2 SYNOPSIS

NAME OF COMPANY: Galderma	***For regulatory use only***
NAME OF FINISHED MEDICINAL PRODUCT: Not applicable	
NAME OF ACTIVE INGREDIENT(S): Brimonidine Tartrate	
Title of study:	Patient-Reported Outcomes of Brimonidine Tartrate 0.5% Gel for Treatment of Severe Facial Erythema of Rosacea

Study centers: 14 centers in total: 7 in Germany, 2 in Sweden and 5 in the United Kingdom (UK).

Clinical phase: Phase IIIb

Study period

- Date of first subject screened: 01 Jul 2013
- Date of last subject completed: 14 Nov 2013

Study objectives

The purpose of this study was to evaluate patient-reported outcomes following treatment of severe facial erythema of rosacea with brimonidine tartrate 0.5% gel compared with vehicle gel. The safety and efficacy of the two treatment regimens were also evaluated.

Study design

This study was conducted as a multicenter, randomized, double-blind, vehicle-controlled and parallel-group trial. It involved male or female subjects, aged 18 years or older, with severe erythema of rosacea based on Patient Self-Assessment (PSA) and meeting specific inclusion/exclusion criteria. Subjects were randomized to apply brimonidine tartrate 0.5% gel or its vehicle gel once daily for 8 days. The study consisted of 3 visits: Day 1, Day 2 (+1 day), and Day 8 (± 2 days).

On Day 1, there were two sets of evaluation: Baseline (i.e. prior to study treatment application) and Hour 3 (3 hours after study treatment application). At Baseline, subjects who fulfilled all inclusion and exclusion criteria were randomly assigned to receive either brimonidine tartrate 0.5% gel or its vehicle gel. On Day 2 (+ 1 day) and Day 8 (± 2 days), evaluation was conducted

2-4 hours after study treatment application. On non-clinic day (Days 3-7), all subjects applied study treatment at home once daily in the morning after skin cleansing.

Subjects were instructed to apply one small pea-size amount (approximately 1 g) of gel on the cheeks, forehead, chin and nose, and even the product out to a thin film on the entire face (even if not all facial areas presented erythema).

Total number of subjects

A total of 92 subjects were randomized at 14 centers in 3 countries: 56 subjects in Germany, 10 subjects in Sweden and 26 subjects in the UK. All randomized subjects were included in the ITT and APT populations: 48 subjects in the brimonidine tartrate 0.5% group and 44 in the vehicle group.

Diagnosis and key inclusion and exclusion criteria

- Key inclusion criteria: Male or female subjects, aged 18 or older, with severe facial erythema of rosacea with a PSA score of 4 (severe) and a Clinician's Erythema Assessment (CEA) score of 3 (moderate) or 4 (severe) at Baseline prior to the study drug application
- Key exclusion criteria: Subjects who had more than 5 facial inflammatory lesions (papules or pustules) of rosacea, or particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or concomitant facial dermatoses that shared clinical features with rosacea such as perioral dermatitis, demodicidosis, facial keratosis pilaris, seborrhoeic dermatitis, acute lupus erythematosus, or actinic telangiectasia.

Test product dosage form

	Investigational Product	Comparator
Trade Name or equivalent	Mirvaso® gel	Not applicable
Name of Drug Substance (INN)	Brimonidine tartrate (CD07805/47)	Not applicable
Pharmaceutical Form	Gel	Gel
Concentration	0.5%	Not applicable
Packaging (type and size)	Tube Montebello 30g	Tube Montebello 30g
Storage Conditions	Store below 25º C. Do not freeze. Do not refrigerate.	Store below 25º C. Do not freeze. Do not refrigerate.
Dosage (total daily dose)	Approximately 1 g	Approximately 1 g
Dose regimen		
Route	Cutaneous	Cutaneous
Frequency	Once daily	Once daily
Duration of administration	8 days	8 days
Location of treated area	Face	Face

Patient-reported outcomes assessment

- Euro Quality of Life-5 Dimensional-3 Level (EQ-5D-3L) questionnaire: this validated questionnaire addressed 5 questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, along with a visual analogue score for the overall health state. Subjects completed it at Baseline (prior to study treatment application on Day 1), Day 2 and Day 8 (2-4 hours after study treatment application)
- Dermatology Life Quality Index (DLQI) questionnaire: this questionnaire is a validated Quality-of-Life (QoL) questionnaire specific to dermatological conditions. Subjects completed this questionnaire at Baseline (prior to study treatment application on Day 1) and on Day 8 (2-4 hours after study treatment application)
- Facial Redness questionnaire: this questionnaire focused on the psychosocial impact of the facial erythema of rosacea. Subjects completed the questionnaire at Baseline (prior to study treatment application on Day 1), Day 2 and Day 8 (2-4 hours after study treatment application)
- Subject Satisfaction questionnaire: Subjects completed a satisfaction questionnaire on Day 8/Early Termination (2-4 hours after study treatment application)
- Subject diary: Subjects completed a diary daily regarding the treatment compliance and responded to one question whether they had control of their facial redness.

