0
AESI	0	0	0.0	0	0	0.0	0	0	0.0
All severe AEs	1	1	5.0	1	1	5.0	1	1	5.0
Related severe AEs	0	0	0.0	0	0	0.0	0	0	0.0
All serious AEs	1	1	5.0	1	1	5.0	1	1	5.0
Related serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
All AEs leading to discontinuation	1	1	5.0	1	1	5.0	1	1	5.0
Related AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
Deaths	0	0	0.0	0	0	0.0	0	0	0.0

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

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

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

- Cutaneous Tolerance

Clinical irritation was assessed on each half face prior treatment application at every visit starting on Baseline (Day 1). The highest severity scores recorded over time are detailed in Table 8 .

Overall, occurrence of erythema, scaling, dryness and stinging/burning were higher on the active-treated side than on the vehicle-treated side. Results from active side were comparable between the 3 groups. Somewhat more subjects treated with CD5789 50µg/g gel had more worst scores for irritation signs and symptoms reported than those treated with the creams.

Table 8 Frequency tables for worst score of each signs/symptoms

		CD5789 25µg/g cream B versus vehicle		CD5789 50µg/g cream B versus vehicle		CD5789 50µg/g gel versus vehicle	
		Active (N=18)	Vehicle (N=18)	Active (N=21)	Vehicle (N=21)	Active (N=20)	Vehicle (N=20)
Worst score for Erythema	N	18	18	21	21	20	20
	0-None	2 (11.1%)	10 (55.6%)	3 (14.3%)	13 (61.9%)	0 (0.0%)	6 (30.0%)
	1-Mild	7 (38.9%)	7 (38.9%)	8 (38.1%)	8 (38.1%)	12 (60.0%)	14 (70.0%)
	2-Moderate	9 (50.0%)	1 (5.6%)	10 (47.6%)	0 (0.0%)	8 (40.0%)	0 (0.0%)
Worst score for Scaling	N	18	18	21	21	20	20
	0-None	2 (11.1%)	13 (72.2%)	1 (4.8%)	16 (76.2%)	0 (0.0%)	10 (50.0%)
	1-Mild	10 (55.6%)	4 (22.2%)	8 (38.1%)	5 (23.8%)	7 (35.0%)	8 (40.0%)
	2-Moderate	6 (33.3%)	1 (5.6%)	12 (57.1%)	0 (0.0%)	13 (65.0%)	2 (10.0%)
Worst score for Dryness	N	18	18	21	21	20	20
	0-None	1 (5.6%)	12 (66.7%)	3 (14.3%)	16 (76.2%)	4 (20.0%)	12 (60.0%)
	1-Mild	11 (61.1%)	4 (22.2%)	10 (47.6%)	4 (19.0%)	6 (30.0%)	6 (30.0%)
	2-Moderate	6 (33.3%)	2 (11.1%)	8 (38.1%)	1 (4.8%)	10 (50.0%)	2 (10.0%)
Worst score for Stinging/Burning	N	18	18	21	21	20	20
	0-None	5 (27.8%)	16 (88.9%)	7 (33.3%)	17 (81.0%)	5 (25.0%)	15 (75.0%)
	1-Mild	7 (38.9%)	2 (11.1%)	6 (28.6%)	4 (19.0%)	9 (45.0%)	5 (25.0%)
	2-Moderate	6 (33.3%)	0 (0.0%)	8 (38.1%)	0 (0.0%)	5 (25.0%)	0 (0.0%)
	3-Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)

- Pregnancy

One subject treated with CD5789 50 µg/g cream B and vehicle got pregnant during the study. The subject gave normal birth to a girl, one week earlier than planned. No safety issues were reported during the pregnancy and at the "Day 10" visit of the baby.

- Laboratory measurements, assessments for vital signs and physical findings

Results from laboratory measurements, assessments for vital signs and physical findings at Day 29 /early termination did not show any relevant changes from values at screening.

22. Summary (conclusion)

The use over 4 weeks of CD5789 cream B at 25 µg/g and 50 µg/g as well as CD5789 50 µg/g gel compared to their vehicle provided significant differences in terms of total lesions count and percent reduction from D01.

CD5879 in the cream B and the gel was well tolerated; adverse events and local tolerability were comparable between the 3 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	RD-06-SRE-18237 - A Pharmacokinetic study of CD5789 following dermal application of CD5789 50 µg/g or 100 µg/g Cream under maximal use conditions in subjects 9 to 17 years of age with Acne Vulgaris
6. Clinical study phase	Phase 1
7. Clinical study period	Date of first enrolled: 01 Nov 2012 Date of last subject completed:18 Jul 2013
8. Countries where clinical study was conducted	United States of America (USA)
9. Number of subjects	Approximately 72 subjects were to be screened in order to achieve the target of 36 randomized/enrolled subjects (18 per group) to ensure 32 completers (at least 16 per group). In an attempt for a fair balance among age groups and gender, enrollment of at

<table>
<tr><td></td><td>least 4 subjects between 9 to 11 years of age and approximately 10 females in the study was planned.</td></tr>
<tr><td>10. Aim and secondary purposes of clinical study</td><td>Primary objective
To assess the systemic exposure to CD5789 under maximal use conditions in subjects 9 to 17 years of age with acne vulgaris when CD5789 50 µg/g Cream or 100 µg/g Cream was applied once daily for 29 days.
Secondary objective
To assess the safety and tolerability of CD5789 50 µg/g Cream and 100 µg/g Cream.</td></tr>
<tr><td>11. Clinical study design</td><td>Randomized, double-blind study consisting of 2 parallel groups:
- Group 1: CD5789 50 µg/g Cream applied once daily
- Group 2: CD5789 100 µg/g Cream applied once daily</td></tr>
<tr><td>12. Main inclusion criteria</td><td>Key inclusion criteria:
- Male or female 9 to 17 years of age inclusive.
- If 9 to 11 years of age (prior to 12th birthday), the subject had an Investigator's Global Assessment (IGA) of at least 3 on the face.
- If 12 to 17 years of age, the subject had an IGA of 4 on the face plus at least 25 inflammatory lesions and at least 40 non-inflammatory lesions on the face.
- Female subjects had a negative serum and urine pregnancy test (UPT) at Screening visit and a negative UPT at Baseline/Day 1 visit.
- Female subjects of childbearing potential OR premenarcheal females had to agree to use a highly effective and approved double-barrier contraceptive method(s) for the duration of the study and for at least 1 month after the last study drug application.
- Body mass index (BMI) at the Screening visit was within specified range.</td></tr>
<tr><td>13. Investigational medicinal product, method of administration, strength</td><td>CD5789 cream, topical administration, strength: 50 or 100 µg/g
▪ Test product dosage form
<table>
<tr><th></th><th>Investigational Product</th><th>Investigational Product</th></tr>
<tr><td>Trade Name or equivalent (if applicable)</td><td>Not Applicable</td><td>Not Applicable</td></tr>
<tr><td>Name of Drug Substance (INN)</td><td>Not Applicable</td><td>Not Applicable</td></tr>
<tr><td>Internal code (if applicable)</td><td>CD5789</td><td>CD5789</td></tr>
<tr><td>Pharmaceutical form</td><td>Cream</td><td>Cream</td></tr>
<tr><td>Strength</td><td>50 µg/g</td><td>100 µg/g</td></tr>
<tr><td>Formula number</td><td>0219.0102</td><td>0219.0073</td></tr>
<tr><td>Packaging (type and size)</td><td>Megaplast bottle 50 mL</td><td>Megaplast bottle 50 mL</td></tr>
<tr><td>Storage conditions</td><td>Store below 25°C – Do not freeze or refrigerate</td><td>Store below 25°C – Do not freeze or refrigerate</td></tr>
<tr><td>Dosage (total daily dose)</td><td>1.1 to 2 g based on body weight</td><td>1.1 to 2 g based on body weight</td></tr>
<tr><td>Dose regimen</td><td></td><td></td></tr>
<tr><td>Route</td><td>Topical</td><td>Topical</td></tr>
<tr><td>Frequency</td><td>Once daily in the morning</td><td>Once daily in the morning</td></tr>
<tr><td>Duration of administration</td><td>29 days</td><td>29 days</td></tr>
<tr><td>Location of treated area</td><td>Face, shoulders, upper back, upper chest (except the neck)</td><td>Face, shoulders, upper back, upper chest (except the neck)</td></tr>
</table></td></tr>
<tr><td>14. Reference medicinal product, method of</td><td>Not Applicable</td></tr>
</table>

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-40209 - Evaluation of the Cutaneous Cumulative Irritancy Potential of CD 5789 Cream at 50 µg/g and 100 µg/g and Corresponding Vehicle Following Repeated Applications to the Skin of Healthy Subjects.
6. Clinical study phase	Phase 1, Human pharmacology
7. Clinical study period	Date of first screened: 23-May-2013 Date of last subject completed: 19-Jul-2013
8. Countries where clinical study was conducted	France
9. Number of subjects	Approximately 55 healthy male or female subjects were to be screened in order to randomize 35 subjects to get at least 30 evaluable subjects at the end of the clinical trial.
10. Aim and	To determine the cutaneous cumulative irritancy potential of CD5789 cream at 50 µg/g

secondary purposes of clinical study	and 100 µg/g and corresponding cream vehicle following repeated applications to the skin of healthy subjects.
11. Clinical study design	This was a single-center, randomized, vehicle-, negative and positive-controlled, evaluator blinded, intra-individual design clinical trial enrolling healthy male and female subjects.
12. Main inclusion criteria	Key inclusion criteria - Male or female 18 to 65 years of age inclusive at screening visit. - The subject was, in the opinion of the Investigator, in good general health. - Skin phototype of I to IV (Wolff 2007) - Female of non-childbearing potential (postmenopausal [absence of menstrual bleeding for 1 year prior to screening, without any other medical reason], hysterectomy or bilateral oophorectomy). - Female of childbearing potential with a negative UPT at screening and baseline visits - Female of childbearing potential who agreed to use a double-barrier contraception method during all the study participation until the last study drug application/last study drug administration and for at least one month after the last study drug application/last study drug administration, consisting of use of condom and a highly effective and approved method of contraception.
13. Investigational medicinal product, method of administration, strength	CD5789, tropical (dermal) administration, cream, strength: 50 µg/g & 100 µg/g
14. Reference medicinal product, method of administration, strength	- Comparator: topical (dermal) administration, cream, strength: placebo - Comparator (negative control): white petrolatum (Vaseline), tropical (dermal) administration, ointment, strength: Not Applicable - Comparator (positive control): Sodium Lauryl Sulfate (SLS), topical (dermal) administration, solution, strength: 0.25%
15. Concomitant therapy	Not Applicable
16. Efficacy evaluation criteria	Efficacy was not assessed in this study.
17. Safety evaluation criteria	- Skin Reaction Assessment. - Adverse Events - Vital signs/Physical examination
18. Statistical methods	- Primary efficacy endpoint: Not Applicable - Secondary efficacy endpoints: Not Applicable
19. Demographic indicators of	The mean age of subjects was 38.8 years (see Table 1) at screening (range 20 to 65 years). Most of randomized subjects were female (62.9%) and all were Caucasian. Randomized

the study population (gender, age, race, etc.)	subjects had mainly a skin phototype III (85.7%). **Table 1 Demographic data** See table below
20. Efficacy outcomes	Not Applicable
21. Safety outcomes	• **Adverse Events** An overview of all AEs reported during the study is given in Table 2 below. Eight subjects (8/35; 22.9%) experienced a total of 11 AEs. Five cutaneous AEs were reported and among them, 4 were related to the study drugs. **Table 2 Overview of adverse events (Safety population)** See table below Three AESIs (see Table 3) were reported. One subject experienced moderate eczema-like reaction on both CD5789 50 µg/g and 100 µg/g treated sites 12 days after starting the study drugs applications. Another subject experienced a moderate skin irritation on the CD5789 100 µg/g treated site 14 days after the first study drugs application. These reactions resolved spontaneously 2 weeks after treatment discontinuation. The subjects were challenged with the study drugs under semi-occlusive conditions during 48 hours at least 2 weeks after the last applications. The results were negative at first (30 min) and

		Screened	Randomized
Gender	N	37	35
	Male	13 (35.1%)	13 (37.1%)
	Female	24 (64.9%)	22 (62.9%)
Race	N	37	35
	White	37 (100.0%)	35 (100.0%)
Age (years)	N	37	35
	Mean±SD	38.8±13.8	38.5±13.8
	Median	33.0	33.0
	(Min,Max)	(20,65)	(20,65)
Phototype	N	37	35
	II	4 (10.8%)	4 (11.4%)
	III	32 (86.5%)	30 (85.7%)
	IV	1 (2.7%)	1 (2.9%)

	CD5789 100 µg/g (N= 35)			CD5789 50 µg/g (N= 35)			CD5789 Vehicle (N= 35)			White Petrolatum (N= 35)			Sodium Lauryl Sulfate (N= 35)			Overall (N= 35)		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
All AEs	9	8	22.9	9	8	22.9	7	7	20.0	7	7	20.0	7	7	20.0	11	8	22.9
Related AEs to study drug	2	2	5.7	2	2	5.7	0	0	0.0	0	0	0.0	0	0	0.0	4	2	5.7
Related AEs to protocol procedure	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
All cutaneous AEs	3	3	8.6	3	3	8.6	1	1	2.9	1	1	2.9	1	1	2.9	5	3	8.6
Related cutaneous AEs	2	2	5.7	2	2	5.7	0	0	0.0	0	0	0.0	0	0	0.0	4	2	5.7
Non cutaneous AEs	6	6	17.1	6	6	17.1	6	6	17.1	6	6	17.1	6	6	17.1	6	6	17.1
Related non cutaneous AEs	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
All serious AEs	0	0	0.0	0	0	0.0	0	0	0.0	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	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	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	0	0	0.0	0	0	0.0	0	0	0.0
AESIs	2	2	5.7	1	1	2.9	0	0	0.0	0	0	0.0	0	0	0.0	3	2	5.7
Related AESIs	2	2	5.7	1	1	2.9	0	0	0.0	0	0	0.0	0	0	0.0	3	2	5.7
Deaths	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0

Adverse events are summarized only for events occurred after the first use of medication.
If an AE is not in treated area it will be summarized in each study treatment.
Note: The numbers in the columns cannot be added because a given subject could report more than one AE.
n= number of events - N= Number of patients - %= Percentage of patients.

second (48 hours) readings after patches removal.

