CLINICAL TRIAL PROTOCOL
PROTOCOL NUMBER: RD.06.SPR.118295

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TITLE PAGE

Title A Multi-Center Study to evaluate Subject Reported Outcomes with use of Trifarotene 50 µg/g cream in the treatment of moderate facial and truncal acne vulgaris		
Project Name or CD number: CD5789	**Project Number:** 02232	**Clinical Trial Phase:** IIIb

IND Number 111091

SPONSOR:

Name:	GALDERMA RESEARCH & DEVELOPMENT, LLC
Address:	14501 North Freeway Fort Worth, TX 76177
Telephone:	(817) 961-5000

For any safety questions, please contact the Clinical Safety Officer (CSO) using the contact details provided in Section 7.2.2.2.2.

For any medical questions related to the clinical trial protocol, please contact the Medical Expert using the contact details below:

Name and Title:	PPD , MD, Medical Expert
Address:	Galderma R&D, LLC 14501 North Freeway Fort Worth, TX 76177 USA
Telephone (mobile):	PPD
Fax:	PPD
E-mail:	PPD

This clinical trial will be performed in compliance with applicable regulatory requirements and Good Clinical Practice (GCP). This clinical trial protocol follows guidelines outlined by the International Conference on Harmonisation (ICH) and the Galderma template.

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SYNOPSIS	
Clinical Trial Title: A Multi-Center Study to Evaluate Subject Reported Outcomes with use of Trifarotene 50 µg/g Cream in the Treatment of Moderate Facial and Truncal Acne Vulgaris	
Short Title: Subject Reported Outcomes with use of Trifarotene 50 µg/g Cream in Subjects with Moderate Facial and Truncal Acne Vulgaris	
Lay Title: Studying the Effects of 50µg/g Cream on Subjects who have Acne	
Clinical Trial phase:	IIIb
Clinical Trial Population:	Subjects with moderate acne vulgaris with facial and truncal acne involvement
Clinical Trial objectives:	The purpose of this study is to evaluate subject reported outcomes with Trifarotene cream.
Clinical Trial design:	Multi-center, open label, single arm study of Trifarotene cream applied once daily in the evening for 24 weeks.
Total number of subjects (Planned):	Approximately 50 subjects will be enrolled in order to obtain 40 subjects at completion.
Number of clinical trial centers (Planned):	CCI [redacted]
Region(s) / country(ies) involved (Planned):	United States
Clinical trial duration:	CCI [redacted]
Duration of subject participation:	Clinical trial participation for each subject is approximately 24 weeks of study treatment ±3 days. Note: Subjects, upon study completion/early termination, will return to standard of care with their physician.
Key inclusion criteria	1. Male or female, 9 years of age and older, at the Screening visit. 2. The Subject has a facial acne CCI [redacted]. CCI [redacted]
Key exclusion criteria	1. The subject has severe forms of acne (e.g., acne conglobata, acne fulminans) or secondary acne form (e.g.,chloracne, drug-induced acne, etc.).

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Clinical Trial Title: A Multi-Center Study to Evaluate Subject Reported Outcomes with use of Trifarotene 50 µg/g Cream in the Treatment of Moderate Facial and Truncal Acne Vulgaris	
	CCI [redacted]
	8. The subject has any uncontrolled or serious disease or any medical or surgical condition that may either interfere with the interpretation of the trial results and/or put the subject at significant risk (according to the Investigator's judgment) if the subject takes part to the trial. 9. The subject has known or suspected allergies or sensitivities to any components of any of the study drugs (see Investigator's Brochure).
Investigational product:	CCI [redacted]
Location of treated area:	Face: Chin, left cheek, right cheek, nose, and forehead Truncal region : right and left upper back, right and left shoulders and right and left upper anterior chest CCI [redacted]
Efficacy Assessments :	**Efficacy 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.

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Clinical Trial Title: A Multi-Center Study to Evaluate Subject Reported Outcomes with use of Trifarotene 50 µg/g Cream in the Treatment of Moderate Facial and Truncal Acne Vulgaris	
	▪ 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. ▪ Subject's assessment of facial acne improvement
Safety assessment:	Safety assessments will be conducted for all subjects at Screening/baseline and all subsequent visits until the Week 24 Visit. The safety parameters are Adverse Events, local tolerability assessments.
Measurement criteria	**Subject-reported outcomes** Quality Of Life questionnaires: • *Dermatology Life Index questionniare (DLQI) questionnaires* comparing Baseline to Weeks 12 and 24 or Early termination • CompAQ (for >16 years age) comparing Baseline to Weeks 12 and 24 or Early termination • EQ-5D-5L comparing Baseline to Weeks 12 and 24 or Early termination • *Subject satisfaction questionnaire* at Week 12/24/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. Total lesion, non-inflammatory lesion (open and closed comedones), inflammatory lesion (papules, pustules) on the face (including the nose) at each visit • *Physician Global Assessment (PGA)*: acne severity of the trunk on a scale from 0 (Clear) to 4 (Severe) at each visit. Total lesion, non-inflammatory lesion (open and closed comedones), inflammatory lesion (papules, pustules) on trunk at each visit CCI [redacted] **Safety** • *Local tolerability parameters* (erythema, scaling, dryness and stinging/burning) will be evaluated at each visit on a 4-point scale ranging from 0 (none) to 3 (severe). CCI [redacted] • *Adverse Events* which includes AEs, SAE, AESI and Death **Other** CCI [redacted]

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Analysed variables	**Subject-reported outcomes** • DLQI/cDLQI and CompAQ at Baseline and Week 12, 24/Early termination • Subject satisfaction questionnaires at Week 12, 24/Early termination • EQ-5D-5L at baseline and Week 12, 24/Early termination **Efficacy variable** • CCI Percent change in the facial IL NI CCI lesion count from Baseline to Weeks 12 and 24 • CCI Percent change in the trunk IL, NI CCI lesion count from Baseline to Weeks 12 and 24 • Success rate of IGA as the percentage of subjects who achieved an IGA with a score of 1 (almost clear) or 0 (Clear) AND an at least a 2-grade improvement from Baseline at each study visit. • Success rate of PGA as the percentage of subjects who achieved a PGA with a score of 1 (almost clear) or 0 (Clear) AND an at least a 2-grade improvement from Baseline at each study visit. CCI CCI **Safety variables** • Local tolerability parameters will be assessed at Baseline and each post baseline visits, on all treated areas. CCI • Local tolerance: Raw value at each visit and worst-score across vist, % of Subjects across scores at each post-baseline visit • Incidence of adverse events (AESI, SAEs, Death, leading to discontinuation or early termination) **Other** CCI
Principal statistical method:	The Intent-to-Treat (ITT) population consists of all enrolled subjects. The Safety population (SAF) consists of the ITT population, who applied at least one dose of treatment. The main objective of this study is to evaluate the subject reported outcomes with trifarotene with 12 and up to 24 weeks of treatment. All variables will be descriptively summarized. All safety endpoints will be sumarized based on SAF population and Quality of life and Efficacy endpoints will be sumarized

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	using ITT population. The last observation carried forward (LOCF) method will be used to impute missing efficacy values where applicable. There is no formal hypothesis to be tested. An estimation approach will be performed. Point estimate and 95% confidence interval will be constructed where possible. Approximately 50 subjects will be enrolled to evaluate the subject reported outcomes (quality of life and satisfaction survey). The sample size is not based on any formal hypothesis testing.

Table 1 Clinical trial schematic

Table 2 Schedule of assessments

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	*Term*
°C	Degrees Celsius
°F	Degrees Fahrenheit
AE	Adverse Event
AESI	Adverse Event of Special Interest
CDLQI	Children's Dermatology Life Quality Index
CDMS	Clinical Data Management System
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CSO	Clinical Safety Officer
CSR	Clinical Study Report
DLQI	Dermatology Life Quality Index
DMP	Data Management Plan
EDC	Electronic Data Capture
e.g.	For Example (Latin: exempli gratia)
ET	Early Termination
etc.	*Et cetera*
FDA	Food and Drug Administration
FSI	First Subject In (first subject screened, i.e. who signs the Informed Consent Form)
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
i.e.	That is (Latin: id est)
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intention-to-treat
ITTT	Intent-to-treat on the Trunk
IUD	Intrauterine Device
LOAEL	Lowest-observed-adverse-effect level

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

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

with low concentration and in cream formulation with adequate recommendations for its use, would be appropriate in acne subjects. Skin irritation can lead to poor compliance and subsequently lack of efficacy. Therefore, adapted treatment instructions for use especially during the first weeks of treatment may result in a better tolerability, leading to improved compliance, efficacy, and patient satisfaction. Hence, the addition of a topical gentle moisturizer for these subjects and recommendation for avoiding sun exposure is a part of the skin care regimen for these acne subjects.[12, 13] Minimizing skin irritation and photoprotection can be achieved by the use of non-comedogenic moisturizers with appropriate sun protection factor (SPF) of 30 or higher can hydrate and protect the skin from UV irradiation.[14, 15, 16]

Acne can persist for years and may seriously affect the psychosocial development, resulting in emotional problems, withdrawal from society, and depression.[3] 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.[17] Therefore, this study aims to evaluate acne subject's satisfaction and quality of life with Trifarotene medication, as it is known for topical retinoids to be sensitive on skin. The local tolerance of the treatment in terms of erythema, scaling, dryness, stinging/burning will also be evaluated.

This clinical trial is designed to evaluate the PRO with use of Trifarotene in subjects with moderate facial and truncal acne vulgaris and also to assess the impact of such treatment instructions on overall efficacy, subject satisfaction, and safety, with management of skin irritation which was not specifically evaluated during the clinical development.

1.2 Drug profile

Retinoids play a central part in the treatment of acne due to their keratolytic activity and modulation of proliferation and differentiation of keratinocytes leading to the elimination of the comedone. [18]

Retinoids exert their effects on a molecular level through nuclear receptors: Retinoic Acid Receptor (RAR) and Retinoic X Receptor (RXR), which each have three sub-types α, β and γ.

