2. SYNOPSIS

NAME OF COMPANY: Galderma	***For regulatory use only***
NAME OF FINISHED MEDICINAL PRODUCT: CD5789	
NAME OF ACTIVE INGREDIENT: Trifarotene	
Title of study:	A Multicenter, Randomized, Double-Blind, Parallel-Group, Vehicle-Controlled Study to Compare the Efficacy and Safety of CD5789 50 µg/g Cream Versus Vehicle Cream in Subjects With Acne Vulgaris

Study centers

85 centers: 30 centers in the United States, 39 centers in Europe (Hungary, Spain, Czech Republic, Romania, and Poland), 8 centers in Ukraine, and 8 centers in Russia.

Of the 85 centers, 82 centers screened subjects. At 1 of the US centers, no subjects were randomized leaving 81 centers at which the study was conducted.

Clinical phase

Phase 3

Study period

- Date of first subject screened: 23 Nov 2015
- Date of last subject completed: 12 May 2017

Study objective

The objective of the study was to assess the efficacy and safety of CD5789 50 µg/g cream applied once daily for 12 weeks in subjects with moderate acne vulgaris.

Study design

Multicenter, randomized, double-blind, parallel-group, vehicle-controlled study comparing CD5789 50 µg/g cream applied once daily in the evening versus its Vehicle Cream.

Total number of subjects

A total of 1212 subjects were randomly assigned to either CD5789 50 µg/g cream (602 subjects) or Vehicle Cream (610 subjects). All randomized subjects received at least 1 dose of study medication.

Diagnosis and key inclusion and exclusion criteria

Key inclusion criteria

Male or female subjects, 9 years or older at Screening. Subjects were to have moderate acne vulgaris on the face with Investigator's Global Assessment (IGA) severity score of 3 (moderate) and at least 20 inflammatory lesions and 25 non-inflammatory lesions on the face at Screening and Baseline. Subjects also were to have moderate acne vulgaris on the trunk with Physician Global Assessment (PGA) severity score of 3 (moderate) on the trunk at Screening and Baseline and at least 20 inflammatory lesions and 20 non-inflammatory lesions but not more than 100 non-inflammatory lesions on the trunk (shoulders, upper back and upper anterior chest) reachable to self-application of the study drug. The criteria regarding moderate truncal acne were optional for subjects between 9 and 11 years of age.

Key exclusion criteria

Subjects were excluded if they had severe forms of acne (e.g., acne conglobata, acne fulminans) or secondary acne form (chloracne, drug-induced acne, etc.), and if they had more than 1 nodule on the face or trunk, or any acne cysts on the face or trunk at Screening and Baseline.

Test product dosage form

	Investigational Product	Comparator Product
Trade name or equivalent *(if applicable)*	N/A	N/A
Name of drug substance (INN)	Trifarotene	Vehicle
Internal code	CD5789	N/A
Pharmaceutical form	Cream	Cream
Strength / Concentration	50 μg/g	N/A
Packaging (type and size)	50 mL bottle with pump and overcap	50 mL bottle with pump and overcap
Storage conditions	Store below 25°C (77°F), do not freeze or refrigerate	
Dosage (total daily dose)	▪ 1 pump actuation was applied as a thin layer on the face ▪ 2 pump actuations were applied as a thin layer on the trunk	▪ 1 pump actuation was applied as a thin layer on the face ▪ 2 pump actuations were applied as a thin layer on the trunk
Dose regimen Route Frequency Duration of administration	 Topical Once daily after washing 12 weeks	 Topical Once daily after washing 12 weeks
Location of treated area	Face: chin, left cheek, right cheek, nose, and forehead Trunk: right and left shoulders, right and left upper anterior chest, and right and left upper back, reachable to self-application by the subject.	Face: chin, left cheek, right cheek, nose, and forehead Trunk: right and left shoulders, right and left upper anterior chest, and right and left upper back, reachable to self-application by the subject.

C=Celsius; F=Fahrenheit; INN=International Non-proprietary names; N/A=not applicable.