Table 3 Related adverse events (Safety population)

Subject	Treatment	Location	System Organ Class/ Preferred Term	Date of onset/ Date of Recovery	Serious/ Severity	Action taken/ Outcome	Study drug/ Procedure	AESI
5074-131	CD5789 100 µg/g	Z3	Skin and subcutaneous tissue disorders/ Eczema	(D13)/(D29)	No/ Moderate	Drug withdrawn/ Recovered	Related/ Not related	Yes
	CD5789 50 µg/g	Z5	Skin and subcutaneous tissue disorders/ Eczema	(D13)/(D29)	No/ Moderate	Drug withdrawn/ Recovered	Related/ Not related	Yes
5074-132	CD5789 100 µg/g	Z5	Skin and subcutaneous tissue disorders/ Skin irritation	(D15)/ (D31)	No/ Moderate	Drug withdrawn/ Recovered	Related/ Not related	Yes
	CD5789 50 µg/g	Z3	Skin and subcutaneous tissue disorders/ Skin irritation	(D15)/ (D31)	No/ Mild	Drug withdrawn/ Recovered	Related/ Not related	No

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

There was no SAE and no death.

- **Cutaneous tolerance**

Worst skin irritation score and MCII are presented for each study drug in Table 4 below.

Table 4 Worst skin reaction score and MCII

		CD5789 100 µg/g	CD5789 50 µg/g	CD5789 Vehicle	White Petrolatum	Sodium Lauryl Sulfate
Worst score	N	35	35	35	35	35
	0-No response	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (42.9%)	4 (11.4%)
	0.5-Indistinct erythema	0 (0.0%)	0 (0.0%)	24 (68.6%)	12 (34.3%)	20 (57.1%)
	1-Well-defined erythema	3 (8.6%)	6 (17.1%)	10 (28.6%)	8 (22.9%)	11 (31.4%)
	2-Slight to moderate edema	19 (54.3%)	18 (51.4%)	1 (2.9%)	0 (0.0%)	0 (0.0%)
	3-Vesicles or papules	2 (5.7%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4-Bullous	11 (31.4%)	10 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Mean±SD	2.6 ± 1.0	2.4 ± 1.1	0.7 ± 0.3	0.4 ± 0.4	0.6 ± 0.3
	Median	2.0	2.0	0.5	0.5	0.5
	(Min,Max)	(1,4)	(1,4)	(1,2)	(0,1)	(0,1)
Cumulative Irritancy Index	N	35	35	35	35	35
	Mean±SD	1.36 ± 0.37	1.25 ± 0.36	0.31 ± 0.20	0.08 ± 0.14	0.22 ± 0.18
	Median	1.26	1.17	0.24	0.03	0.17
	(Min,Max)	(0.9,2.3)	(0.8,2.3)	(0.0,1.0)	(0.0,0.6)	(0.0,0.8)

During this study, 31.4% (11/35) and 28.6% (10/35) of subjects had a worst score equal to 4 on the CD5789 100 µg/g and CD5789 50 µg/g treated sites respectively.

The worst score did not exceed 2 with the Vehicle (1/35; 2.9%) and 1 with the White Petrolatum and the positive control (SLS 0.25%).

Both concentrations of CD5789 50 µg/g and 100 µg/g induced cumulative irritant reaction under semi-occlusive conditions. A slight dose-dependent cumulative irritancy profile was observed.

22. Summary (conclusion)	This study was conducted to determine the cumulative irritancy potential of CD5789 cream at 50 µg/g and 100 µg/g and corresponding cream vehicle following repeated applications to the skin of healthy subjects under semi-occlusive conditions.

	This was a single-center, randomized, vehicle-, negative and positive-controlled, evaluator blinded, intra-individual design clinical trial enrolling healthy male and female subjects carried out in a specialized phase 1 unit (CPCAD, Nice in France). The methodology used was standard for this type of Dermal Safety Study. The subjects were exposed to the study drugs i.e. CD5789 cream at 50 µg/g and 100 µg/g, CD5789 vehicle, white petrolatum as negative control and 0.25% SLS aqueous solution as positive control, under semi-occlusive conditions 6 days a week for 3 consecutive weeks. Thirty-five subjects were randomized and 33 completed the study. Two subjects discontinued the study for non-related reasons. Most subjects were females and all were Caucasian. Subjects had mainly a skin phototype III. At Screening visit, the mean age was 38.8 years (range 20 to 65 years). This 21-Day tolerance study showed that CD5789 cream has a dose-dependent irritancy profile when applied under semi-occlusive conditions. In this study, SLS 0.25% in aqueous solution was used as positive control as classically recommended. However, due to the therapeutic class of the studied molecules (topical retinoids), the study was designed using semi-occlusive dressings and not occlusive patches (maximized skin penetration). The irritant potential of 0.25% SLS aqueous solution was reduced compared to occlusive conditions (Feldmann 1965, Maibach 1992). Nevertheless, the skin reaction profile over time is in favor of a slight cumulative irritant reaction. The irritancy potential of CD5789 at 50 µg/g and 100 µg/g was definitely higher than those of the negative control (white petrolatum) and the Vehicle. This observation of an irritant reaction with a small incremental effect at two doses validates that a positive reaction can be documented under the conditions of the study. In conclusion, within the study conditions, the skin irritancy potential of CD5789 cream at 50 µg/g and 100 µg/g seems similar to that of current topical retinoids.

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

Annex 30

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

(clause 4 of Section IV)

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD-06-SPR-18223 - A randomized, multi-center, Investigator-blind, vehicle- and active-controlled, phase 2 study to assess the efficacy and safety of different concentrations of CD5789 Cream applied once daily in subjects with moderate to severe acne vulgaris
6. Clinical study phase	Phase 2
7. Clinical study period	Date of first screened: 20-JUN-2012 Date of last subject completed:24-JUL-2013
8. Countries where clinical study was conducted	United States ofAmerica
9. Number of subjects	**Planned:** Approximately 150 subjects were planned to be randomized into each of Strata 1 and 2, and approximately 28 subjects to Stratum 3. In total, across all 3 Stratum, 328

16. Efficacy evaluation criteria	**Primary efficacy endpoints:** - Success Rate 1 (SR1), defined as the percentage of subjects who achieve at least a two-point reduction in the IGA score from Baseline at Week 12, Last Observation Carried Forward (LOCF), Intent to Treat (ITT) population. - Absolute and percent change in total lesion counts from Baseline to Week 12 (LOCF, ITT). **Secondary efficacy endpoints:** - Success Rate 2 (SR2), defined as the percentage of subjects rated "Clear" (Grade 0) or "Almost clear" (Grade 1) with at least a two-point reduction on the IGA scale at Week 12 (LOCF, ITT). - Absolute and percent change in inflammatory lesion counts from Baseline to Week 12 (LOCF, ITT). - Absolute and percent change in non-inflammatory lesion counts from Baseline to Week 12 (LOCF, ITT). Other efficacy endpoints: - IGA and Change in IGA from Baseline to Week 12 (LOCF, ITT) - Subject's assessment of acne at Week 12 (LOCF, ITT) - Absolute and percent change in lesion counts by type of lesion (observed data, ITT).
17. Safety evaluation criteria	Adverse events (AEs) reported at each visit after the subject signs the informed consent form; routine hematology and blood chemistry; general physical examination and vital signs; electrocardiograms (ECGs) and local tolerability (erythema, scaling, dryness, and stinging/burning).
18. Statistical methods	**Efficacy:** The primary comparisons were those of each dose versus the placebo in the combined pre-defined strata. Both the intention to treat (ITT) and per protocol (PP) populations were analyzed. For the ITT population, the LOCF was used to impute missing data up to Week 12. An analysis of covariance (ANCOVA) model with terms for treatment, stratum, and Baseline lesion count as covariate was used to analyze the changes from Baseline in lesion counts. An additional model included the treatment by stratum interaction to investigate whether there was evidence of differing treatment effects between strata. The Cochran-Mantel-Haenszel (CMH) test stratified by stratum was used to analyze the success rate (SR1 and SR2), IGA (full scale), changes from Baseline in IGA, percent changes in lesion counts, and subject assessment of acne. The untransformed Table score and general association statistic was used for success rates, and the RIDIT score and row mean difference for the other ordinal or continuous parameters. Similar analyses were performed separately per stratum as exploratory subgroup analyses. All tests were two-sided and used the 0.05 level to declare significance. No adjustment for multiplicity was made. Exploratory analysis was performed using Cochran-Armitage trend test on SR1 and SR2, and regression analysis for change and percent change in total lesion count. Dose (0 µg/g, 25 µg/g, 50 µg/g, and 100 µg/g) was an independent variable in the model to test for dose effect. **Safety:** Adverse events (AEs) and local tolerability data were collected per stratum, and for all strata combined. All AEs occurring during the study were recorded and classified on the basis of MedDRA terminology for the safety population. Treatment-emergent AEs

(TEAEs) were summarized by the number and percentage of subjects reporting AEs, serious AEs, AEs of special interest, AEs leading to discontinuation, AEs related to study medication, and severe AEs, by system organ class and preferred term. Each subject was counted only once within a system organ class or a preferred term.

Clinical laboratory parameters including ECG were descriptively summarized using standard statistics and shift tables. For local tolerability, descriptive statistics were used to summarize the assessments at Baseline and Weeks 1, 2, 4, 8, and 12 for each treatment group. Frequencies and percentages for each outcome category were included in these statistics. Similarly, frequencies and percentages for the scores worse than Baseline were summarized. Mean values were presented graphically versus time by treatment group. Physical examination data were listed and vital signs were summarized descriptively.

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

The ITT population demographic and disease characteristics at Baseline were similar across the treatment groups (Table 1). Mean age was 18.2 years and age ranged from 12 to 35 years (more subjects were aged 12 to 17 years [60.9%] than ≥18 years [39.1%]). Most subjects were male (78.6%) and Caucasian (81.9%). Demographic characteristics for Strata 1 and 2 were similar to the overall ITT population.

At Baseline, in the overall ITT population, mean (SD) of total lesions was 86.6 (27.42), inflammatory lesions was 39.2 (13.60) and non-inflammatory lesions was 47.0 (22.27); see Table 2. The mean (SD) of nodules at Baseline was 0.5 (0.99). Mean and median non-inflammatory lesion count and total lesion count at Baseline were lower in the CD5789 50 µg/g Cream group than other treatment groups, predominantly in Stratum 2 subjects in this group. There were no other differences in disease characteristics at Baseline across the treatment groups.

The proportions of ITT population subjects in the subgroups were similar for Strata (1 and 2) and Baseline IGA (3 and 4). Consistent with the criteria for stratification, subjects in Stratum 2 had more severe disease at Baseline (100% subjects with IGA of 4; inflammatory lesion mean of 49.8; non-inflammatory lesions mean of 47.8) than subjects in Stratum 1 (98% subjects with IGA of 3; inflammatory lesion mean of 28.2; non-inflammatory lesions of 45.9).

Table 1 Demographic data (ITT population)

	CD5789 25 µg/g Cream (N=61)	CD5789 50 µg/g Cream (N=61)	CD5789 100 µg/g Cream (N=60)	Tazarotene 0.1% Gel (N=61)	Vehicle (N=61)	Total (N=304)
Mean Age	18.1	18.2	18.3	18.3	18.3	18.2
12-17 years	42 (68.9)	36 (59.0)	37 (61.7)	36 (59.0)	34 (55.7)	185 (60.9)
≥18 years	19 (31.1)	25 (41.0)	23 (38.3)	25 (41.0)	27 (44.3)	119 (39.1)
Male	46 (75.4)	53 (86.9)	48 (80.0)	44 (72.1)	48 (78.7)	239 (78.6)
Female	15 (24.6)	8 (13.1)	12 (20.0)	17 (27.9)	13 (21.3)	65 (21.4)
Race						
White	52 (85.2)	51 (83.6)	52 (86.7)	47 (77.0)	47 (77.0)	249 (81.9)
Black or African American	9 (14.8)	7 (11.5)	8 (13.3)	12 (19.7)	13 (21.3)	49 (16.1)
Asian	0	2 (3.3)	0	0	1 (1.6)	3 (1.0)
American Indian or Alaskan Native	0	0	0	2 (3.3)	0	2 (0.7)
Other	0	1 (1.6)	0	0	0	1 (0.3)
Ethnicity						
Hispanic or Latino	16 (26.2)	18 (29.5)	15 (25.0)	10 (16.4)	22 (36.1)	81 (26.6)
Japanese Origin	0	0	0	0	1 (1.6)	1 (0.3)

Data source: Table 14.1.3.1

Note: Percentages are based on the number of enrolled subjects in the ITT population with available data in each treatment group.