Trifarotene, developed by GALDERMA R&D for topical administration, shows selective binding to RAR and not to RXR. CCI [redacted]

1.3 Risk/benefit assessment

The most serious risk associated with retinoids is related to teratogenicity and embryotoxicity. Systemic exposure to Trifarotene, like all retinoids, may cause fetal harm following systemic exposure in pregnant women.

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[redacted]

Taken the documented effectiveness of Trifarotene cream 50µg/g in the treatment of acne, the risk/ benefit assessment is supportive of the study.

2 CLINICAL TRIAL OBJECTIVES AND CLINICAL HYPOTHESIS

2.1 Clinical trial objectives

The purpose of this study is to evaluate subject reported outcomes with Trifarotene cream.

2.2 Clinical hypotheses

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[redacted]

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]

CCI

[redacted]

CCI [redacted]

4 CLINICAL TRIAL DURATION AND TERMINATION

The planned clinical trial duration (from FSI to LSO) is approximately CCI [redacted]. The date of end of the clinical trial is defined as the date of the last visit of the last subject who participates in the trial.

The planned duration of recruitment (i.e. From FSI to LSI) is approximately CCI [redacted].

Prior to subject enrolment, a screening period lasting CCI [redacted] at the maximum is authorized.

Clinical trial participation for each subject is approximately CCI [redacted]

GALDERMA may decide to prematurely terminate or suspend the participation of a particular clinical trial center (e.g., for non-inclusion or non-compliance with protocol, regulations, or GCP) or prematurely suspend the clinical trial (e.g., for safety, study drug quality, regulatory, efficacy, or logistical reasons) at any time, with appropriate notification.

5 SELECTION AND DISPOSITION OF CLINICAL TRIAL POPULATION

5.1 Number of subjects

CCI [redacted]

5.2 Clinical trial population characteristics

In order to be eligible for the trial, subjects must fulfill all of the following criteria at Baseline visit. Some criteria are to be checked at the Screening visit. Subjects may be re-screened once unless the reason for screen failure is related to acne severity (IGA or PGA) or lesion counts.

5.3 Inclusion criteria

1. The subject is a male or female, 9 years of age and older, at Screening visit.
2. Subject with clinical diagnosis of acne vulgaris, CCI [redacted]

a) Investigator's Global Assessment (IGA) score of 3 (Moderate) CCI [redacted]

b) Truncal acne severity grade of 3 (moderate) on the Physician Global assessment (PGA) scale CCI [redacted]

3. In general good health (physical, mental, and social well-being, not merely the absence of disease/infirmity), according to subject self-report.
4. Having Fitzpatrick skin phototype I-VI (refer to Fitzpatrick Skin Classification).
5. The subject is a female of non-childbearing potential (pre-menarcheal or postmenopausal [absence of menstrual bleeding for 1 year prior to Screening, without any other medical reason], hysterectomy or bilateral oophorectomy).
6. The subject is a female of childbearing potential:
   - 6.1. With a negative urine pregnancy test (UPT) at Screening and Baseline visits,
   - 6.2. Who are willing to take UPTs throughout the course of the study.
   - 6.3. Who has been strictly abstinent for 1 month prior to Screening/Baseline and agrees to continue for the duration of the clinical trial and at least 1 month after the last study drug application,

     OR

     Who agrees to use an effective and approved contraceptive method(s) for the duration of the study and at least 1 month after the last study drug application. An effective method of contraception is defined as:

     - 6.3.a. bilateral tubal ligation;
     - 6.3.b. approved combined oral contraceptives (estrogens and progesterone), implanted or injectable contraceptives, or hormonal contraceptive vaginal rings with a stable dose for at least 1 month prior to the Screening/Baseline visit;
     - 6.3.c. hormonal intra uterine device (IUD) inserted at least 1 month prior to the Screening/Baseline visit;
     - 6.3.d. vasectomized partner for at least 3 months prior to the Screening/Baseline visit.
7. If a female of childbearing potential uses combined oral contraceptives approved as acne treatments (e.g., Ortho Tri-Cyclen®, Yaz®, Diane-35®), the dose should be stable for at least 6 months prior to the Screening/Baseline visit.
8. For a pre-menstrual female who begins menses during the study:

8.1. Agrees to be strictly abstinent for the duration of the clinical trial and at least 1 month after the last study drug application,

OR

8.2. Agrees to use an effective and approved contraceptive method(s) for the duration of the study and at least 1 month after the last study drug application and agrees to undergo pregnancy tests. An effective method of contraception is defined as approved combined oral contraceptives (oestrogens and progesterone), implanted or injectable contraceptives, or hormonal intra-uterine device (IUD) or hormonal contraceptive vaginal rings.

CCI

10. The subject agrees to participate in the study, verified by dating and signing an approved written Informed Consent Form (ICF) or for subjects under age of majority, an assent form signed by the subject (if required) in conjunction with an ICF signed by the parent(s)/legal representative at the Screening visit before any study procedures.

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12. Apprised of HIPAA (Health Insurance Portability and Accountability Act) and is willing to share personal information and data, as verified by signing a written authorization at the Screening/Baseline visit.

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For subjects under the age of 18:

15. Having a parent or legal guardian who is 18 years of age or older and presents proof of guardianship (eg, insurance card, certificate of residence, or copy of officially issued family registration) at screening/baseline visit.

5.4 Exclusion criteria

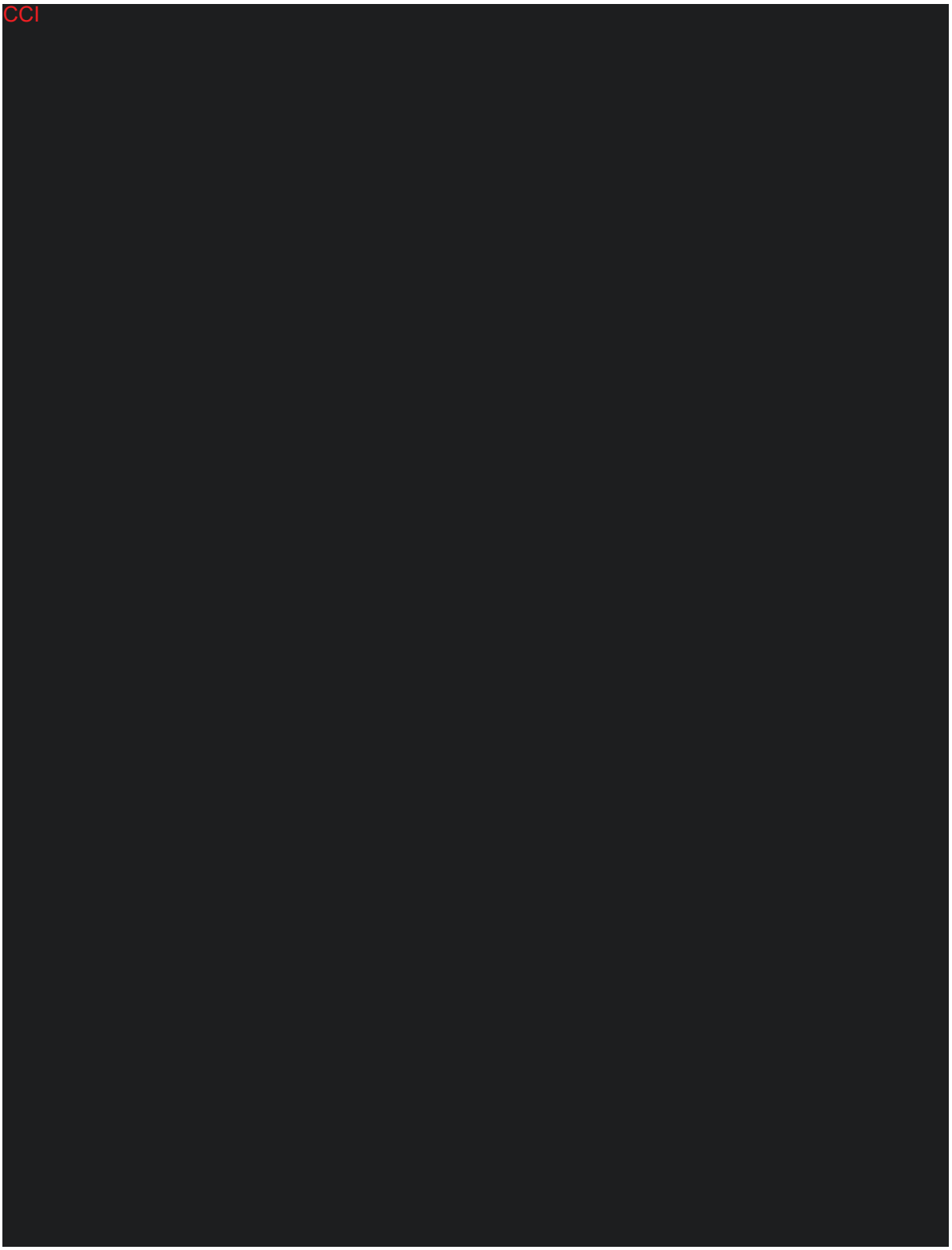
1. Subject with severe acne (IGA or PGA > 3).
2. The subjects has severe forms of acne (eg, acne conglobate, acne fulminans) or secondary form (eg. Chloracne, drug-induced acne, etc).

3. The subject has any acne cyst on the face at Screening and Baseline.
4. The subject has any acne cysts on the trunk at Screening and Baseline.

CCI

[redacted]

CCI



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[redacted]

5.5 Previous and concomitant therapies

5.5.1 Definition

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[redacted]

Concomitant therapies are defined as follows:

- any existing therapies ongoing at the baseline visit or starting after the baseline visit, 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 with start on or after the baseline 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 (done during visit or by call) for a chronic condition, etc.

