

Efficacy Comparison of Ivermectin 1% Topical Cream Associated with Doxycycline 40 mg Modified Release (MR) Capsules Versus Ivermectin 1% Topical Cream Associated with Placebo in the Treatment of Severe Rosacea.

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Date: 10 Feb 2017

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Protocol N° RD.03.SPR.113322

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Page 1 of 106 CONFIDENTIAL

CLINICAL TRIAL PROTOCOL

PROTOCOL NUMBER: RD.03.SPR.113322

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TITLE PAGE

Title: Efficacy comparison of Ivermectin 1% topical cream associated with Doxycycline 40 mg Modified release (MR) capsules versus Ivermectin 1% topical cream associated with Placebo in the treatment of severe Rosacea.

Project Name:	Project Number:	Clinical Trial Phase:
Ivermectin 1% cream and Doxycycline 40 mg MR capsules	838	IV for US IIIb For Canada and Europe

EUDRACT NUMBER: 2017-000157-40

IND NUMBER: 076064 (Ivermectin 1% cream); 067833 (Doxycycline 40mg MR capsules)

Version Number: Final - 10 Feb 2017

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details provided in Section 8.2.2

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

CLINICAL TRIAL ADMINISTRATIVE STRUCTURE

The following table contains the details of GALDERMA R&D employees involved in the conduct of the trial.

SPONSOR PERSONNEL		
Name/Title	Affiliation/Address/Tel./Fax	Responsibilities
<div></div> <div></div>	GALDERMA R&D SNC, <div></div> <div></div> <div></div> <div></div> <div></div> <div></div>	Responsible for clinical management and monitoring of clinical trial and for overall coordination of clinical project
<div></div> <div></div>	Galderma R&D, SNC Same as above <div></div> <div></div> <div></div>	Responsible for administrative follow-up and management of Trial Master File
<div></div> <div></div> <div></div>	Galderma R&D, SNC Same as above <div></div> <div></div> <div></div>	Responsible for study medical management and safety surveillance

GALDERMA RESEARCH & DEVELOPMENT

Protocol N° RD.03.SPR.113322

version Final dated 10-FEB-2017

Page 5 of 106 CONFIDENTIAL

<div></div> <div></div>	<p>GALDERMA R&D SNC,</p> <p>Same as above</p> <div></div> <div></div> <div></div>	<p>Responsible for the Phase IV group</p>
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<div></div> <div></div>	<p>GALDERMA R&D SNC,</p> <p>Same as above</p> <div></div> <div></div> <div></div>	<p>Responsible for quality assurance and audits</p>

<div>██████████</div> <div>████████████████████</div>	<div>GALDERMA R&D SNC,</div> <div>Same as above</div> <div>████████████████████</div> <div>████████████████████</div> <div>██</div>	<div>Responsible for the</div> <div>management of all clinical</div> <div>supplies activities</div>
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SIGNATURE PAGE

Investigator's Agreement

I agree to:

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

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

PRINCIPAL INVESTIGATOR

PRINTED NAME:

SIGNATURE DATE

SIGNATURE

DATE

GALDERMA R&D

MEDICAL EXPERT

PRINTED NAME:

████████████████████

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Protocol N° RD.03.SPR.113322

version Final dated 10-FEB-2017

Page 8 of 106 CONFIDENTIAL

SPONSOR REPRESENTATIVE

PRINTED NAME:

████████████████████

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Protocol N° RD.03.SPR.113322

version Final dated 10-FEB-2017

Page 10 of 106 CONFIDENTIAL

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Original Protocol:

Archives (GALDERMA R&D Sophia Antipolis)

TABLE OF CONTENTS

TITLE PAGE	2
CLINICAL TRIAL ADMINISTRATIVE STRUCTURE.....	4
SIGNATURE PAGE	7
DISTRIBUTION	9
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS.....	16
1. SYNOPSIS	20
2. BACKGROUND AND RATIONALE	28
2.1 Medical background and rationale for the clinical trial	28
2.2 Investigational product profile	31
2.3 Risk/Benefit assessment	31
3. CLINICAL TRIAL OBJECTIVES AND CLINICAL HYPOTHESIS	31
3.1 Clinical trials objectives.....	31
3.2 Clinical hypothesis	31
4. SELECTION AND DISPOSITION OF CLINICAL TRIAL POPULATION.....	32
4.1 Number of subjects	32
4.2 Clinical trial population	32
4.2.1 Inclusion criteria	32
4.2.2 Exclusion criteria	33
4.3 Prior and concomitant therapies	36
4.3.1 Definition.....	36
4.3.2 Categories.....	36
4.3.3 Recording	36
4.3.4 Authorised therapies during the clinical trial.....	37
4.3.5 Prohibited therapies during the clinical trial	37

4.4	Procedures / reasons for discontinuation.....	38
5.	INVESTIGATIONAL PLAN	40
5.1	Overall clinical trial design.....	40
5.2	Discussion of clinical trial design	40
5.3	Clinical trial duration and termination.....	41
5.4	Clinical trial flow chart.....	42
5.5	Clinical trial visit description and procedures	43
5.5.1	Visit 1 – Screening/Baseline visit	43
5.5.2	Visit 2 and 3 – Week 4 and Week 8.....	45
5.5.3	Visit 4- Week 12 / Last clinical trial visit	46
6.	CLINICAL SUPPLIES	48
6.1	Investigational product identification and use	48
6.1.1	Product identity	48
6.1.2	Method of treatment assignment.....	49
6.1.3	Subject Identification Number (SIN)	50
6.1.4	Instructions for use and administration	50
6.2	Other supplies	51
6.3	Investigational product packaging and labeling	52
6.4	Investigational product management.....	52
6.4.1	Accountability.....	53
6.4.2	Dispensing.....	53
6.4.3	Investigational product compliance management and record	54
6.4.4	Storage of investigational product.....	54
6.4.5	Return of investigational product.....	54
6.5	Blinding	55

6.5.1	Verification of blinding	55
6.5.2	Unblinding during the clinical trial	55
7.	EFFICACY AND SAFETY ASSESSMENT	56
7.1	Efficacy assessments	56
7.1.1	<i>Inflammatory Lesion Count</i>	56
7.1.2	<i>Clinician's Erythema Assessment (CEA)</i>	56
7.1.3	<i>Investigator's Global Assessment (IGA)</i>	57
7.1.4	<i>Stinging/Burning sensation</i>	57
7.1.5	<i>Ocular Signs and Symptoms</i>	58
7.1.6	<i>Flushing</i>	58
7.1.7	<i>Subject's Global Improvement in Rosacea</i>	60
7.2	Safety assessments	61
7.2.1	<i>Adverse Events</i>	61
7.3	Patient related outcomes	61
7.3.1	<i>Dermatology Life Quality Index (DLQI) questionnaire</i>	61
7.3.2	<i>EQ-5D-5L questionnaire</i>	61
7.3.3	<i>Work Productivity and Activity Impairment Questionnaire: General Health Problem (WPAI:GH) modified for Rosacea</i>	62
7.3.4	<i>Subject satisfaction questionnaire</i>	62
7.4	Other assessments	62
7.4.1	<i>Photography</i>	62
7.4.2	<i>Facial redness colorimetric measurements</i>	62
7.5	Appropriateness of measurements	63
8.	ADVERSE EVENT	64
8.1	Definitions	64
8.1.1	<i>Adverse Events (AE)</i>	64

8.1.2	Serious Adverse Events (SAE).....	64
8.1.3	Unexpected adverse drug reaction.....	65
8.1.4	Adverse event reporting period.....	65
8.1.5	Severity.....	66
8.1.6	Relationship to the study drug(s) and/or clinical trial procedure.....	66
8.2	Reporting procedures.....	67
8.2.1	Procedures for reporting adverse events	67
8.2.2	Procedure for reporting a serious adverse event	68
8.2.3	Procedure for suspected allergic contact reaction	69
8.3	Procedures for reporting pregnancies.....	72
9.	STATISTICAL METHODS PLANNED	74
9.1	Statistical and analytical plans	74
9.1.1	<i>Variables to be statistically analysed</i>	74
9.1.2	<i>Populations analysed, evaluability and limitations / evaluation of Bias</i>	75
9.1.3	Data presentation and graphics.....	76
9.1.4	Statistical analyses	76
9.2	Sample size determination	77
9.2.1	Historical data and assumptions.....	77
9.2.2	Sample size calculation	77
10.	TRAINING / MONITORING / DATA MANAGEMENT / QUALITY ASSURANCE	78
10.1	Personnel training	78
10.2	Clinical monitoring	78
10.3	Data management.....	78
10.4	Quality assurance / audit / inspection.....	79
11.	ETHICS AND GENERAL CLINICAL TRIAL CONDUCT CONSIDERATIONS.....	79

11.1	Institutional review board (IRB) or ethics committee (EC)	79
11.2	Ethical conduct of the clinical trial	80
11.3	Subject information sheet / informed consent	80
11.4	Contractual requirements	80
11.5	Data collection and archiving	80
11.5.1	Data Collection	80
11.5.2	Source documentation	81
11.5.3	Archives	81
11.6	Insurance	81
12.	REFERENCE LIST	82
13.	ATTACHMENTS	84
13.1	ATTACHMENT# 1	84
13.2	ATTACHMENT# 2	88
13.3	ATTACHMENT# 3	92
13.4	ATTACHMENT# 4	94

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse Event
APT	All Subjects Treated (Safety Population)
CDMS	Clinical Data Management System
CEA	Clinician's Erythema Assessment
CMH	Cochran-Mantel-Haenszel
CPM	Clinical Project Manager
CRA	Clinical Research Associate
CRF	Case Report Form
COPD	Chronic Obstructive Pulmonary Disease
CRO	Contract Research Organization
DLQI	Dermatology Life Quality Index
DMP	Data Management Plan
EC	Ethics Committee
EQ-5D	EuroQol-5 Dimension-5 Level questionnaire
FDA	Food and Drug Administration
FSI	First Subject In (<i>first subject who signs the Informed Consent Form</i>)
GCP	Good Clinical Practice

Abbreviation	Term
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
i.e.	That is (Latin: id est)
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IPL	Intense Pulsed Light
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-To-Treat
IUD	Intra Uterine Device
IVM	Ivermectin
LOCF	Last Observation Carried Forward
LSI	Last Subject In (Last subject randomized/assigned to treatment)
LSO	Last Subject Out (Last subject who completed last clinical trial visit)
MedDRA	Medical Dictionary for Regulatory Activities
MR	Modified Release

Abbreviation	Term
NSAID	Non-steroidal anti-inflammatory drug
OTC	Over-The-Counter
PI	Prescribing Information or Principal Investigator
PIPEDA	Personal Information Protection and Electronic Documents Act
PRO	Patient Reported Outcome
PP	Per Protocol
QD	Once Daily (Latin: quaque die)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System (SAS Institute Inc., Cary, NC)
SD	Standard Deviation
SIN	Subject Identification Number
SOC	System Organ Class
SOP	Standard Operating Procedure
SPF	Sun Protection Factor
SmPC	Summary of Product Characteristics
TOC	Table of Contents
UPT	Urine Pregnancy Test

GALDERMA RESEARCH & DEVELOPMENT

Protocol N° RD.03.SPR.113322

version Final dated 10-FEB-2017

Page 19 of 106 CONFIDENTIAL

Abbreviation	Term
UV	Ultraviolet
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health

1. SYNOPSIS

Clinical trial title: Efficacy comparison of Ivermectin 1% topical cream associated with Doxycycline 40 mg Modified release (MR) capsules versus Ivermectin 1% topical cream associated with Placebo in the treatment of severe rosacea.		
Short title (± acronym): ANSWER study - oracea soolaNtra aSsociation in patients With severE Rosacea		
Project number: 838	Clinical trial phase: IV for US IIIb For Canada and Europe	Clinical trial period Planned First Subject In: Q2 2017 Planned Last Subject Out: Q1 2018
Objective(s):	The main objective of this study is to evaluate the efficacy of Ivermectin 1% topical cream associated with Doxycycline 40 mg Modified release (MR) capsules versus Ivermectin 1% topical cream associated with Placebo in the treatment of severe Rosacea. The Safety and Patient Reported Outcomes (PRO) will be also evaluated.	
Methodology:	This is a multi-center, randomized, investigator-blind, controlled and parallel-group study in subjects with severe rosacea characterized by persistent diffuse facial erythema and inflammatory lesions (papules and pustules).	
Total number of planned subjects:	A total of 270 subjects will be enrolled (i.e. 135 subjects in each group).	
Total number of planned sites:	Approximately 50 sites	
Approximate number of subjects/site:	Approximately 5 subject/site	
Country(ies) involved:	USA, Canada and Europe (ie: Germany, Czech Republic, Hungary, and Poland).	