Table 2 Baseline disease characteristics (ITT population)

Baseline parameter	CD5789 25 µg/g Cream (N=61)	CD5789 50 µg/g Cream (N=61)	CD5789 100 µg/g Cream (N=60)	Tazarotene 0.1% Gel (N=61)	Vehicle (N=61)	Total (N=304)
IGA Score 3	30 (49.2)	30 (49.2)	29 (48.3)	28 (45.9)	31 (50.8)	148 (48.7)
IGA Score 4	31 (50.8)	31 (50.8)	31 (51.7)	33 (54.1)	30 (49.2)	156 (51.3)
Mean Total Lesions	90.8	80.5	86.3	88.9	86.7	86.6
Mean Inflammatory Lesions	39.4	38.4	38.8	39.2	40.1	39.2
Mean Non-Inflammatory Lesions at Baseline	51.0	41.6	47.1	49.3	45.9	47.0
Mean Nodules at Baseline	0.4	0.5	0.5	0.3	0.7	0.5

Data source: Table 14.1.3.1

Note: Percentages are based on the number of enrolled subjects in the ITT population with available data in each treatment group.

20. Efficacy outcomes

Primary efficacy criteria:

- SR1

The SR1 at Week 12 using LOCF was higher in subjects receiving active treatment than in subjects receiving Vehicle; the difference was statistically significant for subjects receiving CD5789 50 µg/g Cream (p=0.040) and Tazarotene 0.1% Gel (p=0.041) at the 5% level using the CMH test on the ITT population (Table 3).

Table 3 Primary efficacy endpoint: Success Rate 1: % of subjects with at least a 2-point reduction in IGA score from Baseline to Week 12 using LOCF (ITT population)

Success rate 1 (SR1)	CD5789 25 µg/g Cream (N=61)	CD5789 50 µg/g Cream (N=61)	CD5789 100 µg/g Cream (N=60)	Tazarotene 0.1% Gel (N=61)	Vehicle (N=61)
Success Rate	29.51	32.79	26.67	32.79	16.39
Difference from Vehicle	13.115	16.393	10.273	16.393	-
95% CI [a]	(-3.266, 29.495)	(-0.249, 33.036)	(-5.923, 26.470)	(-0.249, 33.036)	-
P-value vs. Vehicle [b]	0.096	0.040	0.184	0.041	-
Treatment by Stratum Interaction [c]	0.630	0.438	0.822	0.675	-

Data source: Table 14.2.1.1

[a] The 95% confidence interval on the difference between Vehicle and the specified treatment group success rates was based on normal approximation with continuity correction (Fleiss 1981).

[b] P-value vs. Vehicle is based on Cochran-Mantel-Haenszel test with general association statistic, controlling for stratum.

[c] P-value for treatment by stratum interaction is from Breslow-Day test for homogeneity of the odds ratio across stratum.

- Total lesion count

Mean decreases in absolute total lesion count from Baseline to Week 12 were greater in subjects receiving active treatment than in subjects receiving Vehicle; the difference was statistically significant for subjects receiving Tazarotene 0.1% Gel (LS mean -59.84; p=0.002; Table 4). The results showed a trend towards a statistically significant difference versus Vehicle for subjects receiving CD5789 50 µg/g Cream (LS mean -54.75; p=0.060; Table 4) and CD5789 100 µg/g Cream (LS mean -54.99; p=0.054; Table 4).

The percent changes from Baseline in total lesion count at Week 12 were also greater in subjects receiving active treatment than in subjects receiving Vehicle; the differences were statistically significant for subjects receiving CD5789 100 µg/g Cream (mean -50.72%; p=0.038; Table 4) and Tazarotene 0.1% Gel (mean -55.07%; p=0.003; Table 4). The results showed a trend towards a statistically significant difference versus Vehicle for subjects receiving CD5789 25 µg/g Cream (mean -47.59%; p=0.067; Table 4) and CD5789 50 µg/g Cream (mean -49.87%; p=0.054; Table 4).

Table 4 **Primary efficacy endpoint: absolute and % change in total lesion count from Baseline to Week 12 using LOCF (ITT population)**

Total lesion count Change from Baseline		CD5789 25 µg/g Cream (N=61)	CD5789 50 µg/g Cream (N=61)	CD5789 100 µg/g Cream (N=60)	Tazarotene 0.1% Gel (N=61)	Vehicle (N=61)
Absolute change	Mean (SD)	-44.16 (31.441)	-40.02 (19.412)	-43.18 (24.282)	-49.41 (33.262)	-35.84 (27.226)
	LS Mean (SE)	-53.61 (8.314)	-54.75 (8.261)	-54.99 (8.296)	-59.84 (8.301)	-46.87 (7.934)
	Difference from Vehicle	-6.74	-7.88	-8.11	-12.97	-
	95% CI [a]	(-14.96, 1.48)	(-16.11, 0.34)	(-16.35, 0.13)	(-21.18, -4.76)	-
	P-value vs. Vehicle [b]	0.108	0.060	0.054	0.002	-
	Treatment by Stratum Interaction [c]	0.414	-	-	-	-
% change	Mean (SD)	-47.59 (28.474)	-49.87 (24.731)	-50.72 (24.885)	-55.07 (26.295)	-40.48 (28.968)
	P-value vs. Vehicle [d]	0.067	0.054	0.038	0.003	-

Data source: Table 14.2.1.1

[a] The 95% confidence interval on the difference between Vehicle and the specified treatment group LS means.

[b] P-value vs. Vehicle is from the pairwise comparisons of LS means between Vehicle and the specified treatment group using analysis of covariance (ANCOVA) with terms for treatment, stratum, and Baseline lesion count as covariate.

[c] P-value for treatment by stratum interaction is from analysis of covariance (ANCOVA) with terms for treatment, stratum, treatment*stratum, and with Baseline lesion count as covariate.

[d] P-value vs. Vehicle is from the pairwise comparisons of percent changes in lesion counts using Cochran-Mantel-Haenszel test stratified by stratum with row mean score statistic and RIDIT scores.

Secondary efficacy criteria

- SR2

At Week 12, achievement of SR2 was also higher in subjects receiving active treatment than in subjects receiving Vehicle; the difference was statistically significant for subjects receiving Tazarotene 0.1% Gel ($p<0.05$ in the ITT population; Table 5). A modest numerical dose-response relationship was observed with active CD5789 Cream with SR2 increasing with increasing dose strength.

Table 5 **Secondary efficacy endpoint: Success Rate 2: % of subjects rated "Clear" (Grade 0) or "Almost clear" (Grade 1) with at least a 2-point reduction in IGA score from Baseline to Week 12 using LOCF (ITT population)**

Success rate 2 (SR2)	CD5789 25 µg/g Cream (N=61)	CD5789 50 µg/g Cream (N=61)	CD5789 100 µg/g Cream (N=60)	Tazarotene 0.1% Gel (N=61)	Vehicle (N=61)
Success Rate	13.11	14.75	16.67	21.31	8.20
Difference from Vehicle	4.918	6.557	8.470	13.115	-
95% CI [a]	(-7.637, 17.473)	(-6.333, 19.448)	(-4.858, 21.798)	(-0.894, 27.123)	-
P-value vs. Vehicle [b]	0.382	0.261	0.168	0.046	-
Treatment by Stratum Interaction [c]	0.885	0.636	0.447	0.190	-

Data source: Table 14.2.1.1

[a] The 95% confidence interval on the difference between Vehicle and the specified treatment group success rates was based on normal approximation with continuity correction (Fleiss 1981).

[b] P-value vs. Vehicle is based on Cochran-Mantel-Haenszel test with general association statistic, controlling for stratum.

[c] P-value for treatment by stratum interaction is from Breslow-Day test for homogeneity of the odds ratio across stratum.

- Inflammatory and non-inflammatory lesion counts

Trends observed with total lesion count were comparable with the trends seen in non-inflammatory lesion counts with statistical significance in subjects receiving CD5789 100 µg/g Cream and Tazarotene 0.1% Gel ($p<0.05$ for absolute and % change in the ITT population; Table 6). Changes in inflammatory lesion count also showed similar overall trends but with statistical significance in subjects receiving CD5789 50 µg/g Cream ($p<0.05$ for % change in the ITT population only; Table 6).

In subjects receiving CD5789, the greatest mean decrease in absolute and percentage inflammatory lesion count from baseline was seen with CD5789 50 µg/g Cream (LS

mean -24.87, p=0.074 and mean -53.14%, p=0.031; Table 6) and the greatest mean absolute and percentage decrease in non-inflammatory lesion count from baseline was seen with CD5789 100 µg/g Cream (LS mean of -32.72, p=0.035, and mean -49.57%, p=0.015; Table 6); no apparent dose relationship was observed.

Table 6 **Secondary efficacy endpoints: absolute and % change in inflammatory and non-inflammatory lesion counts from Baseline to Week 12 using LOCF (ITT population)**

Lesion count change from Baseline		CD5789 25 µg/g Cream (N=61)	CD5789 50 µg/g Cream (N=61)	CD5789 100 µg/g Cream (N=60)	Tazarotene 0.1% Gel (N=61)	Vehicle (N=61)
Inflammatory lesion count: absolute change	Mean (SD)	-19.67 (14.874)	-21.11 (13.268)	-19.32 (11.566)	-21.03 (13.890)	-17.74 (15.073)
	LS Mean (SE)	-23.26 (4.178)	-24.87 (4.172)	-23.10 (4.179)	-24.64 (4.177)	-21.10 (4.005)
	Difference from Vehicle	-2.16	-3.77	-2.00	-3.54	-
	95% CI [a]	(-6.30, 1.98)	(-7.92, 0.38)	(-6.16, 2.16)	(-7.68, 0.60)	-
	P-value vs. Vehicle [b]	0.306	0.074	0.345	0.094	-
	Treatment by Stratum Interaction [c]	0.422	-	-	-	-
% change	Mean (SD)	-49.16 (35.711)	-53.14 (30.187)	-51.93 (27.255)	-53.09 (29.484)	-41.70 (35.898)
	P-value vs. Vehicle [d]	0.154	0.031	0.107	0.059	-
Non-inflammatory lesion count: absolute change	Mean (SD)	-24.30 (21.633)	-18.69 (12.895)	-23.70 (18.390)	-28.26 (26.346)	-17.70 (17.745)
	LS Mean (SE)	-30.97 (5.380)	-30.90 (5.352)	-32.72 (5.370)	-35.95 (5.373)	-26.98 (5.131)
	Difference from Vehicle	-3.99	-3.92	-5.74	-8.98	-
	95% CI [a]	(-9.33, 1.34)	(-9.25, 1.41)	(-11.09, -0.40)	(-14.31, -3.65)	-
	P-value vs. Vehicle [b]	0.142	0.149	0.035	0.001	-
	Treatment by Stratum Interaction [c]	0.491	-	-	-	-
% change	Mean (SD)	-46.34 (30.888)	-45.26 (29.331)	-49.57 (29.786)	-55.88 (28.913)	-38.20 (30.368)
	P-value vs. Vehicle [d]	0.049	0.192	0.015	<0.001	-

Data source: Table 14.2.1.1

[a] The 95% confidence interval on the difference between Vehicle and the specified treatment group LS means.

[b] P-value vs. Vehicle is from the pairwise comparisons of LS means between Vehicle and the specified treatment group using analysis of covariance (ANCOVA) with terms for treatment, stratum, and Baseline lesion count as covariate.

[c] P-value for treatment by stratum interaction is from analysis of covariance (ANCOVA) with terms for treatment, stratum, treatment*stratum, and with Baseline lesion count as covariate.

[d] P-value vs. Vehicle is from the pairwise comparisons of percent changes in lesion counts using Cochran-Mantel-Haenszel test stratified by stratum with row mean score statistic and RIDIT scores.

- Other efficacy analyses

There was a decrease in IGA score (improvement) from Baseline to Week 12 in 63.9% to 75.3% subjects across the treatment groups. Improvements in subject assessment of acne were statistically significant compared to Vehicle in subjects receiving CD5789 100 µg/g Cream ($p<0.05$). Absolute and percentage mean decreases in lesion count from Baseline to Week 12 were observed with each lesion type in all treatment groups.

- Exploratory efficacy analyses
    - Subgroup analyses

Summaries of the co-primary efficacy endpoints (SR1 and total lesions counts) across the subgroups showed a greater response in Stratum 2 subjects compared to Stratum 1 subjects, in subjects with Baseline IGA 4 (severe) compared to IGA 3 (moderate), and in females compared to males; however, the trends across the subgroups were not consistent within each active treatment group when comparing differences to Vehicle. A greater response was seen in adult subjects (18 to 35 years) compared to children (12 to 17 years) except for with CD5789 25 µg/g Cream. A greater SR1 response was seen in non-Caucasians compared to Caucasians except for with CD5789 50 µg/g Cream and no differences were observed between the races for changes in total lesion counts.

