Effect of Adapalene 0.3% - Benzoyl Peroxide 2.5% Gel Versus Vehicle Gel on the Risk of Formation of Atrophic Acne Scars in Moderate to Severe Acne Subjects

NCT Number: NCT02735421

Date: 27 June 2017

INTERIM STATISTICAL ANALYSIS PLAN FOR RD.03.SPR.105061 (6-MONTH (Week 24) AFTER BASELINE)

EFFECT OF ADAPALENE 0.3% - BENZOYL PEROXIDE 2.5% GEL VERSUS VEHICLE GEL ON THE RISK OF FORMATION OF ATROPHIC ACNE SCARS IN MODERATE TO SEVERE ACNE SUBJECTS

APPROVALS

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Original: GALDERMA RESEARCH & DEVELOPMENT Archives, Sophia-Antipolis site

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1. STUDY OBJECTIVE

The purpose of this study was to evaluate the efficacy of Adapalene 0.3% - benzoyl peroxide 2.5% gel (ABPO Forte) versus vehicle gel on the risk of formation of atrophic acne scars in moderate to severe acne subjects.

2. INTERIM STATISTICAL ANALYSIS OBJECTIVE

The purpose of this interim analysis is to test the superior efficacy of ABPO Forte compared to its vehicle at week-24, in terms of *Total atrophic acne scar* per half-face (primary efficacy criterion).

The interim analysis will be performed when all subjects have completed the week-24 visit. For this interim analysis, all available variables at week-24 will be analyzed. It will have no impact on the type I error as this corresponds to primary analysis. This interim analysis is dedicated to provide topline results and is not meant to condition to any premature study termination.

3. INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN

Part I: This study was to be conducted as a multi-center, randomized, investigator-blinded, and vehicle-controlled trial using intra-individual comparison (right half-face versus left half-face) involving subjects of any gender or race, aged 16 to 35 years inclusive, with moderate to severe acne vulgaris and atrophic acne scars, and meeting other specific eligibility criteria.

A total of 60 subjects were to be enrolled at approximately 7 sites in Canada and France. Approximately 8-15 subjects were planned from each site. Subjects were to be treated for 24 weeks and each of their half-face randomized to one of the two following treatments:

- once-daily Adapalene 0.3% - BPO 2.5% gel.
- once-daily “Adapalene 0.3% - BPO 2.5%” vehicle gel .

There were 8 study visits: at baseline, week 1, 4, 8, 12, 16, 20 and week 24.

Part II: This is an open-label trial. At the decision of the investigator based on his/her medical assessment of efficacy during part I (effect on acne lesions and/or acne scars) and if the subject agrees, the subjects will have the possibility to continue to be treated with once-daily ABPO Forte for up to 24 additional weeks on the whole face with 2 additional visits, week 36 and 48

3.2 SAMPLE SIZE CONSIDERATION

3.2.1 Historical data and assumptions

Results from a previous intra-individual trial designed as a right-left comparison of Adapalene 0.1% - BPO 2.5% gel versus vehicle gel in acne subjects (protocol RD.03.SPR.40183E) showed a standard deviation (SD) of the bilateral differences in terms of *total atrophic acne scar count* at week 24 of around 4.8 with a mean bilateral difference around 2.

3.2.2 Sample size calculation

Using the historical data mentioned above, 50 evaluable subjects will be required, with 80% power. To allow about 20% rate of subjects excluded from analysis (major deviation, drop out, lost to follow-up, etc.) at week 24, 60 subjects should be enrolled.

4. ANALYZED VARIABLES

4.1 EFFICACY VARIABLES

4.1.1 Primary efficacy variable

- *Total atrophic acne scar count per half-face at week 24*: The scars were counted according to their size defined in 2 categories using 2- and 4-mm punch biopsy tools for size classification: scars 2-4 mm and scars > 4 mm.

4.1.2 Secondary efficacy variables

- *Total atrophic acne scar count per half-face at each intermediate visit*
- *Percent change from baseline in total atrophic acne scar count per half-face at each post-baseline visit*
- *Investigator's Scar Global Assessment (SGA) per half-face at each post-baseline visit*: % of subject across score. The evaluator assessed the severity of atrophic acne scars of each half-face, performing a static ("snapshot") evaluation of the severity based on the scale below:

Grade	Score	Clinical Description
Clear	0	No visible scars from acne
Almost Clear	1	Hardly visible scars from 50 cm away
Mild	2	Easily recognizable; less than half the affected face area* involved
Moderate	3	More than half and less than 75% of the affected face area* involved
Severe	4	More than 75% of the affected face area* affected

* The affected face area corresponds to a half-face.