GALDERMA RESEARCH & DEVELOPMENT

Protocol N° RD.03.SPR.113322

version Final dated 10-FEB-2017

Page 21 of 106 CONFIDENTIAL

Clinical trial title: Efficacy comparison of Ivermectin 1% topical cream associated with Doxycycline 40 mg Modified release (MR) capsules versus Ivermectin 1% topical cream associated with Placebo in the treatment of severe rosacea.		
Short title (± acronym): ANSWER study - oracea soolaNtra aSsociation in patients With severE Rosacea		
Project number: 838	Clinical trial phase: IV for US IIIb For Canada and Europe	Clinical trial period Planned First Subject In: Q2 2017 Planned Last Subject Out: Q1 2018
Population and main inclusion criteria:	Male or female subjects with severe rosacea, age of 18 years or older, with >20 to maximum 70 inflammatory lesions (papules and pustules) on the face & Investigator's Global Assessment (IGA) score 4; meeting specific inclusion/exclusion criteria.	
Clinical trial duration per subject	12 weeks	
Number of visits:	Up to 5 visits for subjects at Screening/Baseline, Week 4, Week 8, and Week 12.	

Clinical trial title: Efficacy comparison of Ivermectin 1% topical cream associated with Doxycycline 40 mg Modified release (MR) capsules versus Ivermectin 1% topical cream associated with Placebo in the treatment of severe rosacea.		
Short title (± acronym): ANSWER study - oracea soolantra association in patients With severe Rosacea		
Project number: 838	Clinical trial phase: IV for US IIIb For Canada and Europe	Clinical trial period Planned First Subject In: Q2 2017 Planned Last Subject Out: Q1 2018
Investigational product: Name: Pharmaceutical form: Dose/concentration: Total daily dose: Mode and frequency of administration: Location of treated area: Duration of treatment:	Ivermectin 1% cream (<i>Soolantra® 1% Cream in the US, Soolantra® 10mg/g in Europe and Rosiver® 10mg/g in Canada</i>) associated with Doxycycline 40 mg MR (30 mg Immediate Release & 10 mg Delayed Release beads) capsules (<i>Oracea® in the US, Oraycea®/Efracea® in Europe and Aprilon® in Canada</i>) Ivermectin 1% cream: Topical to the face, approximately one small pea size amount per facial region (right and left cheeks, forehead, chin, and nose) once a day Doxycycline 40 mg MR (30 mg Immediate Release & 10 mg Delayed Release beads): 1 Capsule once-daily 12 weeks	

Clinical trial title: Efficacy comparison of Ivermectin 1% topical cream associated with Doxycycline 40 mg Modified release (MR) capsules versus Ivermectin 1% topical cream associated with Placebo in the treatment of severe rosacea.		
Short title (± acronym): ANSWER study - Oracea Soolantra Association in patients With severe Rosacea		
Project number: 838	Clinical trial phase: IV for US IIIb For Canada and Europe	Clinical trial period Planned First Subject In: Q2 2017 Planned Last Subject Out: Q1 2018
Comparator product: Name: Pharmaceutical form: Strength/concentration: Total daily dose: Mode and frequency of administration: Location of treated area: Duration of treatment:	Ivermectin 1% cream (<i>Soolantra® 1% Cream in the US, Soolantra® 10mg/g in Europe and Rosiver® 10mg/g in Canada</i>) associated with CD2475-101 (<i>Oracea®</i>) oral placebo capsules. Ivermectin 1% cream: Topical to the face, approximately one small pea size amount per facial region (right and left cheeks, forehead, chin, and nose) once a day CD2475-101 (<i>Oracea®</i>) placebo: 1 Capsule once-daily 12 weeks	
Non-investigational product to be provided for the clinical trial:	Gentle Skin Cleanser Facial Moisturizer SPF 30 Urine Pregnancy Kits	

Clinical trial title: Efficacy comparison of Ivermectin 1% topical cream associated with Doxycycline 40 mg Modified release (MR) capsules versus Ivermectin 1% topical cream associated with Placebo in the treatment of severe rosacea.		
Short title (± acronym): ANSWER study - oracea soolaNtra aSsociation in patients With severE Rosacea		
Project number: 838	Clinical trial phase: IV for US IIIb For Canada and Europe	Clinical trial period Planned First Subject In: Q2 2017 Planned Last Subject Out: Q1 2018
Measurement criteria	Efficacy <ul style="list-style-type: none"> Inflammatory lesion count by investigators at each visit Severity on the diffuse persistent facial erythema of rosacea based on Clinician's Erythema Assessment (CEA) evaluated by investigators at each visit Severity of rosacea based on Investigator's Global Assessment (IGA) evaluated by investigators at each visit Severity of stinging/burning sensation evaluated by subjects at each visit Global assessment of Ocular signs and symptoms, if present at baseline, evaluated by investigator at each visit Number of flushing per week evaluated by subject using diary throughout the study Severity of flushing evaluated by subject using diary throughout the study Global improvement in rosacea evaluated by subjects at the last visit Safety <ul style="list-style-type: none"> Adverse Events (AEs) throughout the study Others <ul style="list-style-type: none"> Dermatology Life Quality Index (DLQI) questionnaire at Baseline and the last visit 	

Clinical trial title: Efficacy comparison of Ivermectin 1% topical cream associated with Doxycycline 40 mg Modified release (MR) capsules versus Ivermectin 1% topical cream associated with Placebo in the treatment of severe rosacea.		
Short title (± acronym): ANSWER study - oracea soolaNtra aSsociation in patients With severE Rosacea		
Project number: 838	Clinical trial phase: IV for US IIIb For Canada and Europe	Clinical trial period Planned First Subject In: Q2 2017 Planned Last Subject Out: Q1 2018
Analysed variables	Primary efficacy variable <ul style="list-style-type: none"> Percent change from Baseline in Inflammatory Lesion count at Week 12. Secondary efficacy variables <ul style="list-style-type: none"> Percent change from Baseline in Inflammatory Lesion count at each intermediate visit <ul style="list-style-type: none"> CEA at each post-Baseline visit: % of subjects across scores IGA at each post-Baseline visit: % of subjects across scores Stinging/burning at each post-Baseline visit: % of subjects across scores Percent change from Baseline (medical history) in terms of flushing count per week Change from Baseline (medical history) in mean score severity per week Global improvement in rosacea at the last visit: % of subjects across scores Exploratory efficacy variables <ul style="list-style-type: none"> Global assessment of Ocular signs and symptoms at each post-Baseline visit: % of subjects across scores 	

Clinical trial title: Efficacy comparison of Ivermectin 1% topical cream associated with Doxycycline 40 mg Modified release (MR) capsules versus Ivermectin 1% topical cream associated with Placebo in the treatment of severe rosacea.		
Short title (± acronym): ANSWER study - oracea soolaNtra aSsociation in patients With severE Rosacea		
Project number: 838	Clinical trial phase: IV for US IIIb For Canada and Europe	Clinical trial period Planned First Subject In: Q2 2017 Planned Last Subject Out: Q1 2018
Principal statistical methods and sample size calculation:	Centers considered too small may be combined to create analysis-center. The Per Protocol (PP) population will consist of all enrolled and randomized subjects, except subjects who have major deviations from the protocol. The Intent-to-Treat (ITT) population will consist of the entire population enrolled and randomized. The last observation carried forward (LOCF) method will be used to impute missing values of lesion counts. Analysis population definitions and pooling of centers will be decided before the database lock and unblinding. The primary objective of this trial is to demonstrate the superiority of Ivermectin associated with Doxycycline MR vs. Ivermectin associated with Placebo, in terms of % change from Baseline in Inflammatory Lesion count at Week 12. The primary efficacy criterion will be analyzed by using the Cochran-Mantel-Haenszel (CMH) statistic, stratified by center (or analysis-center) after ridit transformation with the row mean difference statistics, testing the hypothesis of equality. The p-value will have to be inferior to 0.05 at Week 12, on ITT/LOCF population. PP analysis will be also performed to assess the robustness of the results obtained on ITT/LOCF population. The other variables will be analyzed similarly as primary analysis on appropriate population. Each test will be two-sided, at the 0.050 significance level. The subject characteristics (previous medication, concomitant medication, demographics, baseline characteristics...), lesion counts and adverse events, will be summarized by descriptive statistics (usual statistics and frequency distribution)	

GALDERMA RESEARCH & DEVELOPMENT

Protocol N° RD.03.SPR.113322

version Final dated 10-FEB-2017

Page 27 of 106 CONFIDENTIAL

2. BACKGROUND AND RATIONALE

2.1 MEDICAL BACKGROUND AND RATIONALE FOR THE CLINICAL TRIAL

Rosacea is a chronic inflammatory disease that affects around 10% of the population in Europe. Clinical characteristics include diagnostic features (persistent centrofacial erythema, phymatous changes); primary features (transient erythema or flushing, inflammatory papules/pustules, telangiectasia, ocular manifestations) and secondary features (burning sensation, stinging sensation, oedema, dry sensation) in various combinations^{1,1,1,2}. Following the onset of the disease, patients with rosacea will experience cycles of relapse and remission of symptoms throughout their lives. Rosacea usually presents in the second or third decade of life, with prevalence of rosacea varying from less than 1% to more than 20%^{1,3,1,4}. It is reported more frequently in fair-skinned people^{1,5,1,6,1,7}. Rosacea is known to have a negative impact on quality of life and is associated with depression and social isolation, hampering both social and professional lives. In a recent National Rosacea Society survey of 1675 patients, 95% in patients with severe symptoms reported an adverse impact on their general outlook on life, highlighting that the emotional impact on patients appears to increase as symptoms become more severe^{1,8}.

Patients with inflammatory lesion of rosacea (papulo-pustular) show a chronic and recurrent course of their disease and it is usually accompanied by a persistent central facial erythema, potentially associated with telangiectasia. Eruptions usually occur on the center of the face with frequent involvement of the forehead and chin. The etiology of rosacea remains unknown, with both genetic and environmental factors potentially impacting pathogenesis. These etiological factors include enhanced vasomotor lability, immune system and sebaceous gland abnormalities, and greater susceptibility to heat and ultraviolet (UV) light exposure^{1,9}. Patients with rosacea are reported to have an upregulated innate immune system, which can be triggered by various factors (including certain foods, UV exposure and temperature changes). This heightened immune response induces signaling cascades associated with inflammatory and vasoregulatory pathways. In addition, microorganisms such as the hair follicle mite *Demodex folliculorum* have been suggested to play a key role. Penetration of the mite into the dermis may stimulate a delayed hypersensitivity reaction and inflammation. Several published studies report abnormally high numbers of *Demodex* in subjects with papulo-pustular rosacea^{1,8}.

In rosacea, the frequency of outbreaks varies with time, ranging from once or twice a year to continuous presence of symptoms. Management of the inflammatory lesions and the associated erythema warrants adherence with continued therapy^{1,10}. Treatment options for rosacea with inflammatory lesions include various topical therapies such as ivermectin, metronidazole, azelaic acid, and sodium sulfacetamide-sulfur^{1,11,1,12}. Systemic treatment with sub- antimicrobial dose formulation of doxycycline (referred to as doxycycline 40 mg modified release) incorporating 30-mg immediate-release and 10-mg delayed-release beads administered once daily; first FDA-approved (2006) as oral treatment for rosacea with papulopustular lesions. Doxycycline 40 mg modified-release (Oracea®) has shown to decrease both gene expression and protein levels of MMPs, KLK, and cathelicidin, which resulted in a reduction in inflammatory lesion counts. By inhibiting the production and activity of MMPs, doxycycline 40 mg modified-release blocks multiple inflammatory pathways, which inhibits the production of proteins contributing to the pathophysiology of inflammation and thus exhibits anti-inflammatory properties while not exhibiting any antibiotic effect in rosacea patients^{1,10}.