Efficacy assessment

- CEA: The evaluator (i.e. the Investigator or designee) evaluated the subject's erythema of rosacea by performing a static evaluation of erythema severity using the 5-grade CEA

(0: Clear skin with no signs of erythema to 4: Severe erythema with fiery redness). A subject had to have a CEA of 3 (moderate) or 4 (severe) at Baseline (prior to study treatment application) to be eligible for the study. On Day 1, CEA assessments were completed at 2 time points by the evaluator at Baseline (prior to the study treatment application) and Hour 3 (3 hours after the study treatment application). On Day 2 and Day 8, CEA assessments were completed once by the evaluator at each visit 2-4 hours after the study treatment application

- PSA: Subjects performed static ("snap shot") evaluations of their erythema of rosacea using the 4-grade PSA (0: no redness to 4: severe redness). A subject had to have a PSA of 4 (severe) at Baseline (prior to study treatment application) to be eligible for the study. On Day 1, PSA assessments were completed at two time points by the subject: at Baseline (prior to the study treatment application) and Hour 3 (3 hours after the study treatment application). On Day 2 and Day 8, PSA assessments were completed once by the subject at each visit 2-4 hours after the study drug application
- Facial inflammatory lesion counts: Facial inflammatory lesions (including papules and pustules) of rosacea were counted by the evaluator at Baseline (prior to study treatment application on Day 1), Day 2 and Day 8. A subject had to have less than 5 facial inflammatory lesions at Baseline to be eligible for the study.

Safety assessment:

Adverse Events (AEs) were recorded at each study visit and monitored throughout the course of the study.

Principal statistical methods

The main objective of this study was to evaluate the patient-reported outcomes following the treatment of severe facial erythema of rosacea with brimonidine tartrate 0.5% gel compared with its vehicle gel.
The following populations were analyzed:

1. The Intent-to-Treat (ITT) efficacy population: this population consisted of the entire population enrolled and randomized.

2. The All Patient Treated (APT) safety population: this population consisted of the ITT population, after exclusion of subjects who never took the treatment with certainty based on monitoring report.

Missing values were not imputed in this study.

Patient-reported outcomes and efficacy assessments

All patient-reported outcomes and efficacy variables were analyzed in the ITT population at each evaluation time point, using the Cochran-Mantel-Haenszel (CMH) test, stratified by center (or analysis-center) after ridit transformation with the row mean difference statistics, testing the hypothesis of equality. Each test was two-sided, at the 0.050 significance level.
CEA and PSA successes were defined as a 2-CEA or 2-PSA grade of improvement compared from Baseline (Hour 0 on Day 1).

Safety assessments

The AEs were descriptively summarized for the APT population (n, %) by relationship to study treatments within System Organ Class (SOC) and Preferred Term and by intensity (i.e. mild, moderate and severe). Deaths and serious AEs (SAEs) were also reported as well as withdrawals due to AEs.

Results

- **Demographics and baseline disease characteristics**

Table 1 Demographic Data – ITT Population

	Brimonidine (N=48)	Vehicle (N=44)	Total (N=92)
Gender n (%)			
Female	30 (62.5)	26 (59.1)	56 (60.9)
Male	18 (37.5)	18 (40.9)	36 (39.1)
Age			
18-65 years old n (%)	37 (77.1)	34 (77.3)	71 (77.2)
>65 years old n (%)	11 (22.9)	10 (22.7)	21 (22.8)
Mean ± SD	53.4 ± 12.9	54.9 ± 12.8	54.1 ± 12.8
Median	54.5	54.5	54.5
(Min, Max)	(25.0, 74.0)	(19.0, 79.0)	(19.0, 79.0)
Race n (%)			
White	48 (100.0)	44 (100.0)	92 (100.0)
Skin phototype n (%)			
I	3 (6.3)	6 (13.6)	9 (9.8)
II	34 (70.8)	27 (61.4)	61 (66.3)
III	11 (22.9)	11 (25.0)	22 (23.9)

ITT: Intent-to-Treat; SD: Standard Deviation; Min: Minimum; Max: Maximum.
Data Source: Section 14, Table 6

At Baseline, the distribution of gender, age, race and skin phototype in the ITT population was comparable for both treatment groups (Table 1). The majority of subjects were female (56/92 subjects, 60.9%), and of skin phototype II (61/92 subjects, 66.3%). All subjects were Caucasian. The overall mean (±SD) age was 54.1 (±12.8) years, with a minimum of 19 years and a maximum of 79 years.

