Subject Reported Outcomes with use of Adapalene 0.3% - Benzoyl peroxide 2.5% in Moderate to Severe Acne in Dark Skin Phototype subjects

NCT Number: NCT02932267

Date: 23 March 2017

CLINICAL TRIAL PROTOCOL

PROTOCOL NUMBER: RD.03.SPR.110232

CONFIDENTIAL

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TITLE PAGE

Title: Subject Reported Outcomes with use of Adapalene 0.3% - Benzoyl peroxide 2.5% in Moderate to Severe Acne in Dark Skin Phototype subjects		
Project Name:	**Project Number:**	**Clinical Trial Phase:**
Epiduo® Forte gel / TactuPump™ Forte gel	816	IV

EUDRACT NUMBER: N/A

IND NUMBER: IND067801

Version Number: 03

Sponsor Contact details:

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For any urgent medical questions, including safety reasons, please use the contact details provided in Section 8.2.2

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 *GALDERMA R&D* employees involved in the conduct of the trial.

SPONSOR PERSONNEL		
Name/Title	**Affiliation/Address/Tel./Fax**	**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, [redacted]	Responsible for medical management and safety surveillance
[redacted]	GALDERMA R&D SNC, Same as above [redacted]	Responsible for the Phase IV group
[redacted]	GALDERMA R&D SNC, Same as above [redacted]	Clinical Operation Manager for the Phase IV group
[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
[redacted]	GALDERMA R&D SNC, Same as above [redacted]	Responsible for the management of all clinical supplies activities
[redacted]	GALDERMA US Fort Worth [redacted]	Responsible for safety surveillance

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 subject's electronic Case Report Forms (eCRFs) in a timely manner on an ongoing basis.
- Use the investigational product(s) 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 *GALDERMA R&D*.
- Allow authorized 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.

SIGNATURE

PRINCIPAL INVESTIGATOR

PRINTED NAME:

SIGNATURE DATE

SIGNATURE **DATE**

GALDERMA R&D

[redacted]

RETURN THE ORIGINAL SIGNED COPY TO G*ALDERMA R&D* AND KEEP A COPY AT YOUR SITE

DISTRIBUTION

Copy of the Protocol:

All signatories and,

[redacted], GALDERMA R&D
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[redacted], GALDERMA Fort Worth US
[redacted], GALDERMA USA Ldta.
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[redacted], GALDERMA Mauritius
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[redacted], GALDERMA International
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[redacted], GALDERMA Medical Affairs
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[redacted], GALDERMA R&D
[redacted], Galderma Laboratories, L.P. USA
[redacted], Regulatory Affairs, Galderma Laboratories, L.P. USA

Copy of the Synopsis:

[redacted], GALDERMA R&D

[redacted] GALDERMA Marketing

[redacted], GALDERMA International

[redacted], GALDERMA R&D SNC

Original Protocol:

Archives (GALDERMA R&D Sophia Antipolis)

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse Event
APT	All Subjects Treated (Safety Population)
BPO	Benzoyl peroxide
CDMS	Clinical Data Management System
CPM	Clinical Project Manager
CRA	Clinical Research Associate
CRO	Contract Research Organization
CTD	Clinical Trial Dossier
DLQI	Dermatology Life Quality Index questionnaire
cDLQI	Children's Dermatology Life Quality Index questionnaire
DMP	Data Management Plan
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FSI	First Subject In *(first subject who signs the Informed Consent Form)*
GAI	Global Assessment of Improvement
GBU	Global Business Unit
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICDRG	International Contact Dermatitis Research Group
i.e.	That is (Latin: id est)
IEC	Independent Ethic Committee

Abbreviation	Term
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator Site File
IUD	Intra Uterine Device
IU/L	International Unit/Liter
ITT	Intent-To-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
LOCF	Last Observation Carried Forward
LSI	Last Subject In (Last subject randomized/assigned to treatment)
LSO	Last Subject Out (Last subject who completed its last clinical trial visit)
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
OTC	Over-The-Counter
PIH	Post-Inflammatory Hyperpigmentation
PRO	Patient Reported Outcome
R&D	Research & Development
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System (SAS Institute Inc., Cary, NC)
SIN	Subject Identification Number
SOC	System Organ Class
SOP	Standard Operating Procedure
SPF	Sun Protection Factor
UPT	Urine Pregnancy Test
USA	United State of America
UV	Ultraviolet
W	Week

1. SYNOPSIS

Clinical trial title: **Subject Reported Outcome with use of Adapalene 0.3% - benzoyl peroxide 2.5% in moderate to severe acne in Dark Skin Phototype subjects**		
Short title (± acronym): **Subject Reported Outcome in Dark Skin Phototype subjects with acne**		
Project number: 816	**Clinical trial phase:** IV	**Clinical trial period** Q1 2017 – Q4 2017
Objective(s):	The main objective of this trial is to evaluate subject reported outcomes with a fixed combination treatment containing Adapalene 0.3% - Benzoyl Peroxide (BPO) 2.5%, in the treatment of moderate to severe acne vulgaris in dark skin phototypes (IV to VI). The safety of the treatment will also be evaluated.	
Methodology:	This is a multicenter open-label, prospective trial in subjects with dark skin from one of the 3 ethnic/race backgrounds: Asian, Latin American and Black/African-American and with moderate to severe acne vulgaris on the face. All eligible subjects will receive Adapalene 0.3% - BPO 2.5% gel (Epiduo® Forte/TactuPump™Forte) once daily on whole face. **One third** of subjects should have dark skin with **Asian** ethnic/race background. **One third** of subjects should have dark skin with **Latin American** ethnic/race background. **One third** of subjects should have dark skin with **Black/African-American** ethnic/race background In each ethnic/race backgrounds at least **one third** of subjects should have "Severe acne" severity (IGA 4) and **two third** "Moderate acne" severity (IGA 3).	
Total number of planned subjects:	Approximately 60 subjects will be enrolled	
Total number of planned sites:	4 sites	
Approximate number of subjects/site:	Approximately 10 to 20 subjects per site	
Country(ies) involved:	Mauritius, Singapore and USA	
Population and main inclusion criteria:	Male or female subjects with moderate to severe acne vulgaris, aged at least 12 years old inclusive with dark skin phototypes IV to VI meeting specific inclusion/ exclusion criteria.	
Clinical trial duration per subject	16 weeks, with 5 trial visits	
Number of visits:	Baseline, W2, W8, W12 and W16	
Investigational product:		
Name:	Epiduo® Forte / TactuPump™ Forte (CD0271 0.3% / CD1579 2.5%)	
Pharmaceutical form:	Gel	
Dose/concentration:	Adapalene 0.3% - BPO 2.5%	
Total daily dose:	4 pea-sized amounts (to cover whole face, e.g. one on the forehead, one on the chin and one on each cheek),	
Mode and frequency of administration:	Topical, once daily in the evening after washing	
Location of treated area:	Whole face	
Duration of treatment:	16 weeks	

<table>
<tr><td colspan="3">Clinical trial title:
Subject Reported Outcome with use of Adapalene 0.3% - benzoyl peroxide 2.5% in moderate to severe acne in Dark Skin Phototype subjects</td></tr>
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Subject Reported Outcome in Dark Skin Phototype subjects with acne</td></tr>
<tr><td>Project number:
816</td><td>Clinical trial phase:
IV</td><td>Clinical trial period
Q1 2017 – Q4 2017</td></tr>
<tr><td>Non-investigational product to be provided for the clinical trial:</td><td colspan="2">Cetaphil® DermaControl™ Oil control Foam Wash twice daily in the morning and in the evening)

Cetaphil® DermaControl™ Oil control Moisturizer SPF 30 once daily in the morning after washing (using Cetaphil® DermaControl™ Oil control Foam Wash) and to re-apply if sun exposure during the day.

