Abbreviation	*Term*
LOCF	Last Observation Carried Forward
LSI	Last Subject In (Last subject enrolled/randomized)
LSO	Last Subject Out (Last subject who completed his/her last clinical trial visit)
MI	Multiple Imputation
MD	Medical Doctor
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
NOAEL	no observed adverse effect level
OTC	Over-the-Counter
PGA	Physician Global Assessment
PK	Pharmacokinetics
PP	Per-Protocol
PT	Preferred term
RAR	Retinoic Acid Receptor
RXR	Retinoic X Receptor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety
SAFT	Safety Population on the Trunk
SIN	Subject Identification Number
SOC	System Organ Class
SOP	Standard Operating Procedure
SPF	Sun Protection Factor
TEAE	Treatment-Emergent Adverse Event
UPT	Urine Pregnancy Test
USA	United States of America
UV	Ultraviolet

3 OVERALL CLINICAL TRIAL DESCRIPTION

Multi-center study for Trifarotene cream applied once daily for 24 weeks in the evening.

Trifarotene 50µg/g cream applied once daily

3.1 Efficacy assessment

The efficacy endpoint consists of the following endpoints:

- Success Rate, defined as the percentage of subjects who achieve an IGA score of 1 (Almost Clear) or 0 (Clear) AND at least a 2-grade improvement from Baseline to Week 12 and Week 24

CCI [redacted]

- Success Rate, defined as the percentage of subjects who achieve a PGA score of 1 (Almost Clear) or 0 (Clear) AND at least a 2-grade improvement from Baseline to Week 12 and Week 24

CCI [redacted]

- Percent change in facial non–inflammatory lesion counts from Baseline to week 12 and week 24.
- Percent change in facial inflammatory lesion counts from Baseline to week 12 and week 24.
- Percent change in truncal non-inflammatory lesion counts from Baseline to week 12 and week 24.
- Percent change in truncal inflammatory lesion counts from Baseline to week 12 and Week 24.

3.2 Safety Assessment

Safety evaluations will be performed at Baseline and at Weeks 1, 4, 12, 18, and 24/Early Termination (ET)/Unscheduled visits. These evaluations will consist of assessment of local tolerability and adverse events at each visit.

CCI [redacted]

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

Concomitant therapies (including preferred or provided moisturizer) are to be recorded, reviewed, and updated at each visit. Every attempt should be made to keep concomitant therapy dosing and regimen constant during the trial.

5.5.4 Authorized concomitant therapies

Unless listed under the exclusion criteria (Section 5.4 item [15]) or in prohibited concomitant therapies, the following therapies are allowed, as long as they are not indicated for the treatment of acne vulgaris (see Section 5.5.5):

Topical treatments:

In addition to the study drug, the following CCI products are authorized on the treated areas if they are not indicated for the treatment of Acne Vulgaris:

CCI

5.5.5 Prohibited concomitant therapies

CCI

CCI [redacted]

7.1.1.1 IGA (Investigator's global assessment) of facial acne

The areas defined for IGA assessment are forehead, each cheek, chin, and nose. IGA will be confined to a global assessment of each area defined above.

CCI [redacted]

The IGA will be assessed CCI [redacted] according to the following scale:

Investigator's Global Assessment Scale (IGA) Face		
0	Clear	Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost Clear	A few scattered comedones and a few small papules.
2	Mild	Easily recognizable; less than half the surface is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the surface is involved. Many comedones, papules and pustules. One nodule may be present.
4	Severe	Entire surface is involved. Covered with comedones, numerous papules and pustules. Few nodules may be present.

7.1.1.2 PGA (Physician Global Assessment) of truncal acne

The areas defined for PGA assessment are shoulders, upper back, and upper anterior chest which are accessible to self-application by the subject, i.e., the regions that the subject can easily reach and apply the study drug without assistance. CCI [redacted]

PGA will be confined to a global assessment of each areas defined above. The PGA is a snapshot static assessment to be done prior to detailed lesion counts. CCI [redacted]

CCI

- Success Rate, defined as the percentage of subjects who achieve a PGA score of 1 (Almost Clear) or 0 (Clear) AND at least a 2-grade improvement from Baseline to Week 12 and Week 24

CCI

- Percent change in facial non–inflammatory lesion counts from Baseline to week 12 and week 24.
- Percent change in facial inflammatory lesion counts from Baseline to week 12 and week 24.
- Percent change in truncal non-inflammatory lesion counts from Baseline to week 12 and week 24.
- Percent change in truncal inflammatory lesion counts from Baseline to week 12 and Week 24.

7.2 Safety assessment

The safety parameters are the recording of adverse events and local tolerability scores as specified in section 7.2.1.

7.2.1 Local tolerability assessment (of face and of trunk)

Erythema, scaling, dryness will be evaluated by the investigator separately on the face and trunk,

CCI

These tolerability signs and symptoms will be assessed for the face and the trunk separately and will be graded at baseline and at each follow up visit based on the below scale:

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

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 any clinically significant worsening of an existing sign, symptom or disease compared to the condition at the first visit (including disease treated), should be considered as an AE. Lack of efficacy is not considered as an AE.

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

Notes:

- 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 is not to be considered as an AE; however, is an important medical event that must be monitored as described in Section 7.2.2.2.5.

7.2.2.1.2 Serious Adverse events

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

- Results in death,
- Is life-threatening,
- Requires inpatient 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 that hypothetically might have caused death if it was more severe.

Inpatient hospitalization is considered to have occurred if the subject has had to stay for a night at the hospital. The criterion for prolongation of hospitalization is also defined as an extra night at the hospital. Hospitalization may not constitute sufficient grounds to be considered as an SAE if it is solely for the purpose of a diagnostic tests (even if related to an AE), elective hospitalization for an intervention that was already planned before subject enrollment 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).