Table 2 Baseline Disease Characteristics – ITT Population

	Brimonidine (N=48)	Vehicle (N=44)	Total (N=92)
Clinician erythema assessment			
3: Moderate	20 (41.7%)	25 (56.8%)	45 (48.9%)
4: Severe	28 (58.3%)	19 (43.2%)	47 (51.1%)
Mean ± SD	3.6 ± 0.5	3.4 ± 0.5	3.5 ± 0.5
Median	4.0	3.0	4.0
(Min, Max)	(3.0, 4.0)	(3.0, 4.0)	(3.0, 4.0)
Patient self-assessment			
4: Severe	48 (100.0%)	44 (100.0%)	92 (100.0%)
Mean ± SD	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.0
Median	4.0	4.0	4.0
(Min, Max)	(4.0, 4.0)	(4.0, 4.0)	(4.0, 4.0)
Inflammatory lesion counts			
Mean ± SD	0.9 ± 1.7	0.8 ± 1.3	0.8 ± 1.5
Median	0.0	0.0	0.0
(Min, Max)	(0.0, 5.0)	(0.0, 5.0)	(0.0, 5.0)

ITT: Intent-to-Treat; SD: Standard Deviation; Min: Minimum; Max: Maximum.
Data Source: Section 14, Table 14.

At Baseline, all subjects had a PSA score of 4 and a CEA score of 3 or 4 in accordance with the inclusion criteria. The percentage of subjects with a CEA score of 4 i.e. severe erythema/rosacea was higher in the brimonidine tartrate 0.5% group than in the vehicle group (28/48 subjects, 58.3% *vs.* 19/44 subjects, 43.2%) (Table 2). At Baseline, all subjects had less than 5 inflammatory lesions in accordance with the exclusion criteria.

- **Patients-reported outcomes**
  - EQ-5D-3L questionnaire

There was no difference in the domains of 'mobility', 'self-care', 'usual activities' or in the overall health state of the subjects before and after treatment or between the two treatments groups, with the majority of subjects reporting having "no problems" in each of the above-mentioned domains, and a mean (±SD) health state score of 76.0 (±19.3) in the brimonidine tartrate 0.5% group and 80.2 (±13.1) in the vehicle group. A slight improvement in the brimonidine tartrate 0.5% group compared with vehicle was observed in the 'pain/discomfort' and 'anxiety/depression' domains between Baseline and Day 8.

- DLQI questionnaire

At Baseline, the mean (±SD) total DLQI scores were relatively high in both treatment groups (7.9 [±6.7] in the brimonidine tartrate 0.5% group and 9.1 [±6.0] in the vehicle group). After 8 days of treatment, improvement in DLQI score was observed for both groups, with no difference between the two treatment groups: the mean (±SD) total DLQI scores were 5.8 (±6.3) in the brimonidine tartrate 0.5% group and 6.0 (±5.4) in the vehicle group.

- Facial Redness questionnaire

At Baseline, the percentages of subjects in each satisfaction category were relatively similar in both treatment groups. Almost all subjects were dissatisfied with their facial appearance, embarrassed and self-conscious with their facial redness.

Table 3 Facial Redness Questionnaire on Day 8, Descriptive and p-Value – ITT Population