- *Investigator's preference on overall scar severity at week 12 and at week 24/early termination*: At week 12, week 24 and in case of early termination, the evaluator assessed his/her preference in terms of overall acne scars severity between the two half faces

Overall efficacy (in terms of acne scars)	Left a lot better than right	Left a little bit better than right	No preference	Right a little bit better than left	Right a lot better than left
Score	-2	-1	0	1	2

- *Percent change from baseline in total lesion count per half-face at each post-baseline visit*: sum of inflammatory and non-inflammatory acne lesion count
- *Percent change from baseline in inflammatory lesion count per half-face at each post-baseline visit*:
- *Percent change from baseline in non-inflammatory lesion count per half-face at each post-baseline visit*:
- *Investigator's Global Assessment (IGA) per half-face at each post-baseline visit*: % of subject across score. The evaluator assessed the severity of acne for each half-face using the scale below and adapted for half-faces:

Grade	**Score**	**Clinical Description**
Clear	0	Clear skin with no inflammatory or non-inflammatory lesions
Almost Clear	1	A few scattered comedones and a few small papules
Mild	2	Easily recognizable; less than half the face is involved. Some comedones and some papules and pustules.
Moderate	3	More than half of the face is involved. Many comedones, papules and pustules. One small nodule may be present.
Severe	4	Entire face is involved. Covered with comedones, numerous papules and pustules. Few nodules may or may not be present.

4.1.3 Exploratory efficacy variables

- *Investigator's assessment of skin roughness per each half-face at baseline, week 12 and week 24/early termination*: The evaluator evaluated skin roughness for each half-face at baseline, week 12, week 24 and in case of early termination by using the five-point scale below:

Category	**Score**	**Description**
None	0	Very smooth
Minimal	1	Smooth
Mild	2	Somewhat smooth
Moderate	3	Slightly rough
Severe	4	Very rough

- *Investigator's assessment of skin texture change per half-face at week 12 and week 24/early termination*: Overall facial skin texture change will be graded by the evaluator for each half-face at week 12, week 24 and in case of early termination as follows:

Score	Description
0	Worse
1	No change
2	1-25% = slight improvement
3	26-50% = moderate improvement
4	51-75% = marked improvement
5	76-90% = almost complete improvement
6	91-100% = complete improvement

- *Skin microrelief variables:* percent change from Baseline per half-face at week 24/early termination

4.2 PATIENT-REPORTED OUTCOMES VARIABLES

- *Acne scar questionnaire per each half-face at baseline, week 12 and week 24/early termination*: using the SCARS questionnaire (Self-assessment of Clinical Acne Related Scars)

- *Subject's satisfaction questionnaire per each half-face at week 24/early termination*

4.3 SAFETY VARIABLES

- *Adverse events*: Incidence of adverse events - All clinical medical events, whether observed by the investigator or reported by the subject and whether or not thought to be study product -related were to be considered adverse events.

➢ *Local tolerability per half-face at each post-baseline visit:* % of subjects across scores. Erythema, scaling, dryness, and stinging/burning were graded at each visit as follows (Stinging/Burning at the baseline visit should be assessed as none):

Erythema – abnormal redness of the skin.		
0	None	No erythema
1	Mild	Slight pinkness present
2	Moderate	Definite redness, easily recognized
3	Severe	Intense redness
Scaling – abnormal shedding of the stratum corneum.		
0	None	No scaling
1	Mild	Barely perceptible shedding, noticeable only on light scratching or rubbing
2	Moderate	Obvious but not profuse shedding
3	Severe	Heavy scale production
Dryness – brittle and/or tight sensation.		
0	None	No dryness
1	Mild	Slight but definite roughness
2	Moderate	Moderate roughness
3	Severe	Marked roughness
Stinging/Burning – prickling pain sensation immediately after (within 5 minutes) dosing.		
0	None	No stinging/burning
1	Mild	Slight warm, tingling/stinging sensation; not really bothersome
2	Moderate	Definite warm, tingling/stinging sensation that is somewhat bothersome
3	Severe	Hot, tingling/stinging sensation that has caused definite discomfort

5. POPULATIONS ANALYZED

The definition of the populations and the pooling center will be finalized after a blind data review meeting, during which the distribution of subjects per site will be reviewed.

5.1 INTENT TO TREAT POPULATION (ITT)

This population consists of the entire population enrolled and randomized (i.e., assigned a kit number). The ITT population will be used for all variables except the safety variables.

5.2 PER PROTOCOL POPULATION (PP)

The PP Population is defined as comprising the ITT subjects who have no major protocol deviations that will be refined during a blind review meeting. Only the primary efficacy endpoint will be analyzed based on this population.