7.2.2.1.3 Adverse Events of Special Interest

An AESI is a noteworthy event for the particular study drug that can be appropriate to monitor closely. It could be serious or non-serious and AESIs could include events that might be potential precursors or prodromal symptoms for more serious medical conditions in susceptible individuals.

CCI

For AESIs, the Investigator is required to complete the Adverse Event Form and follow the AESI reporting procedures in Section 7.2.2.2.3 even if the event is considered non-serious according to the usual regulatory criteria. For suspected sensitizations follow challenge and re-challenge patch test procedures in Section 7.2.2.2.4.

7.2.2.1.4 Unexpected adverse drug reaction

According to ICH E6, an unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable study drug information (e.g., IB for an unapproved investigational product or the package insert/summary of product characteristics for an approved product).

7.2.2.1.5 Adverse event reporting period

The clinical trial period during which AEs must be reported is the period from when the subject signed the ICF 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 may not appear until a medication has been discontinued.

7.2.2.1.6 Severity

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

The Investigator is to 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 signs or symptom, but easily tolerated.
Moderate	Discomfort, enough to cause interference with usual activity
Severe	Incapacitating with inability to work or perform usual activity

7.2.2.1.7 Relationship to the study drug

The Investigator is to determine whether there is a reasonable causal relationship between the study drug and the AE. Medical judgment should be used to determine the relationship, considering all relevant factors including the pattern of reaction, temporal relationships, positive challenge or rechallenge, relevant medical history, and confounding factors such as co-medication or concurrent diseases.

The expression “reasonable causal relationship” is meant to convey in general that there are facts or arguments to suggest a causal relationship (ICH E2A, Section IIIA 1).

The relationship assessment for an AE is to be completed using the following definitions as a guideline for all AEs occurring during clinical trials conducted or sponsored by GALDERMA R&D:

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 study drug (investigational product and the AE),
- The clinical trial protocol procedure (such as blood test) and the AE.

Investigator contact: PPD

3. Complete the Adverse Event Form provided in the CRF as fully as possible.
4. Ensure that the event is classified as an SAE in the CRF.
5. Print and complete the Serious Adverse Event Form available in the electronic data capture (EDC) system as PDF document. Fax or scan and send by e mail the completed form, accompanied by any other relevant information or medical records (e.g., laboratory test results) within 24 hours to the CSO. The demographics, medical history, previous and concomitant therapies, and adverse event pages of the CRF must be completed and available for review in the EDC system at the time of the report.
6. 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, first inform the CSO of the outcome by telephone, then fax or scan and send by e-mail all additional follow-up information to the CSO within 24 hours. Serious Adverse Events will be monitored until the Investigator and Sponsor agree that the event is satisfactorily resolved.
7. 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.
8. Inform the CSO of the final outcome of the event. Send a revised or updated Serious Adverse Event Form and Adverse Event Form, if appropriate.
9. Comply with the applicable regulatory requirement(s) related to the reporting of SAEs to the Institutional Review Board (IRB) / Independent Ethics Committee (IEC).

7.2.2.2.3 Procedure for reporting an adverse event of special interest

For any AESI (see Section 7.2.2.1.3) occurring during the period of the clinical trial, whether related to the treatment or not, and whether expected or not, the Investigator is to do the following:

1. Take prompt and appropriate medical action, if necessary. The safety of subjects is the first priority.
2. Immediately inform the CSO of the event by fax or email and discuss further actions to be taken.
3. Investigator contact: Refer to Section 7.2.2.2.2.
4. Complete the Adverse Event Form provided in the CRF as fully as possible.
5. Ensure that the event is classified as an AESI in the CRF.
6. Print the Adverse Event form. Fax or scan and send by e mail the completed form, accompanied by any other relevant information or medical records (e.g. laboratory test

results) within 24 hours to the CSO. The demographics, medical history, previous and concomitant therapies, and adverse event pages of the CRF must be completed and available for review in the EDC system at the time of the report.

7. Monitor and record the progress of the event until it resolves or reaches a clinically stable outcome, with or without sequelae. For all the additional follow-up evaluations, first inform the CSO of the outcome by telephone, then fax or scan and send the additional follow-up information by e-mail to the CSO within 24 hours. AESIs will be monitored until the Investigator and Sponsor agree that the event is satisfactorily resolved.
8. 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.
9. Inform the CSO of the final outcome of the event. Send a revised or updated Adverse Event Form, if appropriate.

7.2.2.2.4 Procedures for suspected sensitization (Re-Challenge and patch Ingredient Test)

If a subject experiences suspected skin sensitization (contact allergy), the following actions should be taken to characterize the event:

CCI

CCI

[redacted]

7.3.2 Dermatology Life Quality Index (DLQI) / Children's Dermatology Life Quality Index (C-DLQI)

Dermatology Life Quality Index (cDLQI/DLQI) will be completed by the subject at the baseline and week 12 and 24/early termination prior to any Investigator assessments to not impact the subject's answers to the quality of life questionnaire. Subjects 16 years and younger (at baseline) should complete the cDLQI (and 17 years and older complete the DLQI) throughout the study.

Prior to any acne assessments, the Investigator or designee should provide the subject with the age appropriate DLQI Form and instruct the subject to read and answer all 10 quality-of-life questions. **The designated study personnel will then check the questionnaire for completeness prior to the subject leaving the office**.