5.5.2 Categories

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

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

5.5.3 Recording

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

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5.5.5 Prohibited concomitant therapies

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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:

Table 3 Exit Form reasons for discontinuation

Pregnancy:	**Withdraw the Subject from the clinical trial and follow the procedure described in Section 7.2.2.2.5.**
Lack of Efficacy:	Investigator judgment only: based on therapeutic/disease-state expectations. If subject opinion only, mark “subject request” and document it in the comment section of the Exit Form.
Adverse Event:	Complete an Adverse Event Form.
Subject Request[a]:	Includes consent withdrawal, subject relocation, schedule conflicts. Explain the reason for withdrawal in the comment section of the Exit Form. If a subject withdraws consent because of an adverse event, the reason for discontinuation should be Adverse Event
Protocol Violation:	Explain the violation in the comment section of the Exit Form.
Lost to Follow-up:	Confirmed with two documented phone calls and a certified letter (delivery receipt requested) without answer. Explain in the comment section of the Exit Form.
Other[a]:	This category is to be used for a subject who discontinues due to a reason other than as specified in the predefined categories above. Explain the reason for discontinuation in the comment section of the Exit Form.

a) If reason for discontinuation is “subject request” or “other”, the subject will be questioned to rule out the possibility of an AE (this should be documented in the comment section of the Exit Form).

6 CLINICAL SUPPLIES

6.1 Clinical supply identification and use

6.1.1 Study drug description

Table 4 Description and usage of the study drug

	Investigational Product
Trade Name or Equivalent	N/A
Name of Drug Substance	Trifarotene
Internal Code	CCI
Pharmaceutical Form	Cream
Strength/ Concentration	50 µg/g
CCI	
Location of Treated Area	Face and truncal region CCI
CCI	

N/A=not applicable

6.1.2 Subject identification number

Upon signature of the ICF (and Assent for minor subjects) each subject will be assigned a Subject Identification Number (SIN) by the designated study personnel.

CCI [redacted]

6.1.3 Kit number

The kit number, a unique number corresponding to the number on the label of the study drug, will be assigned to each eligible subject at Baseline. CCI [redacted]

CCI [redacted]

6.1.4 Instructions for use and application

Each subject will receive both oral and written instructions for the proper dosing and study treatment application techniques. CCI [redacted] As well, the dosing calendar completion will be explained to each subject at each dispensation visit.

Applications will be done by the subjects themselves at home in the evening. CCI [redacted]

Application on the face:

CCI [redacted]

CCI [redacted]

The study drug will be applied to the facial region which includes the forehead, nose, chin and each cheek once daily in the evening after washing and drying.

The objective is to cover the face with a thin layer of the study drug, CCI [redacted] One pump actuation should be enough to cover the forehead, right cheek, left cheek, nose, and chin. Avoid application in/close to eyes, or angles of the mouth, lips and mucous membrane.

CCI [redacted]

Application on the trunk:

CCI [redacted]

The study drug will be applied to the upper truncal regions CCI [redacted] once daily in the evening after washing and drying.

The objective is to cover the reachable upper truncal region with a thin layer of the study drug, CCI [redacted] Two actuations of the pump should be enough to cover right and left upper back area CCI [redacted] and upper anterior right and left chest. Avoid application on the axillary region and anterior and posterior neck.

The study drug should not be applied to cuts, abrasions, eczematous, or sunburned skin.

The daily dairy is to be completed by the subject (if needed, with the help of the legal guardian) and returned to the site at each study visit.

6.1.5 Other supplies

CCI [redacted]

CCI

[redacted]

6.2 Study drug packaging and labeling

Each subject kit is comprised of an outer box enclosing CCI dispensing boxes labeled with an affixed and a tear-off portion.

Each dispensing box will contain CCI pumps, also with labeling.

CCI

[redacted]

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

6.3 Supplies management

6.3.1 Accountability

Upon receipt of the study drug, the site personnel responsible for managing the supplies must conduct a complete inventory of all study drugs.

The investigator or designee will maintain accurate records of supplies received, inventoried at the clinical trial site and used per subject.

CCI

[redacted]

All study drug sent to the Investigator/Institution will be accounted for and no unauthorized use is permitted. CCI

[redacted]

6.3.2 Storage of clinical study drug

Study drug must be stored in a safe and secure area with restricted access; under the storage conditions specified by GALDERMA R&D (see Table 4).

6.3.3 Dispensing and return

6.3.3.1 Dispensing

Designated study personnel at each investigational site will be responsible for dispensing the study drug at the appropriate visits and will record the dispensing information for each subject.

CCI [redacted]

6.3.3.2 Return

Each subject will be instructed on the importance of returning their study drug bottle pumps (used and/or unused) CCI [redacted] Drug accountability will be done upon return by the designated clinical trial center personnel.

CCI [redacted]

For subjects who do not complete the entire clinical trial, all used and unused study drug should be returned by the subjects to the defined personnel at the clinical trial center.

6.3.4 Treatment compliance management and record

Subjects will be instructed by study personnel on the importance of being compliant with the use of the study drug throughout the clinical trial.

A subject daily diary will be provided to the subject with clear direction from the study site personnel at each dispensation visit. Each subject will complete the daily diary CCI [redacted] Subjects will also be questioned about the number of missed applications (if any) between study visits.

Treatment compliance will be assessed using the subject daily diary. CCI [redacted]

CCI [redacted]

6.4 Dose modification

Subjects are encouraged to use from the Baseline visit and throughout the study the provided moisturizer, CCI [redacted]

Signs and symptoms of local cutaneous irritation assessed with a local tolerability scale will be considered as Adverse Events CCI [redacted]

7 CLINICAL TRIAL ASSESSMENT

7.1 Efficacy assessments

IGA and PGA assessments are to be performed by a qualified evaluator. CCI [redacted]

CCI [redacted]

7.1.1 Efficacy measurements

IGA/PGA and Lesion Counts will be performed for face and trunk separately. CCI [redacted] Refer to Appendix 13.8.

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]

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]

CCI

[redacted]

7.1.2 Efficacy endpoints

- Efficacy Endpoint: The efficacy endpoint consists of the following:
  - 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]

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

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

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.

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.

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]

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

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

CCI

[redacted]

b) 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.

7.2.2.2.5 Procedures for reporting pregnancies

Any pregnancy occurring during clinical trials, where the fetus could have been exposed to the study drug, must be monitored until its outcome in order to ensure the complete collection of safety data on GALDERMA R&D products.

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

1. Withdraw the subject from the clinical trial.

CCI

[redacted]

5. At the outcome of the pregnancy, complete the Pregnancy Surveillance Form – Part II: Course and Outcome of Pregnancy, as fully as possible. Inform the CSO by telephone, then fax or scan and send by e-mail this pregnancy form to the CSO within 24 hours.
6. If the pregnancy leads to an abortion (voluntary, spontaneous or therapeutic), in-utero death, or congenital anomaly, follow the procedure for declaration of an SAE (see Section 7.2.2.2.2).

7.3 Other assessments

7.3.1 Photographs

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

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.

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

At baseline and weeks 12 and 24/Early termination, subject will complete the EQ-5D-5L (Appendix 13.6).

EQ-5D-5L is a validated questionnaire for the assessment of the general health state. It contains two parts: a descriptive system and a VAS. The descriptive system is made up of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The VAS consists of a vertical line where the subject can assess his or her own health status. EQ-5D-5L will be administered according to the schedule of assessments only to the subset of subjects who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries).

7.3.5 Subject satisfaction questionnaire

At weeks 12 and 24/Early termination, subject will complete a satisfaction questionnaire regarding the investigational products they have been using in this trial (see Appendix 13.1). CCI [redacted]

7.3.6 Study drug acceptability questionnaire

At weeks 12 and 24/Early termination, subjects will complete an acceptability questionnaire regarding use of the study drug (see Appendix 13.2).

8 CLINICAL TRIAL VISITS DESCRIPTIONS AND PROCEDURES

8.1 Description of clinical trial visits

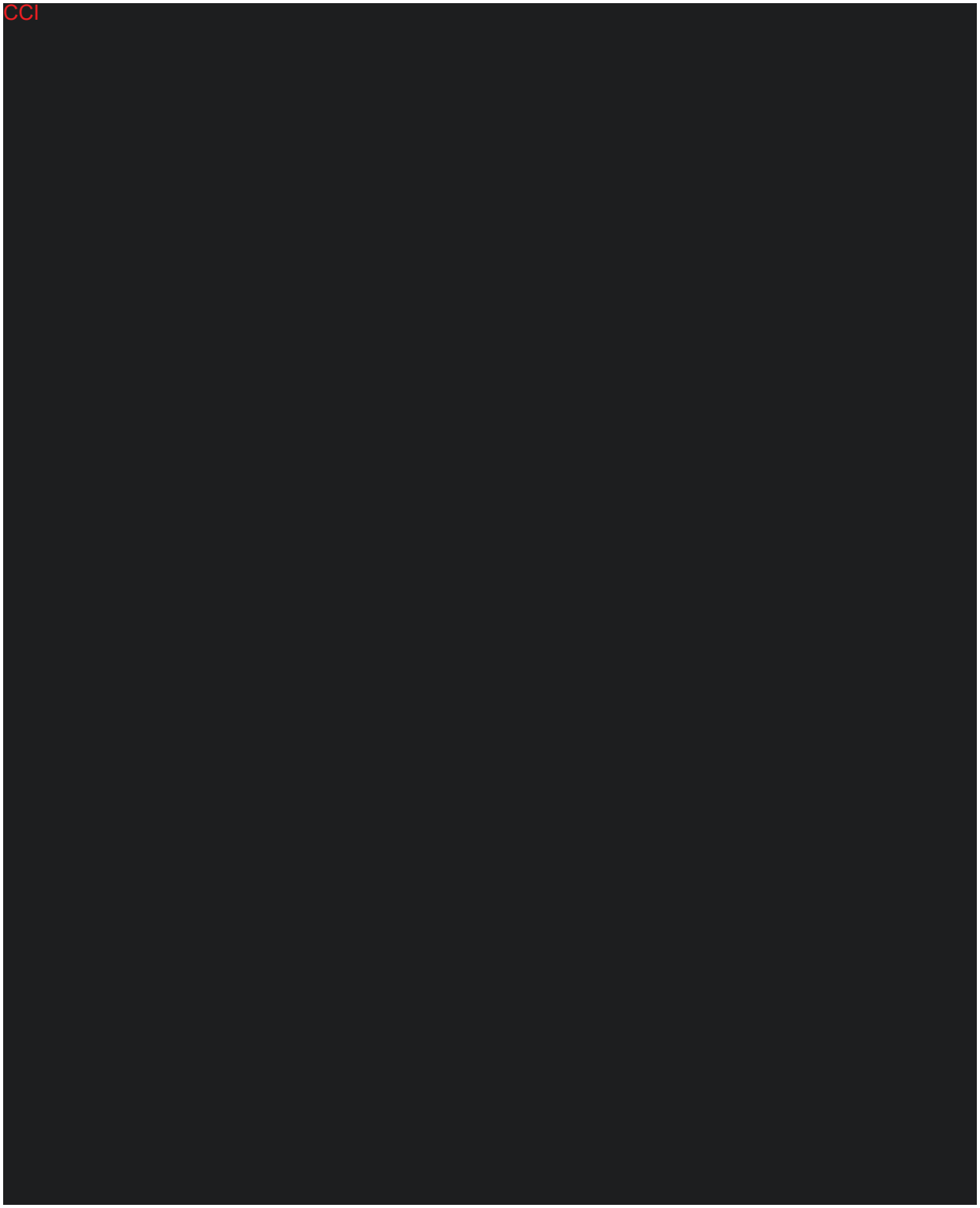
Please refer to the Schedule of Assessments table in the Synopsis (Table 2).