5.3 SAFETY POPULATION (APT)

This population consists of the intent-to-treat population, after exclusion of subjects who never took the treatment with certainty based on monitoring report. The APT population will be only used for the safety variables (AEs)

5.4 MISSING VALUES

In order to evaluate the effect of major deviations or of data exclusions, the last observation carried forward (LOCF) method will be used to impute missing values of acne scar and lesion counts and global assessment scores (SGA and IGA). If no post-baseline data are available, baseline will be carried forward. Thus, the number of subjects will not vary at each visit. The other missing values will not be replaced (observed data).

6. STATISTICAL METHODS AND DATA CONSIDERATIONS

SAS version 9.3 will be used for all analyses. All tests will be two-sided and significance will be declared at a 0.05 level.

6.1 DATA PRESENTATION

All continuous data will be summarized at each visit using usual statistics: number of values, mean, median, standard deviation, minimum and maximum, and by frequency distribution (n, %) for qualitative data. For ordinal data, both frequency distribution and usual statistics will be presented.

Therapies that have been stopped before the baseline visit will be presented as prior therapies. Those reported at baseline and still continuing after baseline will be classified as concomitant therapies.

The adverse events will be descriptively summarized (n, %). All summaries are based on the safety population (APT). The adverse events will be descriptively summarized (n, %) by relationship to study treatments within System Organ Class (SOC) and preferred term (MedDRA). Subjects will be descriptively summarized (n, %) by intensity (*i.e.* mild, moderate and severe) of adverse event, SOC and preferred term. Deaths and serious adverse events will be reported as well as withdrawals due to adverse events. A subject will be counted once per System Organ Class (SOC) and once per preferred term even if more than one occurrence of an event was reported within a SOC or preferred term. In the summary by categories of intensity, the adverse event with the highest intensity will be used. The subject will be counted once per SOC (highest intensity whatever the AE within the SOC) and once per preferred term (highest intensity whatever the AE within the preferred term).

All tables will be presented by overall, treatment group (if appropriate), treatment bilateral difference (if appropriate) and by visit (if appropriate). For AE tables, if too few AEs are recorded, a listing can be provided including subject number, treatment group, SOC, preferred term, date of onset, severity, subject discontinued, outcome, date of resolution and relationship.

6.2 STUDY SUBJECTS

6.2.1 Subject disposition

Normal completion as well as early discontinuation will be described on the ITT population. Reasons for withdrawals and normal completions will be summarized using frequency distribution (n, %). All withdrawals will be detailed in a subject-by-subject listing.

6.2.2 Protocol deviation

Major protocol deviations will be summarized using frequency distribution (n, %) detailed in a subject-by-subject listing in the ITT population.

6.2.3 Data sets analyzed

Number of subjects included in each analysis (PP, ITT) and number of subjects included in the safety analysis will be presented.

6.2.4 Demographic data

Demographic data collected at baseline will be descriptively summarized for ITT population.

6.2.5 Medical history

Medical history is defined as the relevant or ongoing conditions and major illnesses/operations (at the discretion of the investigator). Acne disease duration will be descriptively summarized by duration classes on the ITT population. Frequency distribution of subjects with at least one previous and/or concomitant disease at baseline will be tabulated (n, %).

6.2.6 Previous and concomitant drug and procedure therapies

Previous drugs/procedures therapies are defined as drugs/procedures that have been stopped within the 6 months preceding the baseline visit and that may have an impact on inclusion/exclusion criteria. Concomitant drugs/procedures are defined as drugs/procedures taken between the baseline visit and the last visit. Previous and Concomitant drugs/procedures will be descriptively summarized on the ITT population, by ATC text for drugs and Lower Level Term for procedures. Frequency distribution of subjects with at least one previous drug/ procedure at baseline and/or with at least one concomitant drug/procedure will be tabulated (n, %).

6.2.7 Compliance

Compliance will be calculated as follows, based on the data from the Study Companion tablet analysis (a tablet on which the subjects record daily applications) complemented with information collected in the eCRF (treatment compliance pages). It will be considered that a subject has not used the product only when it will be confirmed (by Study Companion tablet analysis or in the eCRF). It will be summarized in terms of frequency percentages by products.

$$\text{Compliance \%} = \frac{\text{Total number of days when treatment was used}}{\text{Date of last use} - \text{date of Baseline visit}} \text{ X } 100$$

6.2.8 Baseline disease characteristics

The characteristics of the disease collected at baseline will be descriptively summarized on ITT population.

