

2. SYNOPSIS

NAME OF COMPANY: Galderma		<i>For regulatory use only</i>
NAME OF FINISHED MEDICINAL PRODUCT: CD5789		
NAME OF ACTIVE INGREDIENT(S): Trifarotene		
Title of study:	A multicenter, randomized, double-blind, parallel-group vehicle controlled study to compare the efficacy and safety of CD5789 50µg/g cream versus vehicle cream in subjects with acne vulgaris	

Study centers

A total of 119 investigational centers in the United States, Canada, Puerto Rico, and Europe screened subjects in the study.

Clinical phase

Phase 3

Study period

- Date of first screened: 30 November 2015
- Date of last subject completed: 17 November 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 1208 subjects were randomly assigned to either CD5789 50 µg/g cream (612 subjects) or Vehicle Cream (596 subjects). All randomized subjects received at least 1 dose of study medication.

Diagnosis and key inclusion and non-inclusion 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 in the evening after washing 12 weeks	Topical Once daily in the evening 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 (shoulders, upper back, and upper anterior chest) by PGA. Both IGA and PGA assessments were based on a 5-point scale from 0 (clear) to 4 (severe).
- Lesion counts (inflammatory and non-inflammatory) were performed separately on the face and on the trunk at all visits by Investigators or qualified study personnel, who used both visual observations and palpation strictly, after assessing the IGA and the PGA. Inflammatory lesions included papules and pustules, and non-inflammatory lesions included open and closed comedones.
- Subject's self-assessment of facial acne improvement was conducted at Week 12/ET based on a 6-point scale (ranging from 0 [complete improvement] to 5 [worse]), and was to occur before any Investigator assessment.

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.
- A facial skin oiliness questionnaire was completed by the subject and returned at the Baseline and 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 ITT population. The p-value for the treatment comparison was generated from the general association statistic of the stratified CMH test. Difference in success rate between treatment groups (CD5789 50 µg/g cream – Vehicle Cream) and the 95% confidence interval (CI) of the difference were based on the large sample approximation method for binary data.

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

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

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

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

Analysis of secondary efficacy endpoints:

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

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

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

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

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

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 1524 subjects who were screened, 1208 were randomized to receive cutaneous administration of CD5789 50 µg/g cream (612 subjects) or Vehicle Cream (596 subjects) once daily for 12 weeks. A total of 1075 (89.0%) subjects completed the study; 540 subjects (88.2%) in the CD5789 50 µg/g cream group and 535 (89.8%) subjects in the Vehicle Cream group.

There were 133 (11.0%) subjects who were prematurely discontinued from the study; 72 subjects (11.8%) in the CD5789 50 µg/g cream and 61 (10.2%) subjects in the Vehicle Cream. Seventy-one (5.9%) subjects voluntarily withdrew from the study; 39 subjects (6.4%) and 32 subjects (5.4%) in the CD5789 and Vehicle Cream groups, respectively. Additional reasons for study discontinuation in the CD5789 50 µg/g cream and Vehicle Cream groups included the following:

- lost to follow-up (13 subjects [2.1%] and 23 subjects [3.9%], respectively),
- adverse event (14 subjects [2.3%] and 1 subject [0.2%], respectively),
- protocol violations (3 subjects [0.5%] and 1 subject [0.2%], respectively),
- pregnancy (0 subjects and 2 subjects [0.3%], respectively),
- lack of efficacy (1 subject [0.2%] and 1 subject [0.2%] respectively), and
- “other” (2 subjects [0.3%] and 1 subject [0.2%], respectively).

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 19.4 (SD = 6.41) years, ranging from 9 to 58 years (median = 18 years). There were 592 (49.0%) subjects who were <18 years old, including 573 (47.4%) subjects age 12 to 17 years, and 19 subjects (1.6%) age 9 to 11 years. There were 616 (51.0%) adult subjects (≥18 years), including 418 (34.6%) subjects aged 18 to 24 years. As expected considering the studied indication, there were no subjects aged ≥65 years. There were more females (629 [52.1%] subjects) than males (579 [47.9%] subjects), and the majority of subjects were white (992 [82.1%] subjects), Not Hispanic or Latino (925 [76.6%] subjects), and had skin phototype I to III (904 [74.8%] subjects).

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

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

Max=maximum; Min=minimum; N=number of subjects; SD=standard deviation.

Note: Baseline was defined as the last measurement prior to the first application of study drug.

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 1185 (98.1%) subjects had moderate truncal acne (PGA grade = 3). At Baseline, there were 17 subjects who had a PGA score of 0, 3 subjects who had a PGA score of 1, and 3 subjects who had a PGA score of 2.

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

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

- On the face, 34.7 (SD = 13.02) and 53.0 (SD = 28.55), respectively
- On the trunk, 36.9 (SD = 17.89) and 46.4 (SD = 21.57), respectively.

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

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

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

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

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

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.

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

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

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

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

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

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

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

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

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

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

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

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

^f Additional analyses were conducted to evaluate the overall success rate at Week 12 in the ITTT population using the MI dataset.

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

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

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 14.2.10, 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, and Table 14.2.6.4.1

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

Safety

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

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

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

Treatment-emergent adverse events with incidence $\geq 1\%$ (at the preferred term level) of subjects in the Vehicle Cream group were (by decreasing frequency): nasopharyngitis (4.6%), headache (2.0%), influenza (1.5%), upper respiratory tract infection (1.4%), and application site pruritus (1.4%).