Both products are topical and will be used on the whole face for 16 weeks</td></tr>
<tr><td>Measurement criteria</td><td colspan="2">Subject-reported outcomes
• Dermatology Life Quality Index questionnaire (DLQI) or Children's Dermatology Life Quality Index (cDLQI) questionnaires at Baseline, Week 12 and at Week 16/Early termination
• Subject satisfaction questionnaire at Week 12 and Week 16/Early termination

Efficacy
• Investigator's Global Assessment (IGA): acne severity of the face on a scale from 0 (Clear) to 4 (Severe) at each visit
• Investigator's Global Assessment of Improvement from baseline (GAI): improvement compared with baseline on a scale from 0 (Excellent improvement) to 5 (Worse) at Week 12 and Week 16/Early termination

Safety
• Post-inflammatory hyper-pigmentation (PIH) severity at each visit (if present at Baseline)
• Local tolerance (erythema, scaling, dryness, stinging/ burning): severity score on a scale from 0 (None) to 3 (Severe) at each trial visit
• Adverse Events throughout the trial

Other
• Photographs (visible light photos) at each visit
• Cosmetic acceptability questionnaire regarding the non-investigational products, at Week 16/Early termination</td></tr>
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<tr><td>Project number:
816</td><td>Clinical trial phase:
IV</td><td>Clinical trial period
Q1 2017 – Q4 2017</td></tr>
<tr><td>Analysed variables</td><td colspan="2">Subject-reported outcomes
• DLQI/cDLQI at Baseline and at each evaluation time
• Subject satisfaction questionnaire at each evaluation time

Efficacy variable
• IGA score: % of subjects across scores at each visit
• GAI score: % of subjects across scores at Week 12 and last visit

Safety variables
• PIH severity: Raw value at each visit and % change from baseline at each post-baseline visit
• Local tolerance: Raw value at each visit and worst-score across visit, % of Subjects across scores at each post-baseline visit
• Incidence of adverse events

Other
• Cosmetic acceptability questionnaire at Week 16/Early termination</td></tr>
<tr><td>Principal statistical methods and sample size calculation:</td><td colspan="2">The Intent-to-Treat (ITT) population consists of all enrolled subjects. The safety population (APT) consists of the ITT population, after exclusion of subjects who never took the treatment. Population definitions will be decided before the database lock.

The objective of this trial is to evaluate the subject reported outcome with Adapalene 0.3% - BPO 2.5% gel during 16 weeks of treatment.

No inferential statistics will be performed. All variables will be descriptively summarized on ITT population and on APT population for the safety variables. The last observation carried forward (LOCF) method will be used to impute missing efficacy values.

As no inferential statistics will be performed, no statistical rationale of sample size can be used. However, the subject reported outcomes (quality of life and satisfaction survey), can be evaluated with a total of 60 subjects.</td></tr>
</table>

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 (Usatine R.P., 1998) (Leyden J J., 1995). Skin of color patients (typically Fitzpatrick skin types IV–VI) are no exception as shown in an epidemiological trial (Alexis A.F., 2007) that the diagnosis of visits from patients of different racial/ethnic backgrounds seen at a hospital-based dermatology practice in New York City were compared and acne was the most common reason for visits for both African American (28.4%) and Caucasian (21%) patients. It is the sequelae of the disease that are the distinguishing characteristics of acne in skin of color, namely Post Inflammatory Hyperpigmentation (PIH) or hypertrophic scarring.

Currently, it is believed that acne in skin of color develops largely by the same pathogenesis that occurs in Caucasian patients. However, there is controversy over whether differences exist in certain biological characteristics of skin (such as sebum production and bacterial colonization) among various racial/ethnic groups. Several studies have been published evaluating racial/ethnic differences in sebaceous gland size and activity compared to Caucasians. (Kligman A.M., Shelley W.B. 1958) (Pochi P.E., Strauss JS. 1988). However, results have been contradictory. The trial evaluated 18 African-American and 19 Caucasian patients for differences in certain skin surface properties, such as sebum level, pH, moisture content, and barrier function and found no significant differences in sebum production between African-American and Caucasian patients. Another trial (Warrier A.G., 1996) examined facial skin microflora in 30 African-American and 30 Caucasian women. The authors found a higher density of P. acnes in African-American patients compared to Caucasian patients; however, the results were not statistically significant. As acne is a chronic and relapsing disease normalizing follicular desquamation is then the key to achieve and maintain control of acne. Today it is established that retinoids such as Adapalene aid the differentiation and reduction of keratinocytes.

Adapalene with Benzoyl Peroxide (BPO) is a unique antibiotic-free combination of Adapalene, a well-tolerated and efficacious topical retinoid, and BPO, a well-established antimicrobial agent. The complementary modes of action, efficacy and safety profiles of these two agents make Adapalene-BPO the most logical choice for once-daily treatment for all types of acne but the most severe. Adapalene possesses anti-comedogenic, comedolytic, and anti-inflammatory properties, whereas BPO, the most potent bactericidal agent, is more effective than topical antibiotics against P. acnes. (Brown J.M., Poston S.M. 1983) (Eady E.A., Cove J.H., Holland K.T., Cunliffe W.J. 1989) (Leyden J.J., 1983) (Lucky, A. W., 1987).

Adapalene 0.3% - BPO 2.5% gel is efficacious to treat moderate to severe acne with a trend of superiority compared to other topical preparations in subjects with severe acne (Stein Gold L., 2010). This suggests that the combination Adapalene - BPO both prevents the formation of new acne by reducing the number of primary and secondary lesions. However, it is also important to assess the local tolerability in terms of skin irritation and other skin barrier impairments in dark skin phototypes that might be caused by the treatment or by acne it-self.

Maintaining skin hydration and avoiding sun exposure is recommended as part of the skin care regimen in acne patients. Minimizing skin irritation and photo-protection can be achieved by the use of non-comedogenic moisturizers with appropriate SPF that hydrate and protect the skin from UV irradiation (Schorr E.S., 2012) (Whitney P., Bowe M.Da. 2014) (Del Rosso, J. Q., 2013) (Zeichner, J., 2011). Using an appropriate cleanser will reduce oil on the face and will not affect skin hydration or the skin barrier function.

Acne can persist for years and may affect seriously the psychosocial development, resulting in emotional problems, withdrawal from society, and depression (Koo , J Y et Smith, L L. 1991).If not treated, acne may cause serious physical and emotional scarring and can significantly impact the quality of life of those affected by the disease (Brown J.M., Poston S.M. 1983) (Usatine, R.P., 1998) Therefore this trial aims to evaluate acne medication for assessment of subject satisfaction and quality of life in the dark skin subjects known to be sensitive with topical retinoids. The local tolerance of the treatment regimen in terms of erythema, scaling, dryness, stinging/burning will also be evaluated.

This clinical trial is designed to evaluate the patient reported outcome with use of Adapalene 0.3% - BPO 2.5% gel (Epiduo® Forte/TactuPump™ Forte) in subjects with dark phototype with moderate to severe acne vulgaris and also to assess this sub-population which was not specifically evaluated during the clinical development of Adapalene 0.3% - BPO 2.5% gel.

2.2. INVESTIGATIONAL PRODUCT PROFILE

The product used in this clinical trial (Adapalene 0.3% - BPO 2.5% gel) is marketed under the name Epiduo® Forte in USA and TactuPump™ Forte in Canada. TactuPump™ Forte is used for for sites in Mauritius and Singapore. Adapalene 0.3% - BPO 2.5% gel is well tolerated in subjects with acne vulgaris. See product monograph for detailed safety information.

2.3. RISK/BENEFIT ASSESSMENT

2.3.1. Risk-benefit statement related to the clinical trial products

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

2.3.2. Risk-benefit statement related to the clinical trial

Adapalene 0.3% - BPO 2.5% gel is an established and widely used marketed product and considered standard of care by many physicians and expert bodies for the treatment of acne vulgaris. It is therefore considered that exposure to the treatment over 4 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 Epiduo® Forte / TactuPump™ Forte gel include mild to moderate application site reactions, such as skin irritation characterized by scaling, dryness, erythema, atopic dermatitis, eczema, and burning/stinging. These reactions usually occur early in the treatment, and tend to gradually lessen over time.

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 method will be conducted during this trial.

Subjects will be followed (especially for Adverse events) regularly during all the trial, approximately once a month for 4 months.