- Phase 3 endpoints for acne vulgaris

	The efficacy results of the 148 subjects with moderate acne (Baseline IGA of 3) in terms of success rate (clear/almost clear with at least a 2 grade improvement from baseline) and inflammatory and non-inflammatory lesion counts (absolute and % changes) support the use of CD5789. - Relationship between CD5789 dose and success rate The exploratory analyses on relationship between CD5789 dose and success rate (SR1 and SR2) did not show a dose-response relationship. A modest numerical dose-response relationship was observed with SR2 (Table 5). - Other analyses No changes of any clinical relevance were observed in atrophic acne scar assessments, truncal acne assessments, dermatology life quality indices, or acute health surveys.
21. Safety outcomes	Median study duration was 99 days (approximately 14 weeks) and median study treatment duration was 84 days (12 weeks). The total number of applications on the face was consistent with once daily treatment over the 12 week study. The percentages of subjects who reported TEAEs in the CD5789 25 µg/g Cream and CD5789 50 µg/g Cream groups were similar to Vehicle (26.2% and 27.9% versus 29.5%), and higher than Vehicle in the CD5789 100 µg/g Cream and Tazarotene 0.1% Gel groups (38.3% and 39.3%) (Table 7). No deaths were reported during the study. Three SAEs were reported by 3 subjects, all of which were considered unrelated to study treatment and led to study withdrawal: pregnancy led to study withdrawal and was followed by the SAE of abortion spontaneous in 2 subjects (CD5789 25 µg/g Cream and Vehicle) and depression in 1 subject (CD5789 50 µg/g Cream). Adverse events led to the withdrawal of a further 3 subjects with non-serious AESIs of local tolerability, all of which were considered to be related to study treatment (Tazarotene 0.1% Gel in 1 subject and CD5789 100 µg/g Cream in 2 subjects). One further subject who was receiving Tazarotene 0.1% Gel had an AESI of lymphadenopathy, however the subject continued study drug and completed the study. Most TEAEs reported were within the SOC Infections and infestations in all treatment groups with a similar frequency across each treatment group (between 11.5% and 18.3%). The TEAEs reported by the highest proportion of subjects in this SOC were nasopharyngitis (CD5789 25 µg/g Cream, CD5789 100 µg/g Cream, and Tazarotene 0.1% Gel) and upper respiratory tract infection (Vehicle). Treatment-emergent AEs in the SOC Skin and subcutaneous tissues disorders were reported by more subjects in the active treatment groups, with the greatest frequency in subjects receiving CD5789 100 µg/g Cream and Tazarotene 0.1% Gel compared to Vehicle (18.3% and 14.8% versus 1.6%). The TEAE with the greatest difference between active treatment and Vehicle was skin irritation which was only reported in subjects receiving CD5789 100 µg/g Cream or Tazarotene 0.1% Gel (10.0% and 8.2%). The drug-related TEAE reported by the highest proportion of subjects was also skin irritation, which was considered to be related in all but one of the subjects who reported it as a TEAE (Table 8). Analysis of TEAEs by stratum showed some differences in the overall number of subjects who reported at least one TEAE in the CD5789 25 µg/g Cream and CD5789 100 µg/g Cream groups, however the differences seen were not consistent between the two groups. The frequency and type of TEAEs reported in each stratum were similar to the overall population. Analysis of TEAEs by age group, suggested that TEAEs were more common with active treatment than compared to Vehicle in the 18 to 35 year age group but not in the 12 to 17 year age group and in females than in males, except for in the CD5789 50 µg/g Cream

group where the opposite trend was observed. There did not appear to be any differences in TEAEs reported by subjects receiving CD5789 when analyzed by race.

Table 7 Overview of adverse events (safety population)

AE Category	CD5789 25 µg/g Cream (N=61)			CD5789 50 µg/g Cream (N=61)			CD5789 100 µg/g Cream (N=60)			Tazarotene 0.1% Gel (N=61)			Vehicle (N=61)		
	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
Any TEAE	16	(26.2)	23	17	(27.9)	24	23	(38.3)	32	24	(39.3)	43	18	(29.5)	27
TEAE Leading to Study Withdrawal	0		0	1	(1.6)	1	2	(3.3)	2	1	(1.6)	3	0		0
SAE	1	(1.6)	1	1	(1.6)	1	0		0	0		0	1	(1.6)	1
AESI	0		0	0		0	2	(3.3)	2	2	(3.3)	4	0		0

Source data: Table 14.3.2.1

Note: If a subject has multiple AEs within the same category, the subject is presented only once in the respective subject count [n (%)]. Each event reported is included in the event count (E). Treatment-emergent AEs are defined as AEs that started after the first dose of study treatment. Percentages are based on the number of subjects in the safety population in each treatment group.

Table 8 Related adverse events (safety population)

AE Category Preferred Term	CD5789 25 µg/g Cream (N=31)			CD5789 50 µg/g Cream (N=31)			CD5789 100 µg/g Cream (N=30)			Tazarotene 0.1% Gel (N=31)			Vehicle (N=31)		
	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
Any Drug-Related Treatment-Emergent Adverse Events	2	(3.3)	2	1	(1.6)	1	9	(15.0)	12	7	(11.5)	15	0	-	0
Skin irritation	0	-	0	0	-	0	6	(10.0)	7	4	(6.6)	4	0	-	0
Skin burning sensation	0	-	0	1	(1.6)	1	0	-	0	2	(3.3)	2	0	-	0
Erythema	0	-	0	0	-	0	1	(1.7)	1	1	(1.6)	1	0	-	0
Pain of skin	0	-	0	0	-	0	1	(1.7)	1	1	(1.6)	1	0	-	0
Pruritus	0	-	0	0	-	0	1	(1.7)	1	1	(1.6)	1	0	-	0
Skin exfoliation	0	-	0	0	-	0	1	(1.7)	1	1	(1.6)	1	0	-	0
Cheilitis	0	-	0	0	-	0	0	-	0	1	(1.6)	1	0	-	0
Dry skin	1	(1.6)	1	0	-	0	0	-	0	0	-	0	0	-	0
Dyshidrosis	0	-	0	0	-	0	0	-	0	1	(1.6)	1	0	-	0
Lymphadenopathy	0	-	0	0	-	0	0	-	0	1	(1.6)	1	0	-	0
Overdose	0	-	0	0	-	0	0	-	0	1	(1.6)	1	0	-	0
Pityriasis alba	0	-	0	0	-	0	0	-	0	1	(1.6)	1	0	-	0
Rash	1	(1.6)	1	0	-	0	0	-	0	0	-	0	0	-	0
Skin hypopigmentation	0	-	0	0	-	0	1	(1.7)	1	0	-	0	0	-	0

Source data: Table 14.3.3.4.1

Note: Adverse events are coded using MedDRA version 13.0. If a subject has multiple occurrences of an AE, the subject is presented only once in the respective subject count. Events are counted each time in the event (E) column. Treatment-emergent AEs are defined as AEs that started after the first dose of study treatment. Percentages are based on the number of subjects in the safety population in each treatment group.

The proportions of subjects with no signs or symptoms of local tolerability at Baseline were similar across the treatment groups. The proportions of subjects experiencing signs or symptoms post-Baseline (worst scores) were higher than at Baseline in all treatment groups, particularly with active treatment. In all active treatment groups, the mean scores for the signs and symptoms of local tolerability were increased from Baseline over the 12 weeks of treatment, with a peak at Week 1, compared to Vehicle for which mean scores remained similar to Baseline throughout the 12 week treatment period. The only exception to this trend was seen with CD5789 100 µg/g Cream in which mean scores of erythema peaked at Week 4. For all treatment groups, the mean scores represented mild signs and symptoms. Worst post-Baseline scores for all signs and symptoms were moderate or severe and worse than Baseline in a similar proportion of subjects receiving CD5789 100 µg/g Cream or Tazarotene 0.1% Gel and higher than in subjects receiving CD5789 25 µg/g Cream or CD5789 50 µg/g Cream (Table 9).

Table 9 **Local tolerability signs and symptoms –scores worse than Baseline that were moderate or severe (safety population)**

Sign/symptom	CD5789 25 µg/g Cream (N=61)	CD5789 50 µg/g Cream (N=61)	CD5789 100 µg/g Cream (N=60)	Tazarotene 0.1% Gel (N=61)	Vehicle (N=61)
Worse than Baseline with worst score post-Baseline moderate or severe					
n	61	61	59	61	60
Erythema	12 (19.7)	10 (16.4)	17 (28.8)	16 (26.2)	4 (6.7)
Scaling	13 (21.3)	18 (29.5)	22 (37.3)	23 (37.7)	2 (3.3)
Dryness	14 (23.0)	17 (27.9)	17 (28.8)	16 (26.2)	3 (5.0)
Stinging / burning	13 (21.3)	9 (14.7)	15 (25.4)	20 (32.8)	1 (1.7)

There were no clinically significant mean changes from Baseline to Week 12 in blood hematology or chemistry, vital signs, or ECG parameters. In the overall safety population, shifts from normal to low AST were greater than shifts from low to normal AST and were notably different from Vehicle for subjects receiving CD5789 25 µg/g Cream. For all blood chemistry and hematology parameters, no shifts were observed in the majority of subjects and no clinically significant changes compared to Vehicle were observed. There were no clinically significant changes in vital signs from Baseline to Week 12 in any individual subject.

22. Summary (conclusion)

In subjects with moderate or severe acne vulgaris, facial treatment with CD5789 50 µg/g Cream, CD5789 100 µg/g Cream, or Tazarotene 0.1% Gel was shown to have a positive effect versus Vehicle on the reduction of IGA scores and/or reduction in absolute or percent total lesion count. CD5789 50 µg/g was shown to be more effective than CD5789 25 µg/g and CD5789 100 µg/g Cream in terms of 2-point reduction of IGA scores (SR1) and percent decrease in inflammatory lesion count, but less effective on total lesion count and SR2 ('Clear' or 'Almost Clear' on IGA) than CD5789 100 µg/g Cream.

As expected with topical retinoids, local tolerability signs and symptoms were increased in all active treatment groups and were comparable in subjects receiving CD5789 100 µg/g Cream or Tazarotene 0.1% Gel. Mean local tolerability signs and symptoms peaked in severity at Week 1, except for in subjects receiving CD5789 100 µg/g Cream in which elevated mean scores of erythema were more prolonged, with a peak at Week 4. Local tolerability of CD5789 50 µg/g Cream was better than with CD5789 100 µg/g Cream and Tazarotene 0.1% Gel. This was also observed with spontaneously reported AEs where skin and subcutaneous tissue disorders were reported in fewer subjects receiving CD5789 50 µg/g Cream than subjects receiving CD5789 100 µg/g Cream.

The objective of this study was to identify a safe and effective concentration of CD5789 Cream to be evaluated in Phase 3 studies. Over 12 weeks of treatment, in the overall study population the dose strength of CD5789 25 µg/g Cream represented the minimally effective dose, whereas CD5789 50 µg/g Cream and CD5789 100 µg/g Cream were both determined to be efficacious with only a modest efficacy advantage in favor of the higher dose. Although both doses of 50 µg/g and 100 µg/g of CD5789 provide a positive benefit risk ratio in the treatment of acne vulgaris, the superior safety and local tolerability profile of CD5789 50 µg/g Cream argues in favor of carrying this dose forward in Phase 3.

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

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

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD-06-SPR-40182 - Pharmacokinetics study of CD5789 cream 50 and 100 µg/g in subjects with severe acne vulgaris under maximal use conditions
6. Clinical study phase	Phase 1
7. Clinical study period	Date of first screened: 25 October 2012 Date of last subject completed: 23 August 2013
8. Countries where clinical study was conducted	Germany – Hungary – United States of America (USA)
9. Number of subjects	A total of 68 subjects were screened and 39 were randomized at 6 centers in 3 countries (3 in Germany, 2 in Hungary and 1 in the USA) to receive CD5789 50 µg/g (21 subjects) or CD5789 100 µg/g (18 subjects). All 39 subjects comprised the Safety population.

	In total, 36 subjects completed the study: there were 2 study withdrawals in the CD5789 50 µg/g group early in the study (after 1 and 3 days) and 1 in the CD5789 100 µg/g group (after 29 days). Data from the 2 subjects who withdrew from the CD5789 50 µg/g group were not included in the PK analysis. One subject in the CD5789 100 µg/g group missed his visit at Day 10 and his data were still included in the PK analyses for the other PK time points (Table 1 below)
10. Aim and secondary purposes of clinical study	To assess the systemic exposure of CD5789 after repeated once daily topical application of CD5789 50 µg/g and 100 µg/g cream in subjects with severe acne vulgaris i.e. an Investigator's Global Assessment (IGA) of 4, with at least 30 non-inflammatory lesions and at least 40 inflammatory lesions on the face over 4 weeks. This assessment was done through determination of the pharmacokinetic (PK) parameters under maximized conditions of use (subjects treated with 2 g of cream on zones potentially affected by acne lesions: face, shoulders, upper back and upper chest except the neck) (Guidance for Industry: Acne Vulgaris: Developing Drugs for Treatment, 2005).
11. Clinical study design	This study was a Phase 1, multicenter, randomized, double-blind, parallel group study involving subjects with acne vulgaris on the face with a severity of 4 on the IGA scale with at least 30 non-inflammatory lesions and at least 40 inflammatory lesions on the face at Screening Visit and Day 1 (Baseline) Visit. The study consisted of a screening period of maximum 14 days, a 29-day period of once daily treatment, followed by a 3-day follow-up period. At Baseline, subjects who fulfilled all inclusion and exclusion criteria were randomly assigned to either the CD5789 50 µg/g group or the CD5789 100 µg/g group. During the treatment period between Day 1 and Day 29 Visits, the study treatment application i.e. 29 applications in total were performed by a qualified person on the face, shoulders, upper back, and upper chest except the neck and starting in the acne-affected areas. The total amount of CD5789 50 µg/g or 100 µg/g cream applied per application was 2 g. The study treatment application was performed on Day 1 between 7:30 and 9:30 AM and at the same time as the first day ±30 min for the following 28 days. During the treatment period, blood samples for determination of CD5789 concentration in plasma were drawn at specific times on Days 1, 2, 10, 15, 16, 22, and 29 (Table 1). Blood samples for PK analysis were also drawn during the 3-day follow-up period, 24, 48, and 72 hours after the last treatment application. **Table 1 Pharmacokinetic Selected Study Periods and Time Points** | PK Sampling Day	Day 1	Day 2	Day 10	Day 15	Day 16	Day 22	Day 29 / Early Termination	Day 30	Day 31	Day 32
---	---	---	---	---	---	---	---	---	---	---
Plasma samples time points [a]	2, 4, 6, 8, 10, 12, and 16 hours after the initial dose	24 hours after initial dose (Pre-dose)	Pre-dose	Pre-dose, 2, 4, 6, 8, 10, 12, and 16 hours after the morning dose	24 hours after Day 15 dose (Pre-dose)	Pre-dose	Pre-dose, 2, 4, 6, 8, 10, 12, and 16 hours after the morning dose	24 hours after last dose on Day 29	48 hours after last dose on Day 29	72 hours after last dose on Day 29
Systemic PK parameters	C_{max}, T_{max}, AUC_{0-24h}	C_{trough}	C_{trough}	C_{trough}, C_{max}, T_{max}, AUC_{0-24h}	C_{trough}	C_{trough}	C_{trough}, C_{max}, T_{max}, AUC_{0-24h}, AUC_{0-t}, AUC_{0-inf}, K_{el}, $T_{1/2}$				 PK = Pharmacokinetic; C_{trough} = Residual drug concentration (pre-dose level); C_{max} = Observed peak drug concentration; T_{max} = Time at which C_{max} occurred; AUC_{0-24h} = Area under the concentration-time curve from pre-dose through 24 hours post-dosing; AUC_{0-t} = Area under the concentration-Time curve from T0 up to the sampling time corresponding to the last quantifiable concentration; AUC_{0-inf} = Area under the concentration-time curve from T0 to extrapolated to time infinity; K_{el} = Elimination rate constant value; $T_{1/2}$ = Terminal half-life value; T0 = Pre-dose time. [a]. Sampling times were determined from time of the application start.
12. Main inclusion criteria	Key inclusion criteria: Male and female subjects, aged 18-35 years, with acne vulgaris on the face with a severity grade of 4 on the IGA scale with at least 30 non-inflammatory lesions and at least 40 inflammatory lesions on the face at Screening and Baseline Visits.
13. Investigational medicinal	CD5789 cream, topical administration, strength: 50 or 100 µg/g