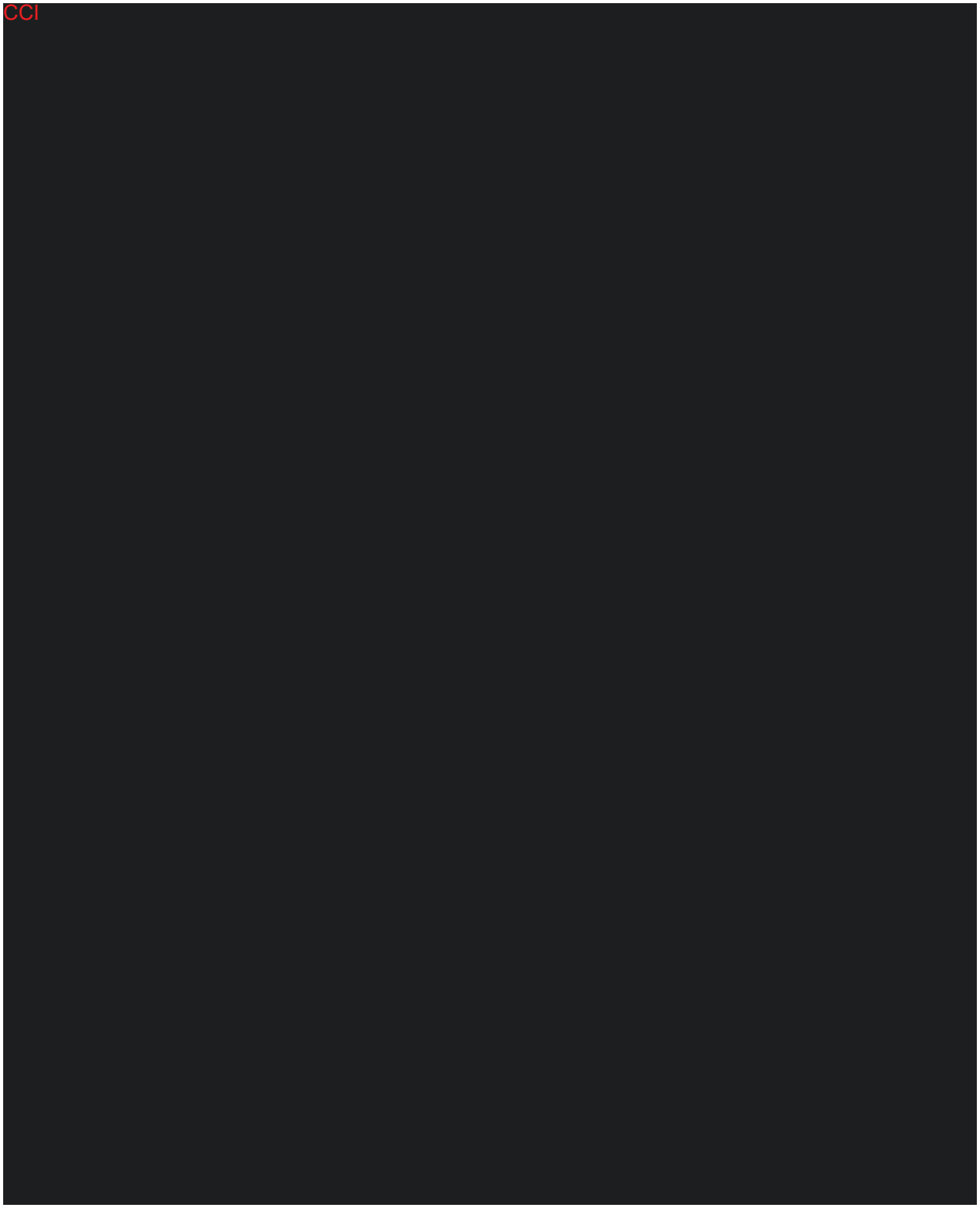
This QOL instrument is not acne specific. The DLQI/C-DLQI are validated instruments that measure the dermatology-related limitations of functional ability and the frequency, severity, and impact of general inflammatory skin conditions on the quality of life.

The six domains addressed in the questionnaire are:

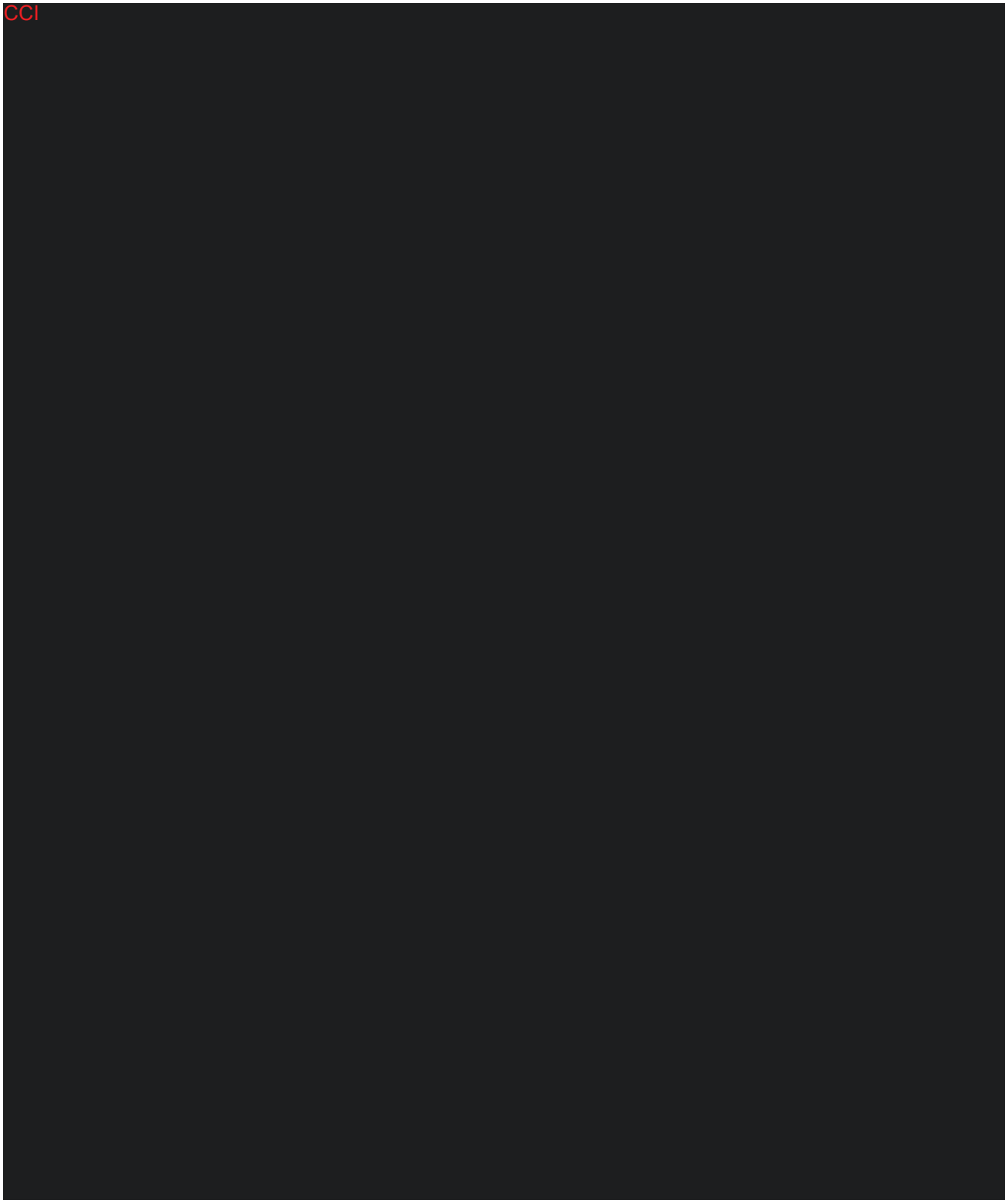
- symptoms and feelings;
- daily activities;
- leisure;
- work/school;
- personal relationships;
- treatment.