Consequently, based on available safety data and the proposed trial design, no safety issues other than those reported by the labelling are expected following topical administration of Adapalene 0.3% - BPO 2.5% gel.

3. CLINICAL TRIAL OBJECTIVES AND CLINICAL HYPOTHESIS

3.1. CLINICAL TRIAL OBJECTIVES

The purpose of this trial is to evaluate subject reported outcomes with the combination of Adapalene 0.3% - BPO 2.5%, Epiduo® Forte / TactuPump™ Forte gel, after 16 weeks of treatment of moderate to severe acne in dark skin phototypes (IV to VI).

3.2. CLINICAL HYPOTHESIS

The trial hypothesis is that daily acne treatment with Epiduo® Forte / TactuPump™ Forte is well tolerated as a treatment in moderate to severe acne in dark phototypes and improves subject's quality of life.
This trial has been designed to provide evidence in support of this hypothesis.

4. SELECTION AND DISPOSITION OF CLINICAL TRIAL POPULATION

4.1. NUMBER OF SUBJECTS

Approximately 60 subjects presenting moderate to severe acne vulgaris with dark skin phototype will be enrolled at 1 site located in Mauritius, 2 sites in USA and 1 site in Singapore.

One third of subjects should have dark skin with **Asian** ethnic/race background.

One third of subjects should have dark skin with **Latin American** ethnic/race background.

One third of subjects should have dark skin with **Black/African-American** ethnic/race background.

In each ethnic/race backgrounds (Asian, Latin American and Black/African-American) approximately one third of subjects **at least** should have "Severe acne" and two third "Moderate acne".

4.2. CLINICAL TRIAL POPULATION

Male or female subjects with a dark skin phototype of any ethnic background (Asian, Latin American and/or Black /African) with a diagnosis of moderate to severe acne vulgaris on the face and meeting the following specific eligibility criteria.

4.3. INCLUSION CRITERIA

1. Male or female subject of one of the 3 ethnic background (see Inclusion **criterion # 4**) of at least 12 years old inclusive,

2. Subject with clinical diagnosis of moderate to severe facial acne vulgaris, defined by:

    a) Investigator's Global Assessment (IGA) score of 3 (Moderate) **OR** 4 (Severe); and

    b) A minimum of 25-100 inflammatory lesions (papules and pustules); and

    c) A minimum of 30-150 non-inflammatory lesions (open and closed comedones) in total (excluding the nose); and

    d) No more than two acne nodules (≥ 1 cm),

3. Subject with skin phototype IV to VI (according to T.B. Fitzpatrick skin phototype [i.e IV-burns minimally; always tans well (moderate brown); V – rarely burns; tans profusely (dark brown; VI – never burns; deeply pigmented (black) tans profusely)]),

4. Subjects from one of the 3 ethnic/race backgrounds: Asian, Latin American and Black/African-American,

5. Female subjects of childbearing potential must have a negative urine pregnancy test (UPT) at Baseline visit (Visit 1),

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. Females of non-childbearing potential, e.g. Premenses, Post-menopausal (absence of menstrual bleeding for 1 year without any other medical reason), hysterectomy, or bilateral oophorectomy,

8. Subject having read, understood and signed the approved Informed Consent Form (ICF) prior to any participation in the clinical trial. Subject under the age of 18 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. Subject must be willing to be photographed. Subject (and parents/guardian if subject is under 18 years of age) must be willing to sign a Photography Release Consent Form,

4.4. EXCLUSION CRITERIA

Any subject who meets at least one of the following criteria will not be eligible for the trial.

1. Subject with severe acne (IGA > 3) with more than 2 nodules, cysts, or extra-facial lesions,

2. Subject with acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.), nodulo cystic acne, acne requiring systemic treatment,

3. Subject with history of lupus, atopic dermatitis, perioral dermatitis, dermatomyositis, rosacea on the face

4. Prior failure to treatment with Epiduo® Forte/TactuPump™ Forte gel (Adapalene 0.3% - BPO 2.5%),

5. Subject with damaged facial skin (e.g. tattoo, cuts, skin abrasion , eczema or sunburned skin),

6. Subjects with skin phototype < IV,

7. Female subject who is pregnant, lactating or planning a pregnancy during the trial,

8. Female Taking Diane-35 or who is planning to change her contraceptive method or hormone replacement therapy during the trial,

9. Subject with known impaired hepatic or renal functions,

10. Subject with a wash-out period for **topical treatment** or procedures on the face less than:

Topical treatments: Corticosteroids, antibiotics, benzoyl peroxide, azelaic acid, dapsone, hydroxyacids, Zinc containing treatments, , antiseptics, other anti-inflammatory products or other acne treatments (for example salicylic acid treatments/ transdermal contraceptives are forbidden if used to treat acne)	2 weeks
Retinoids	4 weeks
Cosmetic/aesthetic procedures on the face (e.g., comedone extraction, desquamating, or abrasive agents, adhesive cleansing strips)	1 week
Wax epilation	2 weeks
Photodynamic therapy	6 weeks
Laser therapy, microdermabrasion, deep chemical peel, plastic surgery for acne	3 months

11. Subject with a wash-out period for **systemic treatment** less than:

• Corticosteroids, (except locally acting corticosteroids such as inhaled or intrathecal or dermal application at distance from the face), tetracyclines, other antibiotics (except penicillin)	1 month
• Oral retinoids/isotretinoin/ anti-androgens / Cyproterone acetate / Chlormadinone acetate	6 months
• Spironolactone/ Drospirenone (except if at a stable dose for at least 3 months for drospirenone)	3 months
• Immunomodulators	3 months
• Oral contraceptives/ oral dapsone for acne	1 month

12. Subjects with severe PIH (Score > 3 on PIH scale),

13. Subject with active or chronic skin allergies,

14. Subject with known or suspected allergy to the investigational product (See Product Monograph for Epiduo® Forte / TactuPump™ Forte gel),

15. Subject who has used tanning booths or lamps or had excessive ultraviolet (UV) radiation exposure within 1 month prior to clinical trial entry or foresees intensive UV exposure during the trial (mountain sports, sailing, sunbathing, etc.),

16. Subject who is at risk in terms of precautions, warnings, and contraindications (see Product Monograph for Epiduo® Forte/TactuPump™ Forte gel),

17. Subject with a beard or other facial hair that might interfere with trial assessments,

18. Subject with an acute / chronic disease, uncontrolled systemic disease or a history of major medical or psychiatric condition or surgical interventions that, in the opinion of the investigator, might put the subject at risk,

19. Subject under guardianship, hospitalized subject in a public or private institution for a reason other than the research, and subject deprived of his/her freedom,

20. Subject who has participated in another investigational product or device research trial within 30 days prior to enrolment OR is in an exclusion period from a previous clinical trial,

21. Subject who is unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.

4.5. PRIOR AND CONCOMITANT THERAPIES

4.5.1. Definition

Previous therapies (products and/or procedures) are defined as therapies that have been stopped within 6 months preceding baseline visit and prior to the first investigational product application 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 baseline visit (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 baseline visit (first investigational product application).

4.5.2. Categories

The following two categories will be considered for previous and concomitant therapies:

- Products/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.

4.5.3. Recording

Previous and concomitant therapies will 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 electronic case report form (eCRF).

Concomitant therapies will be recorded, reviewed, and updated at each trial visit.

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.

4.5.4. Authorized therapies during the clinical trial

Unless listed under the Exclusion Criteria above (see section 4.4, criteria 10 and 11) or in Prohibited Therapies (see section below 4.5.5), all therapies are authorized.

Subject must use the provided moisturizer and cleanser as required for the symptomatic relief of skin dryness or irritation (use of moisturizer with sunscreen and cleanser other than the provided ones must be recorded in 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 final trial assessments.

Also subjects should be instructed to avoid excessive sun-exposure wind and cold. Cosmetics are to be used minimally and not at all during evaluation visit or photography of the skin.

4.5.5. 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 4.4, criteria 10 and 11),
- 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 at the investigator's judgement are liable to interfere or interact with the efficacy and the safety of Epiduo® Forte / TactuPump™ Forte® gel.

If prohibited therapies become a necessary treatment for the safety or best interest of the subject, *GALDERMA R&D* 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.