	Brimonidine (N=48)	Vehicle (N=44)	p-value
1. Satisfied with appearance?			
N	46	42	0.0328
Very dissatisfied/Dissatisfied	21 (45.7%)	29 (69.0%)	
Neither Dissatisfied or Satisfied/Satisfied/Very satisfied	25 (54.3%)	13 (31.0%)	
2. Appearance acceptable?			
N	46	42	0.5312
Very unacceptable/Unacceptable	22 (47.9%)	25 (59.5%)	
Neither Acceptable or Unacceptable/Acceptable/Very acceptable	24 (52.1%)	17 (40.5%)	
3. Appearance concerned?			
N	46	42	0.0756
Not at all/Slightly	13 (28.2%)	9 (21.4%)	
Somewhat/Moderately/Extremely	33 (71.7%)	33 (78.6%)	
4. Embarrassed with facial redness?			
N	46	42	0.0083
Not at all	13 (28.3%)	4 (9.5%)	
Slightly/Somewhat/Moderately/Extremely	33 (71.7%)	38 (90.4%)	
5. Self-conscious?			
N	45	42	0.0076
Not at all/Slightly/Somewhat	33 (73.4%)	20 (47.6%)	
Moderately/Extremely	12 (26.7%)	22 (52.3%)	
6. Frequency control last 24 hours?			
N	46	41	0.2186
Not at all	11 (23.9%)	13 (31.7%)	
Slightly/Somewhat/Moderately/Extremely	25 (76.1%)	28 (68.2%)	

7. Frustrated?			
N	46	42	0.2373
Not at all	4 (8.7%)	6 (14.3%)	
Slightly/Somewhat/Moderately/Extremely	42 (91.2%)	36 (85.8%)	
8. Cover up or camouflage?			
N	46	42	0.7769
Not at all	28 (60.9%)	26 (61.9%)	
Slightly/Somewhat	11 (23.9%)	5 (11.9%)	
Moderately/A great deal	7 (15.2%)	11 (26.2%)	
9. Pay attention to the known triggers?			
N	46	41	0.8764
Not at all/Rarely	22 (47.8%)	20 (48.8%)	
Some of the time/Often/Constantly	24 (52.2%)	21 (51.2%)	
10. Avoid the known triggers?			
N	46	42	0.6149
Not at all/Rarely	22 (47.8%)	20 (47.6%)	
Some of the time/Often/Constantly	24 (52.2%)	22 (52.4%)	
11. Interfering with social life?			
N	46	42	0.8361
Not at all	16 (34.8%)	9 (21.4%)	
Slightly/Somewhat/Moderately/Extremely	30 (65.2%)	33 (78.5%)	
12. Interfering with work life?			
N	45	42	0.6259
Not at all	12 (26.7%)	10 (23.8%)	
Slightly/Somewhat/Moderately/Extremely/Not applicable/I'm not working	33 (73.4%)	32 (76.2%)	

ITT: Intent-to-Treat.
Note: p-value for between treatment differences by CMH test based on ridit scores stratified by analysis center.
Data Source: Section 14, Table 20.

At Baseline, the percentages of subjects in each satisfaction category were relatively similar in both treatment groups: 6.3% and 4.5% were very satisfied/satisfied/neutral with their facial appearance in the brimonidine tartrate 0.5% and vehicle groups, respectively. However, at Day 8, the percentage of subjects very satisfied/satisfied/neutral with their appearance was significantly higher in the brimonidine tartrate 0.5% group than in the vehicle group (54.3% *vs.* 31.0%, p=0.0328, Table 3).

At Baseline, the percentages of subjects in each embarrassment category were relatively similar in both treatment groups: 8.3% and 4.5% were not embarrassed at all with their facial redness in the brimonidine tartrate 0.5% and vehicle groups, respectively. At Day 8, this percentage was significantly higher in the brimonidine tartrate 0.5% group than in the vehicle group (28.3% *vs.* 9.5%, p=0.0083, Table 3).

At Baseline, the percentages of subjects who were moderately or extremely self-conscious about their facial redness were similar in both groups (62.5% in the brimonidine tartrate 0.5% group *vs.* 61.3% in the vehicle group). At Day 8, this percentage was significantly lower in the brimonidine tartrate 0.5% group than in the vehicle group (26.7% *vs.* 52.3%, p=0.0076, Table 3).

Regardless of the evaluation visit or the treatment group, the majority of subjects did not cover or camouflage their facial redness. At Baseline, the percentages of subjects who covered their facial redness moderately or a great deal were similar in both treatment groups (33.3% and 31.8% in the brimonidine tartrate 0.5% and vehicle groups, respectively). At Day 8, this percentage was lower in the brimonidine tartrate 0.5% group than in the vehicle group (15.2% *vs.* 26.2%) (Table 3).

For the other items including appearance acceptance and concerns, 24-hour frequency control, frustration, paying attention to and avoiding known triggers, and interference with social and working life, at Day 8, the percentages of subjects who provided positive response were higher in the brimonidine tartrate 0.5% group compared with the vehicle group for most of the questions even though the differences between the two treatment groups were not significant (Table 3).