Efficacy endpoints

Primary efficacy endpoints

The primary efficacy endpoint consisted of the following 3 co-primary endpoints:

- Success rate, defined as the percentage of subjects who achieved an IGA score of 1 (Almost Clear) or 0 (Clear) and at least a 2-grade improvement from Baseline to Week 12
- Absolute change in facial non-inflammatory lesion count from Baseline to Week 12
- Absolute change in facial inflammatory lesion count from Baseline to Week 12

Secondary efficacy endpoints

The secondary efficacy endpoint consisted of the following 3 co-secondary endpoints:

- Percentage of subjects who achieved a PGA score of 1 (Almost Clear) or 0 (Clear) and at least a 2-grade improvement from Baseline to Week 12
- Absolute change in truncal non-inflammatory lesion count from Baseline to Week 12
- Absolute change in truncal inflammatory lesion count from Baseline to Week 12

Supportive endpoints

- Percent change in facial non-inflammatory lesion counts from Baseline to Week 12
- Percent change in facial inflammatory lesion counts from Baseline to Week 12
- Percent change in truncal non-inflammatory lesion counts from Baseline to Week 12
- Percent change in truncal inflammatory lesion counts from Baseline to Week 12
- Subject's assessment of facial acne improvement

Efficacy assessments

- IGA and PGA assessments were conducted at Screening, Baseline, and at Weeks 1, 2, 4, 8, and 12/End of Treatment (ET) visits. Efficacy was assessed on the facial region by IGA and on the upper truncal region by PGA. Both IGA and PGA assessments were based on a 5-point scale from 0 (clear) to 4 (severe).
- Lesion counts (inflammatory and non-inflammatory) were performed separately on the face and on the trunk at all visits by Investigators or qualified study personnel, who used both visual observations and palpation strictly, after assessing the IGA and the PGA. Inflammatory lesions included papules and pustules, and non-inflammatory lesions included open and closed comedones.
- Subject's self-assessment of facial acne improvement was conducted at Week 12/ET based on a 6-point scale (ranging from 0 [complete improvement] to 5 [worse]), and was to occur before any Investigator assessment.

Safety assessments

Safety assessments of adverse events and local tolerability were conducted for all subjects at Screening and all subsequent visits until the Week 12/ET Visit. Laboratory tests were performed at Screening and the Week 12/ET visit, and physical examination and vital signs were assessed at Screening, Baseline, and Week 12/ET.

Other assessments

Quality of life assessments**:** Dermatology Life Quality Index (DLQI; for subjects more than 16 years old at the baseline visit) and Children's Dermatology Life Quality Index (C-DLQI; for subjects not more than 16 years old at the baseline visit) questionnaires were completed by the subjects at Baseline and the Week 12/ET visits.

Principal statistical methods

Primary efficacy endpoints:

IGA success rate was analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center based on the Intent-to-treat (ITT) population, which included all randomized subjects. The p-value for the treatment comparison was generated from the general association statistic of the stratified CMH test. Difference in success rate between treatment groups (CD5789 50 μg/g – Vehicle) and the 95% confidence interval (CI) of the difference were based on the large sample approximation method for binary data.

Changes from Baseline in facial lesion counts was analyzed separately by lesion type (inflammatory and non-inflammatory) using an analysis of covariance (ANCOVA) model that included baseline lesion count, analysis center, and treatment as factors. The p-value for the treatment comparison, estimate of the treatment difference (CD5789 50 μg/g – Vehicle), and the 95% CI of the difference was generated from the ANCOVA model.

The superiority of CD5789 50 μg/g cream to Vehicle Cream was declared only if the statistical significance of all 3 co-primary efficacy endpoints were met. That is, the 2-sided p-values for the difference between the 2 treatment groups in all 3 co-primary efficacy endpoints had to be <0.05.

The primary analyses were performed using the ITT population based on the multiple imputation (MI) methodology assuming the data were missing at random (MAR) as the imputation method for missing values.

In addition to the planned analyses, post-hoc analyses of the success rate of IGA at each visit and of change in lesion counts from baseline at each visit were conducted using both MI and observed data.