<table>
<tr><td>product, method of administration, strength</td><td>Test product dosage form
<table>
<tr><th></th><th>Investigational Product</th><th>Comparator</th></tr>
<tr><td>Trade Name or equivalent (if applicable)</td><td>NA</td><td>NA</td></tr>
<tr><td>Name of Drug Substance (INN)</td><td>NA</td><td>NA</td></tr>
<tr><td>Internal code (if applicable)</td><td>CD5789</td><td>NA</td></tr>
<tr><td>Pharmaceutical Form</td><td>Cream</td><td>NA</td></tr>
<tr><td>Concentration</td><td>50 or 100 µg/g</td><td>NA</td></tr>
<tr><td>Packaging (type and size)</td><td>Megaplast Bottle 50 mL</td><td>NA</td></tr>
<tr><td>Storage Conditions</td><td>Store below 25°C – Do not freeze or refrigerate</td><td>NA</td></tr>
<tr><td>Dosage (total daily dose)</td><td>2 g (2 mg/cm²)</td><td>NA</td></tr>
<tr><td>Dose regimen</td><td></td><td></td></tr>
<tr><td>Route</td><td>Topically</td><td>NA</td></tr>
<tr><td>Frequency</td><td>Daily</td><td>NA</td></tr>
<tr><td>Duration of administration</td><td>29 days</td><td>NA</td></tr>
<tr><td>Location of treated area</td><td>Face, shoulders, upper back and upper chest, except the neck</td><td>NA</td></tr>
</table>
NA = Not applicable.</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>- Adverse Events (AEs) monitored throughout the course of the clinical study.
- Laboratory safety tests: hematology and blood chemistry at Screening and Day 29 Visits and urine drug screen (UDS) at the Screening Visit.
- Local tolerability assessment (erythema, scaling, dryness, and stinging/burning) performed on Day 1, Day 15, Day 22 and Day 29 Visits by the Investigator using a 4-point scale (0: none to 3: severe).
- Physical examination at Screening, Day 1, and Day 29 Visits.
- Vital signs at Screening, Day 1, Day 15, and Day 29 Visits.
- Electrocardiograms (ECGs) at Screening and Day 29 Visits.

All randomized subjects who have received the treatment at least once were included in the safety analysis.

Local tolerability was summarized using means over time, frequency by severity over time, and for worst response across visits by zone and treatment. Time to first switch (for any treated areas) was also summarized in terms of frequency by treatment. The incidence of AEs was summarized in frequency tables by System Organ Class (SOC) and Preferred Term (PT) for each treatment. Physical examination, vital signs and ECG results, as well as laboratory parameters, were summarized by descriptive statistics. Shift tables for the laboratory data were prepared for each laboratory parameter.</td></tr>
<tr><td>18. Statistical methods</td><td>This main purpose of this study was to assess the systemic exposure of CD5789 after repeated once daily topical application through determination of PK parameters under</td></tr>
</table>

maximized conditions of use. Therefore, there were no primary or secondary efficacy endpoints.

Inferential statistical analysis

All randomized subjects with no major protocol deviation were included in the PK set. The following analyses were to be performed separately for each treatment group to evaluate the time effect, if sufficient quantifiable data. The parameters including C_{trough}, AUC_{0-24h}, and C_{max} were submitted, after logarithmic transformation (Ln), to an analysis of variance. 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 time points (Days 1, 15 and 29 for AUC_{0-24h} and C_{max}; Days 2, 10, 15, 16, 22, and 29 for C_{trough}) 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 following analyses were to be performed separately by study day to evaluate the group effect, if sufficient quantifiable data. The parameters including C_{trough}, AUC_{0-24h}, and C_{max} were submitted after Ln transformation, to an analysis of variance. The model included Group 1 as factor and 90% CIs of the pairwise differences between groups on the Ln scale were calculated. The limits of the intervals were back-transformed into exponential to obtain 90% CIs of the ratios of geometric means between groups, on the original scale.

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

Table 2 Demographic Data - All Subjects

		CD5789 50 µg/g	CD5789 100 µg/g	TOTAL
Age (Years)	N	21	18	39
	Mean	20.81	21.78	21.26
	SD	3.44	4.25	3.82
	Median	19.00	20.00	20.00
	Min-Max	18-31	18-34	18-34
	Q1-Q3	19-22	19-22	19-22
	18 to 64 Years N (%)	21 (100.0)	18 (100.0)	39 (100.0)
Gender	N	21	18	39
	Female N (%)	5 (23.8)	4 (22.2)	9 (23.1)
	Male N (%)	16 (76.2)	14 (77.8)	30 (76.9)
Race	N	21	18	39
	White N (%)	21 (100.0)	18 (100.0)	39 (100.0)

SD = Standard deviation; Min = Minimum; Max = Maximum; Q1 = First quartile (25%); Q3 = Third quartile (75%).

At Baseline, the distribution of age, gender, and race in the overall population was comparable for both treatment groups. The majority of subjects were male (76.2% and 77.8% in the CD5789 50 µg/g and 100 µg/g groups, respectively), and the 9 women were of childbearing potential: 8/9 women were taking medical contraception and 1/9 women used a hormonal intra-uterine device. The subjects were all Caucasians, and the overall mean age (± standard deviation [SD]) was 21.26 years (±3.82), with a median of 20.00 years and a minimum of 18 years and a maximum of 34 years.

20. Efficacy outcomes

Not Applicable

21. Safety outcomes

Table 6 Overview of Adverse Events - Safety Population

	CD5789 50 µg/g (N=21)		CD5789 100 µg/g (N=18)	
	N events	N(%) subjects	N events	N(%) subjects
All AEs	97	14 (66.7)	114	16 (88.9)
Related AEs	66	12 (57.1)	106	15 (83.3)
All dermatologic AEs	74	13 (61.9)	107	15 (83.3)
Related dermatologic AEs	66	12 (57.1)	106	15 (83.3)
All serious AEs	0	0	0	0
Related serious AEs	0	0	0	0
Severe AEs	0	0	1	1 (5.6)
Related severe AEs	0	0	1	1 (5.6)
AEs of Special Interest	0	0	1	1 (5.6)
Related AEs of Special Interest	0	0	1	1 (5.6)
AEs leading to discontinuation	0	0	0	0
Related AEs leading to discontinuation	0	0	0	0
Deaths	0	0	0	0

AE = Adverse event.

Notes: AEs were defined as events that occurred the day of the first study medication application or after.

Numbers in columns cannot be added because a given subject could report more than one AE.

Overall, when pooling both CD5789 concentrations, 211 treatment-emergent AEs (TEAEs) were reported: 97 in the CD5789 50 µg/g group and 114 in the CD5789 100 µg/g group. The proportion of subjects who reported TEAEs was higher in the CD5789 100 µg/g group (16/18 subjects, 88.9%) than in the CD5789 50 µg/g group (14/21 subjects, 66.7%).

A total of 181 dermatologic TEAEs were reported: 74 reported by 13/21 subjects (61.9%) in the CD5789 50 µg/g group and 107 reported by 15/18 subjects (83.3%) in the CD5789 100 µg/g group.

Table 7 Related Adverse Events - Safety Population

		CD5789 50 µg/g (N=21) N (%)	CD5789 100 µg/g (N=18) N (%)
TOTAL NUMBER OF AEs		66	106
TOTAL NUMBER OF SUBJECTS WITH AEs		12 (57.1)	15 (83.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		12 (57.1)	15 (83.3)
	Erythema	9 (42.9)	13 (72.2)
	Skin irritation	6 (28.6)	9 (50.0)
	Pruritus	2 (9.5)	5 (27.8)
	Skin exfoliation	3 (14.3)	5 (27.8)
	Skin burning sensation	2 (9.5)	3 (16.7)
	Dry skin	-	1 (5.6)
	Pain of skin	-	1 (5.6)
	Skin erosion	1 (4.8)	-

AE = Adverse event; SOC = System organ class; PT = Preferred term.

Notes: Treatment-emergent AEs were defined as events that occurred the day of the first study medication application or after.

A subject was counted once per PT even if more than 1 occurrence of the event was experienced.

A subject was counted once per SOC even if more than 1 event was experienced within the SOC.

Overall, 172/181 dermatologic TEAEs, all of which were in the SOC Skin and Subcutaneous Disorders, were considered related to the study treatment: 66 reported by 12/21 subjects (57.1%) in the CD5789 50 µg/g group and 106 reported by 15/18 subjects (83.3%) in the CD5789 100 µg/g group. The percentage of subjects reporting TEAEs in this SOC was higher in the CD5789 100 µg/g group than in the CD 5789 50 µg/g group. In total, 42.9% and 72.2% of subjects experienced erythema, 28.6% and 50.0% skin

	irritation, and 9.5% and 27.8% had pruritus in the CD5789 50 µg/g and 100 µg/g groups, respectively. All reported TEAEs except one were of mild or moderate severity: one TEAE of skin irritation on the upper back reported on Day 15 by one subject in the CD5789 100 µg/g was severe. There was one AE of special interest (AESI) reported by one subject in the CD5789 100 µg/g group: this AESI of suspected contact allergy on the shoulders and back, which was finally update as a cutaneous irritation, was of moderate intensity and assessed as related to the study treatment by the Investigator. There were no deaths, no serious AEs (SAEs) and no TEAEs leading to discontinuation. Overall, the worst scores for local tolerability including erythema, scaling, dryness, and stinging/burning were higher in the CD5789 100 µg/g group than in the CD5789 50 µg/g group over the treatment period, indicating that the 100 µg/g cream was less well tolerated than the 50 µg/g cream. This trend was confirmed after analysis of the first switch to a different area to be treated: subjects in the 100 µg/g group had to switch to a different area earlier than subjects in the 50 µg/g group and the percentage of subjects who did not have to switch areas was higher in the CD5789 50 µg/g group than in the CD5789 100 µg/g group. No safety concerns with either the 50 or 100 µg/g creams were raised after assessment of clinical laboratory safety tests including hematology, blood chemistry and urine screen test, vital signs, physical examinations or ECGs.
22. Summary (conclusion)	This study was conducted in male and female subjects aged 18 to 34 years old presenting severe acne vulgaris with an IGA score of 4, with at least 30 non-inflammatory lesions and at least 40 inflammatory lesions on the face. It aimed at assessing the systemic exposure of CD5789 after repeated once daily topical application of CD5789 50 µg/g and 100 µg/g creams. This assessment was done through determination of the PK parameters under maximal conditions of use. The study treatment was applied in a once daily regimen over a 29-day period on all skin areas potentially affected by acne (i.e. face, upper back, upper chest and shoulders). Repeated daily topical application of CD5789 cream in adult subjects resulted in very low systemic exposure. Overall, only 37% of subjects in the CD5789 50 µg/g group and 61% in the CD5789 100 µg/g group had quantifiable CD5789 plasma levels after 29 days of application. In the CD5789 50 µg/g group, the most exposed subject had a C_{max} of 7.9 pg/mL and an $AUC_{0\text{-}24h}$ of 104 pg.hr/mL at Day 29 (Male, 19 years old). In the CD5789 100 µg/g group the most exposed subject had a C_{max} of 49 pg/mL and an $AUC_{0\text{-}24h}$ of 456 pg.hr/mL (Female, 21 years old). CD5789 was characterized by a rapid absorption phase with a short and reproducible T_{max} (approximately 4 hours) and a short terminal $t_{1/2}$ (from 2.4 to 9.1 hours). No statistical demonstration of steady state (i.e. time effect) and dose proportionality (i.e. dose effect) could be performed in this study due to a high number of subjects with non-quantifiable plasma levels, specifically in the lower dose group. However, exposure of subjects in the CD5789 100 µg/g group to a higher dose of CD5789 in comparison to those in the CD5789 50 µg/g group increased the systemic exposure. Similarly, the comparable geometric C_{max} and $AUC_{0\text{-}24h}$ means at Day 15 and Day 29 determined in the CD5789 100 µg/g group supported that no accumulation occurred over a 29-day period of topical treatment with CD5789 50 or 100 µg/g creams and that steady state conditions were achieved after 2 weeks of treatment. Furthermore, the absence of accumulation was consistent with the short absorption phase, the short terminal $t_{1/2}$ and the non-quantifiable systemic residual concentrations in most subjects. The overall PK