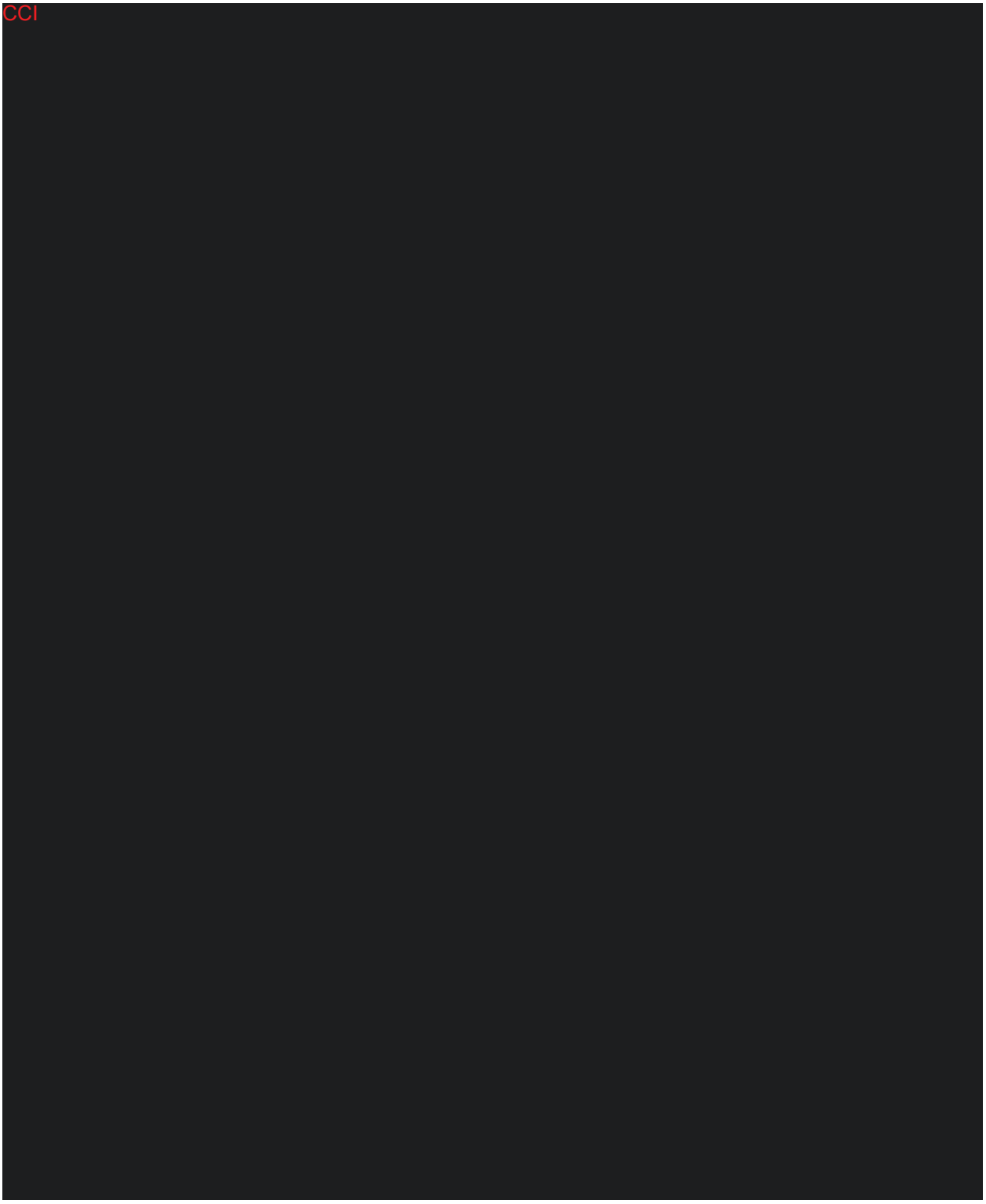
CCI [redacted]

A written, dated, initialed and signed ICF, Assent Form for minors, HIPAA, and Photo Consent Form or Photo Assent form, must be obtained prior to performing any clinical trial-related evaluations and/or procedures.

CCI [redacted]

CCI

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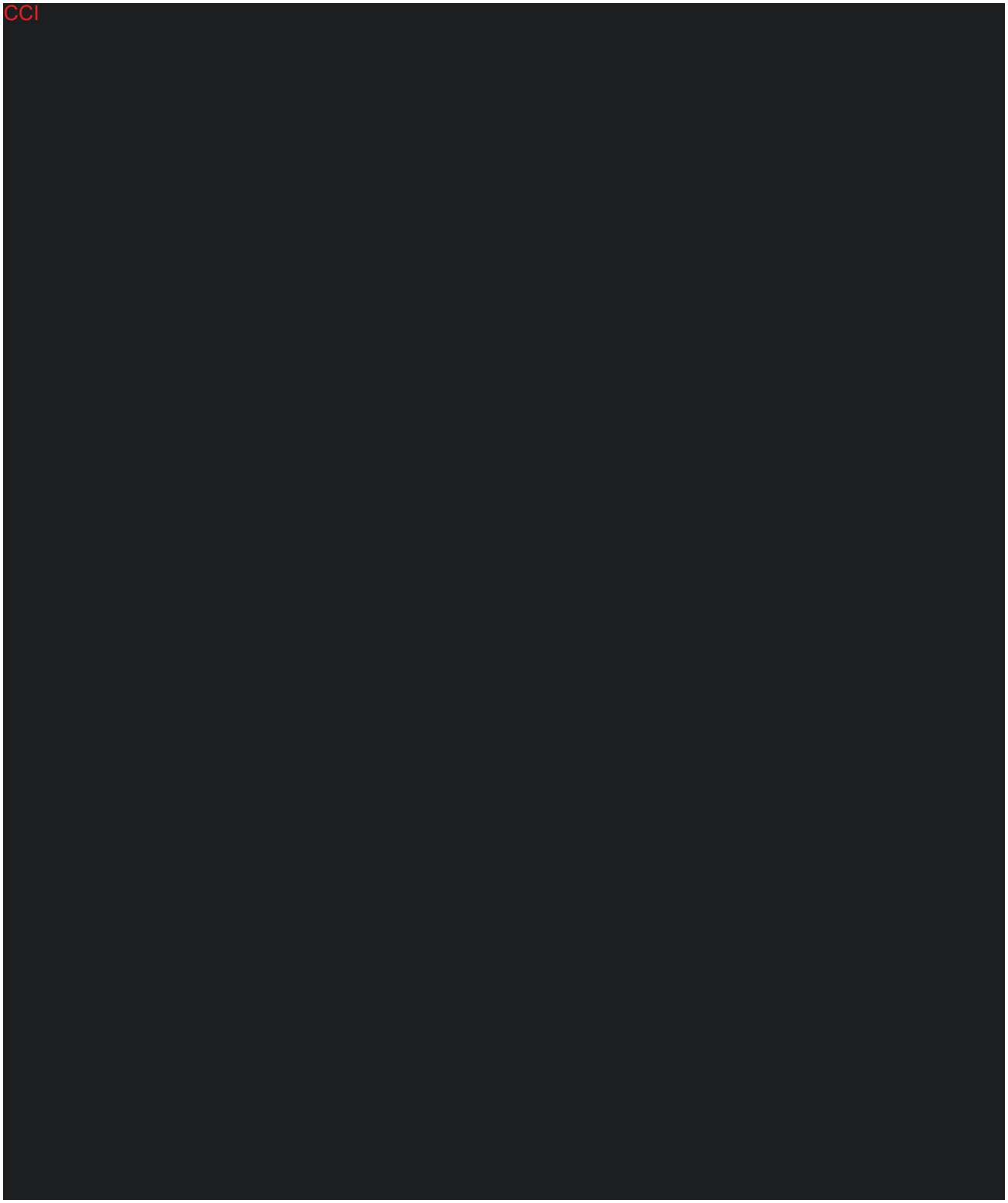

