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: 06 July 2016

GALDERMA

**CLINICAL TRIAL PROTOCOL**
**PROTOCOL NUMBER: RD.03.SPR.105061**

**CONFIDENTIAL**

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## TITLE PAGE

| **Title:** 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 | | |
|---|---|---|
| **Product Name:**<br>CD0271 0.3%/CD1579 Gel, named Tactupump™ Forte in Canada | **Project Number:**<br>816 | **Clinical Trial Phase:**<br>IV |

EUDRACT n°: 2016-002666-31
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***Version Number: 02 FR***

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| | |
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**For any urgent medical questions, including safety reason, please use the contact details provided in Section 8.4.**

This clinical trial will be performed in compliance with applicable regulations, Good Clinical Practice (GCP) and the ethical principles that have their origin in the Declaration of Helsinki. This clinical trial protocol follows guidelines outlined by the International Conference on Harmonization (ICH) and the GALDERMA R&D Phase IV department template

## Clinical Trial Administrative Structure

The following table contains the details of the sponsor's employees involved in the conduct of the trial.

| ***SPONSOR PERSONNEL*** | | |
|---|---|---|
| *Name/Title* | *Affiliation/Address/Tel./Fax/Email* | *Responsibilities* |
| [redacted] | GALDERMA R&D SNC, [redacted] | Responsible for clinical management and monitoring of clinical trial and for overall coordination of clinical project |
| [redacted] | GALDERMA R&D SNC, Same as above [redacted] | Responsible for administrative follow-up and management of Trial Master File |
| [redacted] | GALDERMA R&D SNC, Same as above [redacted] | Responsible for medical management and safety surveillance |
| [redacted] | GALDERMA R&D SNC, Same as above [redacted] | Responsible for the coordination of all data management activities |
| [redacted] | GALDERMA R&D SNC, Same as above [redacted] | Responsible for the management of all statistical activities |
| [redacted] | GALDERMA R&D SNC, Same as above [redacted] | Responsible for quality assurance and audits |

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|---|---|---|
| [redacted] | GALDERMA R&D SNC,<br>Same as above<br>[redacted] | Responsible for safety surveillance |
| [redacted] | GALDERMA R&D SNC,<br>Same as above<br>[redacted] | Responsible for the management of all clinical supplies activities for France |
| [redacted] | Galderma Laboratories, L.P.<br>[redacted] | Responsible for the management of all clinical supplies activities for Canada |

## SIGNATURE PAGE

**INVESTIGATOR'S AGREEMENT**

I agree to:

- Implement and conduct this clinical trial diligently and in strict compliance with the protocol, Good Clinical Practices and all applicable laws and regulations.
- Accurately record all required data on each patient's electronic Case Report Forms (eCRFs) in a timely manner on an ongoing basis.
- Use the investigational products for this clinical trial only. Maintain a complete and accurate inventory during and at the completion of the clinical trial. Maintain records of all investigational product units received, dispensed, returned by the subjects, and the number of product units returned to the Sponsor.
- Allow authorised representatives of GALDERMA R&D or regulatory authorities to conduct on-site visits to review, audit, and copy clinical trial documents. I will personally meet these representatives at mutually convenient times to answer any clinical trial-related questions.
- Comply strictly with the agreement signed for the carrying out of my services within the scope of this protocol, especially with the provisions regarding confidentiality and intellectual property (results and publications).

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

PRINCIPAL INVESTIGATOR

| PRINTED NAME: | SIGNATURE | DATE |
|---|---|---|

*GALDERMA R&D*

SPONSOR REPRESENTATIVE

| PRINTED NAME: [redacted] | SIGNATURE | DATE |
|---|---|---|

SPONSOR MEDICAL EXPERT

| PRINTED NAME: [redacted] | SIGNATURE | DATE |
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Original Protocol:

Archives (GALDERMA R&D – Sophia Antipolis)

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| AE | Adverse Event |
| APT | All Patients Treated (Safety Population) |
| BPO | Benzoyl peroxide |
| CDMS | Clinical Data Management System |
| CPM | Clinical Project Manager |
| CRA | Clinical Research Associate |
| eCRF | Electronic Case Report Form |
| CRO | Contract Research Organization |
| DMP | Data Management Plan |
| EC | Ethics Committee |
| EDC | Electronic Data Capture |
| FSI | First Subject In *(first subject who signs the Informed Consent Form)* |
| GCP | Good Clinical Practice |
| GPRS | General Packet Radio Service |
| hCG | Human chorionic gonadotropin |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IGA | Investigator's Global Assessment |
| i.e. | That is (Latin: id est) |
| IRB | Institutional Review Board |
| ISF | Investigator Site File |
| IUD | Intra Uterine Device |
| ITT | Intent-To-Treat |
| LOCF | Last Observation Carried Forward |
| LSI | Last Subject In (*Last subject who signs the Informed Consent Form*) |
| LSO | Last Subject Out *(last subject last visit)* |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMP | Matrix-degrading metalloproteinases |
| N/A | Not Applicable |
| OTC | Over-The-Counter |
| PIH | Post-Inflammatory Hyperpigmentation |
| PP | Per Protocol |
| PRO | Patient Reported Outcome |
| QA | Quality Assurance |
| QR code | Quick Response code |

| | |
|---|---|
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System (SAS Institute Inc., Cary, NC) |
| SCARS | Self-assessment of Clinical Acne-Related Scars |
| SD | Standard Deviation |
| SGA | Scars Global Assessment |
| SIN | Subject Identification Number |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SPF | Sun Protection Factor |
| UPT | Urine Pregnancy Test |
| UV | Ultraviolet |
| w | Week |

# 1 SYNOPSIS

| | | |
|---|---|---|
| **Clinical trial title:** 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 | | |
| **Short title:** Adapalene 0.3% - benzoyl peroxide 2.5% gel and risk of formation of atrophic acne scars | | |
| **Project number:**<br>816 | **Clinical trial phase:**<br>IV | **Clinical trial period (planned):**<br>Q2 2016 – Q4 2017 |
| **Objective(s):** | The main objective of this trial is to evaluate the effect of Adapalene 0.3% - benzoyl peroxide (BPO) 2.5% gel versus vehicle gel on the risk of formation of atrophic acne scars in moderate to severe acne subjects. | |
| **Methodology:** | This trials is composed of 2 parts:<br><br>**<u>Part I:</u>** This is a multi-centre, international, randomized, investigator blinded, vehicle controlled trial using intra-individual comparison (right half-face versus left half-face).<br><br>All eligible subjects will have each half-face randomized to one of the two following treatments:<br>- once-daily Adapalene 0.3% - BPO 2.5% gel (CD0271 0.3%/CD1579 2.5% Gel, named Tactupump™ Forte in Canada, ).<br>- once-daily "Adapalene 0.3% - BPO 2.5%" vehicle gel (Vehicle gel)<br><br>**<u>Part II:</u>** 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 Adapalene 0.3% - BPO 2.5% gel (CD0271 0.3%/CD1579 2.5% Gel / Tactupump™ Forte) for up to 24 additional weeks on the whole face. | |
| **Total number of planned subjects/sites:**<br>**Approximate number of subjects/site:** | A total of 60 subjects will be enrolled at approximately 7 sites (8-15 subjects per site). | |

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| **Country(ies) involved:** | Canada, France |
| **Population and main inclusion criteria:** | Male or female subjects with moderate to severe acne vulgaris, age of 16 to 35 years inclusive, meeting specific inclusion/exclusion criteria. |
| **Clinical trial duration per subject** | The maximum trial duration for a subject is 48 weeks:<br>Part I: 24 weeks<br>Part II: 24 weeks |
| **Number of visits:** | Part I (8 visits): Baseline, W1, W4, W8, W12, W16, W20 and W24<br>Part II (2 visits): W36 and W48 |
| **Investigational product**<br>**Name:**<br><br>**Pharmaceutical form:**<br>**Dose/concentration:**<br>**Total daily dose:**<br>**Mode and frequency of administration:**<br>**Location of treated area:**<br>**Duration of treatment:** | <br>Tactupump™ Forte (in Canada) / CD0271 0.3%/CD1579 2.5% Gel<br>Gel<br>Adapalene 0.3% - BPO 2.5%<br>2 pea-sized amounts for one half-face<br><br>Topical, once-daily in the evening after washing<br>Face<br>24 weeks (part I) + 24 additional weeks (part II) |
| **Investigational comparator product:**<br>**Name:**<br>**Pharmaceutical form:**<br>**Strength/concentration:**<br>**Total daily dose:**<br>**Mode and frequency of administration:**<br>**Location of treated area:**<br>**Duration of treatment:** | <br><br>Vehicle gel (used only during part I)<br>Gel<br>N/A<br>2 pea-sized amounts for one half-face<br><br>Topical, once-daily in the evening after washing<br>Face<br>24 weeks |
| **Non-investigational product to be provided for the clinical trial:** | Cetaphil® DermaControl™ Oil Control Foam Wash, twice daily (once in the morning, once in the evening). |

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| | Cetaphil® DermaControl™ Oil Control Moisturizer SPF 30 once daily in the morning after using Cetaphil® DermaControl™ Oil Control Foam Wash and applications as needed during the day.<br><br>Both products are topical and will be used on the whole face for the whole duration of the trial (up to 48 weeks). |
| **Measurement criteria** | **Efficacy**<br>• *Atrophic acne scar count* on each half-face at each visit.<br>• *Investigator's scar global assessment (SGA)* of each half-face at each visit on a scale from 0 (Clear) to 4 (Severe).<br>• *Investigator's preference on overall scar severity* (right vs. left) on a scale from -2 to 2 at week 12 and week 24, early termination during part I.<br>• *Non-inflammatory lesion (open and closed comedones), inflammatory lesion (papules, pustules) and nodule count* on each half-face at each visit.<br>• *Investigator's global assessment (IGA)* of each half-face at each visit: severity of acne on a scale from 0 (Clear) to 4 (Severe).<br>• *Investigator's assessment of skin roughness* of each half-face at Baseline, week 12, week 24, week 48, early termination.<br>• *Investigator's assessment of skin texture change* of each half-face at week 12, week 24, week 48, early termination.<br>• *Quantitative evaluation of skin microrelief (skin replica)* for each half-face at Baseline, week 24, week 48, early termination (if after week 8) (done at one selected site only).<br><br>**Safety**<br>• *Adverse Events (AEs)* throughout the trial.<br>• *Local tolerability scores* (Erythema, Scaling, Dryness, Stinging/Burning) at each visit.<br><br>**Patient Reported Outcome (PRO)**<br>• *Acne scar appearance* using the SCARS questionnaire at Baseline, week 12, week 24, week 48, early termination for each half-face. |

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| | • *Subject satisfaction questionnaire* at week 24, week 48, early termination.<br><br>**Other**<br>• *Photographs* at Baseline, week 12, week 24 and week 48 (done at selected sites only). |
| **Analysed variables** | **Efficacy variables**<br><br><u>Primary efficacy endpoint</u><br>*Total atrophic acne scar count* per half-face at week 24<br><br><u>Secondary efficacy endpoints</u><br>• *Total atrophic acne scar count* per half-face at each post-baseline visit (except week 24)<br>• *Percent change from Baseline in total atrophic acne scar count* per half-face at each post-baseline visit<br>• *SGA* per half-face at each post-baseline visit<br>• *Investigator's preference on overall scar severity* (right vs. left) at week 12 and week 24/early termination during part I<br>• *Percent change from Baseline in total lesion count* per half-face at each post-baseline visit<br>• *Percent change from Baseline in inflammatory lesion count* per half-face at each post-baseline visit<br>• *Percent change from Baseline in non-inflammatory lesion count* per half-face at each post-baseline visit<br>• *IGA* per half-face at each post-baseline visit<br><br><u>Exploratory endpoints</u><br>• *Investigator's assessment of skin roughness* for each half-face at Baseline, week 12, week 24, week 48, early termination<br>• *Investigator's assessment of skin texture change* for each half-face at week 12, week 24, week 48, early termination<br>• *Skin microrelief variables: percent change from Baseline* per half-face at week 24, week 48, early termination (if after week 8) |

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| **Analysed variables (continued)** | **Safety variables** on Safety population<br>• *Incidence of Adverse Events*<br>• *Local tolerability: percent of subjects across scores* at each post-baseline visit<br><br>**PRO**<br>• *Acne scar appearance* using the SCARS questionnaire at Baseline, week 12, week 24, week 48, early termination, for each half-face<br>• *Subject satisfaction questionnaire* at week 24, week 48, early termination |
| **Principal statistical methods and sample size calculation:** | The Per Protocol (PP) population will consist of all enrolled and randomized subjects, except subjects who have major deviations from the protocol. The Intent-to-Treat (ITT) population will consist of the entire population enrolled and randomized. The last observation carried forward (LOCF) method will be used to impute missing values of acne scar and lesion counts and global assessment scores. Analysis population definitions will be decided before the database lock and unblinding.<br><br>The primary objective of this trial 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.<br><br>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. PP analysis will be also performed to assess the robustness of the results obtained on the ITT/LOCF population.<br><br>The other efficacy variables of part I will be analyzed similarly as primary analysis on appropriate population. Each test will be |

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| | two-sided, at the 0.050 significance level.<br><br>The subject characteristics (previous medication, concomitant medication, demographics, baseline characteristics…), lesion counts, microrelief, adverse events, local tolerability and questionnaires, and all variables of part II will be summarized by descriptive statistics (usual statistics and frequency distribution).<br><br>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.<br><br>Using the historical data mentioned above, 50 evaluable subjects will be required, with 80% power. To allow about 20% rate of subjects excluded from the analysis (drop out, lost to follow-up, etc.) at week 24, 60 subjects should be enrolled. |

# 2 BACKGROUND AND RATIONALE

## 2.1 MEDICAL BACKGROUND AND SHORT RATIONALE FOR THE CLINICAL TRIAL

Acne vulgaris is a chronic, inflammatory skin disease of the pilosebaceous unit, affecting approximately 80% of young adults and adolescents (Kraining, et al., 1979) (Cunliffe, et al., 1979) (Usatine, et al., 1998) (Leyden, 1995). This is a polymorphic disease in which several types of lesions are usually present at the same time: primary lesions, found in active acne defined by the non-inflammatory and the inflammatory lesions; secondary lesions which came from the first ones and which are defined by scarrings and postinflammatory hyperpigmentation (PIH). It can persist for years and may affect seriously the psychosocial development, resulting in emotional problems, withdrawal from society, and depression (Koo , et al., 1991).

Even if the treatments are efficient in non-inflammatory and inflammatory lesions, secondary acne lesions are not well addressed by the treatments and remain the most unfortunate clinical outcome of acne (Layton, et al., 1994). Acne scars are not uniform and there are several subtypes. Some are more hypertrophic and keloidal in appearance, while others could be more atrophic (Goodman, et al., 2006(a)) (Goodman, et al., 2006(b)). The severity of the acne scars is correlated with the acne grade and also with the delay between the start of the disease and the start of an adapted treatment (Layton, et al., 1994). In her clinical evaluation of acne scarring, Layton indicated that facial scarring occurs to some degree in the majority of acne sufferers (95% of the population) even in the mild to moderate population. Although not universal, acne scars generally occur more with inflammatory acne lesions that were not properly treated (Layton, et al., 1997). Once established, acne scars are believed not to be treatable medically but invasive procedures could offer some improvement (Jacob, et al., 2001) (Jemec, et al., 2004) (Goodman, 2011).

Loss of dermal matrix is a contributing factor in atrophic acne scars (Kang, et al., 2005). This loss of dermal matrix consists in degradation of collagen produced by intracellular pathway activated by inflammation during the acne lesion formation (Kang, et al., 2005) (Trivedi, 2006). This leads to the transcription factor activation coding for matrix-degrading metalloproteinases (MMPs). MMPs degrade extracellular matrix molecules during physiological and pathological tissue remodeling. Three MMPs (MMP-1 [collagenase], MMP-3 [stromelysin] that can initiate collagen degradation and MMP-9 [gelatinase] that can further degrade collagen fragments) have been shown to be increased in inflammatory acne lesion in vivo (Kang, et al., 2005) (Trivedi, 2006) (Fisher, et al., 2000) (Papakonstantinou, et al., 2005). The same enzymes are involved in the remodelling of the dermal matrix in the photoaging process (Kang, et al., 1997) (Kang, et al., 1998) (Fisher, et al., 2000).