	profile of CD5789 supported that accumulation of CD5789 was unlikely to occur after longer duration of treatment. In addition, metabolism investigations performed using validated analytical methods for the three pharmacologically active metabolites in vitro (CD06530, CD06700 and CD09986) and the inactive one (CD09717), showed that all plasma concentrations of CD06700 and CD09717 were below the limit of quantification (<10 pg/mL). For CD06530, only 2 subjects treated with the highest strength of CD5789 cream (i.e. 100 µg/g) displayed low quantifiable levels. For CD09986, only one subject displayed low quantifiable levels. Overall, no metabolites were quantified in adult acne subjects treated under maximal use conditions with 2 g of CD5789 50 µg/g Cream. Assessment of the disease severity confirmed that this study was conducted on subjects with severe acne ensuring an adequate assessment of CD5789 transdermal penetration in the targeted disease population under maximal use conditions. Safety assessment showed that the percentages of subjects with at least one TEAE and with related TEAEs were higher in the CD5789 100 µg/g group than in the CD5789 50 µg/g group. The related AEs were all in the SOC Skin and Subcutaneous Disorders. One subject in the CD5789 100 µg/g group experienced a severe skin irritation considered related to the study treatment by the Investigator. There was one AESI of cutaneous irritation reported by one subject in the CD5789 100 µg/g group. There were no SAEs and no TEAEs leading to discontinuation. Overall, local tolerability evaluation showed that the 100 µg/g cream was less well tolerated than the 50 µg/g cream. This trend was confirmed by a higher number of subjects who had to switch to a different area to be treated in the 100 µg/g group than in the CD5789 50 µg/g group. No safety concerns with either the 50 or 100 µg/g creams were raised after assessment of clinical laboratory safety tests, vital signs, physical examinations or ECGs.

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

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

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD-06-SPR-103918 - A Phase 1, open-label, two-period, single-sequence drug-drug interaction study to evaluate the effects of multiple dose CD5789 cream 100 µg/g, on the pharmacokinetics of single-dose levonorgestrel (0.15 mg) and ethinyl estradiol (0.03 mg) tablets, in healthy adult female subjects.
6. Clinical study phase	Phase 1
7. Clinical study period	- Date of first screened: 21 February 2017 - Date of last subject completed: 12 April 2017
8. Countries where clinical study was conducted	United States of America
9. Number of subjects	A total of 24 subjects were enrolled in the study.
10. Aim and secondary	- To evaluate the effects of multiple-dose CD5789 100 µg/g topical cream (2 g of topical formulation applied once daily for 14 days) on the pharmacokinetics of a

purposes of clinical study	single-dose of levonorgestrel (LNG; 0.15 mg)/ ethinyl estradiol (EE; 0.03 mg) in healthy adult female subjects. - To assess the safety and tolerability of multiple-dose CD5789 100 µg/g topical cream (2 g of topical formation applied once daily for 14 days) in healthy adult female subjects.
11. Clinical study design	This was a Phase 1 open-label, two-period, single-sequence DDI study aimed at assessing the perpetrator potential of CD5789. In particular, this study assessed the CD5789 capability to reduce the systemic exposure of co-administered oral contraceptive steroids that are metabolized by the cytochrome P450 (CYP450) enzyme CYP3A4 (i.e., LNG [0.15 mg]/ EE [0.03 mg]). Towards this end, the pharmacokinetic (PK) profile of each component of the oral contraceptive (i.e., LNG and EE) was assessed before and after repeated applications of CD5789 100 µg/g cream (2 g of topical formulation applied once daily for 14 days). In addition, the PK profile of CD5789 was measured at the end of the treatment period to confirm the exposure to the topical drug. Healthy female subjects were to receive a single-dose of LNG (0.15 mg)/ EE (0.03 mg) on Day 1 and Day 18, and once daily topical applications (n = 14) of CD5789 100 µg/g cream from Day 5 to Day 18. Both the oral contraceptive and CD5789 100 µg/g cream were administered by qualified study personnel at the study center, in the morning. CD5789 100 µg/g cream was applied on the face, shoulders, upper chest and upper back areas as evenly as possible (2 g/day). In case of skin irritation due to CD5789, application location could be temporarily changed to untreated adjacent areas until irritation was resolved, while maintaining the initial total daily dosing and surface area.
12. Main inclusion criteria	- Female ≥18 to ≤35 years of age inclusive at the time of Screening. - Female of non-childbearing potential (post-menopausal [absence of menstrual bleeding for 1 year prior to screening, without any other medical reason], hysterectomy, or bilateral oophorectomy). - Females of childbearing potential had to: ○ Have a negative urine pregnancy test at Screening and Day -1 ○ Be strictly abstinent for 1 month prior to Baseline and agrees to continue for the duration of the clinical trial and 1 week after last dose application OR ○ Agree to use two effective forms of contraception for the duration of the study and at least 1 week after the last study drug application. The two forms of contraception authorized were defined as the use of a barrier method of contraception (condom with spermicide) in association with one of the following methods of contraception: ▪ Bilateral tubal ligation ▪ Non hormonal Intra uterine device inserted at least 1 month prior to the Baseline visit ▪ Vasectomized partner for at least 3 months prior to the Baseline visit - Medically healthy on the basis of medical history, physical examination, and clinical laboratory testing. Clinical laboratory test results had to be within the laboratory normal range or, if outside of the laboratory normal range, deemed not clinically significant by the Principal Investigator or qualified designee. - Body weight between 45 and 100 kg. - Body mass index (BMI) 18 to 30 kg/m^2 - Non-smokers (including no use of nicotine-containing products) for at least 3 months prior to dosing.

<table>
<tr><td>13. Investigational medicinal product, method of administration, strength</td><td>Trifarotene (CD5789), topical (dermal) administration, strength: 100 µg/g cream
Test product dosage form
<table>
<tr><th></th><th>Investigational Test Product</th><th>Investigational Reference Product</th></tr>
<tr><td>Name of Drug Substance</td><td>Trifarotene</td><td>Levonorgestrel/ ethinyl estradiol</td></tr>
<tr><td>Internal Code</td><td>CD5789</td><td>Not applicable</td></tr>
<tr><td>Pharmaceutical Form</td><td>Cream</td><td>Oral tablets</td></tr>
<tr><td>Strength/ Concentration</td><td>100 µg/g</td><td>0.15 mg / 0.03 mg</td></tr>
<tr><td>Formula number</td><td>0219.0073</td><td>-</td></tr>
<tr><td>Batch number</td><td>16.01436</td><td>-</td></tr>
<tr><td>Packaging (type and size)</td><td>30 mL amber glass</td><td>-</td></tr>
<tr><td>Storage conditions</td><td>Store below 25°C (77°F), do not freeze or refrigerate</td><td>Store at controlled room temperature, 20° to 25°C (68°-77°F); excursions permitted between 15° to 30°C (59°-86°F)</td></tr>
<tr><td>Dosage (total daily dose)</td><td>2g</td><td>0.15mg/0.03mg</td></tr>
<tr><td>Route</td><td>Topical</td><td>Oral</td></tr>
<tr><td>Dose Regimen</td><td>Once daily (morning)</td><td>Single dose (morning)</td></tr>
<tr><td>Duration of administration</td><td>14 days</td><td>Single doses at two periods 18 days apart</td></tr>
<tr><td>Location of Treated Area</td><td>Face, shoulders, upper chest and upper back areas</td><td>-</td></tr>
</table></td></tr>
<tr><td>14. Reference medicinal product, method of administration, strength</td><td>Levonorgestrel/ ethinyl estradiol, oral administration, 0.15 mg / 0.03 mg
Test product dosage form
<table>
<tr><th></th><th>Investigational Test Product</th><th>Investigational Reference Product</th></tr>
<tr><td>Name of Drug Substance</td><td>Trifarotene</td><td>Levonorgestrel/ ethinyl estradiol</td></tr>
<tr><td>Internal Code</td><td>CD5789</td><td>Not applicable</td></tr>
<tr><td>Pharmaceutical Form</td><td>Cream</td><td>Oral tablets</td></tr>
<tr><td>Strength/ Concentration</td><td>100 µg/g</td><td>0.15 mg / 0.03 mg</td></tr>
<tr><td>Formula number</td><td>0219.0073</td><td>-</td></tr>
<tr><td>Batch number</td><td>16.01436</td><td>-</td></tr>
<tr><td>Packaging (type and size)</td><td>30 mL amber glass</td><td>-</td></tr>
<tr><td>Storage conditions</td><td>Store below 25°C (77°F), do not freeze or refrigerate</td><td>Store at controlled room temperature, 20° to 25°C (68°-77°F); excursions permitted between 15° to 30°C (59°-86°F)</td></tr>
<tr><td>Dosage (total daily dose)</td><td>2g</td><td>0.15mg/0.03mg</td></tr>
<tr><td>Route</td><td>Topical</td><td>Oral</td></tr>
<tr><td>Dose Regimen</td><td>Once daily (morning)</td><td>Single dose (morning)</td></tr>
<tr><td>Duration of administration</td><td>14 days</td><td>Single doses at two periods 18 days apart</td></tr>
<tr><td>Location of Treated Area</td><td>Face, shoulders, upper chest and upper back areas</td><td>-</td></tr>
</table></td></tr>
<tr><td>15. Concomitant therapy</td><td>Not Applicable</td></tr>
<tr><td>16. Efficacy evaluation criteria</td><td>Not Applicable</td></tr>
<tr><td>17. Safety evaluation criteria</td><td>- Local tolerability (erythema, scaling, dryness, stinging/burning), at each visit from Day 5 visit to the end of the study (Day 28/early termination [ET] visit). Local tolerability was assessed separately on the face and on the trunk using specific 4-point scales (ranging from 0 [none] to 3 [severe])
- Adverse events (AEs) at each visit
- Hematology, blood chemistry and urinalysis at Screening and Day 18 visits
- Vital signs and physical examination at Screening and Day 28/ET visits
- Urine drug screen and alcohol breath test at Screening, Day -1, and Day 17 visits</td></tr>
</table>

	- Pregnancy test at Screening, Days -1, 5, 18 and 28/ET visits, or any other time points at the Investigator's discretion
18. Statistical methods	The PK analysis set included all subjects in the Safety analysis set who provided at least one post Baseline evaluable drug concentration value. Pharmacokinetic analyses were based on observed cases. The safety analysis set included all subjects who applied/were administered the study products at least once. For each component of the oral contraceptive (i.e., LNG and EE), AUC_{0-t}, AUC_{0-inf}, and C_{max} were submitted, after logarithmic (Ln) transformation, to 2 separate analyses of variance. 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 Day 18 visit (oral contraceptive + CD5789) and Day 1 visit (oral contraceptive alone) 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 LNG (0.15 mg)/ EE (0.03 mg), alone and co-administered with CD5789, on the original scale. A DDI could be concluded if the Test (LNG [0.15 mg]/ EE [0.03 mg] + CD5789) to Reference (LNG [0.15 mg]/ EE [0.03 mg] alone) 90% CIs for the geometric least squares mean ratios did not fully fall inside the accepted 80-125% range for AUC_{0-t}, AUC_{0-inf}, and C_{max}. Safety data were summarized descriptively.
19. Demographic indicators of the study population (gender, age, race, etc.)	The majority of the subjects were White (18 [75.0%] subjects), and had skin phototype III (17 [70.8%] subjects). Mean ± SD age was 27.0 ± 4.60 years (ranging from 19 to 35 years), and mean ± SD BMI was 25.1 ± 2.69 kg/m^2 (ranging from 20 to 29 kg/m^2).
20. Efficacy outcomes	Not Applicable
21. Safety outcomes	• **Local tolerability** Skin irritation on the face reached a peak after 4 applications of CD5789 100 µg/g cream (i.e., at Day 9 visit). Skin irritation on the trunk was overall stable, although it seemed to worsen a few days after the last study drug application at Day 18 visit (i.e., at Day 20 and Day 21 visits). For subjects with scores worsened from pre-treatment (Day 5), worst scores were mostly moderate for erythema, scaling and dryness, and mild or moderate for stinging/burning, on both face and trunk. Severe scores were reported in 1 subject for erythema and 2 subjects for stinging/burning on the face, and 2 subjects for stinging/burning on the trunk. At the final visit (Day 28), none of the subjects had local tolerability signs/symptoms on the face, as these had resolved, while mild or moderate erythema (in 10 subjects), scaling (in 14 subjects) and dryness (in 14 subjects) were still observed on the trunk. During the treatment period with CD5789 100µg/g cream, mean scores for erythema, dryness, scaling and stinging/burning were higher on the face than on the trunk, showing a better tolerability profile to CD5789 100 µg/g cream for the trunk compared to the face. • **AEs** A total of 37 AEs were reported in 19 (79.2%) subjects; of these, 32 AEs in 18 (75.0%) subjects were reported during the treatment with CD5789 100 µg/g cream alone and were