The possible answers to the DLQI questions for the effect of acne on QOL were scored as follows: very much (3), a lot (2), a little (1), and not at all (0). The DLQI is calculated by

CCI



CCI



CCI [redacted]

9 STATISTICAL METHODS PLANNED

9.1 Statistical analysis plan

A statistical analysis plan (SAP) will be developed and issued 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 analysis strategies that are specified in the sections of the clinical trial outline below. The SAP will be finalized prior to the database lock. CCI [redacted]

CCI [redacted]

Any changes to analyses made after the SAP has been finalized, along with an explanation as to when and why they occurred, will be documented in the clinical study report. Post hoc exploratory analyses will also be clearly identified in the Clinical Study Report (CSR).

9.1.1 Data transformations

Not applicable

Subject disposition, demographics and baseline characteristics, previous therapies, and concomitant therapies will be summarized by descriptive statistics based on the ITT Population. Treatment exposure and compliance data will be summarized based on the Safety Population.

For statistical analysis purposes, previous therapies/procedures are defined as those ending at Baseline or before; and concomitant therapies/procedures are defined as those ongoing at the Baseline visit or starting after the Baseline visit.

Treatment-emergent Adverse Events (TEAEs) are defined as AEs with onset on or after first dose of study drug; or those AEs with onset prior to first dose of study drug but worsened during treatment.

TEAEs will be tabulated in frequency tables by System Organ Class (SOC) and Preferred Term (PT) based on the Medical Dictionary for Regulatory Activities (MedDRA). Additional summary tables will be provided for SAEs, AEs considered related to the study drug, severe AEs, AESIs, and AEs leading to discontinuation. For a given AE, a subject will be counted once even if he/she has experienced multiple episodes of that particular AE.

In addition, non TEAEs will be summarized or listed separately.

For local tolerability (erythema, scaling, dryness, stinging/burning), data will be summarized for worst score over treatment period, the final score during treatment, as well as scores for each visit.

The quality of life indices, EQ-5D-5L, COMPAQ (including the anchor question), C-DLQI, and DLQI will be summarized descriptively.

Subgroup analyses will be explored by analysis center, age (<18 years, ≥18 years), gender and race if appropriate for efficacy endpoint, and safety endpoints (TEAEs and Local tolerability).

Further details will be provided in the SAP.

9.1.3.1 Imputation of missing data

The last observation carried forward (LOCF) will be used to impute efficacy endpoints, where applicable. Non-responder analysis will also be carried out for Binary endpoints.

Further details will be provided in the SAP.

9.1.3.2 Statistical hypothesis testing and multiplicity adjustment

Analysis of Efficacy Endpoint

All efficacy and patient reported endpoints will be summarized with point estimate and 95% confidence intervals.

Further details will be provided in SAP.

CCI

13.3 Dermatology Life Quality Index (DLQI™)

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	❒ ❒ ❒ ❒ ❒

17. My skin feels bumpy or uneven.									
18. My skin feels dirty.									
19. My skin is red.									
20. My skin causes me discomfort or pain.									

Since your baseline visit in this study, has there been any change in overall quality of life related to your acne?

RESPONSE RANGE:
Patient instructions: Please circle the number that best describes your response where -7 indicates a great deal WORSE and +7 indicates a great deal BETTER

-7 (a great deal WORSE) -6 -5 -4 -3 -2 -1 0 (No change) +1 +2 +3 +4 +5 +6 +7 (a great deal BETTER)

The above is based on this section of the paper for MCID determination for DLQI GRCQ
The GRCQ [4], used as an anchor, allows patients to give a self-assessment of the change since baseline assessment in, for example, overall QoL or severity of skin condition, whether it has improved, remained the same or deteriorated. It has a 15-point scoring system with responses ranging from a very great deal better (+7) to no change (0) to a very great deal worse (-7). The GRCQ with a 15-point scoring system was chosen to maximize the sensitivity of the responses. Respondents with scores of 0, -1 or 1 are classified as unchanged or having a small but unimportant change. Respondents whose scores are 2, 3, -2 or -3 are considered to have experienced a small change equivalent to the minimal important difference. Those with scores of 4, 5, -4 or -5 are considered to have experienced a moderate change, and those with scores of 6, 7, -6 or -7 are considered to have experienced a large change [3,4]. The question posed was: 'Since your first clinic visit, has there been any change in overall quality of life related to your skin disease?'
REF: Basra M, K, A, Salek M, S, Camilleri L, Sturkey R, Finlay A, Y: Determining the Minimal Clinically Important Difference and Responsiveness of the Dermatology Life Quality Index (DLQI): Further Data. Dermatology 2015;230:27-33. doi: 10.1159/000365390