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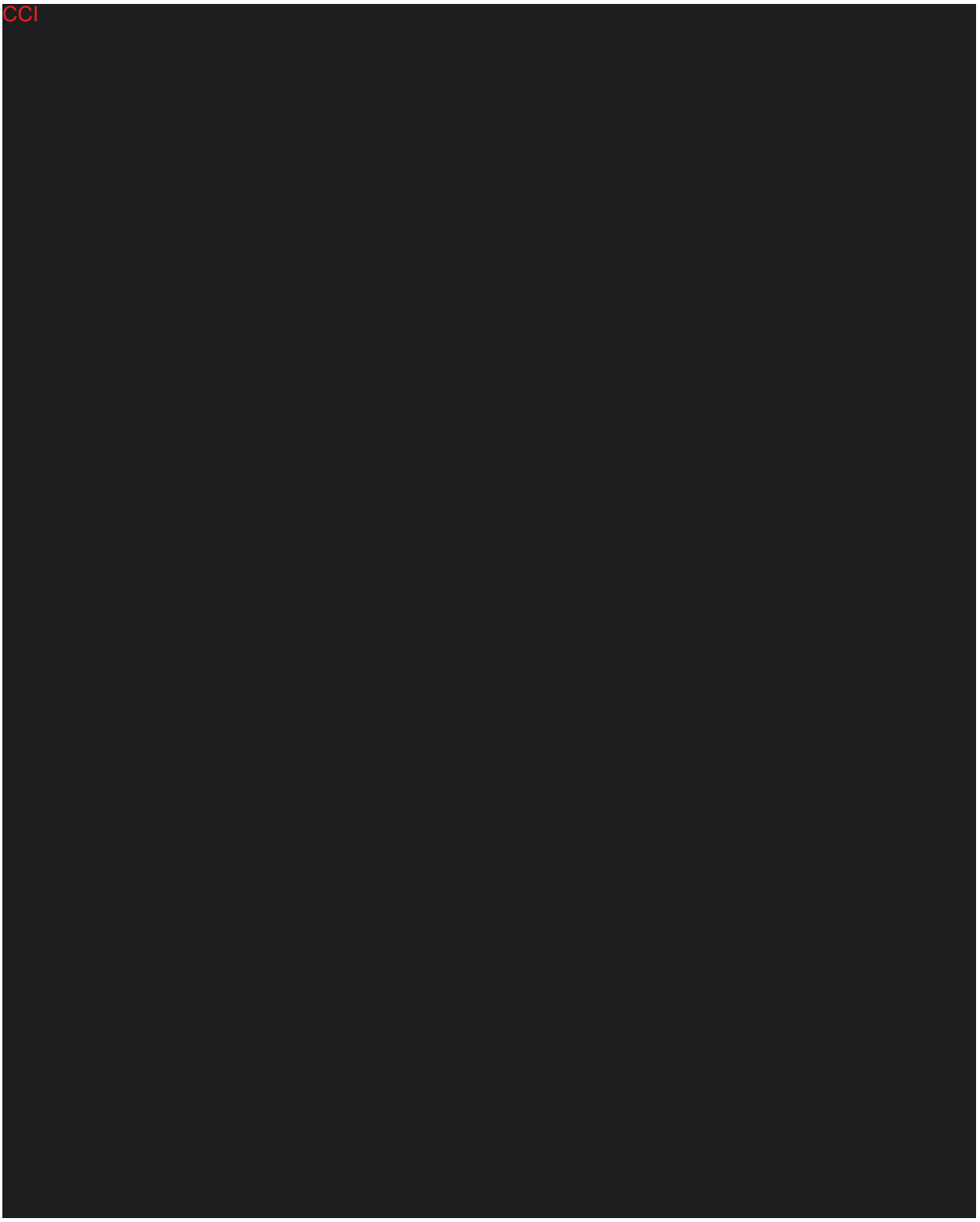

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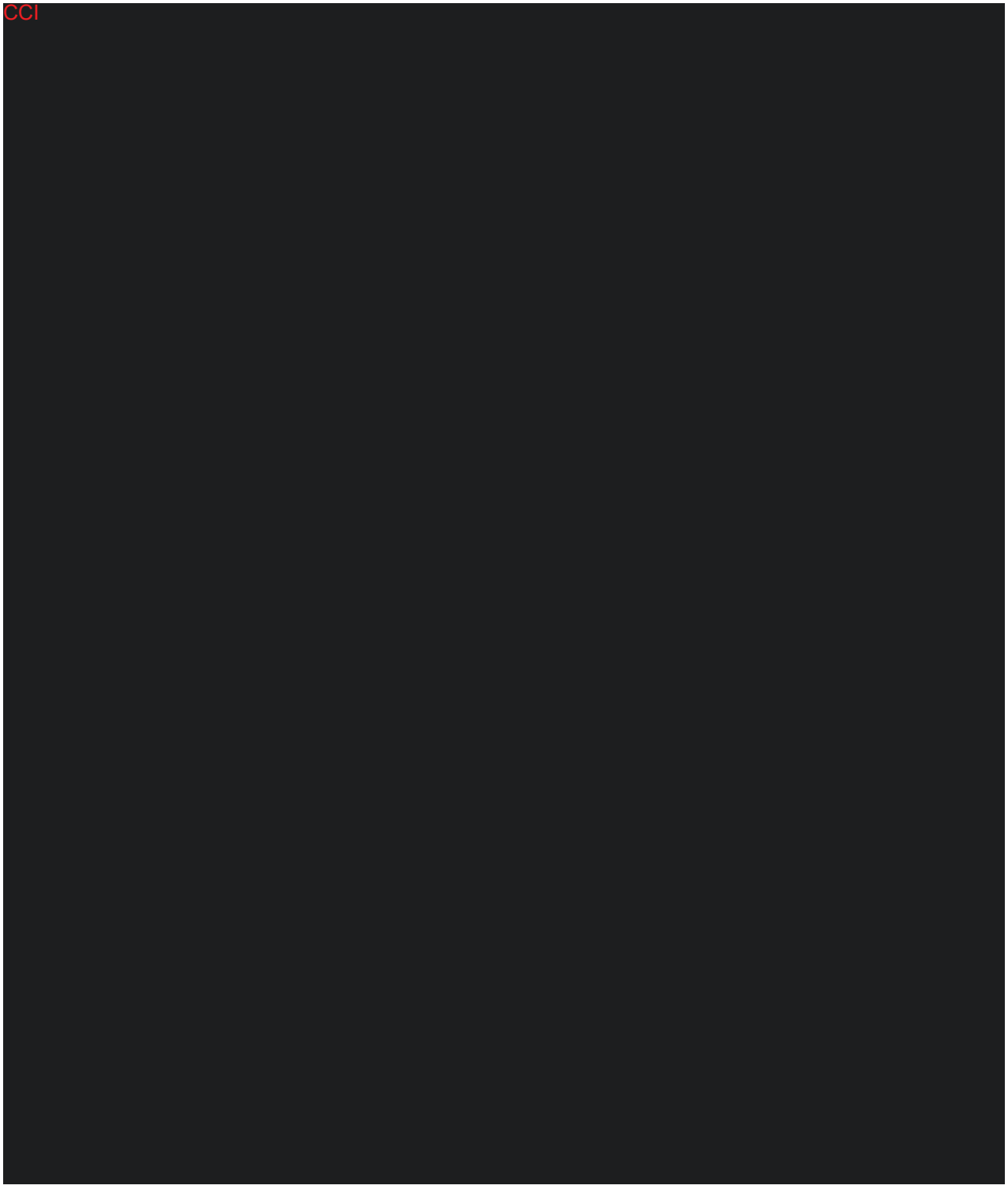

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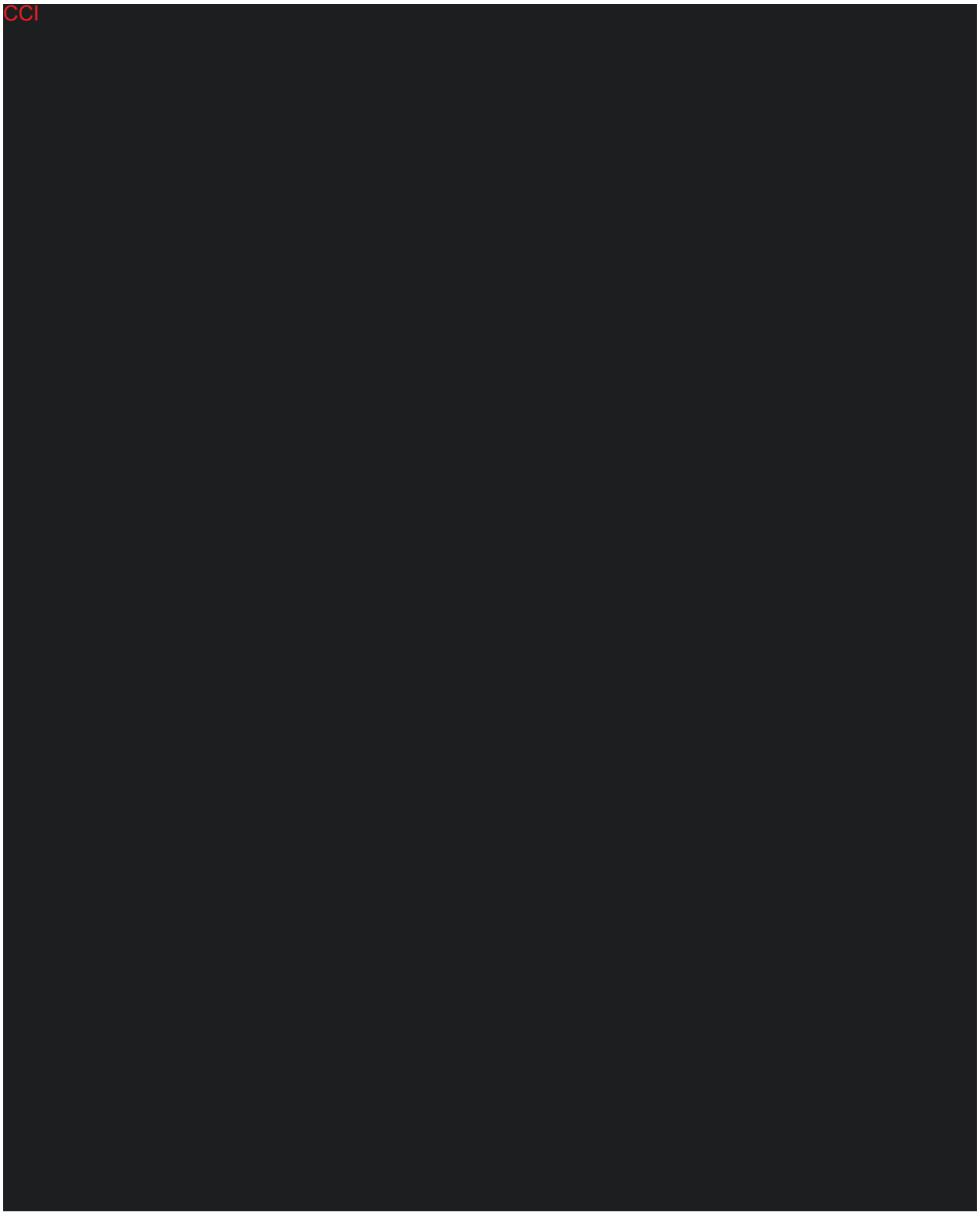


CCI

[redacted]

8.1.9 Unscheduled visits

An unscheduled visit may occur for safety reasons.