Ivermectin is a macrocyclic lactone derivative with dual anti-inflammatory and anti-parasitic properties. Approved for the treatment of onchocerciasis, strongyloidiasis and scabies in humans by oral route, and in lotion foam for topical head lice treatment. Oral ivermectin has been demonstrated to be effective as an anti-parasitic agent in reducing the number of Demodex mites in demodicidosis and in blepharitis. Ivermectin (IVM) has also been shown to exert anti-inflammatory effects by inhibiting lipopolysaccharide-induced production of inflammatory cytokines, including tumor necrosis factor- alpha (TNF- α) and interleukin (IL)-1 β , while increasing the anti-inflammatory cytokine IL-10. Ivermectin is able to suppress production of the inflammatory mediators and modulation of NO, iNOS, COX-2, and PGE-2 release which are major contributing factors during the inflammatory process. It's therapeutic effect as a topical cream in rosacea is assumed to be due to both, its anti-inflammatory and anti-demodex properties^{1,10}.

The approval of Ivermectin 1% cream (FDA, 2015) for the treatment of the inflammatory lesions of rosacea was based upon two identically-designed large vehicle-controlled Phase 3 randomized trials that demonstrated efficacy and safety in adults with moderate to severe papulopustular rosacea on a 12-week treatment period. In both studies, a greater proportion of subjects in the IVM 1% group achieved treatment success. Ivermectin was superior to vehicle in terms of reduction from baseline in inflammatory lesion counts (76% and 75% versus 50% for both vehicle groups, respectively)^{1,13}. For Doxycycline the two placebo-controlled pivotal phase 3 trials evaluated the efficacy and safety of doxycycline 40 mg modified release (MR) once daily versus placebo in participants with moderate to severe rosacea. These participants had 10 to 40 papules and pustules and moderate to severe erythema and telangiectasia. Both studies showed marked reductions in the number of inflammatory lesions compared with placebo. Treatment with doxycycline 40 mg MR significantly reduced the number of lesions from the first follow-up assessment at 3 weeks throughout the entire 16-week study compared with placebo ($P \leq 0.005$). Study by Sanchez et al.^{1,14} using doxycycline with metronidazole versus metronidazole alone did demonstrate in moderate to severe rosacea that adjunctive use of sub-antimicrobial dose doxycycline significantly reduced the clinical signs of rosacea compared with metronidazole alone^{1,6}. Based on the complementary mechanism of action of doxycycline MR and ivermectin^{1,10}, a scientific rationale to assess the combined therapy targeting inflammatory lesions in severe rosacea is planned. Topical ivermectin cream is a promising first-line treatment to target the inflammatory lesions of rosacea, which can be used in combination with systemic doxycycline modified-release as per the recent Canadian Rosacea guideline^{1,15} to provide an optimal treatment approach considering all inflammatory pathways involved in rosacea with inflammatory lesions.

Unlike clinical studies evaluating monotherapy approaches, clinicians often use a combination of topical and oral therapy for patients with severe rosacea, as an increased or additive benefit has been suggested with combination regimens. Topical ivermectin cream 1% and oral anti-inflammatory doxycycline (40 mg MR, modified-release) are both approved for the treatment of rosacea with inflammatory papules and pustules. Associating those two products, each having demonstrated a good safety profile and efficacy on rosacea features, should lead to optimized clinical outcomes in a complex disease that has been proven difficult to manage comprehensively and would reflect a controlled study of that which is already prescribed in clinical practice^{1,15}. In an attempt to further optimize comprehensive management of severe rosacea, this study aims to investigate the efficacy, patient satisfaction and safety of the association of topical Ivermectin 1% cream and oral Doxycycline MR 40mg once a day treatment.

2.2 INVESTIGATIONAL PRODUCT PROFILE

The products used in this clinical trial are Ivermectin 1% cream and Doxycycline MR 40 mg capsules. Both are approved for rosacea treatment and are well tolerated. See respective product information (PI-SmPC) for detailed efficacy and safety information.

2.3 RISK/BENEFIT ASSESSMENT

Rosacea is a chronic, non-life-threatening skin disease characterized by two major features which are a persistent central facial erythema and recurrent eruptions of inflammatory lesions (i.e., papules, pustules, or both).

The two investigational products are marketed individually for rosacea treatment and with proven efficacy and good safety profile including severe rosacea population.

Whatever the randomization arm, all study subjects will benefit from an efficient and safe rosacea treatment.

The association of investigational products is not expected to raise new tolerability issues and has the potential to reach to better and possibly faster efficacy outcome.

3. CLINICAL TRIAL OBJECTIVES AND CLINICAL HYPOTHESIS

3.1 CLINICAL TRIALS OBJECTIVES

The main objective of this study is to evaluate the efficacy of Ivermectin 1% topical cream associated with Doxycycline 40 mg capsules MR compared with Ivermectin 1% topical cream monotherapy in the treatment of severe rosacea with papulopustular lesions.

The Safety and Patient Reported Outcomes (PRO) will be also evaluated.

3.2 CLINICAL HYPOTHESIS

Associating IVM 1% cream and oral Doxycycline 40 mg MR in a comprehensive approach to address the severe inflammatory lesions of rosacea and should lead to an optimized clinical outcome. Both drugs have only been evaluated individually so far, but never as an association.

This study aims to assess both treatment evaluations on rosacea symptoms and will allow for the evaluation of the potential benefit of such treatment association on cumulative efficacy, time to onset of action with 2 products in rosacea, safety, and patient satisfaction needed in severe condition of rosacea.

4. SELECTION AND DISPOSITION OF CLINICAL TRIAL POPULATION

4.1 NUMBER OF SUBJECTS

A total of 270 subjects will be enrolled (i.e. 135 subjects in each group) at approximately 50 sites located in the USA, Canada and Europe (Germany, Czech Republic, Hungary, and Poland).

4.2 CLINICAL TRIAL POPULATION

Subjects who meet all of the following criteria will be eligible for the clinical trial. Some criteria are to be checked at screening visit and/or at baseline visit, as specified by the trial design.

4.2.1 Inclusion criteria

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

1. Male or female subject age ≥ 18 years or older;
2. Subject with a minimum of 20 but not more than 70 inflammatory lesions (papules and pustules) of rosacea on the face at Baseline visit;
3. Subject with severe rosacea with papulopustular lesions (according to the Investigator's Global Assessment, IGA score rated 4);
4. Female Subject of childbearing potential must have a negative urinary pregnancy test (UPT) at baseline visit (UPT should have a sensitivity of 25 IU/L or less). They must agree to use/continue a highly effective and approved contraceptive method(s) for the duration of the study and at least 4 weeks after the last study drug(s) use. A highly effective method of contraception being defined as:
 - bilateral tubal ligation;
 - combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month prior to Baseline visit;
 - hormonal intra-uterine device (IUD) inserted at least 1 month prior to Baseline visit;
 - vasectomized partner for at least 3 months prior to Baseline

OR

5. Is of non-childbearing potential, defined as post-menopausal (absence of menstrual bleeding for one year prior to clinical trial entry without any other medical reasons), hysterectomy or bilateral oophorectomy prior to clinical trial entry.
6. Willing and able to comply with all of the time commitments and procedural requirements of the clinical trial protocol. In particular, subject must adhere to the visit schedule, concomitant therapy prohibitions, and must be compliant with the treatment at study visits.
7. Understand and sign an Informed Consent Form (ICF) and photo consent (when appropriate) at screening, prior to any investigational procedures being performed.
8. Apprised of the Health Insurance Portability and Accountability Act (HIPAA), if in the US, or the Personal Information Protection and Electronic Documents Act (PIPEDA) if in Canada [or the equivalent in other regions] and is willing to share personal information and data, as verified by signing a written authorization at the screening/baseline.

4.2.2 Exclusion criteria

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

1. Subject with particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated pustulosis of the chin, isolated rhinophyma) or other facial dermatoses that may be confounded with papulopustular rosacea, such as perioral dermatitis, facial keratosis pilaris, acute lupus erythematosus, actinic telangiectasia or seborrheic dermatitis and acne vulgaris
2. Subject with more than 2 nodules of rosacea (a circumscribed, elevated, solid lesion more than 1.0cm in diameter with palpable depth) on the face
3. Subject with known allergies or sensitivities to any components of the formulation of the study drugs being tested (either Ivermectin 1% cream or Doxycycline, see package inserts)
4. Female who is lactating.
5. Female who intends to conceive a child during the clinical trial during the study period and for at least 4 weeks after the last study drug(s) use.
6. Currently participating in any other clinical trial of a drug or device OR participated within 30 days prior to baseline OR is in an exclusion period (if verifiable) from a previous clinical trial.
7. The subject has received, applied or taken the following treatments within the specified time frame prior to the Screening/Baseline visit:

Topical facial treatments or procedures on the face:	
Astringents or abrasives (scrubs, exfoliating cleansers and products containing salicylic acid or alcohol)	2 days
Antibiotics (e.g. metronidazole or macrolides)	4 weeks
Benzoyl Peroxide	4 weeks
Anti-rosacea drugs (e.g. azelaic acid, brimonidine, oxymetazoline)	4 weeks
Immunomodulators	4 weeks
Corticosteroids	4 weeks
Retinoids	4 weeks
Any procedure on the face (e.g. laser, intense pulsed light-IPL, facial peel, dermabrasion, electrocoagulation, Thermage®)	6 weeks
Systemic treatments:	
Antibiotics (e.g. cyclines, macrolides, metronidazole)	4 weeks
Corticosteroids	4 weeks
Immunomodulators	4 weeks
Oral Ivermectin	4 weeks

Other drugs used for the treatment of acne or rosacea (eg: spironolactone)	4 weeks
Oral retinoids	12 weeks
Anticoagulants of the dicoumarol type	4 weeks
Sulphonylurea oral antidiabetic agents	1 week
Other treatments:	
Inhaled Corticosteroids (for asthma or chronic obstructive pulmonary disease - COPD)	4 weeks
Oxymetazoline (any route; e.g. eye drops, nasal sprays...) or vasodilators	4 weeks

8. The subject is unwilling to refrain from use of prohibited medication during the clinical trial (see section 4.3.5)
9. Subject who is vulnerable as defined in Section 1.61 of the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP); eg: adult subject under guardianship, hospitalized subject in a public or private institution for a reason other than the research, and subject deprived of his/her freedom
10. The subject has history of alcohol or drug abuse (positive urine drug screen and/or alcohol test) within the previous 12 months.
11. The subject is a study site staff member (investigator, study nurse, etc.) or a relative of one.
12. The initiation of a hormonal method of contraception within 1 month of baseline, or discontinuation during the course of study, or change in the actual product within 1 month of baseline or planned during the study
13. Subject with clinically significant abnormal laboratory finding at the screening/baseline visit or an underlying known disease, a surgical or medical condition, which in the judgment of the Investigator, would put the subjects at risk (e.g., uncontrolled chronic or serious diseases which would normally prevent participation in any clinical study, such as cancer, leukemia or hematologic dyscrasia), or might confound the study assessments (e.g. other dermatological diseases), or might interfere with the subject's study participation (e.g. planned hospitalization during the study)
14. Subject who is at risk in terms of precautions, warnings, and contra-indication (see package insert)

15. Subject with hairs on the treated area that might interfere with study assessments
16. Subject exposed to excessive UV radiation within two weeks prior to the Baseline visit, or subjects planning exposure during the study (e.g. phototherapy, occupational exposure to the sun, planned holidays with excessive sun during the study period, tanning salon)

4.3 PRIOR AND CONCOMITANT THERAPIES

4.3.1 Definition

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

An exception will be made on the last rosacea treatment taken, where no limit on period of time will be applied upon data collection.

Concomitant therapies are defined as follows:

- any existing therapies ongoing at the time of the screening/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 since the screening/baseline visit

4.3.2 Categories

The following two categories will 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, etc.

4.3.3 Recording

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

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

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

4.3.4 **Authorised therapies during the clinical trial.**

Unless listed in the exclusion criteria above or in the prohibited therapies (see sections 4.2.2 and 4.3.5), all therapies are authorized.

Subjects must use the study-provided cleanser, moisturizer/sunscreen for skin care as described in section 6.2.

Subjects may use cosmetics and make-up if they are applied after study drug application.

Subjects may not use foundation make-up or study provided moisturizer/sunscreen on the days of the visits.