4.5.6. 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 (e.g. if a subject discontinues **after** week 2, complete the week 8 visit procedures). Additional final procedures will be conducted for all premature discontinuation 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 enrolled and assigned a kit 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 will be made available to the sponsor.

Reasons for clinical trial completion/discontinuation, as listed on the Exit Form of the eCRF are described below:

Normal trial Completion	Subject completes the clinical trial as planned in the protocol
Pregnancy	Withdraw the subject from the clinical trial following the procedure described in the protocol section 8.2.3.1
Lack of efficacy	Investigator judgment only: based on therapeutic/disease-state expectations. If subject opinion only, mark "withdrawal by subject" and document it in the comment section of the eCRF Exit Form
Adverse Event	Complete eCRF Adverse Event Form
Withdrawal by subject	Includes consent withdrawal, subject relocation, schedule conflicts, etc… Does not include AE. . 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	Confirm 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. Explain the reason for discontinuation in the comments section of eCRF Exit Form.

If reason for discontinuation is "withdrawal by subject" 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

This clinical trial will be conducted as a multi-centre, open-label prospective trial involving subjects aged at least 12 years old inclusive with dark skin type phototype IV to VI from one of the 3 ethnic/race backgrounds: Asian, Latin American and Black/African-American with moderate to severe acne vulgaris on the face and meeting other specific eligibility criteria.

Approximately 60 subjects will be enrolled in 4 sites located in Mauritius, USA and Singapore. 20 subjects are planned from each site.

One third of subjects should have dark skin with **Asian** ethnic/race background:
One third of subjects should have dark skin with **Latin American** ethnic/race background:
One third of subjects should have dark skin with **Black/African-American** ethnic/race background:

In each ethnic/race backgrounds (Asian, Latin American and Black/African-American) approximately **one third** of subjects should have "Severe acne" (IGA 4) and **two third** "Moderate acne" severity (IGA 3).

All eligible subjects will receive Adapalene 0.3% - BPO 2.5% gel (Epiduo® Forte / TactuPump™ Forte gel) once daily on the whole face.
There will be 5 trial visits: at baseline, week 2 (± 1 day), week 8 (± 3 days), week 12 (± 3 days), and week 16 (±5 days).

5.2. DISCUSSION OF CLINICAL TRIAL DESIGN

This clinical trial will assess subject reported outcomes with a product marketed in USA under the name Epiduo® Forte gel and TactuPump™ Forte gel in Canada, used according to its labeling information (indication, selected population, dose regimen). Therefore, this trial will be classified as Phase IV study in USA. Meanwhile, as this product is not marketed in Mauritius and Singapore (CTD recently submitted) therefore this trial is classified as a Phase IIIb trial for Mauritius and Singapore.

According to clinical studies performed with Epiduo® in acne, 3 months treatment is sufficient to treat acne. As this trial aims to treat moderate to severe acne consequently, treatment period is fixed to 4 months as a maximum in order to have a complete cure of acne.

Since acne is a chronic and long-lasting skin condition which could affect seriously the psychosocial development resulting in emotional problems it is deemed important to evaluate subjects' quality of life before and after treatment.

For this subjects will complete DLQI or cDLQI for children, at baseline, Week 12 and at last trial visit.

A satisfaction questionnaire on use of the investigational product will be completed by subjects at Week 12 and at end of the trial.

An acceptability questionnaire on use of the non –investigational products will also be completed by subjects at end of the trial.

This clinical trial should allow evaluation of subjects' reported outcome after use of the investigational product Adapalene 0.3% - BPO 2.5%.

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 11 months. The end date of the clinical trial will be the date of the last visit of the last subject who participates in the clinical trial.

The planned duration of recruitment (i.e. From FSI to Last Subject In (LSI)) is approximately 7 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 the clinical trial site(s) with appropriate notification.

The expected duration of subject participation is 16 weeks.

5.4. CLINICAL TRIAL FLOW CHART

PROCEDURES	CLINICAL TRIAL VISITS				
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
	Baseline	**Week 2** (±1 d)	**Week 8** (±3 d)	**Week 12** (±3 d)	**Week 16** (±5 d)
Informed consent/Photography Consent[b]	X				
Inclusion/Exclusion Criteria	X				
Demographics/ Relevant medical history/ Prior therapies[c]	X				
Urine Pregnancy test (UPT)[d]	X		X	X	X
Investigator's Global Assessment (IGA)	X	X	X	X	X
Global Assessment of Improvement				X	X[a]
PIH evaluation[e]	X	X	X	X	X
Local tolerance assessment	X	X	X	X	X
Photographs[b]	X[h]	X	X	X	X
Concomitant therapies	X	X	X	X	X
Adverse events[f]	X	X	X	X	X
Dispensation of investigational products	X		X		
Dispensation of non-investigational products	X		X		
Return of investigational products			X		X
Subject Diary/Compliance[g]		X	X	X	X
DLQI-cDLQI questionnaire	X			X	X[a]
Subject satisfaction questionnaire				X	X[a]
Cosmetic acceptability questionnaire					X[a]
Exit form					X[a]

a. To be performed at Week 16 or before in case of early termination.
b. Photography consent and standardized photography (mandatory criteria for inclusion in the trial).
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 CRF.
d. UPT will have sensitivity down to at least 25 IU/L for hCG. UPT is mandatory at baseline, week 8, week 12 and week 16/early termination in female subjects
e. If PIH present at baseline visit.
f. Adverse event onsets after subject signature of the informed consent form should be recorded on the AE Form of the CRF.
g. Subject diary is a diary which will be given to the subject to report the treatment application
h. Sponsor Medical Expert will review the clinical evaluation of acne and give his confirmation for inclusion of subjects into the trial.

5.5. CLINICAL TRIAL VISIT DESCRIPTION AND PROCEDURES

5.5.1. Visit 1 – Baseline visit

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 required 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. 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,
6. Inform subject about authorized and prohibited concomitant therapies,
7. Check inclusion/exclusion criteria (see sections 4.3 and 4.4),
8. Log into the IVR/IWR System to check the inclusion rate in terms of balance in ethnic/race background and acne severity,
9. Conduct a urine pregnancy test (UPT) for female subjects of childbearing potential,
10. Log into the eCRF to get a Subject Identification Number (SIN),
11. Perform an Investigator's Global Assessment (IGA) of the whole face (see section 7.2.1),
12. Assess the Post-Inflammatory Hyperpigmentation (PIH) severity if any (see section 7.3.1),
13. Perform the baseline Local Tolerability Assessment (erythema, scaling dryness and stinging/burning; see section),

    Note: *Stinging/burning at the baseline visit should* ***NOT*** be *assessed at baseline,*
14. Take photographs of the face according to the provided procedure (subject and parent/guardian should accept through the approved ICF),
15. 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,
16. If the subject is eligible, assign a kit number (see specific section 0) (to be reported on the prescription form),
17. Fill in a prescription form with the Subject's Identification Number,
18. The Product Dispenser (person in charge of products dispensation) will:

a. Dispense to the subject the baseline investigational product from the adequate subject kit according to the Prescription Form,
b. Affix the tear-off portion of the label 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. Provide appropriate verbal and written instructions on how to properly use the investigational product. The **first application** of investigational product will be conducted by the subject under the direction of the Product Dispenser **before** leaving the investigational site,
f. Remind the subject to not to apply the investigational product the first evening,
g. Dispense a subject Diary and provide verbal instruction on how to complete the Diary after each product application,
h. Emphasize the importance of complying with the given instructions and treatments, instruct the subject to bring back the subject's diary at the next visit,
i. For all female subjects, emphasize the guidelines about contraception and risks in case of pregnancy,

19. Ask the subject to complete baseline DLQI/cDLQI questionnaire,
20. Schedule the next follow up visit in two weeks ± 1 day.