	cutaneous in nature. All AEs resolved during the study, and, except for one moderate event of sinusitis, they were of mild intensity. Of the 9 treatment related AEs, 7 (in 5 [20.8%] subjects) were cutaneous in nature and considered as related to CD5789 100 µg/g cream. The remaining 2 treatment related AEs (PTs: headache and dysmenorrhea) were reported by 2 (8.3%) subjects during the treatment period with CD5789 100 µg/g cream plus LNG/ EE and were considered as related to the oral contraceptive. All of the treatment related AEs were of mild intensity, none led to study discontinuation, and they all resolved during the study. A total of 26 AEs in 16 (66.7%) subjects were considered by the Investigator as related to the study procedure (to the use of Cetaphil products [cleanser and/or lotion/moisturizer lotion]). These AEs included all of the events of application site pain (reported as burning: 24 events in 15 [62.5%] subjects), which was the most frequently reported AE, and of application site discomfort (reported as stinging and burning: 2 events in 1 [4.2%] subject). All of these AEs were of mild intensity, none of them led to study discontinuation, and they all resolved during the study after changing the cleanser/moisturizer (to cream products or petroleum jelly). No serious AEs, AEs of special interest, AEs leading to study discontinuation, or deaths were reported during the study. • **Clinical laboratory evaluations** Overall, hematology and blood chemistry values remained stable over time. Shifts from normal values at Screening to high or low values at Day 18 visit were considered as non-clinically significant. All of the positive urinalysis results were considered as non-clinically significant. • **Vital signs, physical findings, and other observations related to safety** Vital signs remained stable over time and were all within the normal range. All of the abnormal physical findings were considered as non-clinically significant. • **Pregnancies** One subject (i.e., Subject 8596-018) had a positive pregnancy test after the last doses of CD5789 100 µg/g cream and of the oral contraceptive were administered at Day 18 visit. The last menstruation for this subject was on 03 March 2017 and date of delivery is expected to be 08 December 2017; she was exposed to CD5789 from 21 March 2017 to 03 April 2017, so the embryo was exposed for approximately 13 days to CD5789. At the time this report was written, the pregnancy was ongoing. At the latest follow-up (12 July 2017), the pregnancy was progressing well.
22. Summary (conclusion)	This study showed that the PK parameters of LNG and EE before and after repeated daily applications of CD5789 100 µg/g cream were equivalent, confirming the absence of DDI. These results indirectly demonstrated that CD5789 does not induce enzymatic activities mediated by CYP3A4. The safety profile of CD5789 100 µg/g cream was as expected for topical retinoids.
Applicant (Marketing Authorization Holder)	_____ (signature) Régis Schulz (full name) GALDERMA SA Zählerweg 10 CH-6300 Zug 058 455 85 00

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

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD-06-SRE-18213 - Exploratory study to evaluate the safety and efficacy of different formulations and concentrations of CD5789 in subjects with acne vulgaris
6. Clinical study phase	Phase 1 Human Pharmacology study
7. Clinical study period	Date of first subject screened: 17 March 2011 Date of last subject completed:23 May 2011
8. Countries where clinical study was conducted	United States of America
9. Number of subjects	Approximately 60 subjects were to be randomized to ensure that per protocol data of 17 subjects per group were available for evaluation at the end of the study.

10. Aim and secondary purposes of clinical study	To evaluate the safety and efficacy of CD5789 in different formulations and concentrations (50 µg/g gel versus cream A at 25 µg/g or 50 µg/g) in subjects with moderate to severe acne vulgaris after 4 weeks of once daily application, 5 days per week.
11. Clinical study design	Exploratory, multi-center, randomized, investigator blinded, vehicle controlled study using intra-individual comparison (right versus left) in 3 parallel groups: - Group 1: CD5789 25µg/g cream A versus vehicle: subjects were to be treated, with 500 µL of CD5789 25µg/g cream A on one half face and other half face received 500 µL of the vehicle cream. - Group 2: CD5789 50µg/g cream A versus vehicle: subjects were to be treated with 500 µL of CD5789 50µg/g cream A on one half face and other half face received 500 µL of the vehicle cream. - Group 3: CD5789 50µg/g gel versus vehicle: subjects were to be treated, with 500 µL of CD5789 50 µg/g gel on one half face and other half face received 500 µL of the vehicle gel.
12. Main inclusion criteria	Key inclusion criteria - Male or female subjects aged 18-35 years old, with: o Moderate to severe facial acne vulgaris (at least 20 inflammatory lesions and 30 non-inflammatory lesions, excluding nose) at Screening and Baseline; o Investigators' global assessment (IGA) severity grade 3 or 4 at Screening and baseline; o Fitzpatrick a skin phototype of I to IV at Screening.
13. Investigational medicinal product, method of administration, strength	- Cream A: CD5789, cream, topical administration, strength: 50µg/g & 25µg/g - Gel: CD5789, gel, topical administration, strength: 50µg/g
14. Reference medicinal product, method of administration, strength	- Vehicle product: cream A, topical administration, strength: Not Applicable - Vehicle product: gel, topical administration, strength: Not Applicable
15. Concomitant therapy	Not Applicable
16. Efficacy evaluation criteria	**Efficacy measurements:** - Lesion counts: inflammatory lesion count (papules, pustules), non-inflammatory lesion count (open and closed comedones), other acne lesion count (nodules); total lesion count will be calculated as the sum of inflammatory lesions, non-inflammatory lesions and nodules. - Investigator and subject efficacy preference at Final visit (Day 29). Efficacy criteria - Primary efficacy criteria

	○ Total acne lesion count (clinically assessed) and percent reduction at the end of treatment. - Secondary efficacy criteria ○ Inflammatory, non-inflammatory and total acne lesion count as well as percent reduction at each visit per half face. ○ Subject and investigator efficacy preference at the end of treatment Other - Cosmetic acceptability.
17. Safety evaluation criteria	- Adverse events at each visit following Screening visit; - Local tolerance assessed on each half-face using a 4-point skin reaction scale at every visit from Baseline (Day 1) to Final visit (Day 29); - Physical examination and vital signs at Screening, Baseline (Day 1) and Final visit (Day 29); - Laboratory safety testing at Screening and Final visit (Day 29).
18. Statistical methods	Local tolerability scores were summarized using means over time and worst response across visits. Adverse events, general physical examination, vital signs, laboratory parameters and cosmetic acceptability questionnaires were summarized by descriptive statistics. Efficacy data were analyzed at each visit for the per protocol population, and for endpoint response in the ITT population (using the last observation of the treatment period carried forward). Lesion counts (inflammatory, non-inflammatory and total) as well as percent reduction 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.
19. Demographic indicators of the study population (gender, age, race, etc.)	Six US centers screened 95 subjects (ranging from 2 to 43 subjects per center). Among these, 59 were randomized. The ratio of number of subjects between groups was well balanced: 21 in CD5789 25µg/g cream A versus vehicle, 19 in CD5789 50 µg/g cream A versus vehicle and 19 in CD5789 50 µg/g gel versus vehicle. Three subjects (2 in group CD5789 50 µg/g cream A versus vehicle and one in group CD5789 50µg/g gel versus vehicle) had at least one major deviation (one used prohibited medication and 2 had issues with treatment compliance). Those 3 subjects were excluded from the PP population, but included in the ITT and Safety populations. None of the 59 randomized subjects discontinued the study prematurely. As presented in Table 1, most of the randomized subjects were white (89.8%) and 50.8% were female. The mean age was 21.6 years (range 18-31).

Table 1 Demographics

		Screened	Randomized			
			CD5789 25µg/g cream A versus vehicle	CD5789 50µg/g cream A versus vehicle	CD5789 50µg/g gel versus vehicle	All
Gender	N	95	21	19	19	59
	Male	40 (42.1%)	9 (42.9%)	9 (47.4%)	11 (57.9%)	29 (49.2%)
	Female	55 (57.9%)	12 (57.1%)	10 (52.6%)	8 (42.1%)	30 (50.8%)
Race	N	95	21	19	19	59
	White	84 (88.4%)	17 (81.0%)	18 (94.7%)	18 (94.7%)	53 (89.8%)
	Black or African American	4 (4.2%)	2 (9.5%)	0 (0.0%)	0 (0.0%)	2 (3.4%)
	Asian	2 (2.1%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
	Other	5 (5.3%)	1 (4.8%)	1 (5.3%)	1 (5.3%)	3 (5.1%)
Age (years)	N	95	21	19	19	59
	Mean	22.6	21.0	22.3	21.5	21.6
	SD	4.4	3.1	3.3	3.9	3.4
	Median	21.0	21.0	22.0	20.0	21.0
	(Min,Max)	(18,39)	(18,29)	(18,30)	(18,31)	(18,31)
Phototype	N	70	21	19	19	59
	I	4 (5.7%)	0 (0.0%)	0 (0.0%)	3 (15.8%)	3 (5.1%)
	II	24 (34.3%)	8 (38.1%)	8 (42.1%)	4 (21.1%)	20 (33.9%)
	III	26 (37.1%)	7 (33.3%)	6 (31.6%)	8 (42.1%)	21 (35.6%)
	IV	16 (22.9%)	6 (28.6%)	5 (26.3%)	4 (21.1%)	15 (25.4%)
Ethnicity	N	95	21	19	19	59
	Hispanic or Latino	15 (15.8%)	1 (4.8%)	1 (5.3%)	4 (21.1%)	6 (10.2%)
	Not Hispanic or Latino	80 (84.2%)	20 (95.2%)	18 (94.7%)	15 (78.9%)	53 (89.8%)

20. Efficacy outcomes

Primary efficacy criteria

- Total lesion count at the end of treatment

At Day 01, no statistically significant differences were observed between the vehicle treated sides and active treated sides, for the both concentration of CD5789 cream A and for the CD5789 50µg/g gel (PP population).

At the end of treatment (Day 29) for the total lesion count, no statistically significant differences were observed in the PP population between the vehicle and CD5789 cream A treated sides, at any concentration. In group CD5789 50µg/g gel the number of total lesions was statistically significantly (p=0.008) less in the CD5789 50 µg/g gel side compared with the vehicle side with a mean difference of 5.6 lesions and an effect size of 0.68 compared to the clinical expected effect size of 0.8.

Table 3 Total Lesions Count

		CD5789 25µg/g cream A versus vehicle			CD5789 50µg/g cream A versus vehicle			CD5789 50µg/g gel versus vehicle		
Total lesion count		Active	Vehicle	A - V	Active	Vehicle	A - V	Active	Vehicle	A - V
Day 01 (ITT)	N	21	21	21	19	19	19	19	19	19
	Mean	37.1	36.4	0.7	33.1	34.4	-1.3	36.4	39.3	-2.9
	SD	15.7	11.6	7.3	11.1	11.3	3.0	13.8	14.8	6.0
	Median	32.0	32.0	0.0	29.0	31.0	0.0	30.0	34.0	-3.0
	(Min,Max)	(22.0,87.0)	(28.0,64.0)	(-11.0,23.0)	(24.0,62.0)	(25.0,66.0)	(-8.0,3.0)	(25.0,68.0)	(25.0,80.0)	(-12.0,12.0)
	P-value*	-	-	**0.805**	-	-	**0.087**	-	-	**0.044**
Endpoint (ITT)	N	21	21	21	19	19	19	19	19	19
	Mean	31.0	33.3	-2.4	28.1	28.1	0.0	24.4	29.7	-5.3
	SD	18.2	21.5	7.6	18.5	24.3	10.5	15.8	17.6	8.1
	Median	29.0	28.0	-2.0	21.0	20.0	-1.0	18.0	25.0	-4.0
	(Min,Max)	(9.0,89.0)	(13.0,101.0)	(-18.0,15.0)	(9.0,81.0)	(4.0,88.0)	(-22.0,17.0)	(5.0,64.0)	(11.0,76.0)	(-24.0,9.0)
	P-value*	-	-	**0.180**	-	-	**>0.999**	-	-	**0.008**
Day 01 (PP)	N	21	21	21	17	17	17	18	18	18
	Mean	37.1	36.4	0.7	33.6	35.1	-1.4	36.9	39.6	-2.7
	SD	15.7	11.6	7.3	11.7	11.7	3.2	14.1	15.2	6.1
	Median	32.0	32.0	0.0	29.0	31.0	0.0	30.0	34.0	-3.0
	(Min,Max)	(22.0,87.0)	(28.0,64.0)	(-11.0,23.0)	(24.0,62.0)	(25.0,66.0)	(-8.0,3.0)	(25.0,68.0)	(25.0,80.0)	(-12.0,12.0)
	P-value*	-	-	**0.805**	-	-	**0.089**	-	-	**0.072**
Day 29 (PP)	N	21	21	21	17	17	17	18	18	18
	Mean	31.0	33.3	-2.4	28.1	29.1	-0.9	24.3	29.9	-5.6
	SD	18.2	21.5	7.6	19.3	25.6	10.3	16.2	18.1	8.2
	Median	29.0	28.0	-2.0	21.0	20.0	-1.0	18.0	24.0	-4.0
	(Min,Max)	(9.0,89.0)	(13.0,101.0)	(-18.0,15.0)	(9.0,81.0)	(4.0,88.0)	(-22.0,17.0)	(5.0,64.0)	(11.0,76.0)	(-24.0,9.0)
	P-value*	-	-	**0.180**	-	-	**0.770**	-	-	**0.008**

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

A - V is Active – Vehicle

- Percent reduction in total lesion count at the end of treatment

At Day 29, the difference between active and vehicle was not statistically significant for the percent reduction in total lesion count for any treatment (PP population and confirmed in the ITT population).