4.3.5 **Prohibited therapies during the clinical trial**

The following therapies are prohibited because they may interfere with the efficacy and/or safety assessment of the investigational products, or because they may interact with the metabolism of the investigational products:

- All topical or systemic therapies listed as exclusion criteria (section 4.2.2)
- Chronic use (>14 days) of sulpha drugs, erythromycin, cephalosporin, and quinolones
- Use of systemic tetracycline antibiotics or tetracycline-like (doxycycline) antibiotics in conjunction with penicillin (drug interactions with bacteriostatic and bactericidal effects).
- Use of Rifampicin, barbiturates, carbamazepine, diphenylhydantoin, primidone, phenytoin (hepatic enzyme inducers which will thereby decrease doxycycline's half-life) and cyclosporine.
- The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity
- For ocular rosacea if new therapy required like topical ophthalmic treatments (including antibiotics eye drops or steroids); but can continue if stable over the past 2 weeks and planned to be maintained during the study (authorised to use lubricating ointments, artificial tears, eyelid care during the study).
- Chronic use (>14 consecutive days) of NSAIDs, except chronic use of aspirin at sub-analgesic dose ($\leq 325\text{mg QD}$) is permitted for patients requiring platelet aggregation inhibitors (dose modifications on PI discretion, refer SmPC)

- Use of protein pump inhibitors
- Any other drugs/procedures which at the investigator's judgement are liable to interfere or interact with the efficacy and the safety of investigational products.

Antacids and vitamins containing aluminum, calcium, or magnesium are allowed only if are taken at least 1.5 hours before or 3 hours after the intake of study medication. A shorter interval is prohibited because these agents might impair drug absorption.

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

4.4 PROCEDURES / REASONS FOR DISCONTINUATION

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

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

Subjects who discontinue the clinical trial prematurely should be fully evaluated, whenever possible.

The procedures designated for the early termination visit will be completed for all premature discontinuation subjects. The appropriate eCRF pages for the next scheduled visit should be completed.

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

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

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

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

All data gathered on the subject prior to termination will be made available to *GALDERMA R&D*.

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

Normal Study Completion	Subject completes the clinical trial as planned in protocol.
Pregnancy	Withdraw the subject from the clinical trial following the procedure described in the protocol section 8.3
Adverse Event	Complete CRF Adverse Event Form.
Withdrawal by subject	Includes consent withdrawal, subject relocation, schedule conflicts, etc... Does not include AE. . Explain the reason for withdrawal in the comments section of the CRF Exit Form.
Protocol Violation	Explain the violation in the comments section of the CRF Exit Form
Lost to Follow-up	Confirm with 2 documented phone calls and a certified letter (delivery receipt requested) without response. Explain in the comments section of the CRF Exit Form.
Other	This category is to be used for a subject who discontinues for a reason other than those specified in the predefined categories above. Explain the reason for discontinuation in the comments section of CRF Exit Form.

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

5. INVESTIGATIONAL PLAN

5.1 OVERALL CLINICAL TRIAL DESIGN

This clinical trial will be conducted as a multi-center, randomized, investigator-blind, controlled and parallel-group study in subjects with severe rosacea characterized by persistent diffuse facial erythema and inflammatory lesions (papules and pustules), and meeting other specific eligibility criteria.

A total of 270 subjects will be enrolled (ie: 135 in each group) in approximately 50 sites in the USA, Canada and Europe. Approximately 5 subjects are planned from each site.

Subjects will be enrolled at baseline and treated for 12 weeks with either Ivermectin 1% cream associated with Doxycycline 40 mg MR (CD2475-101) capsules or Ivermectin 1% cream associated with CD2475-101 placebo capsules.

There will be two parallel groups, randomized in a ratio of [1:1].

There will be up to 5 trial visits: at baseline, Screening/Baseline, Week 4 (± 3 days), Week 8 (± 3 days), and Week 12 (± 5 days).

5.2 DISCUSSION OF CLINICAL TRIAL DESIGN

IVM 1% cream and oral Doxycycline 40 mg MR have been individually approved for rosacea treatment in US, Canada and Europe, with demonstrated efficacy and good safety profile including in severe rosacea population.

They will be used in this trial in their indication and approved dose and regimen.

Unlike clinical studies evaluating monotherapy approaches, clinicians often use a combination of topical and oral therapy for patients with severe rosacea, as an increased or additive benefit has been suggested with combination regimens.

Topical Ivermectin cream (10 mg/g) and systemic, oral Doxycycline 40 mg MR (modified-release) have only been evaluated individually so far, but never as an association. The combined therapeutic approach of both drugs association may be more beneficial, but has never been assessed for rosacea treatment in a randomized clinical trial.

To ensure an appropriate evaluation of this association benefit, it will be compared to Ivermectin 1% topical cream alone associated to the placebo of Doxycycline 40 mg MR (CD2475-101).

This clinical trial will compare the efficacy and safety of Ivermectin 1% topical cream associated with Doxycycline 40 mg Modified release (MR) capsules compared to Ivermectin 1% topical cream associated with Placebo in the treatment of severe Rosacea.

5.3 CLINICAL TRIAL DURATION AND TERMINATION

The average planned period for the clinical trial from First Subject In (FSI) to Last Subject Out (LSO)] is approximately 9 months. The end date of the clinical trial will be the date of the last visit of the last subject who participates in the clinical trial.

The planned duration of recruitment (i.e. From FSI to Last Subject In (LSI)) is approximately 6 months.

The clinical trial may be terminated by the investigator at his/her clinical trial site at any time with appropriate notification to *GALDERMA R&D*. Likewise, *GALDERMA R&D* may terminate the clinical trial and/or the participation of the clinical trial site(s) with appropriate notification.

The expected duration of subject participation is 12 weeks.

5.4 CLINICAL TRIAL FLOW CHART

PROCEDURES	STUDY VISITS			
	Visit 1	Visit 2	Visit 3	Visit 4
	Screening/ Baseline	Week 4 (±3 d)	Week 8 (±3 d)	Week 12 (±5 d)
Informed Consent/Photography Consent	X			
Inclusion/Exclusion Criteria	X			
Demographics/Medical History (including flushing and co-morbidities) / Previous Therapies (including rosacea last treatment)	X			
Concomitant Therapies	X	X	X	X
Urine Pregnancy Test (UPT) ^a	X			X
Inflammatory (Papules and Pustules) Lesion Counts	X	X	X	X
Clinician Erythema Assessment (CEA)	X	X	X	X
Investigator's Global Assessment (IGA)	X	X	X	X
Severity of Stinging/Burning sensation	X	X	X	X
Global assessment of Ocular signs and symptoms	X	X	X	X
Flushing via diary (frequency and severity)	X	X	X	X
Subject's Global Improvement in Rosacea				X ^d
Standardized Facial photography / facial redness colorimetric measurements ^b	X	X	X	X
Adverse Event (AE) ^c	X	X	X	X
DLQI Questionnaire	X			X ^d

EQ-5D-5L Questionnaire	X			X ^d
WPAI: GH questionnaire	X			X ^d
Subject Satisfaction Questionnaire				X ^d
Dispensation of Investigational Products, Subject Diary and Other Supplies	X	X	X	
Return of Investigational Products and Subject Diary		X	X	X
Exit form				X ^d

a. For subjects of childbearing potential only. UPT is mandatory at Screening/Baseline and at last visit (Week 12 or before if early termination).

b. Photography consent and standardized photography + facial redness colorimetric measurements at selected centers only.

c. AEs are to be collected starting from the signing of the Informed Consent Form.

d. Assessments to be performed in case of early termination visit.

5.5 CLINICAL TRIAL VISIT DESCRIPTION AND PROCEDURES

5.5.1 Visit 1 – Screening/Baseline visit

1. Explain the nature and the constraints of the clinical trial to the subject and to parent.
2. Have the subject read, understand, date and sign an approved informed consent form (ICF). Give a dated and signed copy to each subject and parent/guardian if applicable.
3. If subject female of childbearing potential agrees to participate to the clinical trial, make sure she is using the required method(s) of contraception (see inclusion criteria 4.2.1). Make sure that the urine pregnancy test is done and the result is negative before subject inclusion in the trial
4. Log into the electronic case report form (eCRF) to get a Subject Identification Number.
5. Question the subject about demography, medical history (including flushing and rosacea co-morbidities), prior and concomitant therapies (including rosacea last treatment).

6. Inform the subject about authorized and prohibited concomitant therapies. If the subject requires a medication washout period, the subject's baseline evaluation must be conducted after the washout period has been completed.
7. Check inclusion/exclusion criteria (see sections [4.2.1](#) and [4.2.2](#)).
8. Conduct facial inflammatory lesion count (see section [7.1.1](#)).
9. Assess and record the severity of the diffused facial erythema of rosacea using CEA (see section [7.1.2](#)).
10. Perform and record Investigator's Global Assessment (IGA) (see section [7.1.3](#)).
11. Evaluate and record the severity of subject's facial stinging/burning sensation (see section [7.1.4](#)).
12. Assess and record the severity of the Ocular signs and symptoms (see section [7.1.5](#)).
13. Record in medical history the frequency of flushing (average per week) and the severity as reported by subject for the last week before baseline visit (see section [7.1.6](#)).
14. Ask subject to complete the Dermatology Life Quality Index (DLQI) questionnaire (see [13.1](#)) and review for completion;
15. Ask subject to complete the EQ-5D-5L questionnaire (see [13.2](#)) and review for completion;
16. Ask subject to complete the WPAI:GH questionnaire (see [13.3](#)) and review for completion;
17. For selected sites only, take photographs of the face according to the provided photographic procedure, only if subject has agreed on the approved ICF.
18. For selected sites only, perform facial redness colorimetric measurements.
19. Record the occurrence of any new adverse events and/or any changes to adverse events.
20. If subject is eligible according to the inclusion/exclusion criteria, the smallest subject kit number available must be assigned to the subject by the investigator;
21. Fill in a prescription form, dispense the subject card, including the SIN, kit number and ask the subject to go see the person in charge of study medication, as relevant (hereafter referred to as investigational product dispenser).
22. The person in charge of investigational product dispensation described here as the investigational product dispenser will:
 - a) Dispense to the subject the baseline investigational products from the subject kit according to the prescription form.
 - b) Affix the tear-off portion of the label on the product dispensation log and report the required information on the labels if applicable.

- c) Dispense to the subject associated non-investigational products
 - d) Dispense the Subject diary.
 - e) Provide appropriate verbal and written instructions on how to properly use the investigational products and how to keep a record of missed doses. The first dose of topical investigational products will be applied/taken by the subject under the direction of site personnel before leaving the investigational site.
 - f) Emphasize the importance of complying with the given instructions and treatments; instruct the subject to bring back the dispensed investigational product(s) together with the subject diary at the next visit.
23. For all female subjects, emphasize the guidelines about contraception and risks in case of pregnancy
24. Schedule the next three visits [Week 4 (\pm 3 days), Week 8 (\pm 3 days) and Week 12 (\pm 5 days)].

5.5.2 Visit 2 and 3 – Week 4 and Week 8

- 1. Question the subject and record the occurrence of any new adverse events and/or any changes to adverse events that were ongoing at the previous clinical trial visit. Document all changes in the CRF.
- 2. Enquire whether any concomitant therapies have been added, stopped, or changed since the subject's last visit. Document all changes in the CRF.
- 3. Conduct facial inflammatory lesion count (see section 7.1.1).
- 4. Assess and record the severity of the diffused facial erythema of rosacea using CEA (see section 7.1.2).
- 5. Perform and record Investigator's Global Assessment (IGA) (see section 7.1.3).
- 6. Evaluate and record the severity of subject's facial stinging/burning sensation (see section 7.1.4).
- 7. Assess and record the severity of the Ocular signs and symptoms (see section 7.1.5).
- 8. Check subject's diary and record the frequency and severity of flushing for each week as reported by subject in the diary (see section 7.1.6).
- 9. Take photographs of the face according to provided photographic procedure (for selected sites only).
- 10. For selected sites only, perform facial redness colorimetric measurements.
- 11. Fill in a prescription form and ask the subject to go see the Investigational product dispenser, as relevant.