5.5.2. Visit 2 (week 2) (±1 Day)

1. Question the subject about occurrence of adverse events (AEs) and 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. Perform an Investigator's Global Assessment (IGA) of the whole face (see section 7.2.1).
4. Assess the Post-Inflammatory Hyperpigmentation (PIH) severity if present at baseline (see section 7.3.1),
5. Perform Local Tolerability Assessment (erythema, scaling dryness and stinging/burning; see Section 7.3.2),
6. Take photographs of the face according to the provided procedure,
7. The Product Dispenser will:
    a. Check the returned subject's diary and interview the subject about compliance (number of missed trial product applications),

b. Emphasize again the importance of complying with the given instructions and treatments; instruct the subject to bring back the dispensed investigational product together with the subject's diary at the next visit,

c. For all female subjects, emphasize the guidelines about contraception and risks in case of pregnancy,

8. Schedule the next follow up visit, visit 3 (week 8) 8 weeks after Baseline visit ± 3 days.

5.5.3. Visit 3 (week 8) (±3 Days)

1. Question the subject about occurrence of adverse events (AEs) and 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. Perform an Investigator's Global Assessment (IGA) of the whole face (see section 7.2.1).
5. Assess the Post-Inflammatory Hyperpigmentation (PIH) severity if present at baseline (see section 7.3.1),
6. Perform Local Tolerability Assessment (erythema, scaling dryness and stinging/burning; see section 7.3.2),
7. Take photographs of the face according to the provided procedure,
8. The Product Dispenser will:
    a. Check the returned investigational product, the subject's diary and interview the subject about compliance (number of missed trial Products applications),
    b. Dispense from the subject kit the applicable visit treatment box,
    c. Affix the tear-off portion of the label on the Product Dispensation Log,
    d. Dispense to the subject the associated non-investigational clinical trial product with explanations how and when to use them,
    e. Emphasize again the importance of complying with the given instructions and treatments; instruct the subject to bring back the subject's diary at the next visit,
    f. For all female subjects, emphasize the guidelines about contraception and risks in case of pregnancy,
9. Schedule the next follow up Visit 4 (week 12), 12 weeks after Baseline visit ± 3 days.

5.5.4. Visit 4 (week 12) (±3 Days)

1. Question the subject about occurrence of adverse events (AEs) and 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. Perform an Investigator's Global Assessment (IGA) of the whole face (see section 7.2.1).
5. Evaluate Global Assessment of Improvement of acne **versus baseline** (see section7.2.2),
6. Assess the Post-Inflammatory Hyperpigmentation (PIH) severity if present at baseline (see section7.3.1),
7. Perform Local Tolerability Assessment (erythema, scaling dryness and stinging/burning; see Section7.3.2),
8. Take photographs of the face according to the provided procedure,
9. The Product Dispenser will:
    a. Check the subject's diary and interview the subject about compliance (number of missed trial products applications),
    b. Emphasize again the importance of complying with the given instructions and treatments; instruct the subject to bring back the dispensed investigational product together with the subject's diary at the next visit,
    c. For all female subjects, emphasize the guidelines about contraception and risks in case of pregnancy,
10. Ask the subject to complete Week 12 DLQI/cDLQI questionnaire,
11. Ask the subject to complete Subject Satisfaction questionnaire.

5.5.5. Visit 5 (week 16) (±5 Days)

1. Question the subject about occurrence of adverse events (AEs) and 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. Perform an Investigator's Global Assessment (IGA) of the whole face (see section 7.2.1),
5. Evaluate Global Assessment of Improvement of acne **versus baseline** (see section 7.2.2),

6. Assess the Post-Inflammatory Hyperpigmentation (PIH) if present at baseline (see section 7.3.1),
7. Perform Local Tolerability Assessment (erythema, scaling dryness and stinging/burning; see Section 7.3.2),
8. Take photographs of the face according to the provided procedure,
9. The Product Dispenser will:
    a. Check the returned investigational product, the subject's diary and interview the subject about compliance (number of missed trial Products applications),
    b. Ensure that the subject has returned all used/unused investigational products and the subject Diary. All missing investigational product units must be documented in the Product Dispensation Log comments section and on other accountability form.
    c. For all female subjects, reiterate the guidelines about contraception and risks in case of pregnancy during 1 month after the end of the trial.
10. Ask the subject to complete the week 16/end of the trial DLQI/cDLQI questionnaire,
11. Ask the subject to complete Subject Satisfaction and Cosmetic acceptability questionnaires,
12. Complete the Exit Form in the eCRF and give the reason for clinical trial discontinuation (see section 4.5.6).

5.5.6. Early termination visit

In case of early termination, the procedures corresponding to the next theoretical visit should be performed (e.g. if a subject discontinues after week 2, complete the week 8 visit procedures). Additional final procedures will be conducted as indicated in the trial flow chart section 5.4.

6. CLINICAL SUPPLIES

Investigational product and supplies will be provided by the sponsor and shipped by the clinical supply unit or local depot. The investigational and non-investigational products used during this clinical trial are marketed products.

6.1. INVESTIGATIONAL PRODUCT IDENTIFICATION AND USE

6.1.1. Product identity

	Investigational Product
Trade Name	Epiduo® Forte
Name of Active Ingredient	Adapalene - Benzoyl Peroxide
Pharmaceutical Form	Gel
Dose or Concentration	Adapalene 0.3% - BPO 2.5%
Formula number	534.0201
Total Daily dose	Four pea-sized amounts to cover whole face (e.g. one on the forehead, chin and each cheek)
Mode and frequency of administration	Topical, once daily in the evening
Location of treated area	Face
Manufacturer ***(Name and address)***	Galderma Production Inc. (GPI) 19400 Route Transcanadienne Baie d'Urfé, Québec Canada H9X 3S4
Packaging type and size (primary)	45g airless bottles with polypropylene pump system
Storage Conditions	Store at controlled room temperature 20°C to 25°C (68 °F to 77 °F). Excursions permitted be-tween 15 and 30°C (59°F et 86°F),

	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%
Formula number	534.0201
Total Daily dose	Four pea-sized amounts to cover whole face (e.g. one on the forehead, chin and each cheek)
Mode and frequency of administration	Topical, once daily in the evening
Location of treated area	Face
Manufacturer ***(Name and address)***	Galderma Production Inc. (GPI) 19400 Route Transcanadienne Baie d'Urfé, Québec Canada H9X 3S4
Packaging type and size (primary)	70g airless bottles with polypropylene pump system
Storage Conditions	Store at controlled room temperature 15°C to 25°C

6.1.2. Method of treatment assignment

This will be an open label trial and all subjects will be dispensed with the investigational product.

The kit number, a unique number will be assigned to each eligible subject at baseline according to the Inclusion/Non-inclusion criteria.

A subject kit will be composed of:

- Two visit boxes: One visit box will be dispensed to the subjects at Baseline (Dispensation 1) and one at week 8 visit (Dispensation 2),

  One extra box to be dispensed in case if subjects loose or destroy trial treatment.

Each box will contain:

- Dispensation 1 (Baseline):

- Two Epiduo® Forte / TactuPump™ Forte gel bottles

- Dispensation 2 (Week 8):

- Two Epiduo® Forte / TactuPump™ Forte gel bottles

- Extra box:

- One Epiduo® Forte / TactuPump™ Forte gel bottle

At baseline visit, all eligible subjects will be dispensed a Baseline visit box from the subject kit in a 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 subject.

6.1.3. IVR/IWR System

Once a Subject has fulfilled inclusion/exclusion criteria and is qualified to enter into the trial, the site will call/connect to the IVR/IWR System to check trial inclusion rate as per ethnic/race background and acne severity stratifications and assign the Subject kit number. The IVR/IWR System acts as an automatic central recruitment center.

The IVR/IWR System requires at least the Subject identification number (SIN) and Site number to provide proper treatment assignment number by linking the SIN to ethnic/race backgrounds and acne severity of the included subjects in the eCRF.

6.1.4. Subject Identification Number (SIN)

Upon signature of the informed consent, a subject meeting all inclusion/exclusion criteria will be allocated a unique subject identification number (SIN). 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.

6.1.5. Instructions for use and administration

The Product Dispenser will give each subject verbal and written instructions on how to use the investigational product 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 product on the face and how to record these applications in the subject diary. This procedure will be thoroughly discussed and reviewed at each trial visit.