Over the past decades, significant evidence has been accumulated that topical retinoids can stimulate dermal fibroblasts to produce more procollagen in photoaged skin (Kang, et al., 1997) (Kang, et al., 1998) (Fisher, et al., 2000). Type I and type III procollagen are reduced in photodamaged skin but it

has been demonstrated that isotretinoin, either oral or topical, protects against UV-induced loss of procollagen, leading to MMP-1, 3 and MMP-9 decrease in relation to the duration of the treatment (Kang, et al., 1997) (Kang, et al., 1998) (Fisher, et al., 2000). This increase in collagen production is clinically appreciated as effacement of wrinkles. After 24 weeks of treatment with topical retinoid, an increase of the epidermal thickness has been observed (Griffiths, et al., 1995) (Kang, et al., 2001) (Philips, et al., 2002). Results generally start to be seen over a few weeks, but as the deposition of new collagen takes place slowly, the skin texture does continue to improve over a 12 month period (Fabbrocini, et al., 2010). Adapalene gel 0.1% and 0.3% formulations have been demonstrated to treat actinic keratoses and solar lentigines and to improve fine and coarse wrinkles, mottled hyperpigmentation, and sallow complexion (Kang, et al., 2003). As photodamage lesions and atrophic acne scars are partially linked to a dermal matrix loss, a potential effect of Adapalene-benzoyl peroxide fixed-dose combination (Adapalene - BPO) to prevent secondary acne lesions (scars) of occurring and/or to improve the pre-existing ones might exist.

Adapalene 0.3% - BPO 2.5% gel is efficacious to treat moderate to severe acne (protocol No.: RD.03.SPR18240) with a trend of numerical superiority compared to Adapalene 0.1% - BPO 2.5% gel in subjects with severe acne.
An exploratory trial (Protocol No.: RD.03.SPR.40183E) has been performed and has shown that over a 24 week period treatment, Adapalene 0.1% - BPO 2.5% reduced the inflammatory and non-inflammatory primary lesions more than the vehicle but also stabilized acne scar counts whereas scars continued to increase with vehicle. Moreover the scar global assessment by the investigator improved with the combination Adapalene - BPO whereas it remained stable with the vehicle. This suggests that the combination Adapalene - BPO both prevents the formation of new acne scars by reducing the number of primary lesions and improves the appearance of pre-existing scars.

It is hypothesized that the treatment effect on acne scars might be stronger with the more concentrated combination Adapalene 0.3% - BPO 2.5% gel.

This controlled clinical trial is designed to evaluate the effect of Adapalene 0.3% - BPO 2.5% gel compared with its vehicle in subjects with moderate to severe acne vulgaris on the risk of formation of acne scars and to improve the appearance of pre-existing ones.

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 subject may enter part II of the trial to continue using Adapalene 0.3% - BPO 2.5% gel for up to 24 additional weeks on the whole face.

## 2.2 INVESTIGATIONAL PRODUCT PROFILE

The product used in this clinical trial (Adapalene 0.3% - BPO 2.5% gel) is marketed under the name Tactupump™ Forte in Canada. Adapalene 0.3% - BPO 2.5% gel is well tolerated in subjects with acne vulgaris. See Canadian product monograph for detailed safety information.

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 Risk-benefit statement related to the clinical trial drugs

Adapalene 0.3% - BPO 2.5% gel (marketed under the name Tactupump™ Forte in Canada) is a commercial product in Canada and will be used according to the approved Canadian indications and usage. Warnings and precautions with Adapalene 0.3% - BPO 2.5% gel are well known and documented in the Canadian product monograph. For more details regarding the clinical adverse reactions and/or the post-marketing experience, please refer to the Canadian product monograph.

### 2.3.2 Risk-benefit statement related to the clinical trial

This is a vehicle controlled trial using intra-individual comparison (right half-face versus left half-face) without direct benefit for the subject.

Adapalene 0.1% - BPO 2.5% (marketed under the name Tactupump™ in Canada and Epiduo™ in France) is an established and very widely used marketed product and considered standard of care by many physicians and expert bodies for the treatment of acne vulgaris.
The same safety profile with a long-term use is expected with Adapalene 0.3% - BPO 2.5% than with Adapalene 0.1% - BPO 2.5%. It is therefore considered that exposure to the treatment over 12 months is covered by long-term safety data for the products Adapalene 0.3% and the combination of Adapalene 0.1% - BPO 2.5% which have shown that the safety profile remains stable with a long-term use.

Treatment-related adverse reactions typically associated with use of Adapalene 0.3% - BPO 2.5% include mild to moderate application site reactions, such as skin irritation characterized by scaling, dryness, erythema, and burning/stinging. These reactions usually occur early in the treatment, and tend to gradually lessen over time.

To allow the subject to be treated on the whole face in case of a dramatic difference between right and left sides, a subject will stop the trial at the discretion of the investigator if the global assessment of the scars shows a marked asymmetry in scar severity between both half-faces at two consecutive

visits. In case the subject has prematurely discontinued the study during part I, s/he cannot enter part II.

Any subject is free to discontinue his/her participation in this clinical trial at any time and for whatever reason, specified or unspecified, and without any prejudice. No constraints are to be imposed on the subject, and when appropriate, a subject may be treated with other conventional therapy when clinically indicated.

No invasive methods will be conducted during this trial.
Subjects will be followed (especially for Adverse events) regularly during all the trial, approximately once a month for the first 24 weeks (part I) and every 12 weeks thereafter (part II).

Consequently, based on available safety data and the proposed trial design, no safety issues others than those reported in the Canadian product monograph are expected following topical administration of Adapalene 0.3% - BPO 2.5% or its vehicle.

# 3 CLINICAL TRIAL OBJECTIVES AND CLINICAL HYPOTHESIS

## 3.1 CLINICAL TRIALS OBJECTIVES

The main objective of this clinical trial is to evaluate the effect of Adapalene 0.3% - BPO 2.5% compared to its vehicle on the risk of formation of atrophic acne scars after 24 weeks of treatment in moderate to severe acne subjects assessed by atrophic acne scars count.

Safety will also be evaluated up to 48 weeks.

## 3.2 CLINICAL HYPOTHESIS

Acne scars being a consequence of inflammatory lesions, treatment of acne with Adapalene 0.3% - BPO 2.5% gel should prevent occurrence of new scars as shown in previous trials with Adapalene 0.1% - BPO 2.5% gel (Protocol No.: RD.03.SPR.40183E) and with Adapalene 0.3% - BPO 2.5% (Protocol No.: RD.03.SPR18240, which has shown marked effects on inflammatory lesions).

Formation of atrophic acne scars may be due to dermal matrix loss (degradation of collagen) (Kang, et al., 2005). Significant evidence has been accumulated that topical retinoids can stimulate dermal fibroblasts to produce more procollagen in photoaged skin (Kang, et al., 1997) (Kang, et al., 1998) (Fisher, et al., 2000). As atrophic acne scars are linked to the same process of dermal matrix loss as photodamage lesions, we hypothesize a potential effect of Adapalene 0.3% - BPO 2.5% gel on

atrophic acne scars. This was also suggested in a preliminary trial with Adapalene 0.1% - BPO 2.5% gel.

Since the subject may continue treatment for 24 additional weeks, it will also be possible to continue assessing the skin texture over this time period. Indeed, as the deposition of new collagen takes place slowly, the skin texture will continue to improve over this 48-week period.

As shown in subjects with photodamaged skin, the retinoid included in Adapalene 0.3% - BPO 2.5% gel might have a positive effect on cosmetic outcomes in younger subjects.

# 4 SELECTION AND DISPOSITION OF CLINICAL TRIAL POPULATION

## 4.1 NUMBER OF SUBJECTS

A total of 60 subjects with moderate to severe acne vulgaris and atrophic acne scars will be enrolled at approximately 7 sites located in Canada and France.

## 4.2 CLINICAL TRIAL POPULATION CHARACTERISTICS

Subjects who meet all of the following criteria will be eligible for the clinical trial.

### 4.2.1 Inclusion criteria

In order to be eligible for the clinical trial, the subject must meet all of the following inclusion criteria:

1. Male or female subject aged 16 to 35 years inclusive
2. Subject with clinical diagnosis of moderate to severe acne vulgaris on the face defined by:
   (a) Investigator's Global Assessment score of 3 or 4, with same score on both sides; and
   (b) A minimum of 25 inflammatory lesions (papules and pustules) in total, with at least 10 on each side (excluding the nose); and
   (c) No more than two acne nodules (≥ 1 cm); and
   (d) A minimum of 10 atrophic acne scars in total (upper than 2 mm) (excluding the nose).

3. Subject with a symmetric number of

   (a) both inflammatory and non-inflammatory lesions on the whole face, and

   (b) atrophic acne scars on the whole face

i.e. there are no more than twice as many lesions of each type on one half of the face than on the other half.

4. Subject with skin phototype of I to IV on Fitzpatrick's scale (Fitzpatrick, et al., 1993).
5. Female of childbearing potential with a negative urine pregnancy test (UPT) at the baseline visit.
6. Female subjects of childbearing potential must practice an effective method of contraception during the clinical trial and at least 1 month after the last clinical trial treatment application: medical contraception [combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives] with stable dose for 1 month prior to clinical trial entry, bilateral tubal ligation, hormonal Intra-Uterine Device (IUD) inserted at least 1 month prior to clinical trial entry, strict abstinence (1 month prior to trial entry and agrees to continue for the duration of the trial), condom with spermicide, vasectomized partner (for at least 3 months prior to clinical trial entry).
7. Female of non-childbearing potential, eg: post-menopausal (absence of menstrual bleeding for one year prior to clinical trial entry, without any other medical reason), hysterectomy, bilateral oophorectomy.
8. Subject having read, understood and signed the approved Informed Consent Form (ICF) prior to any participation in the clinical trial. Subjects under 18 years of age having signed an Assent Form to participate in the clinical trial and their parent(s) or legal representative having read and signed the Informed Consent Form prior to any clinical trial related procedure.
9. Subject willing and able to comply with the requirements of the trial protocol, in particular, subject must adhere to the visit schedule, concomitant therapy prohibitions, and must be compliant to the treatment.
10. For Canada: Subject informed of the terms pertaining to the Personal Information Protection and Electronic Documents Act (PIPEDA): the subject is willing to share personal information and data and he/she has provided authorization by signing the ICF.
11. For France: Subject covered by a National Social Security System.

### 4.2.2 Exclusion criteria

Any subject who meets one or more of the following criteria will not be included in this clinical trial.

1. Subject with acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.), nodulo cystic acne, acne requiring systemic treatment.
2. Prior failure to treatment with Tactupump™ Forte (Adapalene 0.3% - BPO 2.5%).
3. Subject with more than 3 excoriated acne lesions.
4. Subject with skin abraded on the treated area or affected by eczema, seborrhoeic dermatitis, cuts or sunburn.
5. Female subject who is pregnant, nursing or planning a pregnancy during the trial or within one month after the last trial treatment application.
6. Female subject who is planning to change her contraceptive method or hormone replacement therapy during the trial.
7. Subject with known impaired hepatic or renal functions.
8. Male subject with a beard or facial hair, which would interfere with the clinical trial evaluations or clinical trial procedures.
9. Subject having received at least one of the following topical treatments on the treated area:

| | |
|---|---|
| • Corticosteroids, antibiotics, benzoyl peroxide, azelaic acid, hydroxyacids, Zinc containing treatments, antibacterials, antiseptics, other anti-inflammatory drugs or other acne treatments (for example, cosmetic products or salicylic acid treatments are forbidden if used to treat acne) | Within 2 weeks |
| • Retinoids | Within 4 weeks |
| • Cosmetic/aesthetic procedures on the face (e.g., peeling, comedone extraction, desquamating, or abrasive agents, adhesive cleansing strips) | Within 1 week |
| • Photodynamic therapy, laser therapy, microdermabrasion for acne | Within 3 months |

10. Subject having received at least one of the following systemic treatments:

| | |
|---|---|
| • Corticosteroids (except locally acting corticosteroids such as inhaled or intrathecal or dermal application at distance from the face), antibiotics (except penicillin) | Within 1 month |
| • Spironolactone / Drospirenone (except if at a stable dose for at least 3 months for drospirenone) | Within 3 months |
| • Oral retinoids | Within 6 months |

| | |
|---|---|
| • Cyproterone acetate / Chlormadinone acetate | Within 6 months |
| • Immunomodulators | Within 3 months |

11. Subject with a condition or who is in a situation which, in the investigator's opinion, may put the subject at risk, may confound the trial results, or may interfere with the subject's participation in the trial.
12. Subject who is at risk in terms of precautions, warnings, and contraindications for the investigational products (see Product Monograph for Tactupump™ Forte).
13. Subject with known or suspected allergy to the investigational products (see Product Monograph for Tactupump™ Forte).
14. Subject who has participated in another investigational product, cosmetic or device research trial within 30 days of enrolment OR is in an exclusion period from a previous clinical trial.
15. Subject who has used tanning booths or lamps or who had excessive ultraviolet (UV) radiation exposure within 1 month prior to clinical trial entry or who foresees intensive UV exposure during the trial (mountain sports, UV radiation, sunbathing, etc...).
16. Adult subject under guardianship, hospitalised subject in a public or private institution for a reason other than the research, and subject deprived of his/her freedom.
17. Subject who is unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.

## 4.3 PRIOR AND CONCOMITANT THERAPIES

### 4.3.1 Definition

Information on previous treatments/procedures that have been stopped within the 6 months preceding the baseline visit and that may have an impact on inclusion/exclusion criteria should be recorded in the eCRF.

Concomitant therapies are defined as follows:

- any existing therapies ongoing at the time of the first investigational product application, or
- any changes to existing therapies (such as changes in dose or formulation) during the course of the clinical trial, or
- any new therapies received by the subject since the first investigational product application

### 4.3.2 Categories

The following two categories are to be considered for prior and concomitant therapies:

- Drugs/therapies including but not limited to, prescription, over-the-counter (OTC), birth control pills/patches/hormonal devices, vitamins, moisturizers, sunscreens, herbal medicines/supplements, and homeopathic preparations.
- Medical and surgical procedures including, but not limited to, laser/radiation procedures, dermal fillers, X-rays, etc.

### 4.3.3 Recording

Previous and concomitant therapies are to be recorded on the Drugs/Therapies Form (for drugs/therapies) and/or on the Medical and Surgical Procedures form (for medical/surgical procedures) in the eCRF.

Concomitant therapies are to be recorded, reviewed, and updated at each visit. Every attempt should be made to keep concomitant therapy dosing and regimen constant during the trial.

Any new concomitant therapy or modification of an existing therapy may be linked to an adverse event (AE). A corresponding Adverse Event Form must be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis, dose modification for a chronic condition, etc.

### 4.3.4 Authorized therapies during the clinical trial

Unless listed under the exclusion criteria (section 4.2.2 items 9 and 10) or in prohibited therapies (section 4.3.5), all therapies are authorized.

Subject may use moisturizer as required for the symptomatic relief of skin dryness or irritation (use of moisturizer other than the one provided for this clinical trial will be captured into the eCRF as concomitant therapy).

Oral vitamin A supplement (up to the recommended daily allowance) and plain penicillin are acceptable.

Systemic anti-inflammatory medication up to 21 days of treatment in total is also acceptable; however, it should be avoided for 1 week prior to the week 24 visit (primary endpoint assessment).