In terms of median percent reduction the difference did not exceed 3.7% for CD5789 50 µg/g gel.

Table 4 Percent reduction in total lesion count

		CD5789 25µg/g cream A versus vehicle			CD5789 50µg/g cream A versus vehicle			CD5789 50µg/g gel versus vehicle		
Percent reduction in total lesion count		Active	Vehicle	A - V	Active	Vehicle	A - V	Active	Vehicle	A – V
Endpoint (ITT)	N	21	21	21	19	19	19	19	19	19
	Mean	17.1	11.5	5.6	19.5	26.7	-7.2	35.1	27.3	7.8
	SD	34.8	37.9	23.8	30.2	39.2	30.4	27.3	22.1	18.2
	Median	21.6	12.5	2.4	25.0	38.2	-7.5	45.2	32.0	3.3
	(Min,Max)	(-50.0,67.9)	(-57.9,56.7)	(-53.4,55.5)	(-30.6,67.9)	(-57.1,87.1)	(-62.1,45.3)	(-24.5,82.8)	(-14.8,62.1)	(-16.4,47.3)
	P-value*	-	-	**0.317**	-	-	**0.395**	-	-	**0.169**
Day 29 (PP)	N	21	21	21	17	17	17	18	18	18
	Mean	17.1	11.5	5.6	21.2	26.1	-4.9	36.7	27.5	9.2
	SD	34.8	37.9	23.8	30.3	41.5	29.0	27.2	22.7	17.7
	Median	21.6	12.5	2.4	25.0	38.2	-7.5	45.3	33.1	3.7
	(Min,Max)	(-50.0,67.9)	(-57.9,56.7)	(-53.4,55.5)	(-30.6,67.9)	(-57.1,87.1)	(-62.1,45.3)	(-24.5,82.8)	(-14.8,62.1)	(-12.6,47.3)
	P-value*	-	-	**0.317**	-	-	**0.579**	-	-	**0.090**

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

A - V is Active – Vehicle

	Secondary efficacy criteria - Inflammatory lesion count and percent reduction in inflammatory lesion count (clinical evaluation) No statistically significant difference between the active and the vehicle was observed in any treatment group at any timepoint, neither in terms of lesion count nor in terms of percent reduction. - Non inflammatory lesion count and percent reduction in non-inflammatory lesion count (clinical evaluation) The difference between active and vehicle was statistically significant for non-inflammatory lesion counts on Day 22 and Day29, but not for percent reduction for the group CD5789 50 µg/g gel versus vehicle. No significant difference was found in non-inflammatory lesion counts and percent reduction at any time point between CD5789 cream A at any dose and the vehicle. - Total lesion count and percent reduction in total lesion count (clinical evaluation) For the CD5789 50 µg/g gel versus vehicle group at Day 08, 22 and 29, the difference between the active and vehicle was statistically significant for total lesion counts but not for the percent reduction. There were no significant differences in total lesion counts and percent reduction at any timepoint between CD5789 cream A at any dose and the vehicle. - Distribution of efficacy preference by Investigator and subjects (clinical evaluation) Investigators preferred CD5789 50 µg/g gel in 38.9 % of subjects compared to 16.7% of subjects treated with the vehicle gel (PP population) 44.4% had no preference. This difference was not significant. For both Cream A vs vehicle groups the majority of investigators had no preference neither for the active nor for the vehicle. Results from the investigators' evaluation were paralleled by those provided by subjects for the CD5789 50 µg/g gel group: 55.6% of subjects preferred the active over its vehicle. When comparing the active and the vehicle in the CD5789 50 µg/g cream A group, notably more subjects preferred the active treated side compared the vehicle treated side (52.9 vs. 17.6%, respectively). However, this difference was not statistically significant. In the CD5789 25 µg/g cream A vs vehicle group, no difference between the active and the vehicle were noted. **Other Assessments** - Cosmetic acceptability The cosmetic acceptability questionnaire completed by the subjects did not show statistically significantly difference between the vehicle and the active treatments, except for "feeling on the face" where the vehicle was statistically significantly better rated ($p = 0.0005$) than CD5789 50 µg/g gel.
21. Safety outcomes	During the course of the study, 2 subjects in the CD5789 50 µg/g gel versus vehicle group had, due to irritation, their dosage regimen modified, the first occurrence was for one subject on Day 05 and for the 2nd subject on Day 11. The mean number of missing applications due to irritation was 3.5 days, with CD5789 50 µg/g gel, only. The mean number of missing applications due to other reasons than irritation (including missing visits) ranged from 1 to 2.4 days for all treatment groups.

The mean number of applications received ranged from 19.4 (CD5789 50 µg/g cream A and gel groups) to 19.8 for the CD5789 25 µg/g cream A group. The theoretical number of applications to be received was 20.

- Adverse Events

Overall there were no deaths, serious adverse events or adverse events of special interest reported. None of the adverse events led to the discontinuation of study subjects.

In the CD5789 25 µg/g cream versus vehicle group, 5 adverse events in 5 subjects were reported. One event, pruritus, was evaluated as mild and considered related to the vehicle.

Six (6) adverse events in 5 subjects were reported with CD5789 50 µg/g cream A; none was considered related or severe.

Five (5) adverse events in 4 subjects were reported in the CD5789 50 µg/g gel versus vehicle group. Two events (skin burning sensation and skin discomfort) in 2 subjects were considered related to the study drug, both were considered severe.

- CD5789 25µg/g cream A versus vehicle group

In the CD5789 25 µg/g cream A versus vehicle group 5 adverse events in 5 subjects were reported. One event, mild pruritus, was considered related to the vehicle (Table 5).

Table 5 Overview of adverse events: CD5789 25µg/g cream A versus vehicle

	CD5789 25µg/g cream A (N= 21)			Vehicle (N= 21)			Total (N= 21)		
	n events	n subj.*	% subj.	n events	n subj.*	% subj.	n events	n subj.*	% subj.
All AEs	4	4	19.0	5	5	23.8	5	5	23.8
Related AEs	0	0	0.0	1	1	4.8	1	1	4.8
All dermatologic AEs	0	0	0.0	1	1	4.8	1	1	4.8
Related dermatologic AEs	0	0	0.0	1	1	4.8	1	1	4.8
AESI	0	0	0.0	0	0	0.0	0	0	0.0
All severe AEs	1	1	4.8	1	1	4.8	1	1	4.8
Related severe AEs	0	0	0.0	0	0	0.0	0	0	0.0
All serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
Related serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
All AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
Related AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
Deaths	0	0	0.0	0	0	0.0	0	0	0.0

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

- CD5789 50µg/g cream A versus vehicle

Six (6) adverse events in 5 subjects were reported with CD5789 50 µg/g cream A. None was considered related or severe (Table 6).

Table 6 Overview of adverse events: CD5789 50µg/g cream A versus vehicle

	CD5789 50µg/g cream A (N= 19)			Vehicle (N= 19)			Total (N= 19)		
	n events	n subj.*	% subj.	n events	n subj.*	% subj.	n events	n subj.*	% subj.
All AEs	6	5	26.3	6	5	26.3	6	5	26.3
Related AEs	0	0	0.0	0	0	0.0	0	0	0.0
All dermatologic AEs	0	0	0.0	0	0	0.0	0	0	0.0
Related dermatologic AEs	0	0	0.0	0	0	0.0	0	0	0.0
AESI	0	0	0.0	0	0	0.0	0	0	0.0
All severe AEs	0	0	0.0	0	0	0.0	0	0	0.0
Related severe AEs	0	0	0.0	0	0	0.0	0	0	0.0
All serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
Related serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
All AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
Related AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
Deaths	0	0	0.0	0	0	0.0	0	0	0.0

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

- CD5789 50µg/g gel versus vehicle

Five (5) adverse events in 4 subjects were reported in the CD5789 50 µg/g gel versus vehicle group. Two events (skin burning sensation and skin discomfort) in 2 subjects were considered related to the study drug, both were considered severe (Table 7).

Table 7 Overview of adverse events: CD5789 50µg/g gel versus vehicle

	CD5789 50µg/g gel (N= 19)			Vehicle (N= 19)			Total (N= 19)		
	n events	n subj.*	% subj.	n events	n subj.*	% subj.	n events	n subj.*	% subj.
All AEs	5	4	21.1	3	2	10.5	5	4	21.1
Related AEs	2	2	10.5	0	0	0.0	2	2	10.5
All dermatologic AEs	2	2	10.5	0	0	0.0	2	2	10.5
Related dermatologic AEs	2	2	10.5	0	0	0.0	2	2	10.5
AESI	0	0	0.0	0	0	0.0	0	0	0.0
All severe AEs	3	3	15.8	1	1	5.3	3	3	15.8
Related severe AEs	2	2	10.5	0	0	0.0	2	2	10.5
All serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
Related serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
All AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
Related AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
Deaths	0	0	0.0	0	0	0.0	0	0	0.0

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

- Local Tolerability

Clinical irritation was assessed on each half face prior to treatment application at every visit from Baseline (Day 01) to the Final visit (Day 29)/early termination visit. The highest severity scores recorded over time are summarized in Table 8.

As expected, occurrence of erythema, scaling, dryness and stinging/burning were higher on the active-treated sides than on the vehicle-treated sides.

The severity and frequency of signs/symptoms were more important with CD5789 50 µg/g gel when compared to the cream A (50 µg/g and 25 µg/g) and the vehicle formulations.

Table 8 Frequency tables for worst score of each signs/symptoms

		CD5789 25µg/g cream A versus vehicle		CD5789 50µg/g cream A versus vehicle		CD5789 50µg/g gel versus vehicle	
		Active (N=21)	Vehicle (N=21)	Active (N=19)	Vehicle (N=19)	Active (N=19)	Vehicle (N=19)
Worst score for Erythema	N	21	21	19	19	19	19
	0-None	12 (57.1%)	13 (61.9%)	5 (26.3%)	9 (47.4%)	1 (5.3%)	10 (52.6%)
	1-Mild	9 (42.9%)	8 (38.1%)	11 (57.9%)	9 (47.4%)	7 (36.8%)	7 (36.8%)
	2-Moderate	0 (0.0%)	0 (0.0%)	3 (15.8%)	1 (5.3%)	11 (57.9%)	2 (10.5%)
Worst score for Scaling	N	21	21	19	19	19	19
	0-None	13 (61.9%)	16 (76.2%)	7 (36.8%)	14 (73.7%)	0 (0.0%)	9 (47.4%)
	1-Mild	5 (23.8%)	5 (23.8%)	10 (52.6%)	5 (26.3%)	8 (42.1%)	9 (47.4%)
	2-Moderate	3 (14.3%)	0 (0.0%)	2 (10.5%)	0 (0.0%)	11 (57.9%)	1 (5.3%)
Worst score for Dryness	N	21	21	19	19	19	19
	0-None	12 (57.1%)	15 (71.4%)	3 (15.8%)	14 (73.7%)	0 (0.0%)	9 (47.4%)
	1-Mild	7 (33.3%)	6 (28.6%)	14 (73.7%)	5 (26.3%)	7 (36.8%)	9 (47.4%)
	2-Moderate	2 (9.5%)	0 (0.0%)	2 (10.5%)	0 (0.0%)	12 (63.2%)	1 (5.3%)
Worst score for Stinging/Burning	N	21	21	19	19	19	19
	0-None	16 (76.2%)	17 (81.0%)	4 (21.1%)	18 (94.7%)	0 (0.0%)	14 (73.7%)
	1-Mild	4 (19.0%)	3 (14.3%)	12 (63.2%)	1 (5.3%)	8 (42.1%)	4 (21.1%)
	2-Moderate	1 (4.8%)	1 (4.8%)	2 (10.5%)	0 (0.0%)	6 (31.6%)	1 (5.3%)
	3-Severe	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	5 (26.3%)	0 (0.0%)

- Physical examination and vital signs

Results for vital signs assessments and physical examinations at Day 29 /early termination were not different from those from Screening and Baseline examinations.

- Laboratory testing

Results from standard laboratory testing at Day 29 /early termination on biochemistry and hematology parameters did not show any relevant changes from laboratory values at screening.

22. Summary (conclusion)

For this exploratory study a total of 95 subjects with acne vulgaris were screened, 59 were randomized in 3 groups as follows: 21 in CD5789 25µg/g cream A versus vehicle, 19 in CD5789 50 µg/g cream A versus vehicle and 19 in CD5789 50 µg/g gel versus vehicle.

None of the 59 randomized subjects discontinued the study prematurely.

Efficacy results demonstrated that there was no significant difference between the active and the vehicle, in total, inflammatory and non-inflammatory lesion counts and respective percent reduction from Day 01 for group CD5789 25 µg/g cream A and group CD5789 50 µg/g cream A. No trend of investigator and subject preference for the active side was detected.

In the CD5789 50 µg/g gel group, only total and non-inflammatory lesion counts were significant different in favor of the active treatment. A slight trend in the investigator preference for the active treated side was detected but was not significant.

Higher severities and frequencies of local signs/symptoms occurred with CD5789 50 µg/g gel, followed by the CD5789 50 µg/g cream A. Two (2) subjects in the CD5789

	50µg/g gel group had related dermatological AEs (skin burning sensation and skin discomfort) leading to missing applications. Local tolerability was best with CD5789 25 µg/g cream A and worse with CD5789 50 µg/g gel. Tolerability with CD5789 50 µg/g Cream was intermediate. Results for standard laboratory testing, vital signs assessments and physical examinations at Day 29 /early termination were not different from results prior to drug application.

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