6.3 EFFICACY ANALYSES

6.3.1 Primary efficacy analyses

The primary objective of this study is to demonstrate the superiority of Adapalene 0.3% - BPO 2.5% gel compared to its vehicle, in terms of total atrophic acne scar count at week 24. The mean bilateral difference between products of primary efficacy endpoint will be analyzed by using the Wilcoxon Rank Signed test, testing the hypothesis of equality. The p-value will have to be inferior to 0.05 at week 24, on ITT/LOCF population. Per Protocol analysis will be also performed to assess the robustness of the results obtained on the ITT/LOCF population.

6.3.2 Secondary efficacy analyses

The secondary efficacy variables will be analyzed similarly as primary analyses on ITT/LOCF population at each post-baseline evaluation time. Lesion counts will be only summarized by descriptive statistics.

6.3.3 Exploratory efficacy analyses

The exploratory efficacy variables will be analyzed similarly as primary analyses on ITT (data observed) population at each post-baseline evaluation time.

6.4 PATIENT-REPORTED OUTCOMES ANALYSES

All subject questionnaire will be descriptively summarized on ITT (data observed) population by investigational products and skin cares.

6.5 SAFETY ANALYSES

6.5.1 Extent of exposure

Treatment duration will be calculated as the number of days between the date of first use and the date of the last use of study treatment. If the date of last use and/or last use are missing the date of first and/or last visit will be used respectively.

6.5.2 Adverse Events

The adverse events will be summarized (n, %) for APT population. Deaths and serious adverse events will be reported as well as withdrawals due to adverse events.

7. CHANGES FROM THE PROTOCOL ANALYSIS PLAN

There is no change from protocol analysis plan.

APPENDIX 1: LIST AND FORMAT OF TABLES

GENERAL FEATURES

- Margins for portrait orientation
    - Top = 3.71 cm
    - Bottom = 3.17 cm
    - Left = 3 cm
    - Right = 1.4 cm
    - Heading = 2.41 cm
    - Footnote = 2.16 cm

- Margins for landscape orientation
    - Top = 3 cm
    - Bottom = 1.4 cm
    - Left = 3.17 cm
    - Right = 3.71 cm
    - Heading = 2.16 cm
    - Footnote = 1.25 cm

8. TABLE SHELLS

14.1. Study Subjects

14.1.1. Conduct of the study

Table 1. Enrolment by center (ITT)

e.g.	Total
Center 1 (n,%) Center 2 (n,%) …..	

Table 2.1 Subjects who discontinued study and reason for discontinuation (ITT)

e.g.	Total
Randomized Premature discontinuation Adverse event Subject's request Protocol violation ….. Completed the study	

Table 2.2. Listing of subjects who discontinued treatment and reason for discontinuation (ITT)
(Included: investigator number, subject number and reason for discontinuation)

Table 3. Adherence to the visit schedule in days (ITT)

	Total
Nb of days between baseline and week 1 N Mean±SD Median (Min,Max)	
……	
Nb of days between baseline and week 24 ……	
Nb of days between baseline and Endpoint* N Mean±SD Median (Min,Max)	

*Endpoint is defined as the last visit

Table 4.1 Major protocol deviations (ITT)

e.g.	Total	
	Deviation n	Subject n (%)
AT LEAST ONE MAJOR DEVIATION Inclusion/exclusion criteria No visit after the baseline Compliance Forbidden concomitant therapies …		

Table 4.2. Listing of subjects and major protocol deviations (ITT)
(Included: investigator number, subject number and deviation)

Table 5. Data sets analysed

	Total
Intent to treat population n Per Protocol population n (%)* Safety population n (%)*	

* Denominator is the number of subjects in the Intent to treat population

14.1.2. Subject characteristics

Table 6. Demographic data (ITT)

	Total
Gender Male n(%) Female n(%)	
Age N Mean ±SD Median (Min,Max) ≤ 18 years 18 – 65 years ≥ 65 years	
Race N White n (%) …	
Phototype I n (%) II n (%) ….	

Table 7. Medical history (ITT)

	Total (N=xxx)
Acne vulgaris: duration in year N Less than 1 year n(%) Between 1 and xx years n(%) More than xx years n(%) Mean ±SD Median (Min,Max)	
With any relevant previous or/and concomitant disease/operation other than Acne vulgaris N Yes: n(%) No: n(%)	

Table 8. Previous drug therapies within the previous 6 months, by ATC text (ITT)

	Total (N=xxx)
Subjects reporting at least one previous drug therapy (n,%) ***List all previous drug therapies by ATC category*** (n,%)	

The numbers in the columns cannot be added because a given subject could report more than one previous drug therapy

Table 9. Previous procedure therapies within the previous 6 months, by Lower Level Term (ITT)

	Total (N=xxx)
Subjects reporting at least one previous procedure therapy (n, %) ***List all previous procedures therapies by LLT.***	

The numbers in the columns cannot be added because a given subject could report more than one previous procedure therapy.