### 4.3.5 Prohibited therapies during the clinical trial

The following drugs/procedures are prohibited because they may interfere with the efficacy/safety assessment of the investigational product, or because they may interact with the metabolism of the investigational product:

- All topical or systemic drugs/procedures listed in exclusion criteria (section 4.2.2, items 9 and 10)
- Any irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have strong skin-drying effect and products with high concentrations of alcohol, astringents, spices, or limes)
- Any other drugs/procedures which in the investigator's judgement are liable to interfere or interact with the efficacy or safety of Tactupump™ Forte (Adapalene 0.3% - BPO 2.5%).

If prohibited therapies become a necessary treatment for the safety or best interest of the subject, the sponsor should be notified to discuss possible alternatives prior to administration of a prohibited therapy and to discuss the pertinence and the modalities for the subject to continue in the clinical trial.

## 4.4 PROCEDURES / REASONS FOR DISCONTINUATION

An investigator may decide to discontinue a subject from the clinical trial for safety reasons.

Although the importance of completing the entire clinical trial should be explained to the subject by the clinical trial personnel, any subject is free to discontinue his/her participation in this clinical trial at any time and for whatever reason, specified or unspecified, and without prejudice.

Subjects who discontinue the clinical trial prematurely should be fully evaluated, whenever possible. The procedures corresponding to the next theoretical visit should be performed (for instance, if a subject discontinues at week 10, complete the week 12 visit procedures). Additional final procedures will be conducted as indicated in the trial flow chart section 5.4. The appropriate eCRF pages should be completed.

For all subjects who prematurely discontinue the clinical trial, the reason must be carefully documented by the investigator on the Exit Form, and, if applicable, on the Adverse Event Form for discontinuation due to an AE.

A subject who has been randomized and assigned a kit number/randomization number cannot be replaced by another subject if he/she discontinues the clinical trial for any reason.

In the case of early termination, the investigator should ensure that the subject receives appropriate therapy for his/her condition.

The sponsor may also decide to prematurely terminate or suspend the clinical trial or the participation of a subject in the clinical trial.

All data gathered on the subject prior to termination should be made available to the sponsor.

Reasons for clinical trial completion/discontinuation, as listed on the Exit Form of the eCRF are described below. Note that there will be 2 separate Exit Forms, one completed at the end of part I (or early termination during part I), and one completed at the end of part II (or early termination during part II).

| | |
|---|---|
| **Normal study Completion** | Subject completes the clinical trial as planned in the protocol. |
| **Adverse Event** | Complete eCRF Adverse Event Form. |
| **Subject's Request** | Includes consent withdrawal, subject relocation, subject has a conflicting obligation. Explain the reason for withdrawal in the comments section of the eCRF Exit Form. |
| **Protocol Violation** | Explain the violation in the comments section of the eCRF Exit Form |
| **Lost to Follow-up** | Confirmed with 2 documented phone calls and a certified letter (delivery receipt requested) without response. Explain in the comments section of the eCRF Exit Form. |
| **Other** | This category is to be used for a subject who discontinues for a reason other than those specified in the predefined categories above. In case the subject discontinues because of a marked asymmetry in scar severity between both half-faces at two consecutive visits (see section 2.3.2), this category should be chosen too.<br>Explain the reason for discontinuation in the comments section of eCRF Exit Form. |
| **Pregnancy** | Withdraw the subject from the clinical trial following the procedure described in the protocol (see section 8.5). |

If reason for discontinuation is “subject request” or “other”, the subject must be questioned to rule out the possibility of an AE; this should be documented in the eCRF.

# 5 INVESTIGATIONAL PLAN

## 5.1 OVERALL CLINICAL TRIAL DESIGN

During part I, this clinical trial will be conducted as a multi-centre, randomized, investigator-blinded, vehicle controlled trial using intra-individual comparison (right half-face versus left half-face) involving subjects 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 will be enrolled at approximately 7 sites located in Canada and France. Approximately 8-15 subjects are planned at each site.

Subjects will be enrolled at baseline and treated for 24 weeks and will have each half-face randomized to one of the two following treatments:

- once-daily Adapalene 0.3% - BPO 2.5% gel (Tactupump™ Forte / CD0271 0.3%/CD1579 2.5% Gel).
- once-daily "Adapalene 0.3% - BPO 2.5%" vehicle gel (Vehicle gel).

During part I, there will be 8 trial visits: at baseline, week 1 (± 1 day), week 4 (± 3 days), week 8 (± 3 days), week 12 (± 1 week), week 16 (±1 week), week 20 (±1 week) and week 24 (±1 week).

At the end of part I, 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 treatment with Adapalene 0.3% - BPO 2.5% gel (Tactupump™ Forte / CD0271 0.3%/CD1579 2.5% Gel) for 12 or 24 additional weeks on the whole face. This second part of the clinical trial (part II) will be conducted as a multi-centre, open-label trial.

During part II, there will be 2 trial visits: week 36 (±2 weeks) and week 48 (±2 weeks).

## 5.2 DISCUSSION OF CLINICAL TRIAL DESIGN

This clinical trial will assess the effect of a marketed product (under the name Tactupump™ Forte in Canada), used according to its labeling information (indication, selected population, dose regimen) and is therefore classified as a Phase IV trial.
No topical product has been described to have an efficacy on the risk of formation of atrophic acne scars, which justifies a vehicle controlled design. Intra-individual comparisons (split-face trial) shall minimize inter-individual variability (increase of study power whilst minimizing the number of subjects).

Since acne is a chronic and long-lasting skin condition, the sponsor considers that 6 months treatment will be sufficient to obtain clinical effect on the basis of the following points:

- Scarring appears secondarily to primary lesions of acne defined by non-inflammatory and/or inflammatory lesions and may correspond to a resolution of these primary lesions;
- It is generally agreed in acne clinical trials that 3 months treatment is sufficient to evaluate the efficacy on the primary lesions of acne. Consequently, to investigate their resolution, the duration of treatment has to be increased to 6 months;
- To observe a relevant effect on scars, a duration of at least 6 months is required.

In addition, some subjects may continue treatment for up to 24 additional weeks with Adapalene 0.3% - BPO 2.5% to improve acne and scar aspect (due to treatment with vehicle).

This clinical trial should allow comparing the efficacy on the risk of formation of atrophic acne scars of the investigational product Adapalene 0.3% - BPO 2.5% to its vehicle.

### 5.3 CLINICAL TRIAL DURATION AND TERMINATION

The average planned period for the clinical trial (from First Subject In (FSI) to Last Subject Out (LSO) is 20 months. The end date of the clinical trial will be the date of the last visit of the last subject (LSO) who participates in the clinical trial.
The planned duration of recruitment (i.e. From FSI to Last Subject In (LSI)) is approximately 8 months.
The clinical trial may be terminated by the investigator at his/her clinical trial site at any time with appropriate notification to GALDERMA R&D. Likewise, GALDERMA R&D may terminate the clinical trial and/or the participation of a clinical trial site with appropriate notification.

The expected duration of subject participation is up to 48 weeks:
- Part I: 24 weeks
- Part II: 24 weeks

## 5.4 CLINICAL TRIAL FLOW CHART

| PROCEDURES | CLINICAL TRIAL VISITS | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Part I | | | | | | | | Part II | |
| | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Visit 8 | Visit 9 | Visit 10 |
| | Baseline | Week 1 (±1 d) | Week 4 (±3 d) | Week 8 (±3 d) | Week 12 (±1 w) | Week 16 (±1 w) | Week 20 (±1 w) | Week 24 (±1 w) | Week 36 (±2 w) | Week 48 (±2 w) |
| Informed Consent/Photography Consent[b] | X | | | | | | | X | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | |
| Demographics/ Relevant medical history/ Prior therapies[c] | X | | | | | | | | | |
| Urine Pregnancy test (UPT)[d] | X | | X | X | X | X | X | X | X | X |
| Atrophic acne scar count | X | X | X | X | X | X | X | X | X | X |
| Investigator's Scar Global Assessment (SGA) | X | X | X | X | X | X | X | X | X | X |
| Investigator's preference on overall scar severity | | | | | X | | | X[a] | | |
| Acne lesion count[e] | X | X | X | X | X | X | X | X | X | X |
| Investigator's Global Assessment (IGA) | X | X | X | X | X | X | X | X | X | X |
| Skin roughness score | X | | | | X | | | X[a] | | X[j] |
| Skin texture change score | | | | | X | | | X[a] | | X[j] |
| Skin microrelief (skin replica)[f] | X | | | | | | | X[i.] | | X[j] |
| SCARS questionnaire | X | | | | X | | | X[a] | | X[j] |
| Subject satisfaction questionnaire | | | | | | | | X[a] | | X[j] |
| Photographs[b] | X | | | | X | | | X | | X[j] |
| Concomitant therapies | X | X | X | X | X | X | X | X | X | X |
| Adverse events[g] / local tolerability assessment | X | X | X | X | X | X | X | X | X | X |
| Dispensation of investigational products | X | | X | X | X | X | X | X | X | |
| Dispensation of non-investigational products | X | | | X | | X | | X | X | |
| Dispensation of "study companion" tablet[h] | X | | | | | | | | | |
| Part I: Review of treatment compliance / return of "study companion" tablet[h] and download of videos | | X | X | X | X | X | X | X | | |
| Part II: Review of treatment compliance | | | | | | | | | X | X |
| Return of investigational products | | | X | X | X | X | X | X | X | X |
| Exit Form part I[a] | | | | | | | | X[a] | | |
| Exit Form part II[j] | | | | | | | | | | X[j] |

a. To be performed at week 24 or before in case of early termination
b. Photography consent and standardized photography at selected sites only.

c. Only prior therapies that were stopped within 6 months of the baseline visit and that may have an impact on inclusion/exclusion criteria should be recorded. Treatment that continues after baseline should be recorded on the Concomitant Treatment Form of the eCRF.
d. UPT will be sourced directly by the investigational sites and will have a sensitivity down to at least 25 IU/L for hCG. UPT is mandatory at baseline, week 24and week 48 or early termination.
e. Papules, pustules, nodules, open and closed comedones will be counted.
f. Skin replica will be performed at one selected site only.
g. Adverse event onsets after subject's signature of the Informed Consent Form should be recorded on the AE Form of the eCRF.
h. "Study companion" is a tablet which will be given to the subject during part I to assess his/her treatment compliance.
i. To be performed at week 24 or before in case early termination occurs after week 8 (during part I).
j. To be performed/completed at week 48 or before in case of early termination from part II

## 5.5 CLINICAL TRIAL VISIT DESCRIPTION AND PROCEDURES

### 5.5.1 Visit 1 (baseline) (part I)

1. Explain the nature and the constraints of the clinical trial to the subject and to his/her parent(s) or guardian if the subject is under the age of 18.
2. If a female subject of childbearing potential agrees to participate to the clinical trial, make sure she is using the requiring method(s) of contraception.
3. Ensure the subject (and parent/guardian for subjects under the age of 18) has read, understood, dated and signed the approved Informed Consent Form (ICF).
4. Give a dated and signed copy of the ICF to each subject and parent/guardian if applicable.
5. Log into the electronic Case Report Form (eCRF) to get a Subject Identification Number (SIN)
6. Question the subject about demography (birthdate, race, skin phototype, gender), relevant medical history, prior therapies (stopped within 6 months of the baseline visit and that may have an impact on the inclusion/exclusion criteria) and concomitant therapies.
7. Inform subject about authorized and prohibited concomitant therapies.
8. Check inclusion/exclusion criteria (see sections 4.2.1 and 4.2.2).
9. Conduct a urine pregnancy test (UPT) for female subjects of childbearing potential.
10. Count atrophic acne scars of each half-face (see section 7.1.1).
11. Perform an Investigator's Scar Global Assessment (SGA) of each half-face (see section 7.1.2).
12. Count inflammatory, non-inflammatory acne lesions and nodules of each half-face (see section 7.1.4).
13. Perform an Investigator's Global Assessment (IGA) of each half-face (see section 7.1.5).
14. Assess the skin roughness score of each half-face (see section 7.1.6).
15. Perform the baseline Local Tolerability Assessment (erythema, dryness, scaling, stinging/burning; see Section 7.2.1). Note: Stinging/burning at the baseline visit should be assessed as None (0).
16. For selected sites only (and only if subject and parent/guardian accept through the approved ICF, if applicable), take photographs of the face according to the provided procedure.
17. For selected sites only, make skin replica for each half-face (if consent given) (see section 7.1.8).
18. Provide guidance on the SCARS questionnaire and ask the subject to fill it out for each half-face (see Appendix 1).
19. Question the subject about the occurrence of any adverse events (AEs) by asking an open ended question taking care not to influence the subject's answer, such as: "have you had any new symptoms, injuries, illness or side-effects or worsening of pre-existing conditions?" Record all events as appropriate on the corresponding AE eCRF pages.

20. If the subject is eligible, assign a kit number (see specific section 6.1.2) (to be reported on the prescription form).
21. The product dispenser (person in charge of products dispensation and not involved in the clinical trial measurement criteria) will:
    a. Dispense to the subject the baseline investigational products from the adequate subject kit according to the Prescription Form.
    b. Affix the tear-off portion of the labels on the product dispensation log.
    c. Dispense to the subject the associated non-investigational products with explanations how and when to use them.
    d. Dispense the subject participation card to the subject.
    e. Dispense the "study companion" tablet to the subject, with appropriate written and verbal instructions.
    f. Provide appropriate verbal and written instructions on how to properly use the investigational products. The first application of investigational products will be conducted by the subject under the direction of the product dispenser before leaving the investigational site.
    g. Remind the subject to not apply the investigational products the first evening.
    h. Emphasize the importance of complying with the given instructions and treatments; instruct the subject to bring back the "study companion" tablet at the next visit.
    i. For all female subjects, emphasize the guidelines about contraception and risks in case of pregnancy.
22. Schedule the next follow up visit in one week ± 1 day

### 5.5.2 Visit 2 (week 1) (part I)

1. Question the subject about occurrence of adverse events (AEs) and assess local tolerability (see section 7.2). Record occurrence of any events and/or any changes in events that were ongoing at the previous clinical trial visit. Document all changes in the eCRF.
2. Enquire whether any concomitant therapies have been added, stopped, or changed since the subject's last visit. Document all changes in the eCRF.
3. Count atrophic acne scars of each half-face (see section 7.1.1).
4. Perform an Investigator's Scar Global Assessment (SGA) of each half-face (see section 7.1.2).
5. Count inflammatory, non-inflammatory acne lesions and nodules of each half-face (see section 7.1.4).
6. Perform an Investigator's Global Assessment (IGA) of each half-face (see section 7.1.5).
7. The product dispenser will:

a. Assess subject's compliance based on the subject's compliance report available on Triacys website and discussion with the subject and report in the eCRF any missing or incomplete product application record as indicated in the product dispensation log.
b. Download data from the "Study Companion" tablet.
c. Emphasize again the importance of complying with the given instructions and treatments; instruct the subject to bring back the dispensed investigational products together with the "study companion" tablet at the next visit.
d. For all female subjects, emphasize the guidelines about contraception and risks in case of pregnancy.

8. Schedule the next follow up visit in three weeks ± 3 days

### 5.5.3 Visit 3 (week 4), 4 (week 8), 6 (week 16) and 7 (week 20) (part I)

1. Question the subject about occurrence of adverse events (AEs) and assess local tolerability (see section 7.2). Record occurrence of any events and/or any changes in events that were ongoing at the previous clinical trial visit. Document all changes in the eCRF.
2. Enquire whether any concomitant therapies have been added, stopped, or changed since the subject's last visit. Document all changes in the eCRF.
3. Conduct a urine pregnancy test (UPT) for female subjects of childbearing potential.
4. Count atrophic acne scars of each half-face (see section 7.1.1).
5. Perform an Investigator's Scar Global Assessment (SGA) of each half-face (see section 7.1.2).
6. Count inflammatory, non-inflammatory acne lesions and nodules of each half-face (see section 7.1.4).
7. Perform an Investigator's Global Assessment (IGA) of each half-face (see section 7.1.5).
8. The product dispenser will:
    a. Check the returned investigational products.
    b. Assess subject's compliance based on the subject's compliance report available on Triacys website and discussion with the subject and report in the eCRF any missing or incomplete product application record as indicated in the product dispensation log.
    c. Download data from the "Study Companion" tablet.
    d. Dispense from the subject kit the applicable visit treatment box.
    e. Affix the tear-off portion of the labels on the product dispensation log.
    f. Dispense to the subject the associated non-investigational clinical trial products with explanations how and when to use them *(only applicable at visit 4 (week 8) and visit 6 (week 16))*.

g. Remind to the subject the importance of complying with the given instructions and treatments and to bring back the investigational products together with the "Study Companion" tablet at the next visit.
h. For all female subjects, emphasize the guidelines about contraception and risks in case of pregnancy.