- Subject Satisfaction questionnaire

Table 4 Subject's Satisfaction Questionnaire at Last Visit, Descriptive and p-Value – ITT Population

	Brimonidine (N=48)	Vehicle (N=44)	p-value
How satisfied are you with the time it took for the treatment to work?			
N	46	42	0.0006
Very satisfied/Satisfied/Somewhat satisfied	32 (69.5%)	14 (33.3%)	
Not satisfied	14 (30.4%)	28 (66.7%)	
How satisfied are you with the improvement of your facial redness since starting the study treatment?			
N	46	42	0.0009
Very satisfied/Satisfied/Somewhat satisfied	31 (67.4%)	14 (33.3%)	
Not satisfied	15 (32.6%)	28 (66.7%)	
How satisfied are you overall with the study treatment?			
N	46	42	0.0065
Very satisfied/Satisfied/Somewhat satisfied	32 (69.6%)	17 (40.4%)	
Not satisfied	14 (30.4%)	25 (59.5%)	
Do you agree that you are able to control your facial redness since starting the study treatment?			
N	45	42	0.0114
Completely agree/Agree/Somewhat agree	27 (60.0%)	14 (33.3%)	
Disagree	18 (40.0%)	28 (66.7%)	

What do you think about your facial appearance since starting the treatment?			
N	46	41	0.0217
A lot better/A little better	29 (63.0%)	11 (26.8%)	
No change/Worse	17 (36.9%)	30 (73.1%)	
Has anyone noticed a change in your facial appearance since starting the treatment?			
N	45	42	0.0163
Yes, positive comments/Yes, neutral comments	21 (46.7%)	11 (26.1%)	
Yes, negative comments	4 (8.9%)	0	
No	20 (44.4%)	31 (73.8%)	
Would you consider using this treatment again?			
N	46	41	0.0012
Yes, once daily as in this study/Yes, more than once daily/Yes, only on days when my facial redness are more severe/Yes, only on special occasions	36 (78.2%)	19 (46.4%)	
No	10 (21.7%)	22 (53.7%)	

ITT: Intent-to-Treat.
Note: p-value for between treatment differences by CMH test based on ridit scores stratified by analysis-center.
(a) 1 = Facial skin cleanser; 2 = Facial moisturizer; 3 = Sunscreen; 4 = Make-up foundation; 5 = Study treatment; 6 = Other facial topical medication.
Data Source: Section 14, Table 24.

At Day 8, when compared with the vehicle group, significantly more subjects in the brimonidine tartrate 0.5% group (Table 4):

- Were satisfied overall with the treatment: 69.6% *vs.* 40.4%, respectively, p=0.0065
- Were satisfied with the improvement in their facial redness since starting the study treatment: 67.4% *vs.* 33.3%, p=0.0009
- Were satisfied with the time to treatment effect: 69.5% *vs.* 33.3%, p=0.0006
- Felt that they had a better facial appearance since starting the treatment: 63.0% *vs.* 26.8%, p=0.0217
- Would consider using the treatment again: 78.2% *vs.* 46.4%, p=0.0012
- Would agree that they were able to control their facial redness since starting the study: 60.0% *vs.* 33.3%, p=0.0114
- Received positive and neutral comments on their facial appearance: 46.7% *vs.* 26.1%, p=0.0163.

    - Facial Redness Control

For the question 'Was I able to control my facial redness today?' in the subject diary, the percentages of subjects stating 'Yes' were higher in the brimonidine tartrate 0.5% group (approximately 80%) than in the vehicle group (approximately 40%) throughout the study duration, confirming the data obtained for a similar question in the Subject Satisfaction questionnaire.

- **Efficacy**
  - CEA

At Baseline, both treatment groups had similar mean CEA scores between 3 and 4 in accordance with the inclusion criteria (Table 5). The mean CEA scores were significantly lower in the brimonidine tartrate 0.5% group than in the vehicle group at all evaluation time points i.e. Hour 3 on Day 1 ($p<0.0001$), on Day 2 ($p=0.0002$) and on Day 8 ($p=0.0006$) (Table 5).