Table 10. Concomitant drug therapies by ATC text (ITT)

	Total (N=xxx)
Subjects with at least one concomitant drug therapy (n, %) ***List all concomitant drug therapies by ATC category***	

The numbers in the columns cannot be added because a given subject could report more than one concomitant drug therapy

Table 11. Concomitant procedure therapies by Lower Level Term (ITT)

	Total (N=xxx)
Subjects with at least one concomitant procedure therapy (n, %) ***List all concomitant procedure therapy by LLT.***	

The numbers in the columns cannot be added because a given subject could report more than one concomitant procedure therapy

Table 12. Compliance for investigational products (ITT)

	ABPO Forte	Vehicle
<25% of compliance n (%) [25%;50%[of compliance n (%) [50%;75%[of compliance n (%) >=75% of compliance n (%)		

Table 13. Baseline disease characteristics (ITT)

	ABPO Forte	Vehicle	ABPO Forte –Vehicle
Acne scar counts (2-4 mm) N Mean ±SD Median Min,Max			
Acne scar counts (>4 mm) …			
Total acne scar counts ….			
Investigator's Scar Global Assessment N …. -2: n (%) -1: n (%) 0: n (%) 1: n (%) 2: n (%) …. Mean ±SD Median Min,Max			
Tota lesion counts ……			
Inflammatory lesion counts ……			
Non-inflammatory lesion counts ……			
Nodule counts ……			
Investigator's Global Assessment N …. -2: n (%) -1: n (%) 0: n (%) 1: n (%) 2: n (%) …. Mean ±SD Median Min,Max			

Table 14. Baseline skin aspect (ITT)

	ABPO Forte	Vehicle	ABPO Forte –Vehicle
Skin roughness score N …. -2: n (%) -1: n (%) 0: n (%) 1: n (%) 2: n (%) …. Mean ±SD Median Min,Max			
Skin microrelief: Sa (µm) N Mean ±SD Median Min,Max			
Skin microrelief: Smax (µm) …			
Skin microrelief: Sz (µm) …			

14.2. Efficacy analyses

14.2.1. Primary efficacy analyses

Table 15. Total atrophic acne scar count: Descriptive and p-value at week 24

		ABPO Forte	Vehicle	ABPO Forte –Vehicle	p-value (1)
Total scar	Week 24 (ITT/LOCF) N Mean ± SD Median (Min,Max)				xxxx
	Week 24 (PP) N Mean ± SD Median (Min,Max)				xxxx
Scar 2-4mm	Week 24 (ITT/LOCF) N Mean ±SD Median Min,Max				xxxx
Scar >4mm	Week 24 (ITT/LOCF) N Mean ±SD Median Min,Max				xxxx

(1) Wilcoxon Rank Signed test

Table 16. Total atrophic acne scar count at week 24: Descriptive by center (ITT/LOCF)

	ABPO Forte	Vehicle	ABPO Forte –Vehicle
Center 1 N Mean ± SD Median (Min,Max)			
Center 2 N Mean ± SD Median (Min,Max)			
…..			

14.2.2. Secondary efficacy analyses

14.2.2.1. Atrophic acne scar

Table 17. Total atrophic acne scar count: Descriptive and p-value by visit (ITT/LOCF)

	ABPO Forte	Vehicle	ABPO Forte –Vehicle	p-value (1)
Baseline N Mean ±SD Median Min,Max				NA
Week 1 N Mean ± SD Median (Min,Max)				xxxx
…..				
Week 20 N Mean ±SD Median Min,Max				xxxx

(1) Wilcoxon Rank Signed test

Table 18. Total atrophic acne scar % change from baseline: Descriptive and p-value by visit (ITT/LOCF)

	ABPO Forte	Vehicle	ABPO Forte –Vehicle	p-value (1)
Week 1 N Mean ± SD Median (Min,Max)				xxxx
…..				
Week 24 N Mean ±SD Median Min,Max				xxxx

(1) Wilcoxon Rank Signed test

Table 19. Investigator's Scar Global Assessment: Descriptive and p-value by visit (ITT/LOCF)

	ABPO Forte	Vehicle	ABPO Forte –Vehicle	p-value (1)
Baseline N Mean ±SD Median Min,Max				NA
…..				
Week 24 N Mean ±SD Median Min,Max				xxxx

(1) Wilcoxon Rank Signed test

Table 20. Investigator's Scar Global Assessment: Descriptive by visit (ITT/LOCF)