During these visits, the assessments will be conducted as appropriate depending on the reason for the visit.

CCI

[redacted]

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]

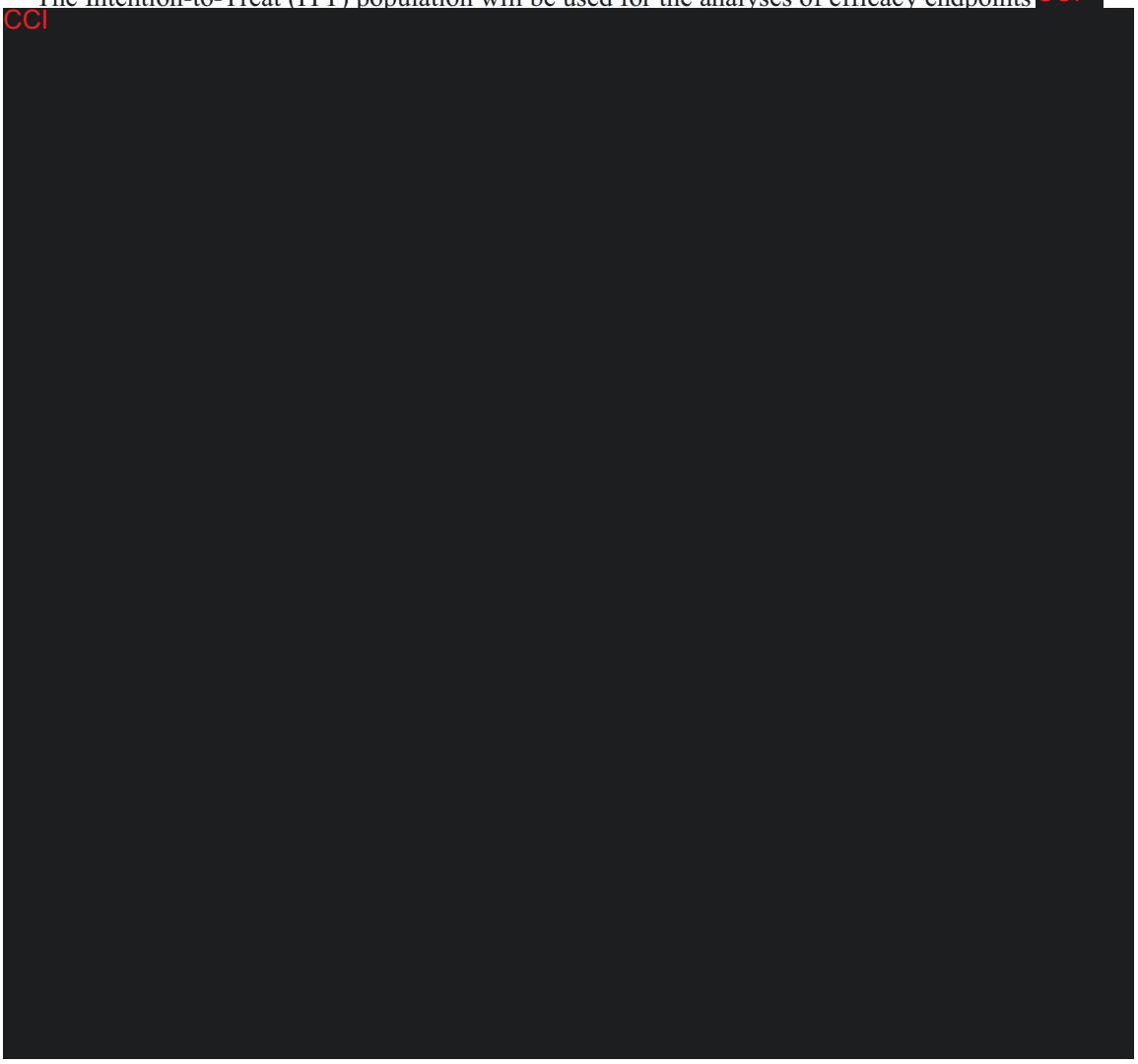
Any changes to analyses made after the SAP has been finalized, along with an explanation as to when and why they occurred, will be documented in the clinical study report. Post hoc exploratory analyses will also be clearly identified in the Clinical Study Report (CSR).

9.1.1 Data transformations

Not applicable

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.

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.

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.

The Investigator will allow the CRO / Sponsor's representatives, to have direct access to all clinical trial records, CRFs, corresponding subject medical records, study drug dispensing records, study drug storage area, clinical trial facilities, and any other documents considered source documentation.

The Investigator also agrees to assist the representative if required.

10.3 Data management

The designated CRO will be responsible for activities associated with the data management of this study.

This will include, but not limited to, setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries.

Study sites will enter data directly into an electronic data capture (EDC) system by completing the CRF via a secure internet connection. Data entered into the CRF must be verifiable against source documents at the study center. Data to be recorded directly on the CRF will be identified and the CRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail.

All data management activities will be detailed in a Data Management Plan (DMP).

10.4 Quality assurance / audit / inspection

The clinical trial is conducted under the sponsorship of GALDERMA R&D in compliance with the applicable international and local regulatory requirements as well as applicable ICH guidelines and in accordance with the SOPs for clinical trial conduct and monitoring from GALDERMA and/or the CRO.

At the completion of the study, digital images will be forwarded to the Sponsor according to individual testing facility SOPs.

Audits of clinical trial centers may be conducted by the Sponsor/CRO representatives, and inspection may be performed by Regulatory Authority inspectorates or IRBs/IECs before, during, or after the clinical trial.

The Investigator will allow and assist the CRO /Sponsor's representatives, IRBs/IECs 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 auditors, audit certificate(s) will be provided by Quality Assurance.

10.5 Changes in clinical trial conduct / amendments

10.5.1 Clinical trial conduct

With the exception of eliminating an immediate hazard to a subject, the Investigator should not deviate from the clinical trial protocol or implement any changes without written approval from the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment.

Changes that involve only logistical or administrative changes to the clinical trial protocol are authorized. The Investigator should document and explain any deviation from the clinical trial protocol.

10.5.2 Amendments

The Sponsor may modify the clinical trial protocol at any time for ethical, medical, or scientific reasons.

10.5.3 Attrition

Clinical studies may experience attrition. Subjects will be made aware that they are free to withdraw from the study at any time for any reason, without prejudice. Otherwise, every effort will be made to have subjects complete the study as stated in this protocol, ensuring subject safety and following the provisions of the ICF. Reasons for subject withdrawal may include an AE, SAE, subject's request, protocol violation, lost to follow-up, and other reasons. Subjects lost from the study will be documented on a screening/enrollment log.

If a subject fails to return for a scheduled examination, a representative of clinical site (site representative/study coordinator) will attempt to contact the subject and determine whether the subject has continued to follow study instructions and intends to continue participation in the study. If so, then the subject will be rescheduled to come into the clinic as soon as possible.

If a rescheduled visit is outside of the specified time frame window, this will be recorded in the screening/enrollment log and as a deviation.

If a subject cannot reschedule in an acceptable time frame and completely misses 1 study visit, the subject may be allowed to continue study participation at the discretion of the Investigator and the Sponsor, provided that the subject has continued to comply with study instructions. If the subject is allowed to continue, the missed visit will be noted in the screening/enrollment log and recorded as a protocol deviation. Subjects will not be allowed to miss the week 12 visit.

11 ETHICS AND GENERAL CLINICAL TRIAL CONDUCT CONSIDERATIONS

11.1 Institutional Review Board or Independent Ethics Committee

This study (protocol, ICF and all addenda) will be reviewed and approved by IntegReview IRB. The study will not be activated and subjects will not be consented, receive any study products, or participate in any study procedures until such time as the IRB has approved the protocol and the ICF. In addition, the IRB will review the study before any significant change in the protocol is initiated. After each review, the IRB's approval will be documented in a letter to the Investigator and a copy of the IRB approval letter will be forwarded to the Sponsor.

11.2 Ethical conduct of the clinical trial

This clinical trial will be conducted in accordance with the protocol, the HELSINKI declaration (1964) and subsequent amendments, and the ICH GCP, and in compliance with applicable regulatory requirements.

11.3 Subject information and consent

All subjects who participate in this clinical trial are required to be fully informed about the clinical trial in accordance with GCPs guidelines, federal regulations, HIPAA (if in the US), or applicable local privacy act if in other countries, and guidelines and in accordance with local requirements.

The ICF, Assent Form, HIPAA or other applicable local privacy act), and Photo Consent Form, approved by an IRB/IEC, will be fully explained to the subject.

Prior to enrolment into the clinical trial, the subject and as needed, the subject's parent/legal representative will sign and date the consent form(s), including assent. The Investigator is responsible for maintaining each subject's consent form(s) in the Investigator's site file and providing each subject, and his/her parent legal representative with a copy of the signed and dated consent form(s) including assent.

11.4 Contractual requirements

A contractual agreement will be signed between the Sponsor/CRO 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 all required records for all subjects. Data for this clinical trial will be recorded in the subject's source documents, subject photographs and on the CRFs provided by the Sponsor. All data should be recorded on the CRFs completely and promptly.