12. Investigational product dispenser will:
- a) Check the investigational products; review the subject's diary for completion and accuracy interview the subject about compliance. All missing tubes must be documented on the eCRF comments section and on other accountability forms.
 - b) Record the investigational products and Facial Moisturizer compliance on the eCRF.
 - c) Dispense to the subject the investigational products from the subject kit according to the prescription form.
 - d) Affix the tear-off portion of the label on the product dispensation log and report the required information on the labels if applicable.
- e) Dispense to the subject associated non-investigational products (if necessary) and give back the subject diary.
- f) Provide appropriate verbal and written instructions on how to properly use the investigational products and how to keep a record of missed dose(s).
 - g) Emphasize the importance of complying with the given instructions and treatments; instruct the subject to bring back the dispensed investigational product(s) together with the subject diary at the next visit.
13. Check and confirm for next follow-up visit schedule until Final visit 4 - Week 12 (\pm 5 days).

In case of early termination of the Clinical Trial for whatever reason:

- a) The subject will be fully evaluated
- b) The procedures designated for the last clinical trial visit should be performed

5.5.3 Visit 4- Week 12 / Last clinical trial visit

- 1. Question the subject and record the occurrence of any new adverse events and/or any changes to adverse events that were ongoing at the previous clinical trial visit. Document all changes in the CRF.
- 2. Enquire whether any concomitant therapies have been added, stopped, or changed since the subject's last visit. Document all changes in the CRF.
- 3. Conduct facial inflammatory lesion count (see section 7.1.1).
- 4. Assess and record the severity of the diffused facial erythema of rosacea using CEA (see section 7.1.2).
- 5. Perform and record Investigator's Global Assessment (IGA) (see section 7.1.3).

6. Evaluate and record the severity of subject's facial stinging/burning sensation (see section 7.1.4).
7. Assess and record the severity of the Ocular signs and symptoms (see section 7.1.5).
8. Check subject's diary and record the frequency of flushing for each week as reported by subject in the diary (see section 7.1.6).
9. Ask the subject to assess her/his Global Improvement in Rosacea (see section 7.1.7) and record the outcome;
10. Ask subject to complete the Dermatology Life Quality Index (DLQI) questionnaire (see 13.1) and review for completion;
11. Ask subject to complete the EQ-5D-5L questionnaire (see 13.2) and review for completion;
12. Ask subject to complete the WPAI:GH questionnaire (see 13.3) and review for completion;
13. Ask subject to complete the Subject Satisfaction questionnaire (see 13.4) and review for completion;
14. Perform a urine pregnancy test (UPT) for female subjects of childbearing potential.
15. For selected sites only, take photographs of the face according to the provided photographic procedure, only if subject has agreed on the approved ICF.
16. For selected sites only, perform facial redness colorimetric measurements.
17. Complete the Exit form in the CRF and give the reason for clinical trial discontinuation.
18. Investigational product dispenser will:
 - a) Check the investigational products; review the subject's diary for completion and accuracy interview the subject about compliance. All missing tubes must be documented on the eCRF comments section and on other accountability forms.
 - b) Record the investigational products and Facial Moisturizer compliance on the eCRF.

6. CLINICAL SUPPLIES

Investigational products and supplies will be provided by the sponsor and shipped by the clinical supply unit or local depot.

6.1 INVESTIGATIONAL PRODUCT IDENTIFICATION AND USE

6.1.1 Product identity

	Galderma Product	Galderma Product	Comparator Product
Trade Name	Soolantra [®] cream	Oracea [®] capsules	Not applicable
Name of Active Ingredient	Ivermectin (CD5024)	Doxycycline monohydrate (CD2475-101)	CD2475-101 placebo capsule
Form	Cream	Capsule	Capsule
Dose or Concentration	1%	40 mg MR (30 mg Immediate Release & 10 mg Delayed Release beads)	Not applicable
Manufacturer (Name and address)	Galderma Production Inc, Montreal (Canada)	Catalent Pharma Solutions, LLC Winchester, Kentucky 40391 USA	Catalent Pharma Solutions, LLC Winchester, Kentucky 40391 USA
Packaging (primary)	30g CRC tube	Bottle of 30 capsules	Bottle of 30 capsules
Storage Requirements*	Store at 20 to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (for US supplies)	Store at room temperature between 59°F to 86°F (15°C to 30°C)	Store at room temperature between 59°F to 86°F (15°C to 30°C)

*the most restrictive storage conditions on the labels will be applied.

6.1.2 **Method of treatment assignment**

Prior to the start of the clinical trial a randomization list will be generated by GALDERMA R&D and transmitted to the assigned clinical packaging organization for labeling. The RANUNI routine of the SAS systems will be used for the kit number generation.

A subject kit will be composed of:

either Ivermectin 1% cream and Doxycycline 40 mg MR (CD2475-101) capsules, or Ivermectin 1% cream and CD2475-101 placebo capsules.

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

Treatments will be balanced in 1:1 ratio for each group. Complete blocks of treatment materials will be sent to the investigational sites.

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

At the baseline visit, all eligible and enrolled subjects will be dispensed treatment (ie: tube of Ivermectin and bottle of Doxycycline 40 mg MR or oral placebo) from the subject kit, which will be allocated in chronological order of inclusion into the clinical trial, without omitting or skipping any numbers.

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

6.1.3 **Subject Identification Number (SIN)**

Upon signature of the informed consent, a subject meeting all inclusion/exclusion criteria will be allocated a unique subject identification number automatically generated by the eCRF.

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

6.1.4 **Instructions for use and administration**

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

In addition, the investigational product dispenser will show the subject how to use/take the investigational products or how to perform the investigational product application at the baseline visit.

Ivermectin 1% cream should be applied once daily in the evening. Subjects will be instructed to apply one small pea size of cream on the forehead, chin, nose, and each cheek (ie a total of 5 pea-sized amounts). The product should be evened out to a thin film on the entire face. Application to the following areas must be avoided: eyes, eyelids, inner nose, mouth, and lips. Should this occur, areas will have to be washed with plenty of water.

Subjects will be instructed to wash hands immediately after product application.

Doxycycline 40 mg MR or its placebo should be taken once daily in the morning on an empty stomach, preferably at least one hour prior to or two hours after meals.

The treatment administration is further described below.

	Investigational Product	Investigational Product	Comparator Product
	Ivermectin	Doxycycline monohydrate	oral placebo
Concentration	1%	40 mg MR (30 mg Immediate Release & 10 mg Delayed Release beads)	NA
Dose regimen	Once daily in the evening	Once daily in the morning	Once daily in the morning
Period of administration	12 weeks	12 weeks	12 weeks
Route of administration	Cutaneous to the entire face	Oral	Oral

6.2 OTHER SUPPLIES

- **Gentle Skin Cleanser:**

Cetaphil Redness Relieving® Foaming Face Wash (or equivalent)

- **Facial Moisturizer SPF 30:**

Cetaphil redness relieving® facial moisturizer¹ (or equivalent)

- **Urine Pregnancy Tests (UPT):**

Arrow™ (or equivalent)

All the above supplies will be provided by the Sponsor.

Gentle Skin Cleanser:

Subjects should use the Gentle Skin Cleanser to wash the face prior to applying the study treatment.

¹ SPF= 30 (per ISO 24444:2010 SPF norm) / SPF= 20 (per FDA Fed Register 2011:76 SPF norm)

No specific labels will be used.

Facial Moisturizer SPF 30:

Subjects will be recommended to use the provided moisturizer/sunscreen during the study, within 1 hour after study drug application, especially for outdoor activities and/or sun exposure. Subjects will be instructed not to apply the provided moisturizer/sunscreen on the days of study visits until the study assessments are performed.

No specific labels will be used.

6.3 INVESTIGATIONAL PRODUCT PACKAGING AND LABELING

All investigational products will be supplied in the subject's kit including visit boxes with an affixed and a tear-off portion.

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

If more than one batch is used with different expiration dates, in order to maintain blinding, only one expiry date, the most conservative, will be listed on the container label.

The same kit number will be printed on each investigational product container and subject kit labels.

The Subject Identification Number and subject's initials will be manually entered onto the subject kit/visit box and the dispensation date will be manually entered onto the visit label box.

The labels (including tear-off part) will also contain information required by Good Manufacturing Practice (GMP), Good Clinical Practice (GCP) and local regulations and will be printed in local languages.

6.4 INVESTIGATIONAL PRODUCT MANAGEMENT

6.4.1 **Accountability**

Upon receipt of the clinical supplies at the site, the investigational product dispenser will conduct a complete inventory of all investigational products and assume responsibility for their storage, accountability and dispensation.

The Investigator or designee will sign the original "Receipt of Clinical Supplies" Form (or any acknowledgment of receipt) upon receipt and inspection of the supplies, send the signed copy and the temperature curve to *GALDERMA R&D* and retain the receipt in the Investigator Site File (ISF).

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

At the end of the trial, all used and unused investigational products will be returned to *GALDERMA R&D* or the designated contractor for further reconciliation, appropriate inventory and destruction.

6.4.2 **Dispensing**

Investigational products will be prescribed only to subjects enrolled into the clinical trial, at no cost and in accordance with the conditions specified in the protocol.

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

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

The investigational product dispenser will follow the accurate prescription according to the allocated kit.

Each Subject kit will contain 3 visit treatment boxes (each for 1 month of treatment) to be dispensed at Baseline, Week 4 and Week 8 visits, respectively.

Each visit treatment box will contain 1 tube of Ivermectin 1% cream and 2 bottles of Doxycycline 40 mg MR or its placebo.

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

The investigational product dispenser must be different from the clinical trial efficacy and safety evaluator in order to maintain the blind (see section 6.4). Treatment kits will be dispensed in ascending sequential order according to the chronological order of enrolment of subjects into the clinical trial.

6.4.3 **Investigational product compliance management and record**

Each subject will be instructed by the investigational product dispenser about the importance of being compliant with clinical trial treatment(s) throughout the clinical trial as well as the importance of returning their investigational product (used and/or not used) at each follow-up visit.

The investigational product(s) will be collected and counted at all visits by the investigational product dispenser.

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

A subject's diary will be given to each subject in order to record the use of investigational products and Facial Moisturizer. The investigational product dispenser will review the subject's diary at every visit.

The return of investigational products will be appropriately documented on the product dispensation log by the investigational product dispenser.

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

6.4.4 **Storage of investigational product**

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

Investigational products should be stored at appropriate storage conditions specified by *GALDERMA R&D* (see section [6.1.1](#)).

6.4.5 **Return of investigational product**

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

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

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

6.5 BLINDING

6.5.1 Verification of blinding

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

1. Oral placebo capsules will be free from marking unlike the Oracea capsules. Aside from this difference, both oral trial products will be filled in the same type of primary packaging materials (ie: bottle) and there will be no other sign that could indicate which one is the active product and which one is the placebo.
2. The investigational products will be dispensed by someone other than the evaluator (investigator or designee) designated as the investigational product dispenser in order to maintain the blind.
3. Additionally, both the investigational product dispenser and the subject will be instructed not to discuss the investigational products with the evaluator (investigator or designee)
4. The investigational product dispenser and the investigator will not have access to the unblinded randomization list.

The randomization list will be maintained secured in a locked cabinet and/or an electronic file with restricted access to only the designated personnel directly responsible for labeling and handling the study drugs at the Sponsor's/designee's location. The independent statistician providing analyses requested will be able to access the randomization list upon request.

6.5.2 Unblinding during the clinical trial

Emergency un-blinding during the clinical trial may be required for therapeutic or for regulatory reasons (e.g. for expedited safety reporting).

A blind-break system will be available for Investigators. At the clinical trial center, the blinded label containing the identification of the assigned study drug(s) will be revealed in emergency situations only. In such an emergency, the Investigator will only break the blind for the subject involved.

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

The investigator must notify the sponsor immediately in the event of such an emergency (see contact details in Section 8.2.2). If possible, the investigator should notify the sponsor before breaking the blind in order to discuss this decision with the sponsor. The investigator is required to document each case of emergency un-blinding on the appropriate form (provided by the Sponsor) and send the completed form to the sponsor immediately.

7. EFFICACY AND SAFETY ASSESSMENT

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

If it is not possible to use the same evaluator to follow a subject, then evaluations should overlap for at least one visit in order to examine the subject together and discuss findings. This should be documented in medical source documents.

7.1 EFFICACY ASSESSMENTS

7.1.1 *Inflammatory Lesion Count*

The evaluator will perform inflammatory lesion count on facial papules and pustules of rosacea at baseline and then at each visit.

Inflammatory lesions are defined as follows:

- Papule – A small, solid elevation less than one centimeter in diameter
- Pustule – A small, circumscribed elevation of the skin, which contains yellow white exudates.