	ABPO Forte	Vehicle
Baseline N 2: Mild n (%) 3: Moderate n (%) 4: Severe n (%) Mean ±SD Median Min,Max		
…..		
Week 24 N 0: Clear n (%) 1: Almost clear n (%) 2: Mild n (%) 3: Moderate n (%) 4: Severe n (%) Mean ±SD Median Min,Max		

Table 21. Investigator's preference on overall scar severity: Descriptive and p-value (ITT)

Week 12 ABPO Forte a lot better than Vehicle (n,%) ABPO Forte a little bit better Vehicle (n,%) No preference (n,%) Vehicle a little bit better ABPO Forte (n,%) Vehicle a lot better than ABPO Forte (n,%) p-value (1)	
Week 24/Early termination ABPO Forte a lot better than Vehicle (n,%) ABPO Forte a little bit better Vehicle (n,%) No preference (n,%) Vehicle a little bit better ABPO Forte (n,%) Vehicle a lot better than ABPO Forte (n,%) p-value (1)	

(1) Wilcoxon Rank Signed test

14.2.2.2. Acne lesions

Table 22. Total lesion, % change from baseline: Descriptive and p-value by visit (ITT/LOCF)

	ABPO Forte	Vehicle	ABPO Forte –Vehicle	p-value (1)
Week 1 N Mean ± SD Median (Min,Max)				xxxx
…..				
Week 24 N Mean ±SD Median Min,Max				xxxx

(1) Wilcoxon Rank Signed test

Table 23. Total lesion count: Descriptive by visit (ITT/LOCF)

	ABPO Forte	Vehicle	ABPO Forte –Vehicle
Baseline N Mean ±SD Median Min,Max			
Week 1 N Mean ± SD Median (Min,Max)			
…..			
Week 24 N Mean ±SD Median Min,Max			

Table 24. Inflammatory lesion, % change from baseline: Descriptive and p-value by visit (ITT/LOCF)
Table 25. Inflammatory lesion count: Descriptive by visit (ITT/LOCF)

Table 26. Non-inflammatory lesion, % change from baseline: Descriptive and p-value by visit (ITT/LOCF)
Table 27. Non-inflammatory lesion count: Descriptive by visit (ITT/LOCF)

Table 28. Investigator Global Assessment: Descriptive and p-value by visit (ITT/LOCF)

	ABPO Forte	Vehicle	ABPO Forte –Vehicle	p-value (1)
Baseline N Mean ±SD Median Min,Max				NA
…..				
Week 24 N Mean ±SD Median Min,Max				xxxx

Table 29. Investigator Global Assessment: Descriptive by visit (ITT/LOCF)

	ABPO Forte	Vehicle
Baseline N 2: Mild n (%) 3: Moderate n (%) 4: Severe n (%) Mean ±SD Median Min,Max		
…..		
Week 24 N 0: Clear n (%) 1: Almost clear n (%) 2: Mild n (%) 3: Moderate n (%) 4: Severe n (%) Mean ±SD Median Min,Max		

14.2.3. Exploratory efficacy analyses

Table 30. Skin roughness score: Descriptive and p-value by visit (ITT)

	ABPO Forte	Vehicle	ABPO Forte –Vehicle	p-value (1)
Baseline N Mean ±SD Median Min,Max				NA
Week 12 N Mean ±SD Median Min,Max				xxxx
Week 24/Early termination N Mean ±SD Median Min,Max				xxxx

Table 31. Skin roughness score: Descriptive by visit (ITT)

	ABPO Forte	Vehicle
Baseline N 1: None n (%) 2: Minimal n (%) 3: Mild n (%) .. Mean ±SD Median Min,Max		
Week 12 …..		
Week 24/Early termination N 1: None n (%) 2: Minimal n (%) 3: Mild n (%) .. Mean ±SD Median Min,Max		

Table 32. Skin texture change score: Descriptive and p-value by visit (ITT)

	ABPO Forte	Vehicle	ABPO Forte –Vehicle	p-value (1)
Week 12 N Mean ±SD Median Min,Max				xxxx
Week 24/Early termination N Mean ±SD Median Min,Max				xxxx

Table 33. Skin texture change score: Descriptive by visit (ITT)

	ABPO Forte	Vehicle
Week 12 N 0: Worse n (%) 1: No change n (%) 2: Slight improvement n (%) .. Mean ±SD Median Min,Max		
Week 24/Early termination N 0: Worse n (%) 1: No change n (%) 2: Slight improvement n (%) .. Mean ±SD Median Min,Max		

Table 34. Skin microrelief, % change from baseline: Descriptive and p-value at week 24/Early termination (ITT)

	ABPO Forte	Vehicle	ABPO Forte –Vehicle	p-value (1)
Skin microrelief: Sa (µm) N Mean ±SD Median Min,Max				xxxx
Skin microrelief: Smax (µm) …				xxxx
Skin microrelief: Sz (µm) …				xxxx