1 BACKGROUND AND RATIONALE

1.1 Medical background and short rationale for the clinical trial

Acne is one of the most common skin disorders treated by dermatologists. While acne is highly prevalent in youth with around 85% of teenagers affected at some point in time.[1] In European populations over 70–80 % of all males will experience acne in some point of their lifetime. In the USA, acne has been reported to affect an estimated number of over 25 (17–45) million Americans.[2] As acne is a chronic and relapsing disease, normalizing follicular desquamation is then the key to achieve and maintain control of acne. It can persist for years and result in disfigurement and permanent scarring, and may have serious adverse effects on psychosocial development, resulting in emotional problems, withdrawal from society, and depression.[3] Teenagers with even mild acne feel stigmatized and frustrated.[4] Today it is established that retinoids acts in the pathology of acne vulgaris: it is a potent modulator of cellular differentiation and keratinisation. Topical retinoids have been the first-line treatment for most forms of acne vulgaris.[5]

Acne is a multifactorial inflammatory disease affecting pilosebaceous follicles.[6, 7, 2] Both clinically and pathophysiologically, truncal acne and facial acne are similar in terms of specific lesions (eg, closed comedones, open comedones, papules and pustules etc.). Further, the management of truncal acne vulgaris warrants an approach similar to what is used for the treatment of facial acne[8]. Truncal acne has been estimated to occur in over half the number of acne patients even if facial acne is the most common and often the most visible form of acne. In one study of patients referred to a dermatology clinic, it was found more than 60 percent of individuals had back acne [9]. In another cohort of 696 patients, half of patients with facial acne were found to have coexistent truncal involvement. Approximately 50% of patients who presented with acne vulgaris demonstrated involvement on the chest and/or back, with more than 3% presenting with truncal acne lesions alone. Interestingly, approximately 1 out of 4 patients who presented with both facial and truncal acne involvement did not voluntarily mention the presence of truncal acne as part of their presenting complaint. In such cases, the presence of truncal acne lesions was detected by clinical examination. The majority of patients presenting with truncal acne vulgaris exhibited mild to moderate severity and more than 75% were interested in treatment for truncal acne lesions. [10]

Trifarotene, a new generation topical retinoid with its unique mechanism of action, binds to specific retinoic acid receptor (RAR-ɤ).[11] Current evidence suggests that topical Trifarotene normalizes the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. It may be an ideal topical agent with high selectivity towards gamma receptors, skin metabolism and with very low systemic absorption for management of acne treatment. Currently under clinical development with studies in acne vulgaris of face and trunk. However, it is also important in terms of patient-reported outcomes (PRO) to assess satisfaction that might be caused by the treatment or by acne itself and to also assess the local tolerability.

Proper skin care is considered to be an important component of the total management plan for patients with acne vulgaris. There are several ways to mitigate adverse effect and prevent further worsening of skin tolerability. These include initiating patients on lower concentrations of topical retinoids, choosing cream or lotion (rather than gel). Trifarotene, being a highly selective RAR-ɤ

CCI

[redacted]

CCI

If prohibited therapies become a necessary treatment for the safety or best interest of the subject, GALDERMA should be notified to discuss possible alternatives prior to administration of a prohibited therapy.

If a subject receives prohibited therapy during the clinical trial, GALDERMA should be notified to discuss the pertinence and the modalities for the subject to continue in the clinical trial.

5.6 Procedures/reasons for subject 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 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.

When a subject does not complete the clinical trial, he/she will be fully assessed, if such assessment is possible. The procedures designated for the Week 24/Early Termination visit should be completed for all subjects discontinuing the clinical trial and the appropriate CRF page should be completed.

All discontinuations and the reason for discontinuation are to be documented by the Investigator on the Exit Form, and also on the Adverse Event Form for discontinuation due to an AE.

For discontinuation due to an AE, the Investigator should ensure that the subject receives suitable therapy for his/her 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.

GALDERMA R&D may also decide to prematurely terminate or suspend a subject's participation in the clinical trial.

Potential reasons for discontinuation, as listed on the Exit Form, are defined in Table 3 below:

The PGA is outlined in the following table CCI [redacted]

Physician Global Assessment Scale (PGA) Trunk		
0	Clear	Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost Clear	A few scattered comedones and a few small papules.
2	Mild	Easily recognizable; less than half the surface is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the surface is involved. Many comedones, papules and pustules. One nodule may be present.
4	Severe	Entire surface is involved. Covered with comedones, numerous papules and pustules. Few nodules may be present.

CCI [redacted]

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		
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

CCI

[redacted]

7.2.2 Adverse events

Adverse events are to be monitored throughout the course of the clinical trial. All AEs are to be reported on the Adverse Event Form 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 center personnel for reporting AEs and medical emergencies.

7.2.2.1 Definitions

7.2.2.1.1 Adverse events

No reasonable possibility:

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

7.2.2.2 Reporting procedures

7.2.2.2.1 Procedures for reporting adverse events

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

At each post-enrollment visit, the Investigator (or sub-Investigator) will question the subject about AEs using an open non-persuasive question to elicit reporting of AEs, for example: "Have you noticed any change in your health since the last visit?" Directed questioning and examination will then be performed, as appropriate.

Any AE occurring during the AE reporting period, whether it is related to the study drug or not, will be recorded immediately in the source document, and described on the Adverse Event Form along with the date of onset, severity, relationship to the study drug, and outcome, without omitting any requested and known information. Additional information may be requested under certain circumstances. Adverse Events 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.