Papules and pustules will be counted separately on each of the five facial regions (forehead, chin, nose, right cheek and left cheek). **Nodules** (defined as a circumscribed, elevated, solid lesion more than 1.0 cm in diameter with palpable depth) **will not be included in the count of inflammatory lesions**, and subjects are not eligible if they have more than 2 nodules on the face at screening/baseline visit.

7.1.2 *Clinician's Erythema Assessment (CEA)*

The evaluator will assess the subject's diffuse persistent facial erythema of rosacea by performing a static ("snap shot") evaluation of erythema severity, at a social distance of approximately 50 cm, using CEA at each visit. The evaluator should make no reference to previous assessments when evaluating the subject's erythema of rosacea and CEA must be evaluated after the inflammatory lesion count.

Grade	Description
0	Clear skin with no signs of erythema
1	Almost clear; slight redness
2	Mild erythema; definite redness
3	Moderate erythema; marked redness
4	Severe erythema; fiery redness

7.1.3 Investigator's Global Assessment (IGA)

The evaluator will assess the subject's rosacea at each visit by performing a static ("snap-shot") evaluation, at a social distance of approximately 50 cm, using IGA score. No reference to previous visits should be made by the evaluator. A subject must have an IGA of 4 (severe) to be eligible for the study.

Grade	Score	Clinical Description
Clear	0	No inflammatory lesions present, no erythema
Almost Clear	1	Very few small papules/pustules, very mild erythema present
Mild	2	Few small papules/pustules, mild erythema,
Moderate	3	Several small or large papules/pustules, moderate erythema,
Severe	4	Numerous small and/or large papules/pustules, severe erythema,

7.1.4 Stinging/Burning sensation

The evaluator will record the severity of subject's facial stinging/burning sensation (a prickling pain sensation) during the last 24h at each visit.

Grade	Score	Clinical Description
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

7.1.5 Ocular Signs and Symptoms

Ocular manifestations will be evaluated by the Evaluator after discussion with the subject. The Evaluator may identify ocular manifestations by looking for tearing, redness of bulbar and/or palpebral conjunctivae, telangiectasia of conjunctiva and lid margin, lid or periocular erythema, or styes, and by inquiring about symptoms of foreign-body sensation, gritty feeling, burning, stinging, itching, dryness, light sensitivity, blurred vision, or decreased visual acuity.

Grading of ophthalmological abnormalities in ocular rosacea will be based on clinical opinion of dermatologist and evaluated at each visit using the below scale.

Grade	Score	Clinical Description
None	0	No ocular sign/symptom
Mild	1	Mild blepharitis with lid margin telangiectasia
Mild-Moderate	2	Blepharoconjunctivitis
Moderate-Severe	3	Blepharo-keratoconjunctivitis
Severe	4	Sclerokeratitis, anterior uveitis

7.1.6 Flushing

At baseline, Investigator will record in medical history the frequency (number) of flushing as reported by subject for the previous week before baseline visit and the corresponding average severity by grading as mild, moderate or severe.

During the study, the number of weekly flushing and the average severity will be recorded from Subject's diary where subject will be asked to report each day the flushing episodes. Investigator or designee will have to check with subject for diary completeness at each visit and report flushing information in the eCRF.

7.1.7 Subject's Global Improvement in Rosacea

The subject will evaluate his/her improvement in rosacea at last visit, compared with his/her rosacea condition before the study.

0	Complete improvement	All signs and symptoms of disease have resolved (100% improvement from Baseline)
1	Excellent Improvement	Nearly all signs and symptoms cleared (90% improvement from Baseline) . Only minimal residual signs and symptoms remain
2	Very good Improvement	Majority of the signs and symptoms have resolved (about 75% improvement from Baseline)
3	Good Improvement	Significant improvement, but many signs and symptoms remain (about 50% improvement from Baseline)
4	Minimal improvement	Slight overall improvement, but not clinically significant (about 25% improvement from Baseline)
5	No Change	Overall severity similar from Baseline
6	Worse	Worse than Baseline

7.2 SAFETY ASSESSMENTS

A safety assessment will be conducted for all subjects at the screening/baseline visit (from the Informed consent signature) and every subsequent visit. The safety parameters and AEs are to be recorded as specified in section 7.2.1.

7.2.1 Adverse Events

Adverse events (AEs) are to be monitored throughout the course of the clinical trial. All AEs occurring after the subject signs the informed consent should be recorded on the AE form on the eCRF.

All AEs are to be reported on an Adverse Event Form of the eCRF with complete information as required. If AEs occur, the main concern will be the safety of the subject. At the time of the ICF signature, each subject must be provided with the name and telephone number of clinical trial center personnel for reporting AEs and medical emergencies.

All clinical medical events, whether observed by the investigator or reported by the subject and whether or not thought to be related to the study drug will be considered AEs. Assessment of seriousness, severity and causality will be based on specific definitions. If the subject discontinues due to an AE, both the AE Form and the Exit Form should be completed.

Subjects reporting a worsening of rosacea (worsening of any signs and symptoms of rosacea including but not limited to inflammatory lesions, persistent erythema and flushing) will be evaluated in detail. This includes the onset, duration and outcomes of those events, as well as a complete history and potential triggers of the concerned signs and symptoms of rosacea.

7.3 PATIENT RELATED OUTCOMES

7.3.1 Dermatology Life Quality Index (DLQI) questionnaire

At Baseline and at last visit, subjects will answer the 10-item DLQI questionnaire (see section 13.1), a validated quality-of-life questionnaire specific to dermatological conditions. The investigator or delegate will then check all questions of the questionnaire for completeness prior to the subject leaving the study visit.

7.3.2 EQ-5D-5L questionnaire

Subjects will answer the quality of life questionnaire EQ-5D-5L at Baseline visit and at last visit. EQ-5D-5L is a 5-level, 5-dimensional format standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. EQ-5D was originally

designed to complement other instruments but is now increasingly used as a 'stand-alone' measure. EQ-5D-5L is designed for self-completion by respondents. It is cognitively simple; taking only a few minutes to complete (see section 13.2). The investigator or delegate will then check all questions of the questionnaire for completeness prior to the subject leaving the study visit.

7.3.3 Work Productivity and Activity Impairment Questionnaire: General Health Problem (WPAI:GH) modified for Rosacea.

Subjects will answer the quality of life questionnaire WPAI: GH at Baseline visit and at last visit. The WPAI: GH questionnaire consists of six questions (see section 13.3). It is an instrument to measure impairments in both paid work and unpaid work. It measures absenteeism, presenteeism as well as the impairments in unpaid activity because of health problem during the past seven days. It has been validated to quantify work impairments for numerous diseases including dermatological diseases such as psoriasis^{1,16}. In addition, the WPAI: GH questionnaire has been used to compare work impairments between treatment groups in clinical studies or between subjects with different disease severity levels. As per WPAI questionnaire adaptation guidelines, the questionnaire has been adapted for rosacea by replacing the term 'your health problems' by 'your rosacea'.

The investigator or delegate will then check all questions of the questionnaire for completeness prior to the subject leaving the study visit.

7.3.4 Subject satisfaction questionnaire

At last visit, subjects will complete a questionnaire (see section 13.4).

7.4 OTHER ASSESSMENTS

7.4.1 Photography

Standardized photographs on the face (1 front view and 2 profile views) will be taken at selected investigational sites at each study visit. Pictures will be used for illustrative purpose and will not be subject to analysis.

7.4.2 Facial redness colorimetric measurements

Complementary facial redness colorimetric measurements will be performed using a Chromameter at selected investigational sites, depending on material availability.

7.5 APPROPRIATENESS OF MEASUREMENTS

The clinical efficacy assessments will be based on inflammatory lesion counts, evaluation of facial erythema, stinging/burning sensation and flushing. The methods are established in the evaluation of rosacea products and used in previous studies with the study products.

Safety is documented by recording adverse events on an ongoing basis as a well-established process in clinical trials. In case of reporting of a worsening of rosacea, specific complementary data will be collected.

Impact of study treatments on subjects' quality of life will be measured by using specific questionnaires. DLQI and EQ-5D-5L are two validated questionnaires for evaluating quality-of-life: While EQ-5D-3L is more general and not disease-specific, the DLQI focuses on the impact of dermatological diseases on the quality-of-life.

The WPAI:GH questionnaire is a validated instrument to quantify work impairments for numerous diseases including dermatological conditions.

To collect specifically the patient satisfaction outcome, a subject satisfaction questionnaire will be used at the end of the study to collect the subjects' feedback on the treatment regimen, the level of satisfaction and future usage.

8. ADVERSE EVENT

8.1 DEFINITIONS

8.1.1 Adverse Events (AE)

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

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

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

Notes:

- Any new sign or symptom reported by the subject that appears after accidental or intentional overdose or misuse should also be reported as an AE.
- There should be an attempt to report a diagnosis rather than the signs, symptoms or abnormal laboratory values associated with the report of an AE. However, a diagnosis should be reported only if, in the Investigator's judgment, it is relatively certain. Otherwise, symptoms, signs, or laboratory values should be used to describe the AE.
- Pregnancy should not be considered as an adverse event but must be followed up as described in section [8.3](#)
- For an AE of irritation, the "date of onset" should be the date that the first symptom occurred.

8.1.2 Serious Adverse Events (SAE)

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

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

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

Note:

- The term “life-threatening” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Inpatient hospitalization is considered to have occurred if the subject has had to stay in hospital overnight. The criterion for the prolongation of hospitalization is also defined as an extra night at the hospital. Hospitalization may not constitute sufficient grounds to be considered as an hospitalization if it is solely for the purpose of diagnostic tests, (even if related to an AE), elective hospitalization for an intervention which was already planned before subject enrolment in the clinical trial, admission to a day-care facility, social admission (e.g., if the subject has no place to sleep), or administrative admission (e.g., for a yearly examination).

8.1.3 **Unexpected adverse drug reaction**

According to ICH E6, an unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable study drug information.

8.1.4 **Adverse event reporting period**

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

The sponsor should be informed if the investigator becomes aware of any unusual safety information or any safety information that appears to be drug-related involving a subject who has

participated in a clinical trial, even after a subject has completed the clinical trial. The investigator should be diligent in looking for possible latent safety effects that do not appear until a medication has been discontinued.

8.1.5 **Severity**

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

The investigator will classify the intensity of AEs using the following definitions as a guideline for all AEs occurring during clinical trials conducted or sponsored by GALDERMA. For this classification, the investigator will take into account the possible range of the intensity of the event and report the grade of intensity which is the most appropriate according his medical judgment.

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

8.1.6 **Relationship to the study drug(s) and/or clinical trial procedure**

The investigator is to determine whether there is a reasonable causal relationship between the occurrence of the AE and exposure to the study drug(s) and/or clinical trial procedure. Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, positive de-challenge or re-challenge, 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 (International Conference on Harmonization (ICH) E2A, section IIIA 1).

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

Reasonable possibility:

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

- The study drug (investigational product, active comparator, or vehicle, etc.) and the AE,

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

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

No Reasonable Possibility:

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

8.2 REPORTING PROCEDURES

8.2.1 Procedures for reporting adverse events

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

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

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

Adverse events assessed as related to the treatment or study procedure will be monitored until they have resolved or reached a stable condition. Other AEs will be monitored until the last visit if they have not resolved or reached a stable condition. The investigator will obtain and maintain in the subject's files all pertinent medical records, information and medical judgment from colleagues who assisted in the treatment and follow-up of the subject. If necessary, the investigator will contact the subject's personal physician or hospital staff to obtain further details. For SAEs (see section 8.2.2) and pregnancies (see section 8.3), the Sponsor is to be informed

immediately by e-mail/fax. The event must be reported by fax or sent by e-mail to the Sponsor within 24 hours of receipt of the information (contact details in section 8.2.2).

8.2.2 Procedure for reporting a serious adverse event

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

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

	GALDERMA R&D
Name	██████████
Title	████████████████████
Address	██████████ ████████████████ ████████████████
Tel. during office hours	██████████████████
Tel. outside office hours	██████████████████████████████
Fax	██████████████
Email	pharmacovigilance@galderma.com

3. Print and complete the Serious Adverse Event form (available in the eCRF system as PDF document). Fax or send by email the completed form, accompanied any other relevant information or anonymized medical records (e.g., laboratory test results) within 24 hours of

receipt of this information to the sponsor (see contact details above). The demographics, medical history, drugs/therapies forms, and adverse event pages of the eCRF must be completed and available for review in the eCRF system at the time of the report.