Table 35. Skin microrelief: Descriptive at week 24/Early termination (ITT)

	ABPO Forte	Vehicle	Total
Skin microrelief: Sa (µm) N Mean ±SD Median Min,Max			
Skin microrelief: Smax (µm) …			
Skin microrelief: Sz (µm) …			

14.2.4. Patient-reported outcomes analyses

Table 36. Acne scar questionnaire at baseline, Descriptive (ITT)

	ABPO Forte	Vehicle
Severity of acne N Mean ±SD Median Min,Max		
Severity of indents/holes N Mean ±SD Median Min,Max		
Face covered by indents/holes N 1: Almost none n (%) 2: A little n (%) 3: Some n (%) 4: A lot n (%) 5: Almost all n (%) Mean ±SD Median Min,Max		
Size of indents/holes N 1: Very small n (%) … 5: Very large n (%) Mean ±SD Median Min,Max		
Quantity of indents/holes N 1: Very few n (%) … 5: Many n (%) Mean ±SD Median Min,Max		
Depth of indents/holes ….		
Visibility of indents/holes ….		

Table 37. Acne scar questionnaire at week 12, Descriptive (ITT)

Table 38. Acne scar questionnaire at week 24/Early termination, Descriptive (ITT)

Table 39. Acne scar questionnaire change from baseline at week 24/Early termination, Descriptive (ITT)

	ABPO Forte	Vehicle
Severity of acne: % change from baseline N Mean ±SD Median Min,Max		
Severity of indents/holes: % change from baseline N Mean ±SD Median Min,Max		
Face covered by indents/holes: change from baseline N …. -2: 2 grade more n (%) -1: 1 grade more n (%) 0: No change n (%) 1: 1 grade less n (%) 2: 2 grade less n (%) ….. Mean ±SD Median Min,Max		
Size of indents/holes: change from baseline N …. -2: 2 grade more n (%) -1: 1 grade more n (%) 0: No change n (%) 1: 1 grade less n (%) 2: 2 grade less n (%) ….. Mean ±SD Median Min,Max		
Quantity of indents/holes: change from baseline ….		
Depth of indents/holes: change from baseline ….		
Visibility of indents/holes: change from baseline ….		

Table 40. Subject satisfaction questionnaire at week 24/Early termination, Descriptive (ITT)

	ABPO Forte	Vehicle
1. How bothered were you by the treatment side effects? N Not bothered at all Bothered a little Bothered somewhat Bothered a great deal		
…..		
6a. Did you use the provided moisturizing lotion? N No (n,%) Yes (n,%)		
6b. If yes N To reduce stg/brg (n,%) to be adherent (n,%) To reduce dryness (n,%) pleasant to use (n,%) None of the above (n,%)		

Table 41. Subject satisfaction questionnaire at week 24/Early termination, Descriptive (ITT)

	ABPO Forte	Vehicle
1. How bothered were you by the treatment side effects? N Not bothered at all (n,%) Bothered a little (n,%) Bothered somewhat (n,%) Bothered a great deal (n,%)		
…..		
6a. Did you use the provided moisturizing lotion? N No (n,%) Yes (n,%)		
6b. If yes N To reduce stg/brg (n,%) to be adherent (n,%) To reduce dryness (n,%) pleasant to use (n,%) None of the above (n,%)		

Table 42. Subject questionnaire about skin cares at week 24/Early termination, Descriptive (ITT)

	Total
1. Both skin care products were easy to incorporate into a daily routine N Strongly agree (n,%) Agree (n,%) Neither agree or disagree (n,%) Disagree (n,%) Strongly disagree (n,%)	
…..	

Table 43. Subject questionnaire about Moisturizer SPF30 at week 24/Early termination, Descriptive (ITT)

Table 44. Subject questionnaire about Wash at week 24/Early termination, Descriptive (ITT)

14.3. Safety analyses

14.3.1. Extent of Exposure

Table 45. Extent of exposure in days (APT)

	ABPO Forte	Vehicle
N Mean±SD Median Min,Max		

14.3.2. Adverse events

Table 46. Overview of adverse events (APT)

e.g.	ABPO Forte treated side		Vehicle treated side		Unspecific treated side		Total	
	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)
All AEs								
AEs related to treatment								
AEs related to procedure								
All dermatologic AEs								
Dermatologic AEs related to treatment								
Dermatologic AEs related to procedure								
All serious AEs								
Serious AEs related to treatment								
Serious AEs related to procedure								
Deaths								
All AEs leading to discontinuation								

Subjects with at least one event. Numbers in columns cannot be added because a given subject may have reported more than one AE.
Column TOTAL is when the subject is considered as a whole

Table 47. Frequency of all adverse events by preferred term (APT)

e.g.	ABPO Forte treated side		Vehicle treated side		Unspecific treated side	
	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)
Subjects with at least one event Diarrhoea nos Peptic ulcer Vomiting nos …..						