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 7.2.2.2.2), AESIs (see Section 7.2.2.2.3), and pregnancies (see Section 7.2.2.2.5), the CSO is to be informed immediately by fax or email. The event must be reported by facsimile or scan and sent by e-mail to the CSO within 24 hours of knowledge of the event (contact details in Section 7.2.2.2.2).

7.2.2.2.2 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 the subject is the first priority.
2. Immediately inform the CSO of the event by fax or email and discuss further actions to be taken.

CCI

[redacted]

Table 5 Suspected sensitization - reaction grading

Score	Morphology	Interpretation
-	No skin changes in the tested area	Negative
?	Faint, non-palpable erythema	Doubtful reaction
+	Palpable erythema (moderate edema or infiltrate), papules not present or scarce, vesicles not present	Weak positive reaction
++	Strong infiltrate, numerous papules, vesicles present	Strong positive reaction
+++	Erythema, infiltration, confluent vesicles, bullae or ulceration	Extreme positive reaction
ir	Inflammation sharply limited to the exposed area, lack of infiltrate, small petechiae, pustules, and efflorescences other than papules and vesicles	Irritant reaction
Nt		Not tested

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

Table 6 Suspected sensitization - conclusion

summing the scores of each question, resulting in a maximum of 30 and a minimum of 0. A lower score on the DLQI indicated increased QOL; therefore, negative changes from Baseline indicate improvement. The meaning of the DLQI total scores were interpreted as: no effect (0-1), small effect (2-5), moderate effect (6-10), very large effect (11-20), or extremely large effect (21-30).
For the cDLQI:

The meaning of the DLQI total scores were interpreted as: no effect (0-1), small effect (2-6), moderate effect (7-12), very large effect (13-18),or extremely large effect (19-30).

The higher the score, the more quality of life is impaired. For instructions of use and scoring: http://sites.cardiff.ac.uk/dermatology/quality-of-life/dermatology-quality-of-life-index-dlqi/dlqi-instructions-for-use-and-scoring

The questionnaires completed will be considered as source data and the answers will be entered into the CRF by the site.

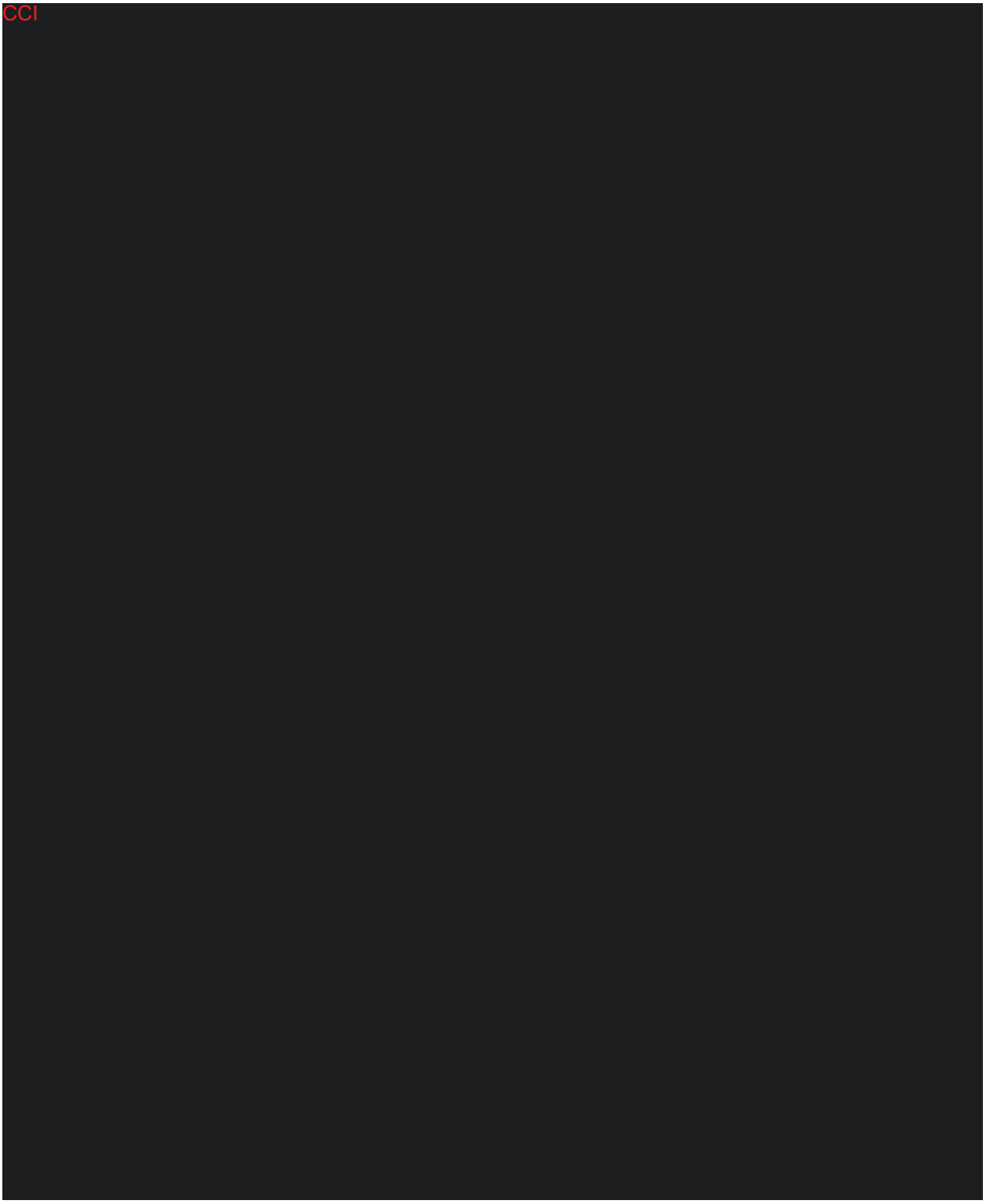
7.3.3 CompAQ for Facial and Truncal Acne

It will be collected at baseline, week 12 and 24/ early termination. The Investigator or designee should provide the subject (16 years of age and older) with the comprehensive QoL measure inclusive of facial and truncal form and instruct the subject to read and answer all 20 quality of life questions. The questionnaire will measure the impact of facial and torso acne on health-related quality of life.

