2. SYNOPSIS

NAME OF COMPANY: Galderma	***For regulatory use only***
NAME OF FINISHED MEDICINAL PRODUCT: CD5789	
NAME OF ACTIVE INGREDIENT(S):	
Title of study:	A long-term safety and efficacy study of CD5789 50 μg/g cream in subjects with acne vulgaris

Study centers

32 centers: 18 centers in Europe and 14 in the United States of America.

Clinical phase

Phase 3

Study period

- Date of first screened: 23 February 2015
- Date of last subject completed: 23 February 2017

Study objectives

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 evaluated as secondary objective.

Study design

Multi-center, open-label, non-comparative, long-term safety study.

Total number of subjects

A total of 455 subjects were enrolled in the study, of whom 453 were treated with CD5789 50 μg/g.

Diagnosis and key inclusion and exclusion criteria

- Key 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.

- Key exclusion criteria:

  Subjects were excluded if they had severe forms of acne (acne conglobata, acne fulminans) or secondary acne form (chloracne, drug-induced acne, etc.), and if they had >1 nodule on the face/ truncal region, or any acne cyst on the face/truncal region at Screening or Baseline visits.

Investigational product

Trade Name or equivalent *(if applicable)*	Not yet defined
Name of Drug Substance (INN)	Trifarotene
Internal code *(if applicable)*	CD5789
Pharmaceutical Form	Cream
Concentration	50 μg/g
Packaging (type and size)	50 mL bottle with pump and overcap
Storage Conditions	Store below 25°C / 77°F, do not freeze, do not refrigerate
Dosage (total daily dose)	▪ A thin layer of study drug (from 1 pump actuation) was applied on the facial region: forehead, nose, chin (including the area between nose and the upper lip if affected by acne) and each cheek. Application in/close to eyes, or angles of the mouth, lips and mucous membrane was to be avoided. If the area could not be covered with 1 actuation, subjects were instructed to get another actuation and gently spread the cream as a thin layer over the whole face. ▪ A thin layer of study drug (from 2 actuations) was applied on the upper truncal region (reachable to self-application): right and left upper back, right and left shoulders and right and left anterior chest. Application in the axillary region, anterior and posterior neck was to be avoided. If the area could not be covered with 2 actuations, subjects were instructed to get another actuation and gently spread the cream as a thin layer over the upper truncal region. ▪ A thin layer of study drug was applied on the middle/lower back on the areas affected with acne vulgaris (if applicable; following protocol amendment #1).
Dose regimen Route/ Frequency/Duration of administration	Topical/ Once daily in the evening after washing the treated areas with preferred mild or soapless cleanser or provided cleanser and allow to fully dry before applying study drug/ Up to 52 weeks.
Location of treated area	▪ Face and upper truncal region (shoulders, anterior chest, and upper back reachable to self-application by the subject). ▪ Middle/lower back, if applicable.

Efficacy assessments:

- **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]).

Pharmacokinetic (PK) assessments:

- **Pharmacokinetic assessment under maximal use conditions** was planned to be performed at Week 4 at selected sites in subjects aged 9-11 years who consented to have a single PK sample taken after a 4-week treatment period under maximal use conditions (i.e., study drug was applied on the face and on the truncal region, whether or not they were affected by acne). These subjects were to apply the study drug at home every day; except at Week 4 visit when the study drug was applied at the study center.
- **Proof-of-exposure (POE) assessment** was planned to be performed at Week 52 (following protocol amendment #2) at any site for subjects aged 9-11 years who consented to provide additional blood sample for this purpose and who were exposed to the study drug the day before Week 52/ET visit.

Quality of life assessments

Dermatology life quality index (DLQI; for subjects aged >16 years at Baseline visit) and **children's dermatology life quality index (**C-DLQI; for subjects aged ≤16 years at Baseline visit) questionnaires were completed by the subjects at Baseline, Weeks 12, 26 and 52/ET visits.

Safety assessments:

- **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.

Principal 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 assessments.
- 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.

Results

▪Subject Disposition

A total of 455 subjects were enrolled in this study; of them, 453 subjects were treated. Of the 455 enrolled subjects, 348 (76.5%) subjects completed the study and 107 (23.5%) subjects discontinued the study. Withdrawal due to subject's request (11.6%) was the most common reason for discontinuation. Of the 453 subjects treated in this study, 342 (75.5%) subjects were in the study for ≥360 days (i.e., 1 year), while 376 (83.0%) subjects were in the study for ≥180 days (i.e., 6 months).

▪Demographics and baseline disease characteristics

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

▪Efficacy

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.

▪PK and POE

Pharmacokinetic samples were collected from 2 subjects aged 10 and 11 years who applied the drug under maximal conditions for 4 weeks; POE samples were collected from 7 subjects aged 11 years who applied the study drug under clinical use conditions for 52 weeks. The CD5789 plasma concentrations were not quantifiable (<5 pg/mL) in any of these 9 subjects; therefore, no further PK/POE analyses were conducted.

▪ Quality of life

The subjects' quality of life improved over time, as shown by the improvement (i.e., decrease) of mean DLQI and C-DLQI total scores over time (2.3 [SD = 2.88] at Week 52 visit vs. 5.2 [SD = 4.59] at Baseline visit for DLQI; 1.9 (SD = 2.25) Week 52 visit vs. 3.7 [SD = 3.38] at Baseline visit for C-DLQI). Similarly, all of DLQI and most of C-DLQI dimensional scores improved (i.e., decreased) over time.

▪Safety

- Local tolerability

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.

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.