Subjects with at least one event. Numbers in columns cannot be added because a given subject may have reported more than one AE.

Table 48. Listing of subjects with with adverse events related to procedure (APT)

(Include: subject number, treatment group, SOC, preferred term, date of onset, severity, serious, subject discontinued, outcome, date of resolution and relationship)

Table 49. Frequency of all adverse events (except SAE) by preferred term (APT)

Table 50. Frequency of related adverse events by preferred term (APT)

e.g.	ABPO Forte treated side		Vehicle treated side	
	Event n	Subject n (%)	Event n	Subject n (%)
Subjects with at least one event Diarrhoea nos Peptic ulcer Vomiting nos …..				

Subjects with at least one event. Numbers in columns cannot be added because a given subject may have reported more than one AE.

Table 51: All adverse events by SOC and preferred term (APT)

e.g.	ABPO Forte treated side		Vehicle treated side		Unspecific treated side	
	Event n	Subject n (%)	Event n	Subject n (%)	Event n	Subject n (%)
ANY ADVERSE EVENT GASTROINTESTINAL DISORDERS Abdominal pain nos ….. IMMUNE SYSTEM DISORDERS Allergic sinusitis …..						

*Subjects with at least one event. 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 preferred term even if more than one occurrence of an event was reported within a SOC or preferred term.

Table 52: Related adverse events by SOC and preferred term (APT)

Table 53. Subject incidence by adverse events intensity, SOC and preferred term (APT)

	ABPO Forte treated side Subject n (%)			Vehicle treated side Subject n (%)			Unspecific treated side Subject n (%)		
e.g.	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
ANY ADVERSE EVENT									
GASTROINTESTINAL DISORDERS									
Abdominal pain nos									
…..									
IMMUNE SYSTEM DISORDERS									
Allergic sinusitis									
…..									

Subjects with at least one event. Numbers in columns cannot be added because a given subject may have reported more than one AE.
A subject was counted once per SOC (highest intensity whatever the AE within the SOC) and once per preferred term (highest intensity if more than one occurrence of an event is reported)

Table 54. Subject incidence by related adverse events, SOC and preferred term (APT)

Table 55. Serious adverse events by SOC and preferred term (APT)

e.g.	ABPO Forte treated side		Vehicle treated side		Unspecific treated side		Total	
	Event n	Subject* n (%)	Event n	Subject* n (%)	Event n	Subject* n (%)	Event n	Subject* n (%)
ANY SERIOUS ADVERSE EVENT								
GASTROINTESTINAL DISORDERS								
Abdominal pain nos								

*Subjects with at least one event. 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 preferred term even if more than one occurrence of an event was reported within a SOC or preferred term.

A listing can be provided with the information of the AE form if too few SAE.

Table 54. Listing of subjects with serious adverse events (APT)

(Include: subject number, treatment group, SOC, preferred term, date of onset, severity, serious, subject discontinued, outcome, date of resolution and relationship)

Table 56. Summary of adverse events leading to discontinuation of study by SOC and preferred term (APT)

e.g.	ABPO Forte treated side	Vehicle treated side	Unspecific treated side	Total
	Subject* n (%)	Subject* n (%)	Subject* n (%)	Subject* n (%)
ANY ADVERSE EVENT				
GASTROINTESTINAL DISORDERS				
Abdominal pain nos				

*Subjects with at least one event. 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 preferred term even if more than one occurrence of an event was reported within a SOC or preferred term.

A listing can be provided with the information of the AE form if too few AE leading to discontinuation of study

Table 55. Listing of subjects with adverse events leading to discontinuation of study (APT)

(Include: subject number, treatment group, SOC, preferred term, date of onset, severity, serious, subject discontinued, outcome, date of resolution and relationship)

14.3.3. Local Tolerance

Table 57. Erythema score by visit, Descriptive (APT)

	ABPO Forte	Vehicle
Baseline		
None		
Mild		
Moderate		
Severe		
Mean±SD		
Median		
(Min,Max)		
…….		
Week 24		
None		
Mild		
Moderate		
Severe		
Mean±SD		
Median		
(Min,Max)		

Table 58. Scaling score by visit, Descriptive (APT)

Table 59. Dryness score by visit, Descriptive (APT))

Table 60. Stinging/Burning score by visit, Descriptive (APT)