Table 5 Clinician's Erythema Assessment: Raw Score at each Evaluation Time, Descriptive and p-Value – ITT Population

	Brimonidine (N=48)	Vehicle (N=44)	p-value
Day 1, Hour 0			
N	48	44	0.1562
3: Moderate	20 (41.7%)	25 (56.8%)	
4: Severe	28 (58.3%)	19 (43.2%)	
Mean ± SD	3.6 ± 0.5	3.4 ± 0.5	
Median	4.0	3.0	
(Min, Max)	(3.0, 4.0)	(3.0, 4.0)	
Day 1, Hour 3			
N	48	43	<0.0001
0: Clear	2 (4.2%)	0	
1: Almost clear	10 (20.8%)	0	
2: Mild	17 (35.4%)	9 (20.9%)	
3: Moderate	16 (33.3%)	22 (51.2%)	
4: Severe	3 (6.3%)	12 (27.9%)	
Mean ± SD	2.2 ± 1.0	3.1 ± 0.7	
Median	2.0	3.0	
(Min, Max)	(0.0, 4.0)	(2.0, 4.0)	
Day 2			
N	47	43	0.0002
1: Almost clear	9 (19.1%)	2 (4.7%)	
2: Mild	21 (44.7%)	10 (23.3%)	
3: Moderate	14 (29.8%)	19 (44.2%)	
4: Severe	3 (6.4%)	12 (27.9%)	
Mean ± SD	2.2 ± 0.8	3.0 ± 0.8	
Median	2.0	3.0	
(Min, Max)	(1.0, 4.0)	(1.0, 4.0)	
Day 8			
N	46	42	0.0006
0: Clear	2 (4.3%)	0	
1: Almost clear	12 (26.1%)	3 (7.1%)	
2: Mild	11 (23.9%)	6 (14.3%)	
3: Moderate	16 (34.8%)	18 (42.9%)	
4: Severe	5 (10.9%)	15 (35.7%)	
Mean ± SD	2.2 ± 1.1	3.1 ± 0.9	
Median	2.0	3.0	
(Min, Max)	(0.0, 4.0)	(1.0, 4.0)	

ITT: Intent-to-Treat. Note: p-value for between treatment differences by CMH test based on ridit scores stratified by analysis-center.
Data Source: Section 14, Table 27.

- PSA

At Baseline, both treatment groups had a mean PSA score of 4 in accordance with the inclusion criteria (Table 6). The mean PSA scores were significantly lower in the brimonidine tartrate 0.5% group than in the vehicle group at all evaluation time points i.e. Hour 3 on Day 1 (p=0.0001), Day 2 (p<0.0001) and Day 8 (p=0.0063) (Table 6).

Table 6 Patient Self-Assessment: Raw score at each Evaluation Time, Descriptive and p-Value – ITT Population

	Brimonidine (N=48)	Vehicle (N=44)	p-value
Baseline			
N	48	44	NA
4: Severe	48 (100.0%)	44 (100.0%)	
Mean ± SD	4.0 ± 0.0	4.0 ± 0.0	
Median	4.0	4.0	
(Min, Max)	(4.0, 4.0)	(4.0, 4.0)	
Day 1, Hour 3			
N	48	43	0.0001
0: No redness	2 (4.2%)	0	
1: Very mild	6 (12.5%)	1 (2.3%)	
2: Mild	14 (29.2%)	3 (7.0%)	
3: Moderate	16 (33.3%)	14 (32.6%)	
4: Severe	10 (20.8%)	25 (58.1%)	
Mean ± SD	2.5 ± 1.1	3.5 ± 0.7	
Median	3.0	4.0	
(Min, Max)	(0.0, 4.0)	(1.0, 4.0)	
Day 2			
N	47	43	<0.0001
0: No redness	1 (2.1%)	0	
1: Very mild	5 (10.6%)	1 (2.3%)	
2: Mild	16 (34.0%)	8 (18.6%)	
3: Moderate	19 (40.4%)	9 (20.9%)	
4: Severe	6 (12.8%)	25 (58.1%)	
Mean ± SD	2.5 ± 0.9	3.3 ± 0.9	
Median	3.0	4.0	
(Min, Max)	(0.0, 4.0)	(1.0, 4.0)	
Day 8			
N	46	42	0.0063
0: No redness	1 (2.2%)	0	
1: Very mild	8 (17.4%)	3 (7.1%)	
2: Mild	10 (21.7%)	7 (16.7%)	
3: Moderate	16 (34.8%)	10 (23.8%)	
4: Severe	11 (23.9%)	22 (52.4%)	
Mean ± SD	2.6 ± 1.1	3.2 ± 1.0	
Median	3.0	4.0	
(Min, Max)	(0.0, 4.0)	(1.0, 4.0)	

ITT: Intent-to-Treat.
Note: p-value for between treatment differences by CMH test based on ridit scores stratified by analysis-center.
Data Source: Section 14, Table 29.