4. **Monitor and record the progress of the event until it resolves** or reaches a clinically stable outcome, with or without sequelae. For all additional follow-up evaluations, fax or send by e-mail all additional follow-up information on the SAE to the sponsor (see contact details above) within 24 hours of receipt of the updated information. SAEs will be monitored until the Investigator and Sponsor agree that the event is satisfactorily resolved.
5. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details
6. **Inform the sponsor of the final outcome of the event.** Send a revised or updated SAE form and AE form, if appropriate.
7. Prompt notification of SAEs by the investigator to GALDERMA is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met. GALDERMA has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GALDERMA will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, IRBs/IECs and investigators. Investigator safety reports are prepared for Suspected Unexpected Serious Adverse Reactions (SUSARs) according to local regulatory requirements and GALDERMA policy and are forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GALDERMA will notify the IRB/IEC, if appropriate according to local requirements.
8. Comply with the applicable regulatory requirements related to the reporting of SAEs to your IRB/EC.

8.2.3 Procedure for suspected allergic contact reaction

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

- Stop the trial product
- Take a picture of the affected area and the non-affected surrounding skin
- Document the event and report it immediately to the sponsor by email/fax, within 24 hours of receipt of the information as described in section [8.2.2](#).

In case of suspicion of allergic contact dermatitis

1. After all signs and symptoms have resolved and after a minimum of two weeks from last dose application, a re-challenge test with the assigned trial product will be performed.
2. Ensure the subject has not been under any treatment with corticosteroids or antihistamines, regardless of the route of administration, the week before testing.
3. Ensure that the skin on the back has not been exposed to the sun or artificial ultraviolet sources the week before testing.
4. Apply an appropriate quantity of the assigned trial product to fill the cupule of the test chamber on the skin of the upper back on either the right or left side of the center line (or the inner forearm if the back cannot be tested). If no test chamber is available on-site, patch test units will be provided. It may be preferable to perform the test under semi-occlusive conditions depending on the irritant potential of the trial product and the intensity of the reaction that was observed. The method to be used will be discussed with the sponsor.
5. Choose a skin site that was not previously involved in the inflammatory skin reaction.
6. Cover it for 48 hours with a hypoallergenic tape.
7. Subject should be informed about avoiding exercise, showers, application of toiletries products, etc. to keep the test system dry
8. After 48 hours, remove the tests and evaluate the site:
 - At approximately 30 minutes after patch test removal (1st reading) and,
 - 24 to 48 hours later (i.e. 72 or 96 hours after application) (2nd reading).
 - A facultative 3rd reading may be performed 96 to 120 hours later (i.e. 6 to 7 days after application of the patch) if the overall assessment so far equivocal or if asked by the sponsor.
 - Pictures of the tested areas will be taken systematically at each reading and properly documented.

Duration of trial product application	1st Reading	2nd Reading	3rd reading (optional)

48 hours	48 hours after trial product application (30 minutes after patch test removal)	72 to 96 hours after trial product application (24 to 48 hours after patch test removal)	6 or 7 days after trial product application (96 to 120 hours after patch removal)
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9. Refer to the scoring system ([Spiewak, R. 2008^{1,17}](#)) used by the International Contact Dermatitis Research Group (ICDRG) to assign a score at each reading:

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

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

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

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

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

8.3 PROCEDURES FOR REPORTING PREGNANCIES

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

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

1. **Withdraw the subject from the clinical trial**
2. Complete all appropriate visit evaluations and CRF pages.
3. **Immediately (no later than 24 hours) contact the Sponsor** to inform them of the pregnancy occurrence and discuss further steps to be taken.
4. **Complete, as fully as possible, the pregnancy surveillance form – Part I:** History and start of pregnancy - provided by the CRA at the beginning of the clinical trial, as fully as possible. Fax or send by email this pregnancy form along with the Exit form within 24 hours of receipt of the information to the Sponsor.

	GALDERMA R&D
Name	██████████
Title	████████████████████
Address	██████████ ████████████████ ████████████
Tel. during office hours	██████████████████
Tel. outside office hours	██████████████████████████████
Fax	██████████████
Email	pharmacovigilance@galderma.com

5. Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask regular follow-up information.
6. **Inform the Sponsor of the progress by tri-monthly updates up** to the final outcome of the pregnancy. For all the additional follow-up evaluations, fax or send by e-mail the additional follow-up information to the sponsor within 24 hours of receipt of the information. If the subject can no longer be reached (lost to follow-up), documentation of the non-response/contact with two phone calls and a letter (certified with return receipt) is required.
At outcome of pregnancy, complete as fully as possible the pregnancy surveillance form – Part II: Course and outcome of pregnancy, as full as possible. Inform the Sponsor by email/ fax, then fax or send by e-mail this pregnancy form to the Sponsor within 24 hours of receipt of the information.
7. If the pregnancy leads to an abortion (voluntary abortion, spontaneous abortion or therapeutic abortion), *in utero* death or congenital anomaly, follow the procedure for declaration of an SAE (see Section 8.2.2).

9. STATISTICAL METHODS PLANNED

9.1 STATISTICAL AND ANALYTICAL PLANS

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

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

The purpose of the trial is to evaluate the efficacy of Ivermectin 1% topical cream associated with Doxycycline 40 mg Modified release (MR) capsules versus Ivermectin 1% topical cream associated with Placebo in the treatment of severe Rosacea.

The Safety and Patient Reported Outcomes (PRO) will be also evaluated.

9.1.1 ***Variables to be statistically analysed***

The following variables will be analysed:

9.1.1.1 Primary efficacy variable

The primary endpoint is the percent change from Baseline in Inflammatory Lesion count at Week 12.

9.1.1.2 Secondary efficacy variables

The secondary efficacy endpoints are:

- Percent change from Baseline in Inflammatory Lesion count at each intermediate visit
- CEA at each post-Baseline visit: % of subjects across scores
- IGA at each post-Baseline visit: % of subjects across scores
- Stinging/burning at each post-Baseline visit: % of subjects across scores
- Percent change from Baseline (medical history) in terms of flushing count per week over 12 weeks
- Change from Baseline (medical history) in terms of flushing severity score per week over 12 weeks
- Global improvement in rosacea at the last visit: % of subjects across scores

9.1.1.3 Exploratory efficacy variable

One exploratory endpoint is planned to be analyzed:

The global assessment of Ocular signs and symptoms at each post-Baseline visit: % of subjects across scores

9.1.1.4 Safety variables

- Incidence of adverse events
- Incidence of serious adverse events

9.1.1.5 Patient Reported Outcomes (PRO)

- DLQI questionnaire at Baseline and the last visit
- EQ-5D-5L questionnaire at Baseline and last visit
- WPAI:GH questionnaire at Baseline and last visit
- Subject Satisfaction Questionnaire at last visit

9.1.2 Populations analysed, evaluability and limitations / evaluation of Bias

The statistical analyses will be performed based on the following subject populations:

9.1.2.1 The Per Protocol efficacy population (PP)

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

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

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

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

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

9.1.2.4 Missing values

The last observation carried forward (LOCF) method will be used to impute missing values of Inflammatory Lesion count, CEA, IGA and Stinging/burning sensation. If no post-baseline data

are available, baseline will be carried forward. Thus, the number of subjects will not vary at each visit. The other missing values will not be replaced (observed data).

9.1.3 Data presentation and graphics

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

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

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

9.1.4 Statistical analyses

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

The definition of the populations will be finalized after a blind data review meeting, during which the distribution of subjects per site will be reviewed. In case of too small sites or in case of severe unbalance between the size of sites, some sites may be combined, *e.g.* per geographical area, to form analysis-center for purpose of stratification of the statistical analyses.

The primary objective of this study will be to demonstrate the superiority of the Ivermectin 1% topical cream associated with Doxycycline 40 mg MR capsules compared to versus Ivermectin 1% topical cream associated with Placebo, in terms of Inflammatory Lesion count at week 12.

The primary efficacy endpoint will be analyzed by using the Cochran-Mantel-Haenszel (CMH, FREQ procedure from SAS®) statistic, stratified by center (or analysis-center) after rdit

transformation with the row mean difference statistics, testing the hypothesis of equality on ITT/LOCF population. PP analysis will also be performed to assess the robustness of the results obtained on ITT/LOCF population. The p-values will have to be inferior to 0.05 at week 12.

The secondary efficacy variables, questionnaires will be analyzed similarly as primary analyses on appropriate population.

The subject characteristics (disposition, previous and concomitant therapies, study treatments duration/ compliance, demographics, baseline characteristics,...), lesion counts and adverse event(s) will only be summarized descriptively, on appropriate population.

9.2 SAMPLE SIZE DETERMINATION

9.2.1 Historical data and assumptions

No previous study exists associating Ivermectin 1% cream and Doxycycline MR. Therefore, this sample size was calculated using the results (% change from baseline in inflammatory lesion counts at Week 12) of previous studies on subjects treated with:

- Ivermectin 1% cream alone, which showed a standard deviation (SD) between 25.4% to 39.9% (with a mean around 35%).
- Doxycycline MR alone, which showed a minimum difference of 26% at Week 12, vs. Placebo

Using this historical data, we can assume that the difference between the association (Ivermectin + Doxycycline MR) and Ivermectin will be at least of 15% with a SD of 35%.

9.2.2 Sample size calculation

With the assumptions mentioned above, a total of 114 evaluable subjects per group will be required to demonstrate at least 15% difference at Week 12, with 90% power. To allow a 15% rate of subjects excluded from analysis (drop out, lost to follow-up, etc.) at Week 12, 135 subjects per group (270 in total) are to be enrolled.

10. TRAINING / MONITORING / DATA MANAGEMENT / QUALITY ASSURANCE

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

10.1 PERSONNEL TRAINING

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

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

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

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

A trial reference manual will be provided to each site as an additional reference tool. These guidelines will contain key CRO and Sponsor contacts and phone numbers and specific instructions for site in order to standardize as much as possible the assessments performed during the clinical trial.

10.2 CLINICAL MONITORING

The conduct of the clinical trial will be closely monitored by representatives of CRO/*GALDERMA R&D* to verify the adherence to the clinical trial protocol, ICH-GCP regulations, applicable SOPs, guidelines, and all local regulations.

The investigator will allow representatives of *GALDERMA R&D/CRO* to have direct access to all clinical trial records, CRFs, corresponding subject medical records, investigational product dispensing records and investigational product storage area, site facilities and any other documents considered as source documentation.

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

10.3 DATA MANAGEMENT

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

All data management procedures will be detailed in the Data Management Plan (DMP).

The DMP will describe the Clinical Data Management System (CDMS) that will be used to collect and validate data. Computerized edit checks and review processes will be performed on an ongoing basis as outlined in the DMP until all data discrepancies are resolved.

After all data discrepancies are resolved, coding is approved, and subject evaluability has been determined, the data will be exported to SAS datasets and will be locked.

After unblinding, the locked SAS database will be used to generate subject listings, tabulations and analyses.

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

10.4 QUALITY ASSURANCE / AUDIT / INSPECTION

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

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

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

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

11. ETHICS AND GENERAL CLINICAL TRIAL CONDUCT CONSIDERATIONS

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

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

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

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

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

11.2 ETHICAL CONDUCT OF THE CLINICAL TRIAL

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

11.3 SUBJECT INFORMATION SHEET / INFORMED CONSENT

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

Prior to any clinical trial procedures, the subject will sign and date the informed consent form(s) which is written in the local language. A copy of the signed and dated form(s) will be given to the subject. The investigator is responsible for maintaining each subject's consent form(s) in the investigator's site file (ISF) and providing each subject with a copy of the consent form.

The informed consent form including photograph release form approved by an IRB/EC will be fully explained to the subject, when applicable.

11.4 CONTRACTUAL REQUIREMENTS

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

11.5 DATA COLLECTION AND ARCHIVING

11.5.1 Data Collection

The investigator must maintain required records on all clinical trial subjects.

Data for this clinical trial will be recorded in the subject's source documents and in the eCRF, the product dispensation logs, the subjects' diaries and questionnaires provided by GALDERMA R&D.

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

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

A complete set of copies will remain at the investigational site.