All subjects will apply the investigational product in the evening after washing their face, for 16 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 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 whole face (e.g. one on the forehead, chin and each cheek),
5. Wash hands,
6. Complete the given subject Diary after each product application.

	Investigational Product
Concentration	Adapalene 0.3% - BPO 2.5%
Dose regimen	Once daily
Period of administration	Evening
Route of administration	Topical

6.1.6. Non-investigational products

Cetaphil® DermaControl™ Oil Control Foam Wash and Cetaphil® DermaControl™ Oil Control Moisturizer SPF 30 and Urine Pregnancy Tests (UPT) will be provided by the sponsor (or designee).

Subjects should use the provided 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 16 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 LABELLING

All investigational products will be supplied in the subject's kit containing 2 visit boxes (one per dispensing visit) plus an extra box.

The subject kit label will be comprised of a single panel fixed label, while the visit box labels will be comprised of a double-panel label with an affixed and a tear-off portion for accountability.

The labels will be printed in the local language. The text of the label will detail the information requested by Good Manufacturing Practice and Good Clinical Practice and local regulations.
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.

6.3. INVESTIGATIONAL PRODUCT MANAGEMENT

6.3.1. Accountability

Upon receipt of the clinical supplies at the site, the investigational 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* 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 Product Dispensation Log by the Product Dispenser at each visit.

It is important that no subject runs out of clinical trial supplies between visits.
Each subject will receive a new visit box containing two bottles of investigational product at baseline and at post-baseline visit week 8.

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 clinical trial treatment(s) throughout the clinical trial as well as the importance of returning their investigational product (used and/or not used) at week 8 and week 16 (or at the end of the trial in case of early termination) visits.

The investigational products will be collected, counted and documented on the Product Dispensation Log or other accountability document as applicable, at post-baseline visits (week 8 and week 16), by the Product Dispenser.

In this trial product compliance will be assessed using a subject diary.

At Baseline visit, subjects will be provided with a subject diary to record on a daily basis the frequency of applications of investigational product (Epiduo® Forte / Tactupump™ Forte gel) and non-investigational products on the face and to record their compliance with the instructed application procedures. Subjects should return the diary at each post-baseline visit for review by the Product Dispenser. At the end of the trial week 16/early termination subjects should return the diary.

The return of investigational products should be appropriately documented on the Product Dispensation Log by the trial Product Dispenser. All subject kits will be collected at the week 16 visit at the latest, if not done before, or at Early Termination.

Subjects will also be questioned regarding the application technique, intake, frequency and missed doses of investigational product and the use of any other additional topical, systemic product as well as OTC product.

During the data review meeting, investigational product compliance for all subjects will be determined and reviewed by the sponsor's clinical team.

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).

6.3.5. Return of investigational product

The Product Dispenser will inform each subject about the importance of returning their investigational products (used and/or not used) at week 8 and week 16 at the latest, if not done before, or at Early Termination.

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

6.3.6. Dose modification

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

Subjects should be instructed to use a moisturizer (the provided one for this trial) and if needed, investigators may reduce temporarily the frequency of the application of Adapalene 0.3% - BPO 2.5% (eg. every other day), or temporarily discontinue use.

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 should be documented in the subject's source data and reported in the eCRF (treatment compliance page).

6.4. BLINDING

6.4.1. Verification of blinding

The trial design is considered as open label trial so blinding is not applicable for this trial.

6.4.2. Unblinding during the clinical trial

Not applicable for this open label trial.

7. SUBJECT REPORTED OUTCOME, EFFICACY AND SAFETY ASSESSMENT

7.1. SUBJECT REPORTED OUTCOMES

The following Subject 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.

7.1.1. Quality of Life Questionnaire

At baseline **before** application of the investigational product, at Week 12 and at Week 16/Early termination subjects will complete a Dermatology Life Quality Index questionnaire (DLQI) or Children Dermatology Life Quality Index questionnaire (cDLQI) (for children age of ≤16 years) (see Attachment 1).

DLQI and cDLQI questionnaires will be used in local language.

7.1.2. Subject Satisfaction Questionnaire

At Week 12 and Week 16/Early termination, subjects will complete a satisfaction questionnaire regarding use of investigational product they used in this trial (see Attachment 2).

Subject satisfaction questionnaire will be translated in local language.

7.2. 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 (Week 16/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).

7.2.1. Investigator's global assessment of acne severity (IGA)

The evaluator will assess the severity of acne for the whole face of the subject using the scale described below. The evaluator will assess subject's acne severity at each visit by performing a static ("snapshot") evaluation of acne. The evaluator should make no reference to baseline or other previous visit when evaluating the subject's acne.

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 of 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.

For the **inclusion criterion** (subjects should have an IGA of 3 or 4).

7.2.2. Global Assessment of Improvement (GAI)

At Week 12 and Week 16/Early termination, the evaluator will evaluate the degree of acne improvement **versus baseline** using the Global Assessment of Improvement score as follows:

Category	Score	Description
Excellent improvement	**0**	All or nearly all signs and symptoms cleared (around and more than **90%** improvement from Baseline). Whether no, or only minimal residual signs and symptoms remain
Very good Improvement	**1**	Majority of the signs and symptoms have resolved (about **75%** improvement from Baseline)
Good Improvement	**2**	Significant improvement, but many signs and symptoms remain (about **50%** improvement from Baseline)
Minimal Improvement	**3**	Slight overall improvement, but not clinically significant (about **25%** improvement from Baseline)
No Change	**4**	Overall severity similar to Baseline
Worse	**5**	Worse than Baseline

7.3. SAFETY ASSESSMENTS

Safety assessments 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 increase in Post inflammatory hyperpigmentation (PIH) and local tolerance severity.

7.3.1. Post inflammatory hyperpigmentation (PIH)

Post inflammatory hyperpigmentation (PIH) is mostly seen in subjects with skin phototypes IV to VI (according to T.B. Fitzpatrick's definitions). PIH lesions may represent the sequel of various

cutaneous disorders as well as therapeutic interventions. The shapes of these lesions closely follow the contours of the original inflammatory dermatosis. Severity of PIH of the treated areas on the face will be evaluated by the evaluator at each visit as follows:

Category	Score	Description
None	**0**	No post inflammatory hyperpigmentation
Very mild	**1**	Few areas of post inflammatory hyperpigmentation, very small in size and only very slightly darker than the surrounding skin
Mild	**2**	Several areas of post inflammatory hyperpigmentation; small in size and slightly darker than the surrounding skin
Moderate	**3**	Many areas of post inflammatory hyperpigmentation; medium in size and much darker than the surrounding skin
Severe	**4**	Large number of areas of post inflammatory hyperpigmentation; large in size and markedly darker than the surrounding skin.

Any increase of PIH score during the trial is to be reported as an Adverse Event.

7.3.2. Local tolerance assessment

Local cutaneous signs and symptoms (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 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 product application (within 5 minutes)?"

Erythema, scaling, dryness will be evaluated by the investigator, and stinging/burning will be recorded by the investigator after discussion with the subject. The four signs and symptoms will be graded at each follow up visit as follows:

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 – pricking pain sensation immediately after dosing (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 should **NOT** be assessed at the baseline visit*

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 first four weeks** of treatment.
- 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.

7.3.3. Adverse Events

Adverse Events will be recorded monitored throughout the course of the clinical trial. All clinical medical events, whether observed by the investigator or reported by the subject and whether or not thought to be product or trial procedure-related will be considered adverse events and

recorded on the appropriate 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.

7.4. OTHERS

7.4.1. Cosmetic acceptability Questionnaire

At Week 16/Early termination, subjects will complete an acceptability questionnaire regarding the non-investigational product they have been using in this trial (see Attachment 3).

Subject cosmetic acceptability questionnaire will be translated in local language.

7.4.2. Photographs

Standardized digital photographs of the whole face (front, right and left) will be taken using a Canfield Scientific stereostatic device (Visia CR®) or equivalent. Detailed procedures will be provided. Subjects will be photographed at baseline and at each post-baseline visit.
At Baseline visit subjects' photograph will be used to confirm the severity of acne (moderate or severe) for inclusion of subjects into the trial. Sponsor Medical Expert will review the clinical evaluation of acne and give his confirmation for inclusion of subjects into the trial.