- Facial inflammatory lesion counts

On Day 2 and Day 8, the majority of subjects had no changes in the inflammatory lesion counts from Baseline and at these evaluation visits, the majority of subjects presented no inflammatory lesions.

- **Safety**

Table 7 Overview of Adverse Events – APT Population

	Brimonidine (N=48)		Vehicle (N=44)		Total (N=92)	
	Event	Subject* n (%)	Event	Subject* n (%)	Event	Subject* n (%)
All AEs	32	15 (31.3)	15	9 (20.5)	47	24 (26.1)
All dermatologic AEs	29	14 (29.2)	13	7 (15.9)	42	21 (22.8)
All severe AEs	1	1 (2.1)	0	0	1	1 (1.1)
All AEs leading to discontinuation	2	1 (2.1)	0	0	2	1 (1.1)
Related AEs	26	14 (29.2)	13	7 (15.9)	39	21 (22.8)
Related dermatologic AEs	25	13 (27.1)	13	7 (15.9)	38	20 (21.7)
Related severe AEs	1	1 (2.1)	0	0	1	1 (1.1)
Related AEs leading to discontinuation	2	1 (2.1)	0	0	2	1 (1.1)

APT: All Patients Treated; AE: Adverse Event.
* Subjects with at least one event.
Note: Numbers in columns cannot be added because a given subject may have reported more than one AE.
Data Source: Section 14, Table 34.

Overall, 47 AEs were reported by 24/92 subjects (26.1%). The percentage of subjects who reported AEs was higher in the brimonidine tartrate 0.5% group than in the vehicle group: 15/48 subjects (31.3%) reported 32 AEs in the brimonidine tartrate 0.5% group while 9/44 subjects (20.5%) reported 15 AEs in the vehicle group (Table 7).

A total of 21/92 subjects (22.8%) reported 39 AEs related to study treatments, 38 of which were dermatological in nature. Higher percentage of subjects in the brimonidine tartrate 0.5% group reported treatment-related AE (14/48 subjects, 29.2%) than the vehicle group (7/44 subjects, 15.9%) (Table 8).

There was one severe related AE and 2 related AEs leading to discontinuation reported by one subject in the brimonidine tartrate 0.5% group (severe erythema and moderate skin swelling). There were no SAEs or deaths in this study.

Table 8 Related Adverse Events – APT Population

	Brimonidine (N=48)		Vehicle (N=44)		Total (N=92)	
	Event	Subject* n (%)	Event	Subject* n (%)	Event	Subject* n (%)
ANY ADVERSE EVENT	26	14 (29.2)	13	7 (15.9)	39	21 (22.8)
INFECTIONS AND INFESTATIONS	1	1 (2.1)	0	0	1	1 (1.1)
Rash pustular	1	1 (2.1)	0	0	1	1 (1.1)
NERVOUS SYSTEM DISORDERS	1	1 (2.1)	1	1 (2.3)	2	2 (2.2)
Headache	1	1 (2.1)	0	0	1	1 (1.1)
Hypoesthesia	0	0	1	1 (2.3)	1	1 (1.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	22	11 (22.9)	12	7 (15.9)	34	18 (19.6)
Erythema	4	4 (8.3)	2	2 (4.5)	6	6 (6.5)
Pain of skin	1	1 (2.1)	0	0	1	1 (1.1)
Pruritus	1	1 (2.1)	1	1 (2.3)	2	2 (2.2)
Rosacea	2	2 (4.2)	1	1 (2.3)	3	3 (3.3)
Skin burning sensation	0	0	2	2 (4.5)	2	2 (2.2)
Skin irritation	0	0	1	1 (2.3)	1	1 (1.1)
Skin tightness	4	3 (6.3)	3	2 (4.5)	7	5 (5.4)
Skin warm	9	2 (4.2)	2	1 (2.3)	11	3 (3.3)
Swelling face	1	1 (2.1)	0	0	1	1 (1.1)
VASCULAR DISORDERS	2	2 (4.2)	0	0	2	2 (2.2)
Flushing	2	2 (4.2)	0	0	2	2 (2.2)

APT: All Patients Treated; AE: Adverse Event; SOC: System Organ Class; PT: Preferred Term.
* Subjects with at least one event.
Note: Numbers in columns cannot be added because a given subject may have reported more than one AE. A subject was counted once per SOC and once per PT even if more than one occurrence of an event was reported within a SOC or PT.
Data Source: Section 14, Table 39.