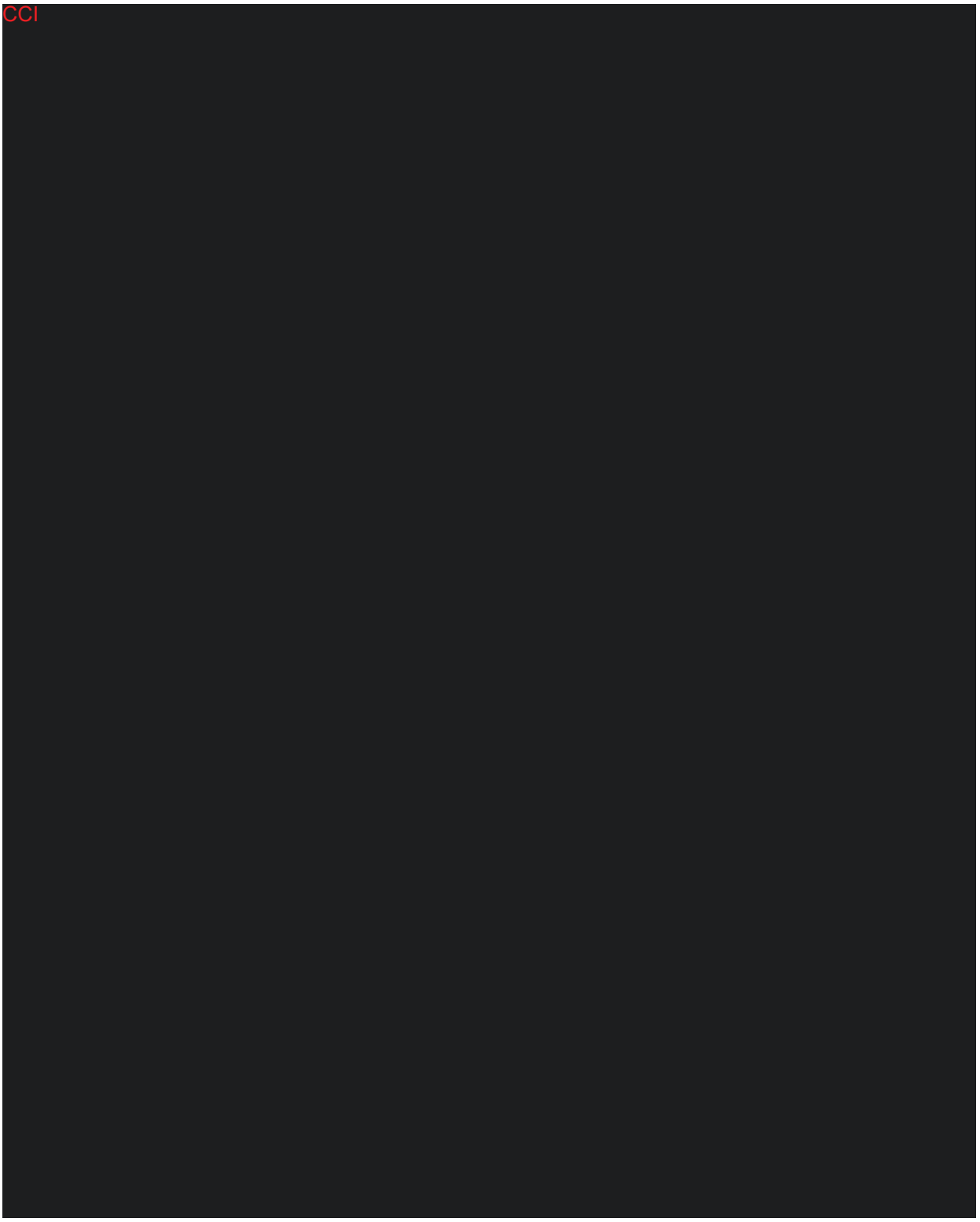
The 20 questions consists of 5 domains that assess a variety of psychosocial and physical impacts of acne: Psychological/Emotional, Social (Judgement From Others), Social Interactions, Treatment Concerns, Physical Symptoms. The score on the CompAQ has a possible range of 0 to 160. The higher the score, the more quality of life is impaired. For instructions of use and scoring (Chelsea McLellan, Marc P. Frey, Diane Thiboutot, Alison Layton, Mary-Margaret Chren, Jerry Tan, Development of a Comprehensive Quality-of-Life Measure for Facial and Torso Acne. Journal of Cutaneous Medicine and Surgery First Published January 31, 2018 https://doi.org/10.1177/1203475418756379)

An anchor question is added in order to detect responsivity with intervention and for Minimal Clinically Important Difference (MCID).

Higher scores indicate greater adverse impact
•The response range for each question is from 0–8 with higher numbers indicating greater adverse impact.
•For each domain, response range is from 0–32.
•For the long form questionnaire, response range is from 0–160
•For the short form questionnaire, response range is from 0–40
The investigator or delegate will then check all questions of the questionnaire for completeness prior to the subject leaving the office.