9. Schedule the next follow up visit in:
   - If at visit 3 (week 4): in four weeks ± 3 days
   - If at visit 4 (week 8), visit 6 (week 16) or visit 7 (week 20): in four weeks ± 1 week

### 5.5.4 Visit 5 (week 12) (part I)

1. Question the subject about occurrence of adverse events (AEs) and assess local tolerability (see section 7.2). Record occurrence of any events and/or any changes in events that were ongoing at the previous clinical trial visit. Document all changes in the eCRF.
2. Enquire whether any concomitant therapies have been added, stopped, or changed since the subject's last visit. Document all changes in the eCRF.
3. Conduct a urine pregnancy test (UPT) for female subjects of childbearing potential.
4. Count atrophic acne scars of each half-face (see section 7.1.1).
5. Perform an Investigator's Scar Global Assessment (SGA) of each half-face (see section 7.1.2).
6. Assess investigator's preference in terms of overall scar severity (see section 7.1.3);
7. Count inflammatory, non-inflammatory acne lesions and nodules of each half-face (see section 7.1.4).
8. Perform an Investigator's Global Assessment (IGA) of each half-face (see section 7.1.5).
9. Assess the skin roughness score of each half-face (see section 7.1.6).
10. Assess the skin texture change score for each half-face (see section 7.1.7).
11. For selected sites only (and only if subject and parent/guardian accept through the approved ICF, if applicable), take photographs of the face according to the provided procedure.
12. Provide guidance on the SCARS questionnaire and ask the subject to fill it out for each half-face (see Appendix 1).
13. The product dispenser will:
    a. Check the returned investigational products.
    b. Assess subject's compliance based on the subject's compliance report available on Triacys website and discussion with the subject and report in the eCRF any missing or incomplete product application record as indicated in the product dispensation log.
    c. Download data from the "Study Companion" tablet.
    d. Dispense from the subject kit the week 12 visit treatment box.

e. Affix the tear-off portion of the labels on the product dispensation log.
f. Remind to the subject the importance of complying with the given instructions and treatments and to bring back the investigational products together with the "Study Companion" tablet at the next visit.
g. For all female subjects, emphasize the guidelines about contraception and risks in case of pregnancy.

14. Schedule the next follow up visit in four weeks ± 1 week

### 5.5.5 Visit 8 (week 24) (end of part I, beginning of part II)

1. Question the subject about occurrence of adverse events (AEs) and assess local tolerability (see section 7.2). Record occurrence of any events and/or any changes in events that were ongoing at the previous clinical trial visit. Document all changes in the eCRF.
2. Enquire whether any concomitant therapies have been added, stopped, or changed since the subject's last visit. Document all changes in the eCRF.
3. Conduct a urine pregnancy test (UPT) for female subjects of childbearing potential.
4. Count atrophic acne scars of each half-face (see section 7.1.1).
5. Perform an Investigator's Scar Global Assessment (SGA) of each half-face (see section 7.1.2).
6. Assess the Investigator's preference on overall scar severity (see section 7.1.3).
7. Count inflammatory, non-inflammatory acne lesions and nodules of each half-face (see section 7.1.4).
8. Perform an Investigator's Global Assessment (IGA) of each half-face (see section 7.1.5).
9. Assess the skin roughness score of each half-face (see section 7.1.6).
10. Assess the skin texture change score for each half-face (see section 7.1.7).
11. For selected sites only (and only if subject and parent/guardian accept through the approved Informed Consent Form, if applicable), take photographs of the face according to provided procedure.
12. For selected sites only, make skin replica for each half-face (if consent given) (see section 7.1.8).
13. Provide guidance on the SCARS questionnaire and ask the subject to fill it out for each half-face (see Appendix 1).
14. Provide guidance on the satisfaction questionnaire part I and ask the subject to fill it out (see Appendix 2).
15. For subjects considered to enter part II of the clinical trial, explain the nature and the constraints of the part II of the clinical trial to the subjects and to his/her parent(s) or guardian if the subject is under the age of 18.

16. If a female subject of childbearing potential agrees to participate in part II of the clinical trial, make sure she agrees to continue using the requiring method(s) of contraception.
17. Ensure the subject (and parent/guardian for subjects under the age of 18) has read, understood, dated and signed the approved ICF for part II.
18. Give a dated and signed copy of the ICF for part II to each subject and parent/guardian if applicable.
19. Fill in the prescription form.
20. The product dispenser will:

For all subjects:

a. Check the returned investigational products.
b. Assess subject's compliance based on the subject's compliance report available on Triacys website and discussion with the subject and report in the eCRF any missing or incomplete product application record as indicated in the product dispensation log.
c. Download data from the "Study Companion" tablet.
d. Ensure that the subject has returned all used/unused investigational products and the "study companion" tablet. All missing investigational product units must be documented in the product dispensation log comments section and on other accountability form.
e. For female subjects, reiterate the guidelines about contraception and risks in case of pregnancy during 1 month after the end of the trial.
f. Complete the Exit Form Part I in the eCRF and give the reason for clinical trial discontinuation (see section 4.4).

For the subjects continuing into part II:

g. Dispense 3 bottles of investigational product and the instructions for use.
h. Affix the tear-off portion of each label on the product dispensation log for part II.
i. Dispense 2 bottles of non-investigational clinical trial products with explanations how and when to use them.
j. Remind to the subject the importance of complying with the given instructions and treatments and to bring back the investigational products at the next visit.
k. For all female subjects, emphasize the guidelines about contraception and risks in case of pregnancy.

21. For subjects continuing into part II, schedule the next follow-up visit in 12 weeks ± 2 weeks.

### 5.5.6 Visit 9 (week 36) (part II)

1. Question the subject about occurrence of adverse events (AEs) and assess local tolerability (see section 7.2). Record occurrence of any events and/or any changes in events that were ongoing at the previous clinical trial visit. Document all changes in the eCRF.

2. Inquire whether any concomitant therapies have been added, stopped, or changed since the subject's last visit. Document all changes in the eCRF.
3. Inquire whether the trial drug regimen has been modified since the last visit.
4. Conduct a urine pregnancy test (UPT) for female subjects of childbearing potential.
5. Count atrophic acne scars of each half-face (see section 7.1.1).
6. Perform an Investigator's Scar Global Assessment (SGA) of each half-face (see section 7.1.2).
7. Count inflammatory, non-inflammatory acne lesions and nodules of each half-face (see section 7.1.4).
8. Perform an Investigator's Global Assessment (IGA) of each half-face (see section 7.1.5).
9. Assess if the subject should continue the treatment for 12 additional weeks on the whole face.
10. Fill in the prescription form
11. The product dispenser will:
    a. Check the returned investigational products.
    b. Assess subject's compliance based on an interview with the subject.
    c. Dispense 3 bottles of investigational product and the instructions for use.
    d. Affix the tear-off portion of each label on the product dispensation log for part II.
    e. Dispense 2 bottles of non-investigational clinical trial products with explanations how and when to use them.
    f. Remind to the subject the importance of complying with the given instructions and treatments and to bring back the investigational products at the next visit.
    g. For all female subjects, emphasize the guidelines about contraception and risks in case of pregnancy.
12. Schedule the next follow up visit in 12 weeks ± 2 weeks.

### 5.5.7 Visit 10 (week 48) (part II)

1. Question the subject about occurrence of adverse events (AEs) and assess local tolerability (see section 7.2). Record occurrence of any events and/or any changes in events that were ongoing at the previous clinical trial visit. Document all changes in the eCRF.
2. Inquire whether any concomitant therapies have been added, stopped, or changed since the subject's last visit. Document all changes in the eCRF.
3. Inquire whether the trial drug regimen has been modified since the last visit.
4. Conduct a urine pregnancy test (UPT) for female subjects of childbearing potential.
5. Count atrophic acne scars of each half-face (see section 7.1.1).
6. Perform an Investigator's Scar Global Assessment (SGA) of each half-face (see section 7.1.2).

7. Count inflammatory, non-inflammatory acne lesions and nodules of each half-face (see section 7.1.4).
8. Perform an Investigator's Global Assessment (IGA) of each half-face (see section 7.1.5).
9. Assess the skin roughness score of each half-face (see section 7.1.6).
10. Assess the skin texture change score for each half-face (see section 7.1.7).
11. For selected sites only (and only if subject and parent/guardian accept through the approved Informed Consent Form, if applicable), take photographs of the face according to provided procedure.
12. For selected sites only, make skin replica for each half-face (if consent given) (see section 7.1.8).
13. Provide guidance on the SCARS questionnaire and ask the subject to fill it out for each half-face (see Appendix 1).
14. Provide guidance on the satisfaction questionnaire part II and ask the subject to fill it out (see Appendix 3).
15. The product dispenser will:
    a. Check the returned investigational products.
    b. Assess subject's compliance based on an interview with the subject.
    c. Ensure that the subject has returned all used/unused investigational products. All missing investigational product units must be documented in the product dispensation log comments section and on other accountability form.
    d. For all female subjects, reiterate the guidelines about contraception and risks in case of pregnancy during 1 month after the end of the trial.
16. Complete the Exit Form for part II in the eCRF and give the reason for clinical trial discontinuation (see section 4.4).

### 5.5.8 Early termination visit

In case of early termination, the procedures corresponding to the next theoretical visit should be performed (for instance, if a subject discontinues at week 10, complete the week 12 visit procedures). Additional final procedures will be conducted as indicated in the trial flow chart section 5.4.

Note: In case the subject has prematurely discontinued the study during part I, s/he cannot enter part II.

# 6 CLINICAL SUPPLIES

Investigational and non-investigational products will be provided by the sponsor and shipped by the assigned clinical packager. The investigational products used during this clinical trial are:

## 6.1 INVESTIGATIONAL PRODUCT IDENTIFICATION AND USE

### 6.1.1 Product identity

**Part I**

| | **Investigational product** | **Investigational comparator product** |
|---|---|---|
| **Trade name** | Tactupump™ Forte | N/A |
| **Name of active ingredient** | Adapalene - Benzoyl Peroxide | N/A (Vehicle Gel) |
| **Pharmaceutical form** | Gel | Gel |
| **Dose or concentration** | Adapalene 0.3% - BPO 2.5% | N/A |
| **Formula number** | 534.0201 | 555.612P |
| **Total daily dose** | 2 pea-sized amounts per half-face | |
| **Mode and frequency of administration** | Topical, once daily in the evening | |
| **Location of treated area** | Face | |
| **Manufacturer** *(Name and address)* | G Production Inc. (GPI)<br>19400 Route Transcanadienne<br>Baie d'Urfé, Québec<br>Canada H9X 3S4 | |
| **Packaging type and size (primary)** | 45g airless pump system | |
| **Storage conditions** | Store below 25°C; excursions permitted to 15°-30°C.<br>Do not freeze or refrigerate | |

**Part II**

| | **Investigational product** |
|---|---|
| **Trade name** | Tactupump™ Forte |
| **Name of active ingredient** | Adapalene - Benzoyl Peroxide |
| **Pharmaceutical form** | Gel |
| **Dose or concentration** | Adapalene 0.3% - BPO 2.5% |

| | **Investigational product** |
|---|---|
| **Formula number** | 534.0201 |
| **Total daily dose** | 2 pea-sized amounts per half-face |
| **Mode and frequency of administration** | Topical, once daily in the evening |
| **Location of treated area** | Face |
| **Manufacturer** *(Name and address)* | G Production Inc. (GPI)<br>19400 Route Transcanadienne<br>Baie d'Urfé, Québec<br>Canada H9X 3S4 |
| **Packaging type and size (primary)** | 45g airless pump system |
| **Storage conditions** | Store below 25°C; excursions permitted to 15°-30°C.<br>Do not freeze or refrigerate |

### 6.1.2 Method of treatment assignment

Prior to the start of the clinical trial, a randomization list will be generated by GALDERMA R&D and transmitted to the assigned clinical packaging organization for labeling. This randomization is used for part I of this clinical trial. The RANUNI routine of the SAS systems will be used for the kit number generation to randomly assign the active treatment or the vehicle to the right of left side of the face.
**The "left" or "right" side of the face is always defined as the subject's left or right.**

For part I, a subject kit will be composed of 7 boxes containing each 1 pump of Tactupump™ Forte / CD0271 0.3%/CD1579 2.5% Gel and 1 pump of CD0271/CD1579 Vehicle Gel (1 box per dispensing visit + 1 extra box).

The kit number indicated on the randomization list will correspond to the kit number indicated on the label of the subject kit.

The randomization list will be secured in a locked cabinet and in an electronic file with restricted access to only the designated personnel directly responsible for labeling and handling the investigational products until the clinical trial database is locked and ready to be unblinded.

At the baseline visit, all eligible subjects will be dispensed a baseline visit box from the subject kit, which will be allocated in chronological order of inclusion into the clinical trial, without omitting or skipping any number.

If a number is omitted by mistake, the skipped kit number should be allocated to the next randomized subject.

For part II, there will be no subject kit. The sites will receive Tactupump™ Forte / CD0271 0.3%/CD1579 2.5% Gel bottles in bulk and dispense 3 bottles to the subjects at both week 24 and week 36 visits (3 bottles for 12 weeks treatment).

### 6.1.3 Subject Identification Number (SIN)

Each subject will be allocated a unique subject identification number (SIN) at the baseline visit. This SIN number will be automatically generated by the eCRF.

During the whole clinical trial, the subject will only be identified using the SIN for all documentation and discussion.

### 6.1.4 Instructions for use and administration

At each product dispensing visit, the product dispenser will give each subject verbal and written instructions on how to use the investigational products and non-investigational products. A specific focus on risks in case of pregnancy will be made for female subjects.

In addition, at the baseline visit the product dispenser will show the subject how to apply the investigational products on each half-face and how to record these applications with the "study companion" tablet. This procedure will be thoroughly discussed and reviewed at each trial visit.

<u>Procedure during part I:</u>
All subjects will apply the investigational products in the evening after washing their face, for 24 weeks, as described in the instructions for use provided to the subjects. The procedure is as follows:

1. Check that the "study companion" tablet has enough battery and put it on the provided holder
2. Wash hands
3. Wash the entire face using the provided Cetaphil® DermaControl™ Oil Control Foam Wash
4. Blot dry the face with a soft towel. Do not rub the face.
5. Take the treatment pump for the RIGHT side of the face (as indicated on the label) and scan the QR code with the "study companion" tablet
6. Follow the instructions given by the "study companion" tablet
7. Record the application (movie)
8. Apply a thin film of this treatment on the RIGHT side of the face avoiding eyes, lips and mucous membranes. DO NOT SPOT APPLY. Two pea-sized amounts should be enough to cover a half of the face.

9. Wash hands
10. Take the treatment pump for the LEFT side of the face (as indicated on the label) and scan the QR code with the "study companion" tablet
11. Follow the instructions given by the "study companion" tablet
12. Record the application (movie)
13. Apply a thin film of this treatment on the LEFT side of the face avoiding eyes, lips and mucous membranes. DO NOT SPOT APPLY. Two pea-sized amounts should be enough to cover a half of the face.