7.5. APPROPRIATENESS OF MEASUREMENTS

Efficacy is evaluated by assessing severity of acne by the investigator (IGA) and the degree of acne improvement versus baseline using the Global Assessment of Improvement (GAI) scores which are current and non-invasive techniques for assessing efficacy of acne treatment.

Post inflammatory hyperpigmentation (PIH) is mostly seen in subjects with skin phototypes IV to VI (according to T.B. Fitzpatrick's definitions). PIH lesions may represent the sequel of various cutaneous disorders as well as therapeutic interventions. Severity of PIH of the treated areas on the face will be evaluated by the the evaluator at each visit.

Acne can persist for years and may affect seriously the psychosocial development, resulting in emotional problems, withdrawal from society, and depression (Koo , J Y., et Smith, L L. 1991). If not treated, acne may cause serious physical and emotional scarring and can significantly impact the quality of life of those affected by the disease (Brown J.M., Poston S.M. 1983) (Usatine, RP., Quan, MA et Strick, R. 1998).

Therefore impact of trial treatments on subjects' quality of life will be assessed using quality of life and satisfaction questionnaires in dark skin subjects known to be sensitive with topical retinoids. For this, subjects will complete the DLQI / cDLQI at baseline, Week 12 and at the end of the trial. A satisfaction questionnaire will also be completed by all subjects at Week 12 and at the end of the trial Week 16/Early termination.

To collect specifically subject's feed-back on the associated non-investigational products used in the trial, a subject cosmetic acceptability questionnaire will be completed at the end of the trial Week 16/Early termination.

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.

8. ADVERSE EVENT

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.) from the screening visit should be reported as a new AE.

Notes:

- Any new sign or symptom reported by the subject that appears after accidental or intentional overdose or misuse should also be reported as an AE.
- There should be an attempt to report a diagnosis 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.
- Pregnancy should not be considered as an adverse event but must be followed up as described in section 8.2.3.1.
- For an AE of irritation, the "date of onset" should be the date that the first symptom occurred.

There may be side effects during treatment with the investigational product, as described in the product monograph for Epiduo® Forte / TactuPump™ Forte gel 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 (after the first 4 weeks of treatment)/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.
- Inpatient 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 at the hospital. Hospitalization may not constitute sufficient grounds to be considered as an hospitalization if it is solely for the purpose of diagnostic tests, (even if related to an AE), elective hospitalization for an intervention which was already planned before subject enrolment 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).

8.1.3. Unexpected adverse drug reaction

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

8.1.4. Adverse event reporting period

The clinical trial period during which AEs must be reported is the period from when the subject signs the Informed Consent Form to the end of the subject's participation.

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 a medication has been discontinued.

8.1.5. Severity

Severity is a clinical determination of the intensity of an AE and not of a disease.
The investigator will classify the intensity of AEs using the following definitions as a guideline for all AEs occurring during clinical trials conducted or sponsored by *GALDERMA*. 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 his 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 trial product(s) and/or clinical trial procedure

The investigator is to determine whether there is a reasonable causal relationship between the occurrence of the AE and exposure to the trial product(s) and/or clinical trial procedure required by the protocol, such as moisturizer use. AE reporting for moisturizer use should be detailed, taking into account whether moisturizer use is recommended or mandatory.

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 AE is to be completed using the following definitions as a guideline for all adverse events occurring during clinical trials conducted or sponsored by *GALDERMA*:

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 vehicle, etc.) and the AE,
- The clinical trial protocol procedure (e.g., UV-induction, biopsy, xylocaine injection, blood test or intraocular pressure measurement, ancillary products provided by the sponsor, such as moisturizers, etc.) and the AE.

The Investigator has to complete these 2 causality assessments on the AE form.

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. REPORTING PROCEDURES

8.2.1. Procedures for reporting adverse events

The collection of AEs is from the time that a subject signs the ICF to their final trial visit.

At each post-baseline 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 trial 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 trial product, and outcome, without omitting any requested and known information. Additional information will be requested under certain circumstances. Adverse Events (AEs) assessed as related to the treatment 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.

Adverse events assessed as related to the treatment or trial procedure will be monitored until they have resolved or reached a stable condition. Other AEs will be monitored until the last visit if they have not resolved or reached a stable condition. 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. For SAEs (see section 8.2.2) and pregnancies (see section 8.2.3.1), the Sponsor is to be informed immediately by e-mail/fax. The event must be reported by fax or sent by e-mail to the Sponsor within 24 hours of receipt of the information (contact details in section 8.2.2).

8.2.2. Procedure for reporting a Serious Adverse Event

For an SAE occurring during the period of the clinical trial, regardless of whether it is related to the treatment or not, and of whether it is expected or not, the investigator must do the following:

1. **Take prompt and appropriate medical action**, if necessary. The safety of subject is the first priority.
2. Ensure that the event is classified as an SAE. **Immediately (no later than 24 hours) inform *the Sponsor*** of the event by email/ fax/, and discuss further actions to be taken:

	GALDERMA R&D
Name	[redacted]
Title	[redacted]
Address	[redacted]
Tel. during office hours	[redacted]
Tel. Outside office hours	[redacted]
Fax	[redacted]
Email	pharmacovigilance@galderma.com

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 demographics, medical history and drugs/therapies forms (if any), and adverse event pages of the eCRF, and any other relevant information (e.g., test results) within 24 hours of receipt of the information to the Sponsor (see contact details above)

4. Print and complete the Serious Adverse Event form (available in the EDC system as PDF document). Fax or send by email the completed form, accompanied any other relevant information or anonymized medical records (e.g., laboratory test results) within 24 hours of receipt of this information to the sponsor (see contact details above). The demographics, medical history, drugs/therapies forms, and adverse event pages of the eCRF must be completed and available for review in the EDC system at the time of the report.

5. **Monitor and record the progress of the event until it resolves** or reaches a clinically stable outcome, with or without sequelae. 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.
6. 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

7. **Inform the sponsor of the final outcome of the event**. Send a revised or updated SAE form and AE form, if appropriate.
8. Prompt notification of SAEs by the investigator to *GALDERMA* is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met. *GALDERMA* has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. *GALDERMA* will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, IRBs/IECs and investigators. Investigator safety reports are prepared for Suspected Unexpected Serious Adverse Reactions (SUSARs) according to local regulatory requirements and *GALDERMA* policy and are forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from *GALDERMA* will file it with the Investigator's Brochure (IB) and will notify the IRB/IEC, if appropriate according to local requirements.
9. **Comply with the applicable regulatory requirements related to the reporting of SAEs to your IRB/EC.**

8.2.3. 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 by email/fax, within 24 hours of receipt of the information as described in section 8.2.2.

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 dose application, a re-challenge test with the assigned trial product will be performed.
2. Ensure the subject has not been under any treatment with corticosteroids or antihistamines, regardless of the 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 center 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 will be discussed with the sponsor.
5. Choose a skin site that was not previously involved in the inflammatory skin reaction.
6. Cover it for 48 hours with a hypoallergenic tape.

7. Subject should be informed about avoiding exercise, showers, application of toiletries products, etc. to keep the test system dry

8. 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 so far equivocal or if asked 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)

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

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

10. At last reading, the investigator will 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

11. Report the results from the re-challenge test as directed by the sponsor and document with photographs.
12. In case of absence of reaction, the subject may resume treatment if appropriate
13. If the re-challenge is positive or equivocal, notify the sponsor immediately. Except 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.
14. 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.

8.2.3.1 Procedures for reporting pregnancies

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

If a subject becomes pregnant, the Investigator is to do the following:

1. **Withdraw the subject from the clinical trial**
2. Complete all appropriate visit evaluations and eCRF pages.

Immediately (no later than 24 hours) contact the Sponsor to inform them of the pregnancy occurrence and discuss further steps to be taken:

	GALDERMA R&D
Name	[redacted]
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), as fully as possible. Fax or send by email this pregnancy form along with the Exit form within 24 hours of receipt of the information 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, as full as possible. Inform the Sponsor by email/ fax, then fax or send by e-mail this pregnancy form to the Sponsor within 24 hours of receipt of the information.
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 8.2.2).
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 8.2.2)

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.