Analysis of secondary efficacy endpoints:

The 3 co-secondary efficacy endpoints were analyzed with the same statistical methods as those used for the co-primary efficacy endpoints, using the intent-to-treat on the trunk (ITTT) population (ie, all subjects in the ITT population who had moderate acne on the trunk at Baseline), with MI as the primary imputation method for missing values.

The testing of the secondary efficacy endpoints was conditional on the success of the 3 co-primary endpoints. Therefore, no adjustment for multiplicity was required in this study.

To claim the superiority of CD5789 50µg/g cream to Vehicle Cream on the trunk, a pre-specified order of hypotheses was tested:

- First, superiority of CD5789 50µg/g to Vehicle Cream on the face was tested ($p<0.05$) for all 3 co-primary efficacy endpoints. If successful then,
- All 3 co-secondary efficacy endpoints were tested ($p<0.05$) for superiority.

The analyses for the secondary efficacy endpoints were repeated using the per protocol (PP) population (ie, all subjects in the ITT population with no major protocol deviations). In addition, post-hoc analysis of PGA success rate at each visit and change in truncal lesion counts from baseline at each visit were conducted for both MI and observed data using ITTT population.

Safety assessments

Summary statistics were provided by treatment group for treatment-emergent adverse events (TEAEs), local tolerability assessments, vital signs and laboratory data.

Results

Subject disposition

Of the 1293 subjects who were screened, 1212 were randomized to receive cutaneous administration of CD5789 50 µg/g cream (602 subjects) or Vehicle Cream (610 subjects) once daily for 12 weeks. A total of 1131 (93.3%) subjects completed the study; 558 subjects (92.7%) in the CD5789 50 µg/g cream group and 573 (93.9%) subjects in the Vehicle Cream group.

There were 81 (6.7%) subjects who were prematurely discontinued from the study; 44 subjects (7.3%) in the CD5789 50 µg/g cream and 37 (6.1%) subjects in the Vehicle Cream. There were no relevant between-group differences regarding reasons for premature discontinuation. The main reason for premature discontinuation was subject's request (30 subjects, 3.2%). Additional reasons for study discontinuation included lost to follow-up (20 subjects, 1.7%), adverse event (10 subjects, 0.8%), protocol violations (5 subjects, 0.4%), "other" (4 subjects, 0.3%), pregnancy (2 subjects, 0.2%), and lack of efficacy (1 subject, 0.1%).

Demographics and baseline disease characteristics

The demographic and baseline characteristics were similar between CD5789 50 µg/g cream and Vehicle Cream as shown in Table 1. The overall mean age of the ITT population was 19.7 (SD [standard deviation] = 6.29) years, ranging from 11 to 49 years (median = 18 years). There were 570 (47.0%) subjects who were <18 years old, including 555 (45.8%) subjects aged 12 to 17 years and 15 (1.2%) subjects aged 9 to 11 years. There were 642 (53.0%) adult subjects (≥18 years), including 419 (34.6%) subjects aged 18 to 24 years. As expected considering the studied indication, there were no subjects aged ≥65 years. There were more

females (695 [57.3%] subjects) than males (517 [42.7%] subjects). The majority of subjects were White (1119 [92.3%] subjects), Not Hispanic or Latino (1090 [89.9%] subjects), and had skin phototype I to III (1077 [88.8%] subjects).

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

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

Max=maximum; Min=minimum; N=number of subjects; SD=standard deviation.
Note: Baseline was defined as the last measurement prior to the first application of study drug.
Data source: Table 14.1.4.1

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

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

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

- On the face, 36.6 (SD = 13.84) and 50.9 (SD = 25.83), respectively
- On the trunk, 39.1 (SD = 16.80) and 45.9 (SD = 19.87), respectively.

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

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

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

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

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

Data source: Table 14.1.4.1

Efficacy

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

Results from this double-blind, randomized, vehicle-controlled study showed that treatment with CD5789 50 µg/g cream once daily for 12 weeks had superior efficacy in treating moderate facial and truncal acne vulgaris compared with Vehicle Cream in subjects 9 years or older. This was observed in IGA success rate, PGA success rate, and change from Baseline in inflammatory and non-inflammatory lesion counts on the face and trunk.