11.5.2 Source documentation

The Investigator must keep accurate separate records (other than the CRFs) of all subject visits, being sure to include all pertinent clinical trial-related information. A statement should be made indicating that the subjects have been included in this clinical trial and have provided signed written Informed Consent and Assent as applicable. All AEs must be thoroughly documented.

Results of any diagnostic tests conducted during the clinical trial should also be included in the source documentation.

11.5.3 Archives

All pertinent data, samples, photographs, correspondence, and reports, the original or amended clinical trial protocol, and all other material relating to the clinical trial will be maintained securely in Sponsor/CRO Investigator/Institution archives for the legally required duration for archiving.

The Investigator/Institution should maintain the essential clinical trial documents as specified in Section 8 of ICH-GCP, and according to the applicable regulatory requirements.

The Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

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

11.6 Insurance

A certificate attesting Third Party coverage of Sponsor/CRO will be provided upon request.

12 LITERATURE REFERENCE LIST

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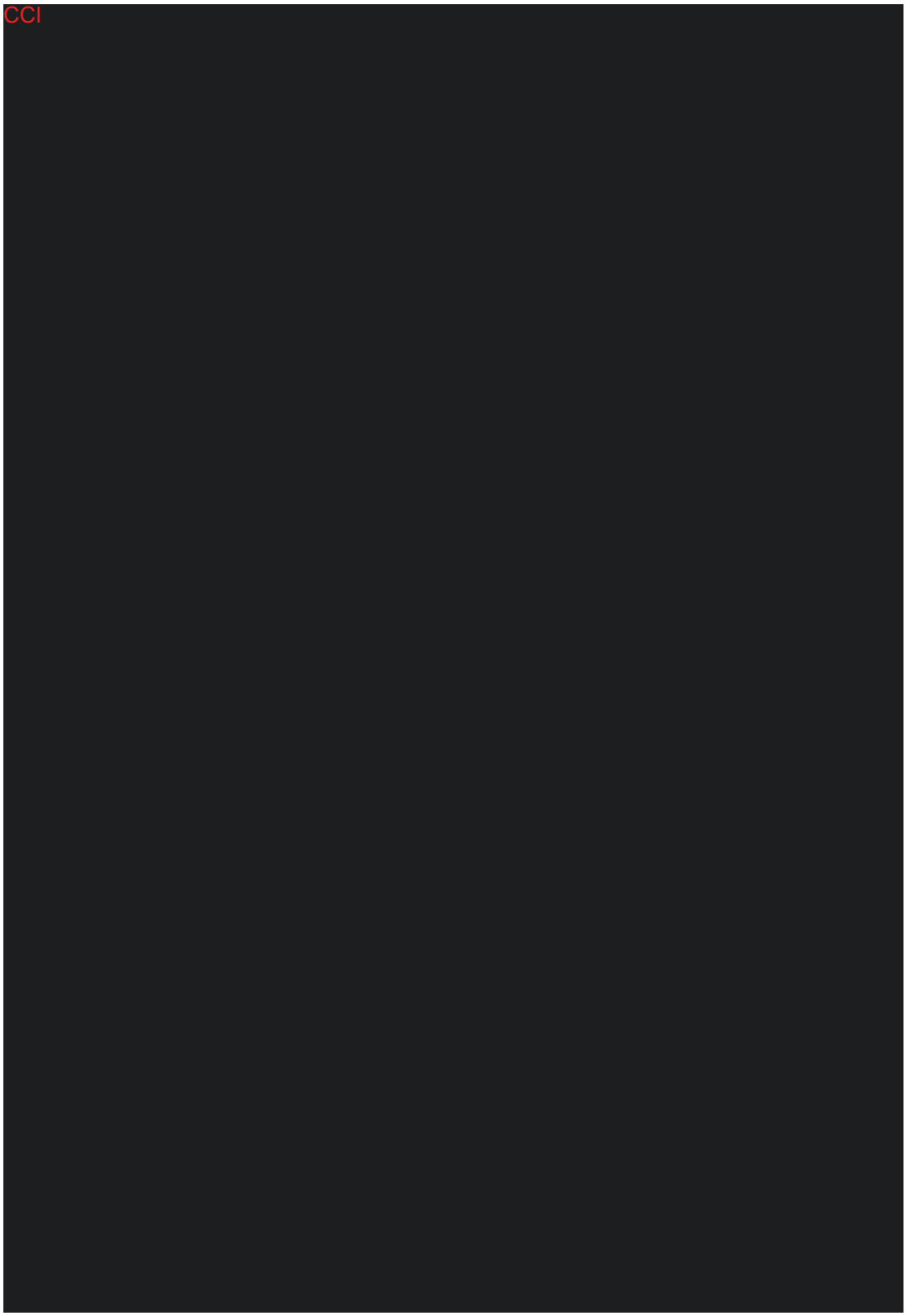

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13.3 Dermatology Life Quality Index (DLQI™)

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	❒ ❒ ❒ ❒ ❒

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.

13.4 Children's Dermatology Life Quality Index (C-DLQI™)

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?** **OR** was it **holiday time?**	**If school time**: Over the last week, how much did your skin affect your **school work**? **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Prevented school ❒ Very much ❒ Quite a lot ❒ Only a little ❒ Not at all ❒ 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.

13.5 QOL Questionnaire for Face and Trunk Acne (16 years of age and older)

CompAQ Measure (Long Form)

We define acne as pimples, zits, or breakouts. We do **not** mean holes, dark spots, or red spots left by acne.

Thinking about the last 7 days, please answer the following questions about acne on your [**face**/**torso** (eg, chest, back, shoulders)] using the following scale:

0	1	2	3	4	5	6	7	8
Never		Rarely		Sometimes		Often		All the time

Items, split by domain	Response Choices								
	0	1	2	3	4	5	6	7	8
A. Psychological/Emotional									
Because of my acne….									
1. I feel depressed, sad, or upset.									
2. I feel embarrassed.									
3. I feel self-conscious.									
4. I feel less confident.									
B. Social (Judgment from others)									
Because of my acne…									
5. I feel that people stare at me.									
6. I feel like people judge me.									
7. People treat me differently.									
8. People think less of me.									
C. Social Interactions									
Because of my acne…									
9. I avoid social interactions.									
10. I spend less time with my friends.									
11. I am concerned about meeting new people.									
12. I am uncomfortable showing affection to others.									
D. Treatment Concerns									
Because of my acne…									
13. I spend a lot time taking care of my skin (at home remedies, treatments, cleansing).									
14. I spend time looking at my skin.									
15. I am concerned that my skin will never be clear.									
16. I am concerned about side effects from treatment.									
E. Physical Symptoms									
Because of my acne…									

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

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

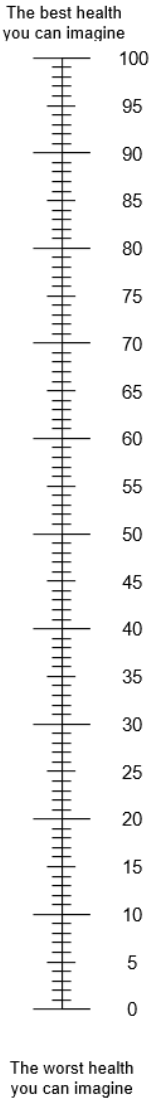
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

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	❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



13.7 Fitzpatrick Skin Classification

The Fitzpatrick skin classification is based on the skin's unprotected response to the first 30 to 45 minutes of sun exposure after a winter season without sun exposure. The categories of skin types are as follows:

I	White; very fair; red or blonde hair; blue eyes; freckles	Always burns easily; never tans
II	White; fair; red or blonde hair; blue, hazel, or green eyes	Always burns easily; tans minimally
III	Cream white; fair with any eye or hair color; very common	Burns moderately; tans gradually
IV	Brown; typical Mediterranean white skin	Burns minimally; always tans well
V	Dark brown; mid-eastern skin types, black hair, olive skin	Rarely burns; tans profusely
VI	Black; black hair, black eyes, black skin	Never burns; deeply pigmented

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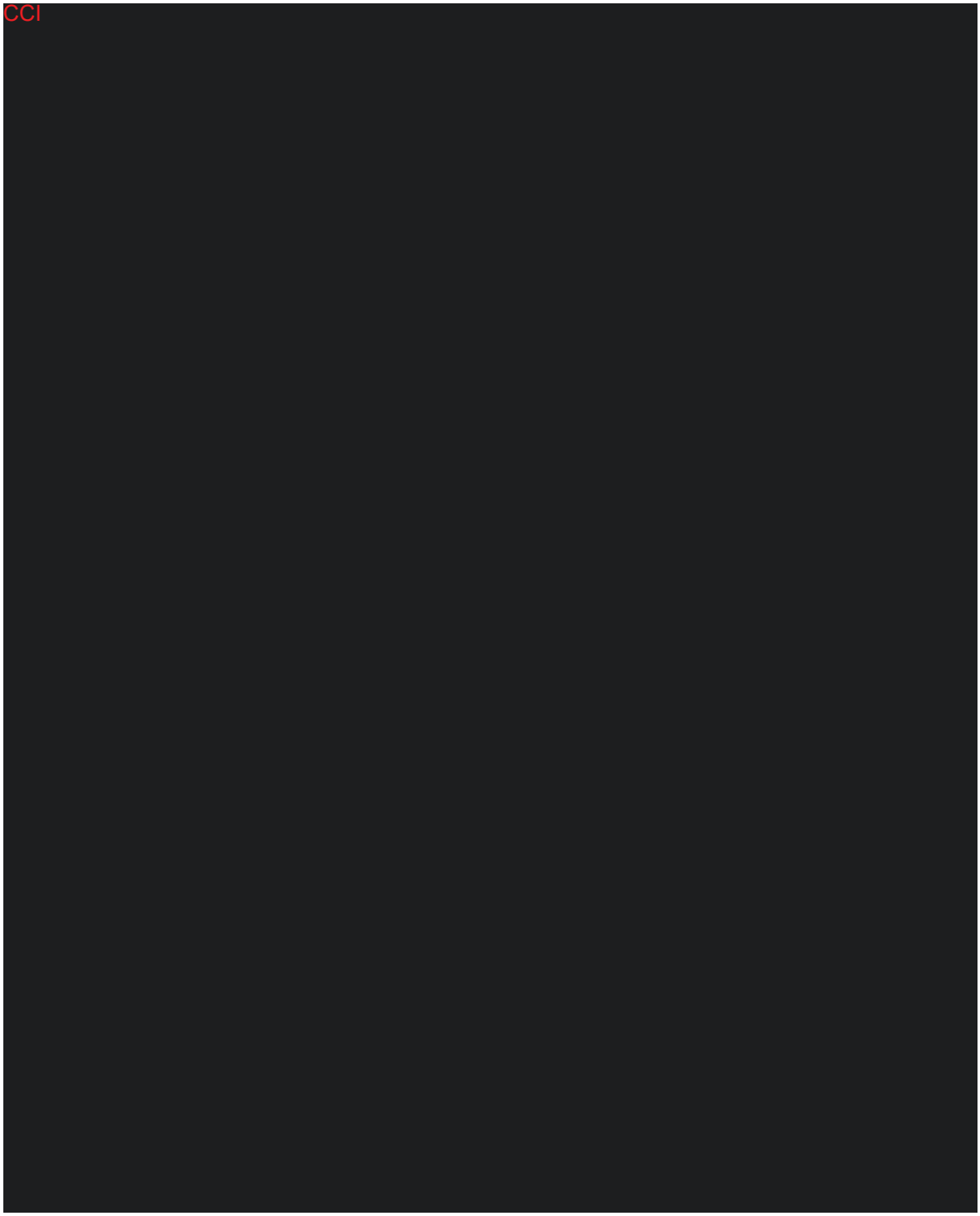