Any change made to the finalized SAP will be documented in the clinical trial report.

The purpose of the trial is to evaluate subject reported outcomes with the combination of Adapalene 0.3% - BPO 2.5%, Epiduo® Forte / TactuPump™ Forte gel, after 16 weeks of treatment of moderate to severe acne in dark skin phototypes (IV to VI).

9.1.1. Variables to be statistically analyzed

The following variables will be analyzed:

Subject reported outcome variable

- *DLQI/cDLQI at Baseline, Week 12 and last visit*
- *Subject satisfaction questionnaire at Week 12 and last visit*

Efficacy variables

- *IGA score: % of subjects across scores at each visit*
- *GAI score: % of subjects across scores at Week 12 and last visit*

Safety variables on safety population

- *PIH: Raw value at each visit and % change from baseline at each post-baseline visit*
- *Local tolerance: Raw value at each visit and worst-score across visit, % of Subjects across scores at each post-baseline visit*
- *Incidence of adverse events*
- *Incidence of serious adverse events*

Other variables

- *Cosmetic acceptability questionnaire at last visit*

9.1.2. Populations analysed, 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 data review meeting.

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

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

9.1.2.2 The Safety population (All subject 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 (AEs).

9.1.2.3 Missing values

The last observation carried forward (LOCF) method will be used to impute missing values of global assessment scores (GAI and IGA). If no post-baseline data are available, baseline will be carried forward. Thus, the number of subjects will not vary at each visit. The other missing values will not be replaced (observed data).

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. All tables will be presented by clinical trial treatment and by visit (when applicable).

Therapies that have been stopped before the baseline visit will be presented as prior therapies. Those reported at screening or starting between screening and baseline visits 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 clinical trial treatments within System Organ Class (SOC) and preferred term (MedDRA). Subjects will be descriptively summarized (n, %) by intensity (*i.e.* mild, moderate and severe) of adverse 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

No inferential statistics will be performed. All variables will be descriptively summarized on ITT population and on APT population for the safety variables. The last observation carried forward (LOCF) method will be used to impute missing efficacy values.

Any changes of the statistical analyses decided after the database lock will be justified and documented.

9.2. SAMPLE SIZE DETERMINATION

As no inferential statistics will be performed, no statistical rationale of sample size can be used. However, a total of 60 subjects to evaluate the subject reported outcomes (quality of life and satisfaction survey), can be considered as sufficient.

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. 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 trial reference 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.

During the Investigator meeting/Initiation visit this document will be discussed and reviewed thoroughly.

10.2. CLINICAL MONITORING

The conduct of the clinical trial will be closely monitored by representatives of *CRO/GALDERMA R&D* 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/CRO* 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 *GALDERMA R&D/* CRO 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.

At the end of the trial 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 and 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 the Contract Research Organization (CRO).

Audits of clinical trial sites may be conducted by the Sponsor/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 CRO/Sponsor's 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 have to 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 12 to 17) and as applicable, photograph release form) approved by an IRB/EC, will be fully explained to the subject and parent/guardian if applicable.

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 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 and in the eCRF, the product Dispensation Logs and the subjects' diary provided by *GALDERMA R&D*.

All data recorded in the documents described above should be recorded completely, promptly, and legibly using black ink.

The appropriate pages will be collected upon clinical trial completion or at any other time specified by CRO/CRA/sponsor.

A complete set of trial documents copies (when applicable) will remain at the investigational site.

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.110232 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.

At the end of the trial a copy of photographs of all subjects will be burned on a CD and archived within trial files.

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.

11.6. INSURANCE

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

12. REFERENCE LIST

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13. ATTACHMENTS

13.1. ATTACHMENT 1: QUALITY OF LIFE QUESTIONNAIRES

DERMATOLOGY LIFE QUALITY INDEX (DLQI) &
CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX (C-DLQI) QUESTIONNAIRES

DERMATOLOGY LIFE QUALITY INDEX QUESTIONNAIRE (DLQI) :

At the beginning and end of the trial, **subjects of 17 years old and over** will answer the 10-item DLQI questionnaire.

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick √ one box for each question

1.	Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒
2.	Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒

6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much	❒
		A lot	❒
		A little	❒
		Not at all	❒
		Not relevant	❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes	❒
		No	❒
		Not relevant	❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot	❒
		A little	❒
		Not at all	❒
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much	❒
		A lot	❒
		A little	❒
		Not at all	❒
		Not relevant	❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much	❒
		A lot	❒
		A little	❒
		Not at all	❒
		Not relevant	❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much	❒
		A lot	❒
		A little	❒
		Not at all	❒
		Not relevant	❒

Please check you have answered EVERY question. Thank you.

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX QUESTIONNAIRE (cDLQI) :

At the beginning and end of the trial, **subjects of 12 to 16 years old included** will answer the 10-item Children's DLQI questionnaire.

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, how **itchy**, **"scratchy"**, **sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
2.	Over the last week, how **embarrassed** or **self-conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
7.	Last week, was it **school time?** ⇨	**If school time**: Over the last week, how much did your skin affect your **school work**?	Prevented School ❒ Very much ❒ Quite a lot ❒ Only a little ❒ Not at all ❒
OR			
	was it **holiday time?** ⇨	**If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Very much ❒ Quite a lot ❒ Only a little ❒ Not at all ❒

8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
9.	Over the last week, how much has your **sleep** been affected by your skin problem?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒

Please check that you have answered EVERY question. Thank you.

13.2. ATTACHMENT 2: SUBJECT'S SATISFACTION QUESTIONNAIRE

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.

Questions about the acne treatment applied every evening:

Whole face

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. How do you measure the improvement of the disease?

Complete improvement	[ ]
Excellent improvement	[ ]
Good Improvement	[ ]
Minimal Improvement	[ ]
No Change	[ ]
Worse	[ ]

5. Overall, are you satisfied with the treatment?

Very satisfied	[ ]
Satisfied	[ ]
Somewhat satisfied	[ ]
Not satisfied	[ ]

6. Would you consider <u>using</u> this treatment <u>again</u>?

Yes [ ]
No [ ]

7. Did you use the provided <u>moisturizing lotion</u>?

Yes [ ]
No [ ]

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 trial treatments
[ ] The moisturizer helped to reduce feeling of **skin dryness**
[ ] The moisturizer was **pleasant to use**
[ ] None of the above

13.3. ATTACHMENT 3: COSMETIC ACCEPTABILITY QUESTIONNAIRE

MOISTURIZER: Cetaphil® DermaControl™ Oil control Moisturizer SPF 30

1. Did you use the provided moisturizer?
   □ Yes □ No

2. Would you say the moisturizer helps you to continue with the treatment?
   □ Yes □ No

3. For each of the characteristics below, please tell us whether you agree or disagree:

The moisturizer:	Strongly disagree	Disagree	Agree	Strongly agree
Makes skin soft and smooth				
Is pleasant to use				
Is gentle enough				
Provides immediate hydration				
Is absorbed quickly by the skin				
Provides long lasting hydration				
Reduces skin dryness				
Relieves itchy skin				
Maintains skin health				
Reduces irritation				
Does not make my skin feel oily				
I feel this is needed as part of my acne treatment				

FACIAL WASH: Cetaphil® DermaControl™ Oil control Foam Wash

1. Did you use the provided facial cleanser?
   □ Yes □ No

2. Would you say the facial cleanser helps you to continue with the treatment?
   □ Yes □ No

3. For each of the characteristics below, please tell us whether you agree or disagree:

The facial cleaning:	**Strongly disagree**	**Disagree**	**Agree**	**Strongly agree**
Leaves my skin feeling clean				
Leaves my skin feeling relieved				
Makes my skin soft and smooth				
Does not leave my skin feeling tight				
Spread easily				
Is gentle enough				
Is pleasant to use				
Increases my skin's luminosity				
Does not dry my skin				
Increases my overall skin appearance				
Helps prepare my skin for treatment				
I feel this is needed as part of my acne treatment				