HCompared with Vehicle Cream, treatment with CD5789 50 µg/g cream resulted in statistically significantly higher IGA and PGA success rates ($p<0.001$) as well as statistically significantly greater reductions in facial and truncal inflammatory ($p<0.001$) and non-inflammatory lesion counts ($p\leq0.001$) from Baseline at Week 12. These results were consistent with the PP and PPT populations for the primary and secondary efficacy endpoints as well as with the sensitivity analyses.

Results of the percent change in facial and truncal inflammatory and non-inflammatory lesion counts from Baseline to Week 12 also showed statistically significant improvement in facial and truncal acne with CD5789 50 µg/g cream compared with Vehicle Cream ($p<0.001$). The proportions of subjects who reported facial acne improvement from Baseline to Week 12 were higher in the CD5789 50 µg/g cream group compared with the Vehicle Cream group.

Subjects were considered to have had overall success if they had an IGA score of “clear” (0) or “almost clear” (1) at Week 12, and at least a 2-grade improvement from Baseline to Week 12, as well as a PGA score of “clear” (0) or “almost clear” (1) at Week 12, and at least a 2-grade improvement from Baseline to Week 12. The overall success rate was higher in subjects who received CD5789 50 µg/g cream compared with subjects who received Vehicle Cream.

Table 3 Summary of efficacy analyses at Week 12

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

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

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

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

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

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

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

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

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

Data source: Table 14.2.1.1, Table 14.2.2.1, Table 14.2.3.1, Table 14.2.4.1, Table 14.2.5.1, Table 14.2.6.1, Table 14.2.7 Table 14.2.8, Table 14.2.9.1, Table 14.2.1.4.1, Table 14.2.2.4.1, Table 14.2.3.4.1, Table 14.2.4.4.1, Table 14.2.5.4.1, Table 14.2.6.4.1, and Table 14.2.10

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

Safety

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

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

A higher proportion of subjects who received CD5789 50 µg/g cream compared with Vehicle Cream reported TEAEs in the General disorders and administration site conditions SOC,

mainly due to application site irritation (CD5789 50 µg/g cream, 18 [3.0%] subjects; Vehicle Cream, 0 subjects), and in the Injury, poisoning and procedural complications SOC, mainly due to sunburn (CD5789 50 µg/g cream, 6 [1.0%] subjects; Vehicle Cream 1 [0.2%] subject).

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

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

Most of the TEAEs reported in both treatment groups were mild or moderate in severity. Few TEAEs were severe (6 TEAEs in 4 [0.7%] subjects in the CD5789 50 µg/g cream group; 7 TEAEs in 7 [0.7%] subjects in the Vehicle Cream group). Severe related TEAEs were reported in 3 (1.6%) subjects in the CD5789 50 µg/g cream group and no subject in the Vehicle Cream group.

Among subjects who received CD5789 50 µg/g cream, the most common TEAEs assessed as related to the study drug were, by decreasing frequency: application site irritation (2.5%), application site pruritus (0.8%), application site pain (0.7%), and application site dryness (0.5%).

No deaths were reported during the study. Three (3) serious TEAEs were reported by 2 (0.3%) subjects in the CD5789 50 µg/g cream group (suicide attempt and major depression in 1 subject; ligament sprain in 1 subject), and 4 serious TEAEs were reported by 4 (0.7%) subjects in the Vehicle Cream group (suicide attempt, appendicitis, sinusitis and asthma, each in 1 subject). None of the serious TEAEs was cutaneous in nature or assessed as related to study drug.

Adverse Events of Special Interest were reported by 9 (1.5%) subjects in the CD5789 50 µg/g cream group, which were all cutaneous in nature and related to the study drug. In this treatment group, the most common AESI was application site irritation (5 [0.8%] subjects). In the Vehicle Cream group, AESIs were reported by 2 (0.3%) subjects (blood bilirubin increase and blood creatinine increase).