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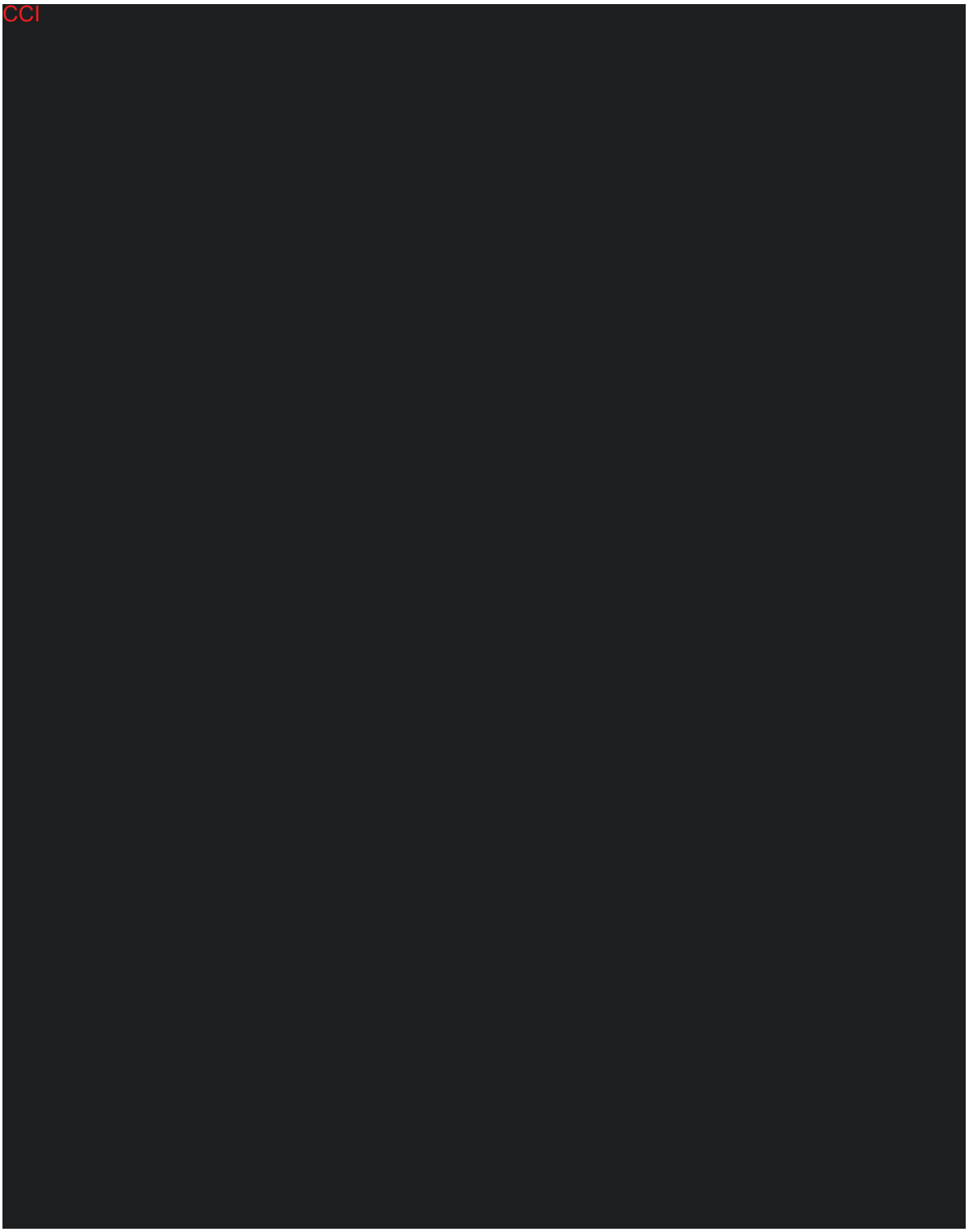
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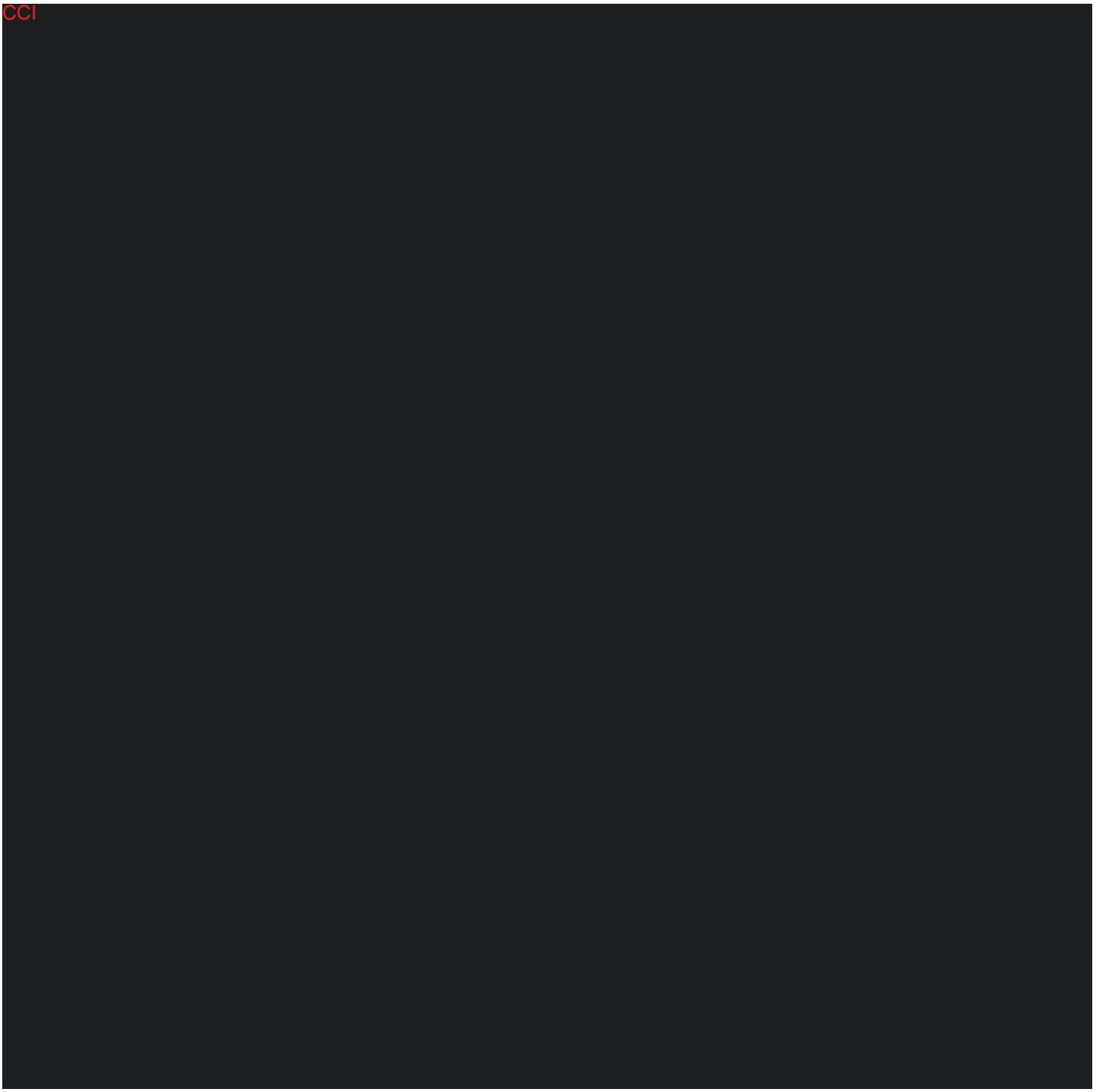
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Protocol Signature Page

I agree to conduct the trial in compliance:

- With the protocol, or any applicable amendment(s), agreed to by the sponsor, regulatory authority and which was given a favorable opinion by the IRB/IEC
- With Good Clinical Practices
- With applicable local and international laws and regulations
- With the instructions I received about
  - ethic principles and subjects protection
  - data collection and reporting
  - study drug(s) and material(s) use and management
  - clinical trial monitoring, audit and inspection

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

Investigator (first name/last name)	**Signature**	**Date:**