Most of the TEAEs reported in both treatment groups were mild or moderate in severity. Few TEAEs were severe (10 TEAEs in 8 [1.3%] subjects in the CD5789 50 µg/g cream group; 1 TEAE in 1 [0.2%] subject in the Vehicle Cream group). Severe related TEAEs were reported in 6 (1.0%) subjects in the CD5789 50 µg/g cream group and 1 (0.2%) subject in the Vehicle Cream group.

Among subjects who received CD5789 50 µg/g cream, the most common (i.e. reported in $\geq 1\%$ of subjects) TEAEs assessed as related to the study drug were, by decreasing frequency: application site irritation (10.4%), application site pruritus (3.7%), sunburn (2.1%), and skin irritation (1.0%).

No deaths were reported during the study. Four serious TEAEs were reported by 4 (0.6%) subjects in the CD5789 50 µg/g cream group and 3 serious TEAEs were reported by 2 (0.3%) subjects in the Vehicle Cream group. None of the serious TEAEs was cutaneous in nature or assessed as related to study drug. The serious TEAEs reported in the CD5789 50 µg/g cream subjects were infectious mononucleosis, procedural dizziness, facial bones fracture, and cellulitis (each in 1 subject); serious TEAEs in the Vehicle Cream group were atypical pneumonia and urinary tract infection in 1 subject; and hereditary angioedema in 1 subject.

Adverse Events of Special Interest were reported by 16 (2.6%) subjects in the CD5789 50 µg/g cream group; they were all cutaneous in nature (application site irritation in 9 subjects [1.5%], dermatitis allergic in 3 subjects [0.5%], acne in 2 subjects [0.3%], and skin irritation in 2 subjects [0.3%]). In the Vehicle Cream group, 5 AESIs were reported in 2 (0.3%) subjects: blood creatinine increased, hyperuricemia, and liver function test abnormal in 1 subject and blood creatinine increased and liver function test abnormal in another subject.

Treatment-emergent adverse events that led to discontinuation were reported by 14 (2.3%) subjects in the CD5789 50 µg/g cream group and 1 (0.2%) subject in the Vehicle Cream group. Of the 14 subjects in the CD5789 50 µg/g cream group, 13 subjects had 13 TEAEs that were cutaneous in nature and related to study drug. One subject in the Vehicle Cream group had a TEAE that led to study drug discontinuation, which was not cutaneous and not related to study drug.

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

There were no clinically significant mean changes from Baseline to Week 12 in vital signs (systolic and diastolic blood pressure, and pulse rate). Four subjects in the CD5789 50 µg/g cream group had treatment-emergent abnormal and clinically significant physical exam findings on the skin that were reported as TEAEs. These were erythematous maculae with severe excoriations on the trunk and face, dermatitis on the skin of chest, erythema, oozing of nostrils on the upper lip, and red itchy rash on the treatment area.

Signs/symptoms of local tolerability (erythema, dryness, scaling, and stinging/burning) on the face and the trunk occurred in a greater proportion of subjects in the CD5789 50 µg/g cream group compared with the Vehicle Cream group. A better local tolerability profile was observed on the trunk compared with the face. These signs/symptoms increased and decreased (crescendo – decrescendo pattern) over the course of the study. On the face, peak irritation was observed at Week 1, except for erythema, which peaked at Weeks 1 to 2, while on the trunk a peak was observed at Weeks 1 or 2, followed by a plateau and then a gradual decrease after Week 4 (truncal erythema or dryness) or Week 8 (truncal scaling or stinging/burning). In the CD5789 50 µg/g cream group, the highest local tolerability scores that worsened from Baseline on the face were graded as mild (34.6% [erythema] to 44.0% [dryness]), moderate (16.3% [stinging/burning] to 23.7% [erythema]), or severe (2.5% [erythema and dryness] to 4.2% [stinging/burning]). On the trunk, the highest local tolerability scores that worsened from Baseline were graded as mild (23.7% [scaling and stinging/burning] to 30.3% [dryness]), moderate (9.0% [stinging/burning] to 14.6% [erythema]), or severe (0.3% [scaling] to 3.3% [erythema]) in the CD5789 50 µg/g cream group.

The percentage of subjects who reported at least 1 TEAE was comparable across most of the subgroup categories. The sign/symptoms of local tolerability worsened from Baseline on the face and trunk at the final visit and also at the worst post-baseline visits were consistent across most of the subgroup categories. The data need to be interpreted with caution given the small number of subjects in some of the subgroup categories.

Dermatitis allergic was diagnosed or could not be ruled out in 3 subjects in CD5789 50 µg/g cream group. All 3 cases of dermatitis allergic were assessed as related to the study drug.

There were 2 pregnancies reported during the study period. One was an uneventful full-term pregnancy with a healthy infant delivered at 41 weeks (Vehicle Cream group); the other subject had an elective abortion (Vehicle Cream group).

Conclusion

All objectives of this pivotal study were met: robust efficacy of CD5789 50 µg/g cream in the treatment of moderate facial and truncal acne vulgaris was demonstrated. Subjects treated with CD5789 50 µg/g cream experienced clinically meaningful and statistically significant improvement in the primary and secondary efficacy endpoints: IGA and PGA success rates (Clear and Almost Clear with at least a 2-grade improvement) at Week 12 and facial and truncal inflammatory and non-inflammatory lesions change from Baseline to Week 12 when compared with corresponding vehicle.

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