Treatment-emergent adverse events that led to discontinuation were reported by 10 (1.7%) subjects in the CD5789 50 µg/g cream group and 1 (0.2%) subject in the Vehicle Cream group. Of the 10 subjects in the CD5789 50 µg/g cream group, 7 subjects had 8 TEAEs that were cutaneous in nature and related to study drug. One (1) subject in the Vehicle Cream group had a TEAE that led to study drug discontinuation, which was not cutaneous and not related to study drug.

There were no clinically significant mean changes from Baseline to Week 12 in hematology or blood chemistry in either treatment group.

There were no clinically significant mean changes from Baseline to Week 12 in vital signs (systolic and diastolic blood pressure, and pulse rate). Three (3) subjects in the CD5789 50 µg/g cream group had treatment-emergent abnormal and clinically significant physical exam findings reported as TEAEs. These were dermatitis on the chest and back, erythematous patches on the chest, and irritant dermatitis.

Signs/symptoms of local tolerability (erythema, dryness, scaling, and stinging/burning) on the face and the trunk occurred in a greater proportion of subjects in the CD5789 50 µg/g cream group compared with the Vehicle Cream group. A better local tolerability profile was observed on the trunk compared with the face. These signs/symptoms increased and decreased (crescendo – decrescendo pattern) over the course of the study. On the face, peak irritation was observed at Week 1, while on the trunk a gradual increase was observed up to Week 4 and then signs/symptoms decreased until the end of the study. In the CD5789 50 µg/g cream group, the highest local tolerability scores that worsened from Baseline on the face were graded as mild (26.4% [erythema] to 36.5% [scaling]), moderate (24.9% [stinging/burning] to 36.4% [dryness]), or severe (6.8% [scaling] to 10.0% [erythema]). On the trunk, the highest local tolerability scores that worsened from Baseline were graded as mild (27.0% [erythema] to 35.7% [scaling]), moderate (12.9% [stinging/burning] to 23.2% [erythema]), or severe (2.5% [dryness] to 7.2% [erythema]).

The TEAEs in the subgroups were consistent with the SAF population. The percentage of subjects who reported at least 1 TEAE was comparable in both treatment groups for most subgroups. The signs/symptoms of local tolerability on the face and trunk were comparable in the majority of the subgroups and consistent with the SAF population. Few subgroups, such as ages 9 to 11 years old, race (Black, Asian, and Other), ethnicity (Hispanic or Latino), and skin phototype (IV-VI) provided variability compared with the SAF population. However, this should be interpreted with caution given the small sample size of these subgroups. A better local tolerability profile was observed on the trunk compared with the face in each demographic subgroup.

Suspected skin sensitization was reported for 1 subject in the CD5789 50 µg/g cream group. Results for the rechallenge skin patch test reached a negative conclusion for contact skin sensitization. Final diagnosis was concluded to be irritant dermatitis on the 4th and 5th digits of both hands; i.e., on non-treated areas. The skin response was considered to be irritant in nature and not indicative of allergic contact skin sensitization.

There were 2 pregnancies reported during the study period. One (1) was an uneventful full-term pregnancy with a healthy infant delivered at 40 weeks and 6 days (Vehicle Cream group); the other subject was lost to follow-up and no further information is available (CD5789 50 µg/g cream group).

Conclusion

All objectives of this pivotal study were met: Compelling and robust efficacy of CD5789 50 µg/g cream in the treatment of moderate facial and truncal acne vulgaris was demonstrated. Subjects treated with CD5789 50 µg/g cream experienced clinically meaningful

and statistically significant improvement in the primary and secondary efficacy endpoints of the study: IGA and PGA success rates (Clear and Almost Clear with at least a 2-grade improvement) at Week 12 and facial and truncal inflammatory and non-inflammatory lesions change from Baseline to Week 12 when compared with corresponding vehicle.

CD5789 50 µg/g cream was safe in all safety assessments performed throughout the study. Most of the TEAEs occurred at the application site. Most of the cutaneous TEAEs and the recorded signs and symptoms of skin irritation followed the well-known pattern of retinoid dermatitis with acceptable and manageable tolerability when CD5789 50 µg/g cream was applied to large body surface areas of face and trunk.