Most of related AEs were in the SOC Skin and Subcutaneous Tissue Disorders. In this SOC, 18/92 subjects (19.6%) reported 34 treatment-related AEs. The percentage of subjects reporting treatment-related AEs in this SOC was higher in the brimonidine tartrate 0.5% group than in the vehicle group (11/48 subjects, 22.9% *vs.* 7/44 subjects, 15.9%).

The treatment-related AEs reported by more than 2 subjects in either group were: erythema (4/48 subjects [8.3%] in the brimonidine tartrate 0.5% group *vs.* 2/44 subjects [4.5%] in the vehicle group), rosacea (2/48 subjects [4.2%] *vs.* one subject [2.3%]), skin burning sensation (0 subjects *vs.* 2/44 subjects [4.5%]), skin tightness (3/48 subjects [6.3%] *vs.* 2/44 subjects [4.5%]) and skin warm (2/48 subjects [4.2%] *vs.* one subject [2.3%]). In the SOC Vascular Disorders, 2 subjects in the brimonidine tartrate 0.5% group reported flushing *vs.* no subject in the vehicle group.

Conclusion

The purpose of this study was to evaluate patient-reported outcomes following the treatment of severe erythema of rosacea with brimonidine tartrate 0.5% gel compared with vehicle gel. The clinical hypothesis was that once-daily application of brimonidine tartrate 0.5% gel was more efficacious than its vehicle gel in improving patient-reported outcomes regarding their QoL, with a good safety profile.

In this study, brimonidine tartrate 0.5% or vehicle was applied once daily on the face over an 8-day period.

First, patient-reported outcomes were assessed using the EQ-5D-3L and DLQI questionnaires, validated for evaluating subjects' general and skin-related QoL, respectively. After an 8-day treatment period, as expected, there was no difference in the EQ-5D-3L domains of mobility, self-care or usual activities or in the overall health state before or after treatment or between the two treatment groups. A slight improvement was observed in the brimonidine tartrate 0.5% group in the EQ-5D-3L domains of pain/discomfort and anxiety/depression. Improvement as reported by total DLQI score was shown for both treatment groups after 8 days of application, compared to baseline, but there was no difference between the groups of brimonidine tartrate 0.5% and vehicle.

The patient-reported outcomes were also assessed using two other questionnaires: the Facial Redness and Subject Satisfaction questionnaires. The Facial Redness questionnaire mainly focuses on the psychosocial impact of rosacea in order to collect outcomes linked to this specific condition. In this questionnaire, after 8 days of treatment, the percentages of subjects who provided positive response were higher in the brimonidine tartrate 0.5% group than in the vehicle group for most of the questions. The majority of subjects in the study did not cover or camouflage their facial redness, regardless of the visit and treatment group. Nevertheless, the percentage of subjects who covered their facial redness moderately or a great deal was lower in the brimonidine tartrate 0.5% group than in the vehicle group after 8 days of treatment. In addition, compared with the vehicle group, significantly more subjects in the brimonidine tartrate 0.5% group were satisfied with their facial appearance, and were not embarrassed or self-conscious with their facial redness (at least $p<0.05$).

The Subject Satisfaction questionnaire aimed at collecting the subjects' feedback on the treatment regimen, the level of satisfaction, and future usage. This specific questionnaire showed that significantly more subjects (at least $p<0.05$) in the brimonidine tartrate 0.5% group than in the vehicle group:

- Were satisfied overall with the treatment
- Were satisfied with the improvement in their facial redness
- Were satisfied with the time to treatment effect
- Felt that they had a better facial appearance since starting the treatment
- Would consider using the treatment in the future
- Agreed they were able to control their facial redness
- Received positive and neutral comments on their facial appearance.

Efficacy was assessed with CEA and PSA scores and successes (defined as a 2-grade improvement compared from Baseline) at each evaluation time point. Despite being similar at Baseline, the mean PSA and CEA scores after 8 days of treatment were significantly lower in the brimonidine tartrate 0.5% group than in the vehicle group ($p<0.001$) while being similar at Baseline. The percentages of subjects with CEA and PSA success were higher in the brimonidine tartrate 0.5% group than in the vehicle group: this difference was statistically significant for the CEA success ($p<0.0001$) but not for the PSA success.

No safety concerns were highlighted with brimonidine tartrate 0.5% in this study. The treatment was well tolerated. Subjects mainly reported cutaneous AEs, of mild severity which resolved spontaneously.

The clinical hypothesis was validated in this study: better efficacy of brimonidine tartrate 0.5% compared with vehicle was confirmed, and this superior efficacy led to an improvement in patient-reported outcomes with a good safety profile.