Procedure during part II:
All subjects will apply the investigational products in the evening after washing their face, for 24 weeks, as described in the instructions for use provided to the subjects. The procedure is as follows:

1. Wash hands
2. Wash the entire face using the provided Cetaphil® DermaControl™ Oil Control Foam Wash
3. Blot dry the face with a soft towel. Do not rub the face.
4. Apply a thin film of the investigational product (Tactupump™ Forte / CD0271 0.3%/CD1579 2.5% Gel) on the whole face avoiding eyes, lips and mucous membranes. DO NOT SPOT APPLY. Four pea-sized amounts should be enough to cover the face.
5. Wash hands

| | **Investigational product** | **Investigational comparator product** (to be used only during part I) |
|---|---|---|
| Concentration | Adapalene 0.3% - BPO 2.5% | N/A |
| Dose regimen | Once daily | Once daily |
| Period of administration | Evening | Evening |
| Route of administration | Topical | Topical |

### 6.1.5 Non-investigational products

In addition, Cetaphil® DermaControl™ Oil Control Foam Wash and Cetaphil® DermaControl™ Oil Control Moisturizer SPF 30 will be provided by the sponsor.

Subjects should use Cetaphil® DermaControl™ Oil Control Foam Wash twice daily (once in the morning and once in the evening) in order to gently wash their face. Face should thereafter be blotted dry with a soft towel.
Subjects should use Cetaphil® DermaControl™ Oil Control Moisturizer SPF 30 once daily in the morning after washing their face, and they may use it as needed during the day (in case of sun exposure for instance).

Both products are topical and will be used on the whole face for the whole duration of the trial (up to 48 weeks).

No specific labels will be used. Subjects will not return these products to the site. No accountability will be conducted on these products.

## 6.2 INVESTIGATIONAL PRODUCT PACKAGING AND LABELING

During part I:
All investigational products will be supplied in the subject's kit containing 7 visit boxes labeled with an affixed and a tear-off portion.

For treatment documentation, the affixed portion of the label will remain on the appropriate packaging. The tear-off portion of the label will be removed at the time of dispensation and attached to the corresponding product dispensation log.

The same kit number will be printed on each product container, visit box and subject kit labels.

Treatment identification for emergency purposes will be possible with "unblinding envelopes" or equivalent, stating the treatment number, investigational product identification, batch number and investigational product expiration date, as applicable.

During part II:
The subjects will receive 3 bottles of investigational products (enough supply for 12 weeks treatment). These bottles will be labeled with an affixed and a tear-off portion. For treatment documentation, the affixed portion of the label will remain on the appropriate packaging. The tear-off portion of the label will be removed at the time of dispensation and attached to the corresponding product dispensation log.

If more than one batch is used with different expiration dates, in order to maintain blinding, only one expiry date, the most conservative, will be listed on the container label as well as on the «scratch-off» field if applicable.

## 6.3 INVESTIGATIONAL PRODUCT MANAGEMENT

### 6.3.1 Accountability

Upon receipt of the clinical supplies at the site, the product dispenser will conduct a complete inventory of all investigational products and assume responsibility for their storage, accountability and dispensation.
The investigator or designee will sign the original "Receipt of Clinical Supplies" Form (or any acknowledgment of receipt) upon receipt and inspection of the supplies, fax the signed copy to GALDERMA R&D or designated contractor and retain the receipt in the Investigator Site File (ISF).

All supplies sent to the investigator site will be accounted for and in no case used in any unauthorized situation.

All used and unused investigational product will be appropriately inventoried by GALDERMA R&D /CRO representative and returned to Galderma R&D /designated contractor for further reconciliation and destruction.

### 6.3.2 Dispensing

All investigational and non-investigational products will be provided only to subjects enrolled into the clinical trial, at no cost and in accordance with the conditions specified in the protocol.

Dispensation will be appropriately documented on the appropriate product dispensation log by the product dispenser at each visit.

It is important that no subject runs out of clinical trial supplies between visits.

The product dispenser will follow the accurate prescription according to the allocated kit (applicable during part I only).

During part I, each subject will receive a new visit box containing one pump of each investigational product at baseline and each post-baseline visit except at week 1 and week 24.
During part II, each subject will receive 3 bottles of Tactupump™ Forte / CD0271 0.3%/CD1579 2.5% gel at the week 24 and week 36 visits.

During part I, all efforts will be taken to keep the evaluator (investigator or designee) blinded by restricting his/her contact with the investigational products.

The product dispenser must be different from the clinical trial efficacy and safety evaluator in order to maintain the blind during part I (see section 6.5).

During part I, treatment kits will be dispensed in ascending sequential order according to the chronological order of enrolment of subjects into the clinical trial.

### 6.3.3 Investigational product compliance management and record

Each subject will be instructed by the product dispenser about the importance of being compliant with the investigational products throughout the clinical trial as well as the importance of returning the products (used and/or not used) at the follow-up visits (except at week 1).

The investigational products will be collected, counted and documented on the product dispensation log or other accountability document as applicable, at all post-baseline visits (except week 1), by the product dispenser.

During part I of this trial, subjects will receive a tablet called “study companion”, developed by Triacys. This tablet will guide them through the product application. The objective is to optimize product compliance and avoid applications on the wrong side of the face.

The product compliance will be assessed using this tablet via daily recording of product applications by the subject. A GPRS card is inserted into this tablet and real-time logs will be sent automatically without any action required from the subject and made available on a website. This will allow monitoring of the use of the tablet by the subjects by Triacys, Galderma R&D/representative and/or the site personnel. At each visit, the product dispenser will review the data available on this website for the subject. In case of missing or incomplete product application records, the product dispenser will impute the missing data in the eCRF after discussion with the subject. At the end of the trial, compliance will be calculated using both data retrieved from the tablet and data in the eCRF.

In addition, videos of product applications will be made every day by the subjects with this “study companion” tablet. At the end of the trial, these videos will be analyzed by qualified operators in order to verify that the subject has applied the correct product on the correct side. At each visit, the subject will return the tablet and videos will be downloaded on a site’s computer by the product dispenser (as data back-up) via a specific application. At the end of the trial, once the videos will have been analyzed and the compliance report will have been finalized, they will be destroyed. This compliance report will be archived at the sites as a transcription of the videos. In no case, personnel other than the qualified operators will have access to the videos.

During part II of this trial, the “study companion” tablet will not be used. The compliance of the subject will be documented in the product dispensation log based on the discussion between the product dispenser and the subject.

During the data review meetings (one after part I and one after part II), investigational product compliance for all subjects will be determined and reviewed by the sponsor's clinical team for possible exclusion from the Per Protocol (PP) population.

### 6.3.4 Storage of investigational product

The investigator has to agree to keep all investigational products in a safe, temperature controlled and secure area with restricted access, in accordance with applicable regulatory requirements (e.g., in the site pharmacy, if applicable).

Investigational products should be stored at appropriate storage conditions specified by GALDERMA R&D (see section 6.1.1). Temperature should be monitored on every working day.

### 6.3.5 Return of investigational product

The product dispenser will inform each subject about the importance of returning the investigational products (used and/or not used) at each trial visit (except week 1 visit).

In the event of early termination/suspension of the clinical trial for safety reasons, a rapid recall of the trial products will be initiated. The investigator or designee must immediately instruct all subjects to stop the clinical trial treatment regimen and return the products to the clinical trial site.

As a general procedure, GALDERMA R&D will provide the investigator with a detailed list of units being recalled so that any of the units remaining on site can be put immediately into quarantine.

## 6.4 DOSE MODIFICATION

Local cutaneous reactions including erythema, scaling, dryness, and stinging/burning may be experienced with use of Adapalene 0.3% - BPO 2.5% gel. All these adverse reactions are easily managed depending upon the severity of these adverse reactions.

Patients should be instructed to use a moisturizer (if possible the one provided for this trial) and if needed, investigators may reduce temporarily the frequency of the application of Adapalene 0.3% - BPO 2.5% gel (eg. every other day), or temporarily discontinue use. In such cases, the treatment on both half-face should be suspended, even if the irritation is only on one half-face.

These are most likely to occur during the first four weeks of treatment but are mostly mild to moderate in intensity, and usually improve with continued use of the medication.

All dose modifications will be documented in the subject's source data and reported in the eCRF (treatment compliance page).
In addition, for part II, at visits Week 36 and Week 48, any dose modification for safety reasons should lead to the collection of additional information (date of onset and resolution, diagnosis, severity, seriousness and treatment(s) if any). The Sponsor should be notified by email (pharmacovigilance@galderma.com) within 24 hours after being informed of this dose modification for safety reasons.

## 6.5 BLINDING

### 6.5.1 Verification of blinding

The clinical trial design is considered investigator-blind during part I based on the following rationale:

1. Both trial products will be filled in the same type of packaging material and there will be no sign that could indicate which one is the active product and which one is the vehicle.
2. The investigational products will be dispensed by someone other than the evaluator (investigator or designee) designated as the product dispenser in order to maintain the blind.
3. Additionally, both the product dispenser and the subject will be instructed not to discuss the investigational products with the evaluator (investigator or designee)
4. The product dispenser and the investigator will not have access to the unblinded randomization list.

These above-mentioned procedures will be followed to ensure the integrity of the blinding of the clinical trial.

Part II is open-label.

### 6.5.2 Clinical trial unblinding

6.5.2.1 Unblinding during the clinical trial (for part I)

At the investigational sites, unblinding forms or equivalent with the identification of the side of the face assigned to one of the investigational products for an individual subject will be made available and may be used in medical emergencies for therapeutic reasons to reveal treatments assigned.

In such a medical emergency, the investigator will break the blind only for the subject involved.

The investigator must notify the sponsor immediately in the event of such an emergency (see contact details in Section 8.4). If possible, the investigator should notify the sponsor before breaking the blind in order to discuss this decision with the sponsor. The investigator is required to document each case of emergency unblinding on the appropriate form (provided by the sponsor) and fax the completed form to the sponsor immediately. Original will be filed in the subject's file.

Note: GALDERMA Clinical Safety department will also have a set of unblinding forms or equivalent.

6.5.2.2 Unblinding at the end of part I of the clinical trial

In general, unblinding will occur after the completion of the following steps:

1. All clinical trial data for part I from the eCRF, "study companion' data, weighing of returned products if necessary, have been entered into the database
2. All data queries, if any, have been resolved.
3. Major deviations or intercurrent events, if any, have been previously defined and identified, i.e. safety and efficacy evaluability have been determined for each subject
4. All coding for adverse events and therapies have been approved and SAE/Pregnancy reconciliation has been completed
5. Data management has integrated the above evaluability information into the database
6. The statistical analysis plan (SAP) has been finalized
7. The database has been formally validated and locked

Written approval from data management, statistician and clinical project manager will be required for unblinding the clinical trial.

Part II is open-label.

# 7 EFFICACY AND SAFETY ASSESSMENT

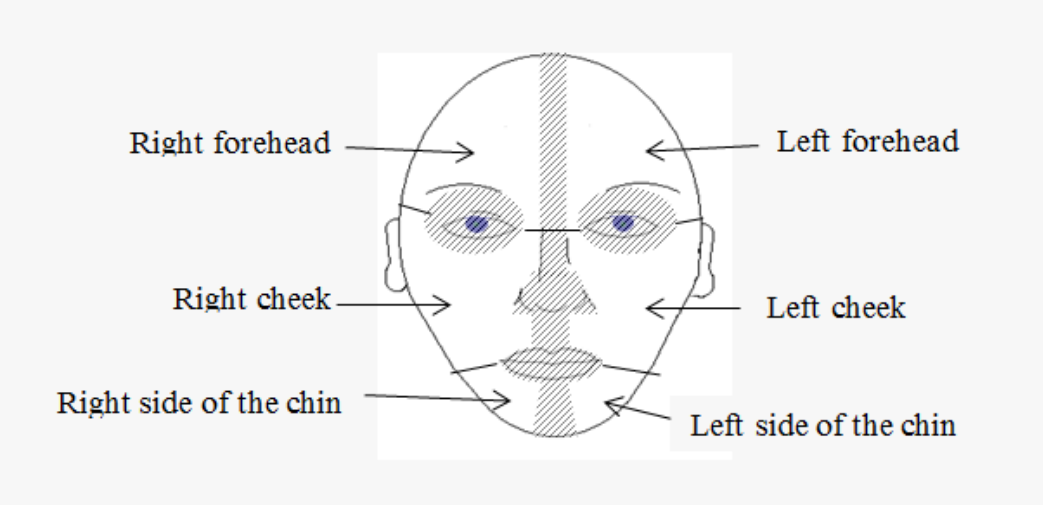
## 7.1 EFFICACY ASSESSMENTS

Clinical evaluations should be performed by the same evaluator (investigator or designee) throughout the clinical trial.

If it is not possible to use the same evaluator to follow a subject, then evaluations should overlap for at least one visit in order to examine the subject together and discuss findings and this should be documented in the source documents. At least for the baseline assessments and the final assessments of part I (week 24/early termination), the evaluator should be the same person.

The evaluated areas must be examined under the same conditions of light exposure at each visit (same angle to avoid shadow and same light source, i.e. artificial or daylight).

Both during part I and part II, the zone in the middle of the face (approximately 2 cm large and the nose) will be excluded for the clinical efficacy evaluations because subjects may apply a mix of both investigational products (active and vehicle) on this zone. See figure below.




### 7.1.1 Atrophic acne scar count

Each type of atrophic acne scars will be counted separately **for each half-face** at each trial visit. The scars will be counted according to their size defined in 2 categories (Jacob, et al., 2001) using 2- and 4-mm punch biopsy tools for size classification:

- Atrophic scars 2-4 mm: includes boxcar (sheer edges), rolling (irregular surface), and undetermined types
- Atrophic scars > 4 mm: includes boxcar (sheer edges), rolling (irregular surface), and undetermined types.

The evaluator will count both types of atrophic scars for each region: left and right forehead, left and right cheeks, and left and right side of the chin above the jaw line (see figure above).

On each half-face, the scar counts will be added together to obtain the total number of scars per half-face.

### 7.1.2 Investigator's scar global assessment (SGA)

The evaluator will assess the severity of atrophic acne scars **of each half-face** at each trial visit, performing a static ("snapshot") evaluation of the severity based on the scale below.
The evaluator should make no reference to baseline or other previous visit when evaluating each subject's half face.

**Table 1: Investigator's Scar Global Assessment (SGA)**

| Category | Score | 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.

### 7.1.3 Investigator's preference in terms of overall scar severity

At week 12, week 24 and in case of early termination (during part I only), the evaluator will assess his/her preference in terms of overall acne scars severity between the two half faces:

**Table 2: Investigator's preference in terms of overall scar severity**

| 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 |

### 7.1.4 Acne lesion count

Each type of lesion will be counted separately **for each half-face** at each trial visit. The evaluator will take the lesion counts from left and right forehead, left and right cheeks, and left and right side of the chin above the jaw line (see figure above).

For each half-face, the lesion counts will be added together to obtain a Total Lesion count per half-face. The following are the definitions of the lesions that will be counted.

*Non-inflammatory lesions*
Open Comedone - A mass of sebaceous material that is impacted behind an open follicular orifice (blackhead).
Closed Comedone - A mass of sebaceous material that is impacted behind a closed follicular orifice (white head).

*Inflammatory lesions*
Papules - A small, solid elevation less than one centimeter in diameter. Most of the lesion is above the surface of the skin.
Pustules - A small, circumscribed elevation of the skin which contains yellow-white exudates.

*Other lesions*
Nodules - A circumscribed, elevated, solid lesion generally more than 1.0 cm in diameter with palpable depth.

### 7.1.5 Investigator's global assessment of acne severity (IGA)

For the **inclusion criterion** (subjects should have an IGA of 3 or 4), the evaluator will assess the severity of acne for the **whole face** of the subject using the scale described in Table 3 below.

For **all other IGA assessments** (at baseline and at each post-baseline visit), the evaluator will assess the severity of acne **for each half-face** using the scale described in Table 3 and adapted for half-faces. The evaluator will evaluate the subject's acne at each visit performing a static ("snapshot") evaluation of acne severity. The evaluator should make no reference to baseline or other previous visit when evaluating the subject's acne.