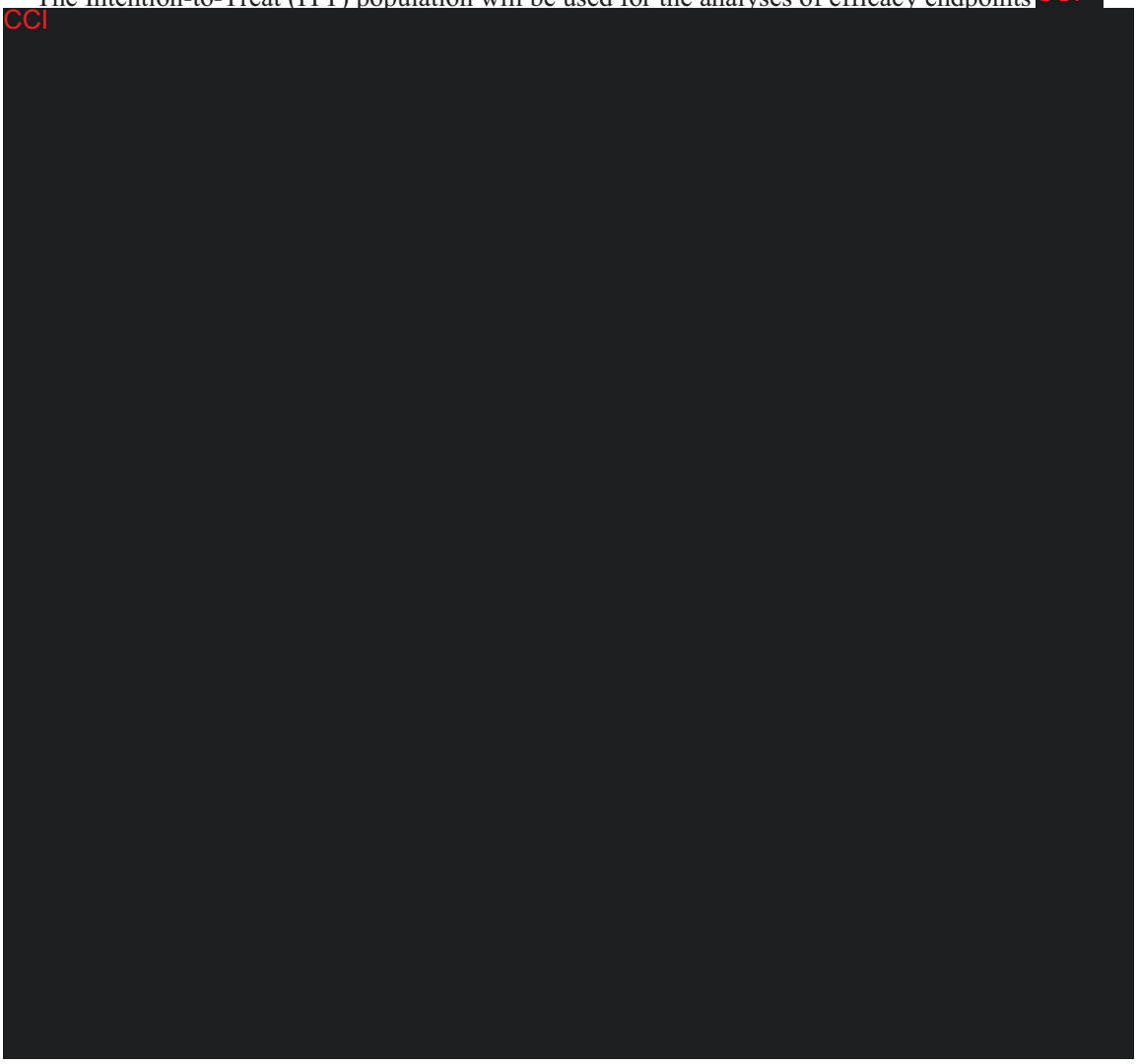

CCI

CCI



9.1.2 Populations analyzed, evaluability and limitation / evaluation of bias

The Intention-to-Treat (ITT) population will be used for the analyses of efficacy endpoints CCI



9.1.3 Data presentation and graphics

For statistical analyses purpose, baseline is defined as the last measurement prior to the first application of the study drug and all analyses will be summarized by visits.

For the summary statistics, the categorical data will be summarized by frequency and percentage of subjects for each response category (N, %) and the continuous data will be summarized using number of subjects, mean, median, minimum, maximum, and standard deviation.

9.2 Sample size determination

There is no formal hypothesis to be tested. An estimation approach will be performed. Point estimate and 95% confidence interval will constructed. Approximately 50 subjects will be enrolled to evaluate the subject reported outcomes (quality of life and satisfaction survey).

10 TRAINING / MONITORING / DATA MANAGEMENT / QUALITY ASSURANCE

10.1 Personnel training

Investigators training will occur on-site during the site initiation visit. It is recommended that all investigators, other evaluators, study coordinators and other applicable personnel attend the site initiation visit. During these meetings/trainings, CCI [redacted]

CCI [redacted]

All sites must complete photography training and submit test photos of all required light conditions CCI [redacted]

The Investigators and study coordinators are expected to attend the Investigator receive on-site training during the site initiation visit prior to participating in the procedures and evaluations in this study. Each site will have a training record as part of the site file and Trial Master File. An Investigator Site File will be provided to each study center.

A study initiation visit will be conducted for each study center prior to enrollment of any subjects.

CRAs and other applicable personnel will be trained prior to study initiation to familiarize CRAs with the disease, the Standard Operating Procedures (SOP), the protocol and other study specific items. Team organization, communication and operational issues will also be discussed.

10.2 Clinical monitoring

The conduct of the clinical trial will be closely monitored by representatives of GALDERMA R&D and/or Contract Research Organization (CRO) to verify adherence to the clinical trial protocol, ICH-GCP guidelines, and applicable SOPs/study procedures.

CCI

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 that you have answered EVERY question. Thank you.

13.6 EuroQoL 5-Dimension (EQ-5D-5L)

EuroQoL 5- Dimension (EQ-5D-5L)

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking	❑
I have slight problems walking	❑
I have moderate problems walking	❑
I have severe problems walking	❑
I am unable to walk	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN / DISCOMFORT

I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