The global severity assessment is outlined in the following table (IGA):

**Table 3: Investigator's global assessment of acne (IGA)**

| Category | Score | 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. |

### 7.1.6 Investigator's assessment of the skin roughness

The evaluator will evaluate skin roughness **for each half-face** at baseline, week 12, week 24, week 48 and in case of early termination by using the five-point scale below:

**Table 4: Skin roughness score**

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

### 7.1.7 Investigator's assessment of the skin texture change

Overall facial skin texture change will be graded by the evaluator **for each half-face** at week 12, week 24, week 48 and in case of early termination as follows:

**Table 5: Skin texture change score**

| 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 |

### 7.1.8 Quantitative evaluation of skin microrelief (skin replica)

At baseline, week 24, week 48 and early termination (in case it occurs after week 8), skin replicas will be performed **on each cheek** (size 5x2 cm) by using specific silicon (Silflo®) and by following the provided detailed procedure. The 5x2 cm region should be chosen - whenever possible - where there are the least scarring and should be equivalent on both sides.
The skin replica will be analyzed for skin microrelief using fringe projection. Roughness parameters will be calculated for the whole replica and on the regions of the replica without any lesion.
This will be performed at one selected site only and if the subject has given consent for this procedure.

## 7.2 SAFETY ASSESSMENTS

A safety assessment will be conducted for all subjects at the baseline visit (after the ICF has been signed) and every subsequent visit. The safety parameters include adverse events (AEs) and assessment of local tolerability.

### 7.2.1 Local tolerability assessment

Signs and symptoms of local cutaneous irritation (erythema, scaling, dryness and/or stinging/ burning) are possible during treatment with Adapalene 0.3% - BPO 2.5%.

The investigator will evaluate erythema, scaling, dryness and/or stinging/burning at each trial visit. The investigator will record stinging/burning after discussion with the subject regarding the previous application days. The investigator will ask an open-ended question, taking care not to influence the subject's answer, such as: "Have you experienced any sensations immediately following products application (within 5 minutes)?"

Erythema, scaling, dryness, and stinging/burning will be graded at baseline and each post-baseline visit as follows (to be done for each half-face):

- **Erythema**: abnormal redness of the skin

None 0: No erythema
Mild 1: Slight pinkness present
Moderate 2: Definite redness, easily recognized
Severe 3: Intense redness

- **Scaling**: abnormal shedding of the stratum corneum

None 0: No scaling
Mild 1: Barely perceptible shedding, noticeable only on light scratching or rubbing
Moderate 2: Obvious but not profuse shedding
Severe 3: Heavy scale production

- **Dryness**: brittle and/or tight sensation.

None 0: No dryness
Mild 1: Slight but definite roughness
Moderate 2: Moderate roughness
Severe 3: Marked roughness

- **Stinging/Burning**: prickling pain sensation immediately after application (within 5 minutes).

None 0: No stinging/burning
Mild 1: Slight warm, tingling/stinging sensation; not really bothersome
Moderate 2: Definite warm, tingling/stinging sensation that is somewhat bothersome
Severe 3: Hot, tingling/stinging sensation that has caused definite discomfort

Note: Stinging/Burning at the baseline visit should be assessed as none (0).

An Adverse Event will be recorded if the severity of the signs and symptoms is such that:

- The subject's participation in the trial is interrupted at his/her request or at the investigator's request after the week 4 visit
- The subject permanently discontinues the treatment at his/her request or at the investigator's request.
- The subject requires concomitant prescription or OTC therapy (other than moisturizers).

Note: Need for increased moisturizer use does NOT constitute an AE.

Any new sign or symptom, which is not included in the scheduled evaluation of tolerability, should be recorded as an Adverse Event, including those of mild intensity.

### 7.2.2 Adverse events

Adverse events (AEs) are to be monitored throughout the course of the clinical trial. All AEs are to be reported on the Adverse Event Form of the eCRF with complete information as required. If AEs occur, the main concern will be the safety of the subjects. At the time of the ICF signature, each subject must be provided with the name and phone number of clinical trial site personnel for reporting AEs and medical emergencies.

## 7.3 PATIENT RELATED OUTCOMES

The following Patient Reported Outcome (PRO) questionnaires should be filled out by the subjects. The investigator or delegate should check all questions of the PRO questionnaires for completeness prior to the subject leaving the office.

### 7.3.1 Questionnaire on acne scar appearance

Subject will assess acne scar appearance **of each half-face** at baseline, week 12, week 24, week 48 and in case of early termination using the SCARS questionnaire (Self-assessment of Clinical Acne Related Scars) provided in Appendix 1.

### 7.3.2 Subject satisfaction questionnaire

At week 24/early termination (in case of early termination during part I), subjects will complete the part I satisfaction questionnaire regarding the treatments and non-investigational products they have been using in this trial (see Appendix 2).

At week 48/early termination (in case of early termination during part II), subjects will complete a satisfaction questionnaire regarding the non-investigational products they have been using in this trial (see Appendix 3).

## 7.4 OTHERS

### 7.4.1 Photographs

Standardized digital photographs of the whole face (front, right and left) will be taken using a Canfield Scientific stereostatic device (Visia CR®) and/or a 3D camera (for instance, 3D Lifeviz™). Detailed procedures will be provided.
Photographs will be taken at baseline, week 12, week 24 and week 48.
This will be performed at selected sites only and if the subject has given consent for this procedure.

## 7.5 APPROPRIATENESS OF MEASUREMENTS

Efficacy is evaluated by assessing the number of inflammatory and non-inflammatory lesions as well as a global assessment of acne severity by the investigator (IGA) which are current and non-invasive techniques for assessing acne severity.

In addition, as this is the main trial objective, atrophic acne scars will also be counted and investigators will make an overall assessment of scars severity (SGA) as it has been previously done in a previous trial (protocol RD.03.SPR.40183E). They will also evaluate the side they prefer in terms of acne scars. These techniques are non-invasive.

Furthermore investigators will assess the skin roughness and the skin texture change using discrete scores. These are non-invasive exploratory assessments. At one selected site, skin replica will be performed to get a quantitative assessment of skin microrelief. This technique is very minimally invasive (silicon imprint of the skin) and has been used in previous trials in a similar subject's population (e.g. RD.03.SPR.29088). These assessments are classified as exploratory efficacy assessments as a possible effect of Adapalene on cosmetic outcomes as shown in subjects with photodamaged skin is hypothesized in younger subjects (Kang, et al., 2003).

Safety will be assessed through the reporting of adverse events and local tolerability assessment on an ongoing basis as a well-established process in clinical trials.

Impact of trial treatments on subjects' assessment of their scars appearance will be assessed using the SCARS questionnaire which has been developed by the Global Alliance to Improve Outcomes in Acne following the recommendations given by FDA guidance for developing patient reported outcome tools with patient interviews (Paper submitted in December 2015). This is the first time this questionnaire is used in a clinical trial but it was designed to be suitable for self-completion and to be rapidly completed (2-5 min) within a clinical research setting. This questionnaire was adapted to a split-face design.

To collect specifically the subject's feed-back on the treatments and on the associated cosmetics products used in the trial, a subject satisfaction questionnaire will be used.

# 8 ADVERSE EVENTS

Throughout the course of the clinical trial, all adverse events will be monitored and reported on an Adverse Event Form of the eCRF disclosing any requested and known information. When adverse events occur, the main concern is the safety of the clinical trial subjects. At the time of the ICF signature, each subject will be given the name and telephone number of clinical trial site personnel to whom AEs and medical emergencies should be reported.

## 8.1 DEFINITIONS

### 8.1.1 Adverse Events (AE)

According to ICH E2A, an AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory value), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Thus any new sign, symptom or disease, or clinically significant increase in the intensity of an existing sign, symptom or disease since the first visit (including the disease being treated), should be considered as an adverse event. Lack of efficacy should not be considered as an AE.

Each new episode of a chronic disease (e.g., hay fever, allergy, etc.) should be reported as a new AE.

**Notes:**

- A diagnosis should preferably be reported rather than the signs, symptoms or abnormal laboratory values associated with the report of an AE. However, a diagnosis should be reported only if, in the investigator's judgment, it is relatively certain. Otherwise, symptoms, signs, or laboratory values should be used to describe the AE.
- Any new sign or symptom appearing after accidental or intentional overdose or misuse should also be reported as an adverse event.
- Pregnancy should not be considered as an adverse event but must be followed up as described in section 8.5.

There may be side effects during treatment with the investigational products, as described in the product monograph for Tactupump™ Forte and in this protocol (mild to moderate application site reactions, such as skin irritation characterized by scaling, dryness, erythema, and burning/stinging).
The course of these expected events will be assessed and reported on the Local Tolerability Assessment Forms. An Adverse Event Form will be completed only if the severity of the expected signs and symptoms is such that an interruption/discontinuation of the subject's participation in the clinical trial, at his/her request or at the investigator's, occurred and/or if a concomitant medication is prescribed to treat the sign/symptom(s).

### 8.1.2 Serious Adverse Events (SAE)

A serious adverse event is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the safety of the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia, or convulsions that do not result in hospitalization.

**Note:**

- The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

- Hospitalization is considered to have occurred if the subject has had to stay in hospital overnight. The criterion for the prolongation of hospitalization is also defined as an extra night in hospital. Hospitalization solely for the purpose of diagnostic tests, even if related to an adverse event, elective hospitalization for an intervention which was already planned before the inclusion of the subject in the clinical trial, admission to a day-care facility, social admission (e.g. if the subject has no place to sleep), or administrative admission (e.g. for a yearly examination) may not themselves constitute sufficient grounds to be considered as a serious adverse event.

### 8.1.3 Unexpected adverse drug reaction

According to ICH E6, an unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable trial drug information (in this clinical trial: the approved Canadian product monograph at the time of AE occurrence).

### 8.1.4 Adverse event reporting period

All AEs occurring during the clinical trial period from when the subject signs the Informed Consent Form to the end of the subject's participation will be reported.

The sponsor should be informed if the investigator becomes aware of any unusual safety information or any safety information that appears to be drug-related involving a subject who has participated in a clinical trial, even after a subject has completed the clinical trial. The investigator should be diligent in looking for possible latent safety effects that do not appear until after the medication has been discontinued.

### 8.1.5 Severity

Severity is the clinical determination of the intensity of an adverse event and not of a disease.

The investigator will classify the intensity of AEs using the following definitions. For this classification, the investigator will take into account the possible range of the intensity of the event and report the grade of intensity which is the most appropriate according to his/her medical judgment.

| | |
|---|---|
| **Mild** | Awareness of sign or symptom, but easily tolerated |
| **Moderate** | Discomfort, enough to cause interference with usual activity |
| **Severe** | Incapacitating with inability to work or perform usual activity |

### 8.1.6 Relationship to the investigational product

The investigator has to determine whether or not there is a reasonable causal relationship between the investigational product and the AE. Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, positive dechallenge or rechallenge, relevant medical history, and confounding factors such as co-medication or co-concurrent diseases.

The expression "reasonable causal relationship" is meant to convey in general that there are facts or arguments to suggest a causal relationship (International Conference on Harmonization (ICH) E2A, section IIIA 1).

The relationship assessment for an adverse event will be completed using the following definitions as a guideline for all adverse events occurring during this clinical trial:

**Reasonable possibility:**

According to the reporting investigator, there is a reasonable possibility (i.e., suggestive evidence or arguments) that there is a causal relationship irrespective of the dose administered between:

- The trial product (investigational product, active comparator, or placebo/vehicle, etc.) and the AE,
- The clinical trial protocol procedure (e.g. UV-induction, biopsy, xylocaine injection, blood test or intraocular pressure measurement, etc.) and the AE.

**No Reasonable Possibility:**

No suggestive evidence or arguments can be identified regarding a causal relationship between the investigational product or the clinical trial protocol procedure and the AE.

## 8.2 PROCEDURES FOR REPORTING ADVERSE EVENTS

Adverse events will be collected from the time that a subject signs the ICF to his/her final trial visit.

At each visit, the investigator (or sub-investigator) will enquire about adverse events using an open question taking care not to influence the subject's answer (e.g., "Have you noticed any change in your health since the last visit?"). Direct questioning and examination will then be performed as appropriate.

Any AE occurring during the AE reporting period, whether it is related to the investigational product or not, will be recorded immediately in the source document, and described in the Adverse Event Form of the eCRF along with the date of onset, severity, relationship to the investigational products, and outcome, without omitting any requested and known information. Additional information may be requested under certain circumstances. Adverse Events assessed as related to the treatments will be monitored until they are completely or satisfactorily resolved. Other AEs will be monitored until the last visit if they are not resolved or satisfactorily resolved.

The investigator will obtain and maintain in the subject's files all pertinent medical records, information and medical judgment from colleagues who assisted in the treatment and follow-up of the subject. If necessary, the investigator will contact the subject's personal physician or hospital staff to obtain further details.

When an AE related to the treatment persists at the end of the clinical trial, the investigator will ensure the subject is followed up until the investigator and GALDERMA R&D agree that the event is satisfactorily resolved.

## 8.3 PROCEDURE FOR SUSPECTED ALLERGIC CONTACT REACTION

This is a general procedure and further details can be discussed with the sponsor.

- Stop the trial product.
- Take a picture of the affected area and the non-affected surrounding skin
- **Document the event and report it immediately** to the sponsor within 24 hours of receipt of the information as described in section 8.4.

### 8.3.1 In case of suspicion of allergic contact dermatitis

1. After all signs and symptoms have resolved and after a minimum of two weeks from last treatment application, perform a re-challenge test with the assigned trial product.
2. Ensure the subject has not been receiving any treatment with corticosteroids or antihistamines of any route of administration the week before testing.
3. Ensure that the skin on the back has not been exposed to the sun or artificial ultraviolet sources the week before testing.
4. Apply an appropriate quantity of the assigned trial product to fill the cupule of the test chamber on the skin of the upper back on either the right or left side of the centre line (or the inner forearm if the back cannot be tested). If no test chamber is available on-site, patch test units will be provided. It may be preferable to perform the test under semi-occlusive conditions depending on the irritant potential of the trial product and the intensity of the

reaction that was observed. The method to be used should be discussed with the sponsor. Choose a skin site that was not previously involved in the inflammatory skin reaction. Cover it for 48 hours with a hypoallergenic tape.

5. The subject should be informed about avoiding exercise, showers, application of toiletries, etc. to keep the test system dry
6. After 48 hours, remove the tests and evaluate the site:
    - at approximately 30 minutes after patch test removal (1st reading) and,
    - 24 to 48 hours later (i.e. 72 or 96 hours after application) (2nd reading).
    - A facultative 3rd reading may be performed 96 to 120 hours later (i.e. 6 to 7 days after application of the patch) if the overall assessment was equivocal or if requested by the sponsor.
    - Pictures of the tested areas will be taken systematically at each reading and properly documented.

| Duration of trial product application | 1st Reading | 2nd Reading | 3rd reading (optional) |
|---|---|---|---|
| 48 hours | 48 hours after trial product application (30 minutes after patch test removal) | 72 to 96 hours after trial product application (24 to 48 hours after patch test removal) | 6 or 7 days after trial product application (96 to 120 hours after patch removal) |

7. Refer to the scoring system used by the International Contact Dermatitis Research Group (ICDRG) to assign a score at each reading (Spiewak, 2008):

| **Score** | **Morphology** | **Interpretation** |
|---|---|---|
| - | No skin changes in the tested area | Negative |
| ? | Faint, non-palpable erythema | Doubtful reaction |
| + | Palpable erythema (moderate edema or infiltrate), papules not present or scarce, vesicles not present | Weak positive reaction |
| ++ | Strong infiltrate, numerous papules, vesicles present | Strong positive reaction |
| +++ | Erythema, infiltration, confluent vesicles, bullae or ulceration | Extreme positive reaction |

| | | |
|---|---|---|
| ir | Inflammation sharply limited to the exposed area, lack of infiltrate, small petechiae, pustules, and efflorescences other than papules and vesicles | Irritant reaction |
| Nt | | Not tested |

8. At last reading, provide an assessment regarding a possible sensitization reaction using the following scale:

| Sensitization Reaction | |
|---|---|
| 0 | Negative (absence of reaction or might be irritant reaction) |
| 1 | Equivocal |
| 2 | Positive |

9. Report the results from the re-challenge test as directed by the sponsor and document with photographs.
10. In case of absence of reaction, the subject may resume treatment if appropriate
11. If the re-challenge is positive or equivocal, notify the sponsor immediately. Except in specific situations, a new series of patch test will be initiated as directed by the sponsor (with individual ingredients at different concentrations if applicable, and possibly *negative and positive controls*) after a minimum of additional two weeks (but not later than 6 months) and after all signs and symptoms have resolved. The patch tests will be placed on the subject's back (or the inner forearm if the back cannot be tested) distant from the site of the re-challenge test (e.g., the left upper back skin if the re-challenge test was done on the right side). Follow the same procedure for the patch test as for the re-challenge.

### 8.3.2 In case of suspicion of immediate contact skin reaction (such as urticaria)

A case by case approach will be applied and the procedure to follow will be discussed with the sponsor.

## 8.4 PROCEDURE FOR REPORTING A SERIOUS ADVERSE EVENT

For any serious adverse event occurring during the clinical trial period, whether or not related to the treatment, expected or not, the investigator will:

1. **Take prompt and appropriate medical action**, if necessary. The safety of the subject is the main priority.
2. **Immediately (no later than 24 hours) inform the sponsor** of the event by fax/email, and discuss further steps to be taken:

| | **GALDERMA R&D** |
|---|---|
| Name<br>Title | [redacted]<br>[redacted]) |
| Address | [redacted] |
| Tel. during office hours | [redacted] |
| Tel. Outside office hours | [redacted] |
| Fax | [redacted] |
| Email | pharmacovigilance@galderma.com |

The treatment allocation may be unblinded for the particular subject under either one or both of the following circumstances:

- If knowledge of the trial treatment is medically necessary in order to manage subject's safety,
- If GALDERMA pharmacovigilance decides that the event requires expedited reporting to the Regulatory Authorities and to the IRBs/ECs, whereby knowledge of the treatment allocation is necessary.

3. **Complete the SAE Form** provided by the CRA (Clinical Research Associate) at the start of the clinical trial (it is also available in the eCRF system as pdf document). Fax or send by email the completed form, accompanied by any other relevant information or anonymized medical records (e.g., laboratory test results) within 24 hours to the sponsor (see contact details above). The demographics, medical history, previous and concomitant therapies, and adverse event pages of the eCRF must be completed and available for review in the EDC system at the time of the report.
4. **Monitor and record the progress of the event until it resolves** or reaches a clinically stable outcome, with or without sequel. For all additional follow-up evaluations, fax or send by e-mail

all additional follow-up information on the SAE to the sponsor (see contact details above) within 24 hours of receipt of the updated information. SAEs will be monitored until the investigator and sponsor agree that the event is satisfactorily resolved.

5. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.
6. **Inform GALDERMA R&D of the final outcome of the event**. Send a revised or updated SAE Form, if appropriate (usually required every ten days) to the sponsor.
7. **Comply with the applicable regulatory requirements related to the reporting of SAEs to IRB/EC.**

## 8.5 PROCEDURES FOR REPORTING PREGNANCIES

Any pregnancy occurring during clinical trials, where the foetus could have been exposed to the investigational products, must be followed-up until outcome in order to ensure the complete collection of safety data on GALDERMA R&D product.

In the case of a pregnancy of a clinical trial subject, the investigator will:

1. **Withdraw the subject from the clinical trial** and complete all appropriate visit evaluations and eCRF pages.
2. **Immediately (no later than 24 hours) contact the sponsor** to inform them of the pregnancy occurrence by fax/email and discuss further steps to be taken.

| | **GALDERMA R&D** |
|---|---|
| Name<br>Title | [redacted] |
| Address | [redacted] |
| Tel. during office hours | [redacted] |
| Tel. Outside office hours | [redacted] |
| Fax | [redacted] |
| Email | pharmacovigilance@galderma.com |

3. **Complete, as fully as possible, the Pregnancy Surveillance Form – Part I:** History and start of pregnancy - provided by the CRA at the beginning of the clinical trial (it is also available in the eCRF system as pdf document), and fax or send by email within 24 hours to the sponsor.
4. Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask regular follow-up information.
5. **Inform the sponsor of the progress by tri-monthly updates up** to the final outcome of the pregnancy. For all the additional follow-up evaluations, fax or send by e-mail the additional follow-up information to the sponsor within 24 hours of receipt of the information. If the subject can no longer be reached (lost to follow-up), documentation of the non-response/contact with two phone calls and a letter (certified with return receipt) is required.
6. **At outcome of pregnancy, complete as fully as possible the Pregnancy Surveillance Form – Part II:** Course and outcome of pregnancy and send it by fax or by email to the sponsor within 24 hours following investigator's or site personnel becoming aware of the outcome of the pregnancy.
7. If the pregnancy leads to an abortion (voluntary abortion, spontaneous abortion or therapeutic abortion), *in utero* death or congenital anomaly, follow the procedure for declaration of an SAE (see section 8.4).
8. If the investigator is informed of a developmental abnormality of the baby, even a long time after the end of the clinical trial, he/she must inform the sponsor and follow the procedure for declaration of an SAE (see section 8.4).

# 9 STATISTICAL METHODS PLANNED

## 9.1 STATISTICAL AND ANALYTICAL PLANS

A Statistical Analysis Plan (SAP) will be developed as a separate document. The SAP will contain a more detailed and technical description of specific data conventions, calculations and of statistical procedures for executing the analyses that are specified in the sections of the clinical trial protocol below. The SAP will be finalized prior to database lock and unblinding. Any change made to the finalized SAP will be documented in the clinical trial report.

### 9.1.1 Variables to be statistically analyzed

The following variables will be analyzed:

**Primary efficacy endpoint:**

- *Total atrophic acne scar count* per half-face at week 24

**Secondary efficacy endpoints:**

- *Total atrophic acne scar count* per half-face at each post-baseline visit (except week 24)
- *Percent change from Baseline in total atrophic acne scar count* per half-face at each post-baseline visit
- *SGA* per half-face at each post-baseline visit
- *Investigator's preference on overall scar severity* at week 12, week 24, early termination during part I
- *Percent change from Baseline in total lesion count* per half-face at each post-baseline visit
- *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¨
- *IGA* per half-face at each post-baseline visit

**Exploratory efficacy endpoints:**

- *Investigator's assessment of skin roughness* of each half-face at Baseline, week 12, week 24, week 48, early termination
- *Investigator's assessment of skin texture change* per half-face at week 12, week 24, week 48, early termination
- *Skin microrelief variables:* percent change from Baseline per half-face at week 24, week 48, early termination (if early termination occurs after week 8)

**Safety endpoints:**

- *Incidence of adverse events*
- *Local tolerability:* percent of subjects across scores at each post-baseline visit

**PRO endpoints:**

- *Acne scar appearance* using the SCARS questionnaire at baseline, week 12, week 24, week 48, early termination, for each half-face
- *Subject satisfaction questionnaire* at week 24, week 48, early termination

### 9.1.2 Populations analyzed, evaluability and limitations / evaluation of bias

The statistical analyses will be performed based on the following subject populations. The definition of the populations will be finalized after a blind data review meeting.

9.1.2.1 The Per Protocol efficacy population (PP)

This population will consist of all enrolled and randomized subjects, except subjects who have major deviations from the protocol. Major deviations will be defined during a data review meeting after data entry and before unblinding the clinical trial treatment. Major protocol deviations will be considered as having a possible effect on the interpretation of primary efficacy results and may include: inclusion criteria not respected, non-available efficacy assessment, interfering therapy at inclusion, etc.
The primary efficacy endpoint will be analyzed based on this population.

9.1.2.2 The Intent-to-Treat efficacy population (ITT)

This population will consist 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.

9.1.2.3 The Safety population (All patients treated [APT])

This population will consist of the Intent-to-Treat population, after exclusion of subjects who never used the treatment with certainty based on monitoring report. The APT population will be only used for the safety variables.

9.1.2.4 Missing values

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) during part I. If no post-baseline data are available, baseline will be carried forward. The other missing values of part I and the data collected during part II will not be replaced (observed data).

### 9.1.3 Data presentation and graphics

All continuous data will be summarized 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. Tables will be presented by investigational product, bilateral difference and visit (when applicable).

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, %) for the safety population (APT). The adverse events will be descriptively summarized (n, %) by relationship to the investigational products 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 events, SOC and preferred terms. Deaths and serious adverse events will be reported as well as withdrawals due to adverse events. A subject will be counted only once per System Organ Class (SOC) and only 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 only 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).

### 9.1.4 Statistical analyses

The primary objective of this trial 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.

The other efficacy variables of part I will be analyzed similarly as the primary analysis on the appropriate population. Each test will be two-sided, at the 0.050 significance level.

The subject characteristics (previous medication, concomitant medication, demographics, baseline characteristics…), lesion counts, microrelief, adverse events, local tolerability and questionnaires and all variables of part II will be summarized by descriptive statistics (usual statistics and frequency distribution).

### 9.1.5 Interim analysis

Interim analysis will be performed when all subjects will have completed the week 24 visit (Part I). For this interim analysis, all available variables will be analyzed. This interim analysis is dedicated to provide the statistical results and is not meant to condition to any premature study termination. As all statistical analyses were planned during part I, this interim analysis will have no impact on the type I error, and the efficacy results will be considered as final.

## 9.2 SAMPLE SIZE DETERMINATION

### 9.2.1 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.

### 9.2.2 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.

# 10 TRAINING / MONITORING / DATA MANAGEMENT / QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for monitoring the clinical trial and the sponsor may perform co-monitoring visits at selected sites.

## 10.1 PERSONNEL TRAINING

Clinical Research Associates (CRA) will be trained prior to clinical trial initiation and as needed during the trial (in particular in case of protocol amendment). During this training, an overview of the disease of interest and treatment will be presented. Specific monitoring guidelines and procedures to be followed during monitoring visits will be discussed.

Initiation visits will be conducted with all principal investigators and site teams. During these visits, an extensive review and discussion of the protocol, procedures and eCRF will be conducted. Evaluation scales will also be reviewed.

A monitoring manual will be provided to each CRA as an additional reference tool.

An eCRF completion guideline will be provided to each CRA and site. These guidelines will contain instructions on how to fill in the eCRF with some examples in order to standardize the eCRF completion as much as possible.

A trial reference manual will be provided to each site as an additional reference tool. These guidelines will contain key CRO and sponsor contacts and phone numbers and specific instructions for site in order to standardize as much as possible the assessments performed during the clinical trial. A manual will also be provided to the product dispenser, with specific instructions detailing use of the “study companion” tablet.

Furthermore during the investigator meeting a specific training on scars assessments will be conducted.

## 10.2 CLINICAL MONITORING

The conduct of the clinical trial will be closely monitored by GALDERMA R&D or representatives to verify the adherence to the clinical trial protocol, ICH-GCP regulations, applicable standard operating procedures (SOPs), guidelines, and all local regulations.

The investigator will allow representatives of GALDERMA R&D to have direct access to all clinical trial records, eCRFs, corresponding subject medical records, investigational product dispensing

records and investigational product storage area, site facilities and any other documents considered as source documentation.

The investigator also agrees to assist the CRO/ GALDERMA R&D representatives, if required.

### 10.3 DATA MANAGEMENT

A CRO will be responsible for data management in connection with the sponsor's data manager.

All data management procedures will be detailed in the Data Management Plan (DMP).
The DMP will describe the Clinical Data Management System (CDMS) that will be used to collect and validate data. Computerized edit checks and review processes will be performed on an ongoing basis as outlined in the DMP until all data discrepancies are resolved.
After all data discrepancies are resolved, coding is approved, and subject evaluability has been determined, the data will be exported to SAS datasets and will be locked (there will be one lock for Part I and one lock for Part II).
After unblinding (part I only), the locked SAS database will be used to generate subject listings, tabulations and analyses.

The data may be audited by the sponsor and/or CRO Quality Assurance department before or after the first statistical analysis results on the primary criteria.

### 10.4 QUALITY ASSURANCE / AUDIT / INSPECTION

The clinical trial will be conducted under the sponsorship of GALDERMA R&D in compliance with all appropriate local regulations as well as ICH guidelines and in accordance with the SOPs for clinical trial conduct and monitoring from GALDERMA R&D and/or CRO.

Audits of clinical trial sites may be conducted by GALDERMA R&D /CRO representatives, and inspection may be performed by Regulatory Authority inspectorates or IRBs/ECs before, during, or after the clinical trial.

The investigator will allow and assist the GALDERMA R&D /CRO representatives, IRBs/ECs and any regulatory agency to have direct access to all requested clinical trial-related records.

For the audits performed by, or on behalf of, GALDERMA R&D auditors, audit certificate(s) will be provided by Quality Assurance.

# 11 ETHICS AND GENERAL CLINICAL TRIAL CONDUCT CONSIDERATIONS

## 11.1 INSTITUTIONAL REVIEW BOARD (IRB) OR ETHICS COMMITTEE (EC)

This clinical trial protocol will be reviewed and approved by IRBs/ECs prior to clinical trial initiation.

This protocol may be modified at any time for ethical, medical or scientific reasons. Such modifications will be documented by a clinical protocol amendment and, if deemed necessary, an amended protocol will be issued.

Before implementation, the amendment should be submitted and approved by applicable IRBs/ECs and, if required by the Regulatory Authority(ies).

No amendment will be required for modification(s) due to a change in logistical or administrative aspects of the clinical trial (e.g., change in monitors, change of telephone numbers). In such a case, the appropriate institution(s) and/or person(s) will be directly notified of the changes.

## 11.2 ETHICAL CONDUCT OF THE CLINICAL TRIAL

This clinical trial will be conducted in accordance with the ethical principles originating from the Declaration of HELSINKI declaration (1964) and subsequent amendments, the International Conference on Harmonization (ICH), Good Clinical Practice (GCP) and in compliance with local regulatory requirements.

## 11.3 SUBJECT INFORMATION SHEET / INFORMED CONSENT

All subjects who participate in this trial will be fully informed about the clinical trial in accordance with the applicable regulations and GCP guidelines and in accordance with local legal requirements.

The Informed Consent Form (including appropriate Assent Form for children (aged 16 to 17) and as applicable, photograph release form or skin replica consent) approved by an IRB/EC, will be fully explained to the subject and parent/guardian if applicable. There will be one ICF for part I (to be signed at the beginning of the trial, before or at the baseline visit) and one ICF for part II (to be signed by the subject at the end of part I, if the subject is considered for part II by the investigator and if s/he is willing to participate to part II).

Prior to any clinical trial procedures, the subject and parent/guardian will sign and date the Informed Consent Form(s) which is written in the local language. A copy of the signed and dated form(s) will

be given to the subject and parent/guardian. The investigator is responsible for maintaining each subject's Informed Consent Form(s) in the investigator's site file (ISF) and providing each subject and parent/guardian with a copy of the consent form.

The Informed Consent Form including photograph release form approved by an IRB/EC will be fully explained to the subject and parent/guardian.

## 11.4 CONTRACTUAL REQUIREMENTS

A contractual agreement will be signed between the CRO/sponsor and each investigator/institution. This document will contain supplementary information, including financial terms, confidentiality, the clinical trial schedule, third party responsibility, and publication rights.

## 11.5 DATA COLLECTION AND ARCHIVING

### 11.5.1 Data Collection

The investigator must maintain required records on all clinical trial subjects.
Data for this clinical trial will be recorded in the subject's source documents, in the product dispensation logs and in the "study companion" tablet allocation log.

All data recorded in the documents described above should be recorded completely, promptly, and legibly using a pen (not a pencil).

Each time a new subject is enrolled, the "study companion" tablet allocation log will be faxed or emailed to Triacys. The real-time data obtained through the "study companion" tablets will be automatically transferred to Triacys servers using specific software elaborated by Triacys. A copy of the videos taken by the subject will be maintained locally by the product dispenser during the trial and eventually destroyed once reconciliation with the central database will have been performed. Special attention will be brought to the videos in order to avoid possible use of those by non-qualified personnel or for reasons other than those related to the trial and indicated in the present protocol.

### 11.5.2 Source documentation

Investigators must keep accurate separate records (other than the eCRF) of all subjects' visits, and all procedures done, being sure to include all pertinent clinical trial related information from which eCRF data will be recorded.

A statement should be made on subject's medical notes indicating that the **subject has been enrolled in GALDERMA R&D protocol RD.03.SPR.105061 and has provided dated and signed informed consent and assent if appropriate.**

All adverse events with the associated concomitant therapies must be thoroughly documented. Results of any diagnostic tests conducted during the clinical trial will be included in the source documentation.

Telephone conversations with the subjects and/or CRO/GALDERMA R&D concerning the clinical trial may be recorded and kept on file.

Once the images from the "study companion" tablets will have been analyzed by qualified operators from Triacys and the report issued by Triacys finalized, they will be destroyed. In no case, personnel other than the qualified operators will have access to the images. The report will be kept on site in the ISF as transcription of the original source data (the videos).

### 11.5.3 Archives

All pertinent data, samples, photos, questionnaires, correspondence, original or amended protocol, all reports and all other material relating to the clinical trial will be maintained securely in GALDERMA R&D / Investigator/Institution archives for the legally-required duration of archiving.

If the investigator retires, relocates, or for any other reason withdraws from the responsibility of keeping the clinical trial records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

A copy of the trial data obtained via the analysis of the videos taken with the "study companion" tablets (the compliance report) will be maintained for a period of 25 years. By contrast, the images will not be maintained after the analysis is completed and the final compliance report is finalized.

## 11.6 INSURANCE

A certificate attesting third party coverage of CRO/GALDERMA R&D will be provided upon request.

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# 13 ATTACHMENTS

## 13.1 APPENDIX 1

# SCARS questionnaire
# (Self-assessment of Clinical Acne-Related Scars)

**RIGHT-HAND SIDE OF THE FACE**

**Part 1**
Please remove all make-up and facial jewellery/piercings, and tie back any loose hair covering your face before answering this questionnaire.
Please begin by answering the questions below. These questions will help you understand the difference between active acne and atrophic acne scars.

**a) Active acne includes zits, breakouts, pimples, whiteheads, and blackheads.**

When looking at the right-hand side of your face in the mirror right now, do you see **zits, breakouts, pimples, whiteheads, or blackheads**?

Yes / No *(please circle one)*

If yes, please **rate the severity** of the **zits, breakouts, pimples, whiteheads, or blackheads** on the right-hand side of your face by putting a vertical line in the place that best describes your acne.

No active acne — Very severe active acne

0 ——————————— 10

The following question asks you about **atrophic acne scars only**. Please **do not** consider active acne (zits, breakouts, pimples, whiteheads, or blackheads), scabs, or flat red or dark marks.

**b) Atrophic acne scars are indents or holes in the skin from previous active acne (not from injury, scratching or picking).**

When looking at the right-hand side of your face in the mirror right now, do you see **indents or holes** in the skin from previous active acne?

Yes / No *(please circle one)*
*If you answered "No" for this question, please go to page 4 to answer questions for the left-hand side of your face.*

If yes, please **rate the severity** of the **indents or holes** on the right-hand side of your face by putting a vertical line in the place that best describes your scars.


**Part 2**

The following questions ask you about **atrophic acne scars only**. Remember, atrophic acne scars are **indents or holes** in the skin from previous active acne. Please **do not** consider active acne (zits, breakouts, pimples, whiteheads, or blackheads), scabs, or flat red or dark marks.

Please read each question, then look in the mirror and think about the indents or holes on the **right-hand side of your face**, and then answer the question. Please mark an "X" in the box (☒) that best describes how the indents or holes on your face look **RIGHT NOW**.

There are no right or wrong answers to these questions. If you want to change your answer, please cross out your original answer and mark an "X" in the correct box.

Please choose only one response.

1. When looking at the right-hand side of your face in the mirror right now, how much of your face looks covered by indents or holes?

| Almost none of the right-hand side of face | A little of the right-hand side of face | Some of the right-hand side of face | A lot of the right-hand side of face | Almost all of the right-hand side of face |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

2. When looking at the right-hand side of your face in the mirror right now, how small or large do the individual indents or holes look?

| Very small | Small | Moderate | Large | Very large |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

3. When looking at the right-hand side of your face in the mirror right now, how many indents or holes do you see?

| Very few indents or holes | A few indents or holes | Some indents or holes | Quite a lot of indents or holes | Many indents or holes |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

4. When looking at the right-hand side of your face in the mirror right now, how deep do the individual indents or holes look?

| Not at all deep | A little deep | Moderately deep | Very deep | Extremely deep |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

5. When looking at the right-hand side of your face in the mirror right now, how visible are the indents or holes to you?

| Not at all visible | A little visible | Moderately visible | Very visible | Extremely visible |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

## LEFT-HAND SIDE OF THE FACE

**Part 3**

Please remove all make-up and facial jewellery/piercings, and tie back any loose hair covering your face before answering this questionnaire.

Please begin by answering the questions below. These questions will help you understand the difference between active acne and atrophic acne scars.

**a) Active acne includes zits, breakouts, pimples, whiteheads, and blackheads.**

When looking at the left-hand side of your face in the mirror right now, do you see **zits, breakouts, pimples, whiteheads, or blackheads**?

Yes / No *(please circle one)*

If yes, please **rate the severity** of the **zits, breakouts, pimples, whiteheads, or blackheads** on the left-hand side of your face by putting a vertical line in the place that best describes your acne.

No active acne — Very severe active acne

0 ——————————— 10

The following question asks you about **atrophic acne scars only**. Please **do not** consider active acne (zits, breakouts, pimples, whiteheads, or blackheads), scabs, or flat red or dark marks.

**b) Atrophic acne scars are indents or holes in the skin from previous active acne (not from injury, scratching or picking).**

When looking at the left-hand side of your face in the mirror right now, do you see **indents or holes** in the skin from previous active acne?

Yes / No *(please circle one)*
*If you answered "No" for this question, you have completed the questionnaire. Thank you for your time.*

If yes, please **rate the severity** of the **indents or holes** on the left-hand side of your face by putting a vertical line in the place that best describes your scars.

No indents or holes — Very severe indents or holes

0 ——————————— 10

**Part 4**

The following questions ask you about **atrophic acne scars only**. Remember, atrophic acne scars are **indents or holes** in the skin from previous active acne. Please **do not** consider active acne (zits, breakouts, pimples, whiteheads, or blackheads), scabs, or flat red or dark marks.

Please read each question, then look in the mirror and think about the indents or holes on the **left-hand side of your face**, and then answer the question. Please mark an "X" in the box (☒) that best describes how the indents or holes on your face look **RIGHT NOW**.

There are no right or wrong answers to these questions. If you want to change your answer, please cross out your original answer and mark an "X" in the correct box.

Please choose only one response.

1. When looking at the left-hand side of your face in the mirror right now, how much of your face looks covered by indents or holes?

| Almost none of the left-hand side of face | A little of the left-hand side of face | Some of the left-hand side of face | A lot of the left-hand side of face | Almost all of the left-hand side of face |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

2. When looking at the left-hand side of your face in the mirror right now, how small or large do the individual indents or holes look?

| Very small | Small | Moderate | Large | Very large |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

3. When looking at the left-hand side of your face in the mirror right now, how many indents or holes do you see?

| Very few indents or holes | A few indents or holes | Some indents or holes | Quite a lot of indents or holes | Many indents or holes |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

4. When looking at the left-hand side of your face in the mirror right now, how deep do the individual indents or holes look?

| Not at all deep | A little deep | Moderately deep | Very deep | Extremely deep |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

5. When looking at the left-hand side of your face in the mirror right now, how visible are the indents or holes to you?

| Not at all visible | A little visible | Moderately visible | Very visible | Extremely visible |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

***Thank you for your time.***

## 13.2 APPENDIX 2

# Subject satisfaction questionnaire – Part I

**INSTRUCTIONS:**

Please complete one questionnaire regarding the trial treatments you have been using in this trial. Please use a pen (not a pencil) to complete this questionnaire. Please give only ONE answer per question.

There are no "Right" or "Wrong" answers. If you are unsure how to answer a question, please give the best answer you can.

If you need to make a change, draw a line through the answer you would like to change, and then record your next response with a checkmark, put your initial and a date next to your correction.

Your answers will not affect your participation in the trial and no prejudice will be shown towards you for completing this document.

**A - Questions about the acne treatment applied every evening**
**Please answer for each side of your face.**

| | Left | Right |
|---|---|---|
| 1. How bothered were you by the treatment side effects? | | |
| Not bothered at all | [ ] | [ ] |
| Bothered somewhat | [ ] | [ ] |
| Bothered | [ ] | [ ] |
| Bothered a great deal | [ ] | [ ] |
| 2. How satisfied were you with the time it took for treatment to work? | | |
| Very satisfied | [ ] | [ ] |
| Satisfied | [ ] | [ ] |
| Somewhat satisfied | [ ] | [ ] |
| Not satisfied | [ ] | [ ] |
| 3. How satisfied were you with the effectiveness of the treatment? | | |
| Very satisfied | [ ] | [ ] |
| Satisfied | [ ] | [ ] |
| Somewhat satisfied | [ ] | [ ] |
| Not satisfied | [ ] | [ ] |
| 4. Overall, are you satisfied with the treatment? | | |
| Very satisfied | [ ] | [ ] |
| Satisfied | [ ] | [ ] |
| Somewhat satisfied | [ ] | [ ] |
| Not satisfied | [ ] | [ ] |

| | Left | Right |
|---|---|---|
| 5. Would you consider using this treatment again? | | |
| Yes | [ ] | [ ] |
| No | [ ] | [ ] |

6. Did you use the provided moisturizing lotion?

**[ ]** Yes
**[ ]** No

a. If yes, would you say (check as many answers as you wish)
**[ ]** The moisturizer helped to reduce stinging / burning sensations
**[ ]** The moisturizer helped you to be adherent to study treatments
**[ ]** The moisturizer helped to reduce feeling of skin dryness
**[ ]** The moisturizer was pleasant to use
**[ ]** None of the above

**B - Questions about <u>both</u> skin care products Cetaphil® DermaControl™ Oil Control Foam Wash and Cetaphil® DermaControl™ Oil Control Moisturizer SPF 30**

1. Both skin care products were easy to incorporate into a daily routine:

[ ] Strongly agree
[ ] Agree
[ ] Neither agree or disagree
[ ] Disagree
[ ] Strongly disagree

2. I would recommend both skin care products to my family or friends:

[ ] Strongly agree
[ ] Agree
[ ] Neither agree or disagree
[ ] Disagree
[ ] Strongly disagree

3. I felt - both skin care products helped my skin look healthier

[ ] Strongly agree
[ ] Agree
[ ] Neither agree or disagree
[ ] Disagree
[ ] Strongly disagree

4. Using both skin care products made for acne made me feel more confident

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

5. I felt - both skin care products made me feel more confident with my skin appearance

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

6. I felt – both skin care products helped make a positive difference in the appearance of my skin

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

7. I would keep using both skin care products

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

8. Both skin care products make my skin more hydrated

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

9. Both skin care products helped my skin to become less oily and less shiny

[ ] Strongly agree
[ ] Agree
[ ] Neither agree or disagree
[ ] Disagree
[ ] Strongly disagree

10. Both skin care products improved the texture of my skin

[ ] Strongly agree
[ ] Agree
[ ] Neither agree or disagree
[ ] Disagree
[ ] Strongly disagree

11. Both skin care products are pleasant to use

[ ] Strongly agree
[ ] Agree
[ ] Neither agree or disagree
[ ] Disagree
[ ] Strongly disagree

**C - Questions about the cosmetic product Cetaphil® DermaControl™ Oil Control Foam Wash**

1. The **Foam Wash** left my skin with a clean healthy feeling:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

2. The **Foam Wash** provided deep cleansing without stripping the skin's moisture:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

3. The **Foam Wash** rinsed off easily:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

4. The **Foam Wash** did not make my skin feel tight or dry:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

**D - Questions about the cosmetic product Cetaphil® DermaControl™ Oil Control Moisturizer SPF 30**

1. The **Moisturizer SPF 30** made my skin feel soft and smooth:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

2. The **Moisturizer SPF 30** improved my skin's texture:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

3. The **Moisturizer SPF 30** left my skin feeling hydrated and protected:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

4. The **Moisturizer SPF 30** provided a comforting sensation on the skin:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

***Thank you for your time.***

## 13.3 APPENDIX 3

# Subject satisfaction questionnaire – Part II

**INSTRUCTIONS:**

Please complete one questionnaire regarding the trial treatments you have been using in this trial. Please use a pen (not a pencil) to complete this questionnaire. Please give only ONE answer per question.

There are no "Right" or "Wrong" answers. If you are unsure how to answer a question, please give the best answer you can.

If you need to make a change, draw a line through the answer you would like to change, and then record your next response with a checkmark, put your initial and a date next to your correction.

Your answers will not affect your participation in the trial and no prejudice will be shown towards you for completing this document.

**A – Not Applicable**

**B - Questions about <u>both</u> skin care products Cetaphil® DermaControl™ Oil Control Foam Wash and Cetaphil® DermaControl™ Oil Control Moisturizer SPF 30**

1. Both skin care products were easy to incorporate into a daily routine:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

2. I would recommend both skin care products to my family or friends:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

3. I felt - both skin care products helped my skin look healthier

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree

[ ] Strongly disagree

4. Using both skin care products made for acne made me feel more confident

[ ] Strongly agree
[ ] Agree
[ ] Neither agree or disagree
[ ] Disagree
[ ] Strongly disagree

5. I felt - both skin care products made me feel more confident with my skin appearance

[ ] Strongly agree
[ ] Agree
[ ] Neither agree or disagree
[ ] Disagree
[ ] Strongly disagree

6. I felt – both skin care products helped make a positive difference in the appearance of my skin

[ ] Strongly agree
[ ] Agree
[ ] Neither agree or disagree
[ ] Disagree
[ ] Strongly disagree

7. I would keep using both skin care products

[ ] Strongly agree
[ ] Agree
[ ] Neither agree or disagree
[ ] Disagree
[ ] Strongly disagree

8. Both skin care products make my skin more hydrated

[ ] Strongly agree
[ ] Agree
[ ] Neither agree or disagree
[ ] Disagree
[ ] Strongly disagree

9. Both skin care products helped my skin to become less oily and less shiny

[ ] Strongly agree
[ ] Agree
[ ] Neither agree or disagree
[ ] Disagree
[ ] Strongly disagree

10. Both skin care products improved the texture of my skin

[ ] Strongly agree
[ ] Agree
[ ] Neither agree or disagree
[ ] Disagree
[ ] Strongly disagree

11. Both skin care products are pleasant to use

[ ] Strongly agree
[ ] Agree
[ ] Neither agree or disagree
[ ] Disagree
[ ] Strongly disagree

**C - Questions about the cosmetic product Cetaphil® DermaControl™ Oil Control Foam Wash**

1. The **Foam Wash** left my skin with a clean healthy feeling:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

2. The **Foam Wash** provided deep cleansing without stripping the skin's moisture:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

3. The **Foam Wash** rinsed off easily:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

4. The **Foam Wash** did not make my skin feel tight or dry:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

**D - Questions about the cosmetic product Cetaphil® DermaControl™ Oil Control Moisturizer SPF 30**

1. The **Moisturizer SPF 30** made my skin feel soft and smooth:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

2. The **Moisturizer SPF 30** improved my skin's texture:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

3. The **Moisturizer SPF 30** left my skin feeling hydrated and protected:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

4. The **Moisturizer SPF 30** provided a comforting sensation on the skin:

   [ ] Strongly agree
   [ ] Agree
   [ ] Neither agree or disagree
   [ ] Disagree
   [ ] Strongly disagree

***Thank you for your time.***