11.5.2 Source documentation

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

A statement should be made on subject's medical notes indicating that the **subject has been enrolled in GALDERMA R&D protocol RD.03.SPR.113322 and has provided dated and signed informed consent.**

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

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

11.5.3 Archives

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

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

11.6 INSURANCE

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

12. REFERENCE LIST

1. Wilkin J, Dahl M, Detmar M, Drake L, Liang MH, Odom R, Powell F, National Rosacea Society Expert Committee. Standard grading system for rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Am Acad Dermatol*. 2004 Jun; 50(6):907-12.
2. Tan J et al. 2016 Updating the diagnosis, classification and assessment of rosacea: Recommendations from the global ROSacea Consensus (ROSCO) panel.
3. Chosidow O, Cribier B. Epidemiology of rosacea: updated data. *Ann Dermatol Venereol*. 2011 Nov;138 Suppl 3:S179-83.
4. Tan J, Berg M. Rosacea: current state of epidemiology. *J Am Acad Dermatol*. 2013;69(6 Suppl 1):S27-35.
5. Culp B, Scheinfeld N. Rosacea: a review. *P T*. 2009 Jan;34(1):38-45.
6. Korting HC, Schöllmann C. Current topical and systemic approaches to treatment of rosacea. *J Eur Acad Dermatol Venereol*. 2009 Aug;23(8):876-82.
7. Powell FC. Clinical practice. Rosacea. *N Engl J Med*. 2005;352(8):793-803.
8. A. Taieb, A. Khemis, T. Ruzicka, W. Baranska-Rybak, J. Berth-Jones, J. Schaubert, P. Briantais, J. Jacovella, T. Passeron on behalf of the Ivermectin Phase III Study Group. Maintenance of remission following successful treatment of papulopustular rosacea with ivermectin 1% cream vs. metronidazole 0.75% cream: 36-week extension of the ATTRACT randomized study. *JEADV* 2016, 30, 829–836
9. David A. Jones. Rosacea, Reactive Oxygen Species, and Azelaic Acid. *J Clin Aesthet Dermatol*. 2009 Jan; 2(1): 26–30.
10. Martin Steinhoff, Marc Vocanson, Johannes J Voegel, Ferial Hacini-Rachinel and Gregor Schäfer Topical Ivermectin 10 mg/g and Oral Doxycycline 40 mg Modified-Release: Current Evidence on the Complementary Use of Anti-Inflammatory Rosacea Treatments. *Adv Ther*. 2016; 33(9): 1481–1501.
11. J Mark Jackson, Melissa Knuckles, John Paul Minni, Sandra Marchese Johnson, and Kevin Tate Belasco. The role of brimonidine tartrate gel in the treatment of rosacea. *Clin Cosmet Investig Dermatol*. 2015; 8: 529–538
12. Pelle MT, Crawford GH, James WD. Rosacea: II. Therapy. *J Am Acad Dermatol*. 2004 Oct;51(4):499-512.

13. Martin Schaller, Thomas Dirschka, Lajos Kemény, Philippe Briantais, and Jean Jacovella. Superior Efficacy with Ivermectin 1% Cream Compared to Metronidazole 0.75% Cream Contributes to a Better Quality of Life in Patients with Severe Papulopustular Rosacea: A Subanalysis of the Randomized, Investigator-Blinded ATTRACT Study. *Dermatol Ther (Heidelb)*. 2016 Sep; 6(3): 427–436.
14. Sanchez J, Somolinos AL, Almodóvar PI, Webster G, Bradshaw M, Powala C. A randomized, double-blind, placebo-controlled trial of the combined effect of doxycycline hyclate 20-mg tablets and metronidazole 0.75% topical lotion in the treatment of rosacea. *J Am Acad Dermatol*. 2005 Nov;53(5):791-7.
15. Asai Y, Tan J, Baibergenova A, Barankin B, Cochrane CL, Humphrey S, Lynde CW, Marcoux D, Poulin Y, Rivers JK, Sapijaszko M, Sibbald RG, Toole J, Ulmer M, Zip C. Canadian Clinical Practice Guidelines for Rosacea. *J Cutan Med Surg*. 2016 Sep;20(5):432-45.
16. Revicki DA, Willian MK, Menter A, Gordon KB, Kimball AB, Leonardi CL, Langley RG, Kimel M, Okun M: Impact of adalimumab treatment on patient-reported outcomes: results from a Phase III clinical trial in patients with moderate to severe plaque psoriasis. *J Dermatolog Treat* 2007, 18:341-350
17. Spiewak R: Patch Testing for Contact Allergy and Allergic Contact Dermatitis. *The Open Allergy Journal*, 2008, 1, 42-51

13. ATTACHMENTS

13.1 ATTACHMENT# 1:

DERMATOLOGY LIFE QUALITY INDEX QUESTIONNAIRE (DLQI)

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

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

1. Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?

Very much	<input type="checkbox"/>
A lot	<input type="checkbox"/>
A little	<input type="checkbox"/>
Not at all	<input type="checkbox"/>

2. Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?

Very much	<input type="checkbox"/>
A lot	<input type="checkbox"/>
A little	<input type="checkbox"/>
Not at all	<input type="checkbox"/>

3. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?

Very much	<input type="checkbox"/>
A lot	<input type="checkbox"/>
A little	<input type="checkbox"/>
Not at all	<input type="checkbox"/>
Not relevant	<input type="checkbox"/>

4. Over the last week, how much has your skin influenced the **clothes** you wear?
- Very much ☐
- A lot ☐
- A little ☐
- Not at all ☐
- Not relevant ☐
5. Over the last week, how much has your skin affected any **social** or **leisure** activities?
- Very much ☐
- A lot ☐
- A little ☐
- Not at all ☐
- Not relevant ☐
6. Over the last week, how much has your skin made it difficult for you to do any **sport**?
- Very much ☐
- A lot ☐
- A little ☐
- Not at all ☐
- Not relevant ☐
7. Over the last week, has your skin prevented you from **working** or **studying**?
- Yes ☐
- No ☐
- Not relevant ☐

If "No", over the last week how much has

your skin been a problem at **work**
or **studying**?

A lot ☐

A little ☐

Not at all ☐

8. Over the last week, how much has your
skin created problems with your **partner** or
any of your **close friends** or **relatives**?

Very much ☐

A lot ☐

A little ☐

Not at all ☐

Not relevant ☐

9. Over the last week, how much has your
skin caused any **sexual difficulties**?

Very much ☐

A lot ☐

A little ☐

Not at all ☐

Not relevant ☐

10. Over the last week, how much of a
problem has the **treatment** for your skin
been, for example by making your home
messy, or by taking up time?

Very much ☐

A lot ☐

A little ☐

Not at all ☐

Not relevant ☐

Please check you have answered EVERY question. Thank you.

GALDERMA RESEARCH & DEVELOPMENT

Protocol N° RD.03.SPR.113322

version Final dated 10-FEB-2017

Page 87 of 106 CONFIDENTIAL

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13.2 ATTACHMENT# 2: EQ-5D-5L QUESTIONNAIRE

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 ☐

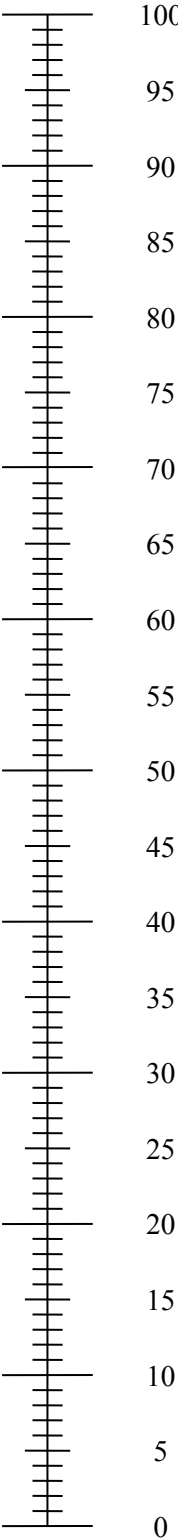
I am moderately anxious or depressed ☐

I am severely anxious or depressed ☐

I am extremely anxious or depressed ☐

The best health you
can imagine

- 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.



GALDERMA RESEARCH & DEVELOPMENT

Protocol N° RD.03.SPR.113322

version Final dated 10-FEB-2017

Page 91 of 106 CONFIDENTIAL

YOUR HEALTH TODAY =

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The worst health
you can imagine

13.3 **ATTACHMENT# 3:**

Work Productivity and Activity Impairment Questionnaire:

General Health V2.0 (WPAI:GH)

modified for Rosacea.

The following questions ask about the effect of your rosacea on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO _____ YES

If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your rosacea? *Include hours you missed on sick days, times you went in late, left early, etc., because of your rosacea. Do not include time you missed to participate in this study.*
_____ HOURS
3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?
_____ HOURS
4. During the past seven days, how many hours did you actually work?
_____ HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your rosacea affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If rosacea affected your work only a little, choose a low number. Choose a high number if rosacea affected your work a great deal.

Consider only how much rosacea affected
productivity while you were working.

Rosacea had no
effect on my
work

0 1 2 3 4 5 6 7 8 9 10

Rosacea
completely
prevented me
from working

CIRCLE A NUMBER

6. During the past seven days, how much did your rosacea affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If rosacea affected your activities only a little, choose a low number. Choose a high number if rosacea affected your activities a great deal.

Consider only how much rosacea affected your ability
to do your regular daily activities, other than work at a job.

Rosacea had no

Rosacea

effect on my daily activities 0 1 2 3 4 5 6 7 8 9 10 completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:GH V2.0 (US English) modified for Rosacea

Reilly MC, Zbrozek AS, Dukes E: The validity and reproducibility of a work productivity and activity impairment measure. Pharmacoeconomics 1993; 4(5):353-365.

13.4 ATTACHMENT# 4: SUBJECT'S SATISFACTION QUESTIONNAIRE

The Subject's Satisfaction Survey will be completed at Week 12 / Early Termination by the Subject.

A- Questions about study drugs (capsules and cream)

1. How satisfied are you with the time the study regimen took to work?

- ☐ Very satisfied
- ☐ Satisfied
- ☐ Somewhat satisfied
- ☐ Not satisfied

2. How satisfied are you with the improvement of your facial lesions since starting the study regimen?

- ☐ Very satisfied
- ☐ Satisfied
- ☐ Somewhat satisfied
- ☐ Not satisfied

3. How satisfied are you with the improvement of your facial redness since starting the study regimen?

- ☐ Very satisfied
- ☐ Satisfied

- ☐ Somewhat satisfied
- ☐ Not satisfied

4. How satisfied are you with the improvement of your ocular symptoms since starting the study regimen?

- ☐ Very satisfied
- ☐ Satisfied
- ☐ Somewhat satisfied
- ☐ Not satisfied
- ☐ Not applicable

5. How satisfied are you with the improvement of your flushing episodes since starting the study regimen?

- ☐ Very satisfied
- ☐ Satisfied
- ☐ Somewhat satisfied
- ☐ Not satisfied
- ☐ Not applicable

6. How bothered are you by the side effects of the study regimen?

- ☐ Not bother at all
- ☐ Bothered a little
- ☐ Bothered somewhat
- ☐ Bothered a great deal

7. How does your face look since starting the study regimen?

- ☐ A lot better
- ☐ A little better
- ☐ No change
- ☐ Worse

GALDERMA RESEARCH & DEVELOPMENT

Protocol N° RD.03.SPR.113322

version Final dated 10-FEB-2017

Page 96 of 106 CONFIDENTIAL

8. How do feel since starting the study regimen?

- ☐ A lot better
- ☐ A little better
- ☐ No change
- ☐ Worse

9. The study regimen was easy to incorporate in your daily routine

- ☐ Strongly agree
- ☐ Agree
- ☐ Disagree
- ☐ Strongly disagree

10. Would you consider using the study regimen again?

- ☐ Yes
- ☐ No

11. How satisfied are you overall with the study regimen?

- ☐ Very satisfied
- ☐ Satisfied
- ☐ Somewhat satisfied
- ☐ Not satisfied

12. How did you find the study regimen compared to the last treatment(s) you received prior starting the study?

- ☐ A lot better
- ☐ Better
- ☐ Similar

GALDERMA RESEARCH & DEVELOPMENT

Protocol N° RD.03.SPR.113322

version Final dated 10-FEB-2017

Page 98 of 106 CONFIDENTIAL

- ☐ Worse
- ☐ Never treated with a previous treatment

B- Questions about both provided skin care products Cleanser and Moisturizer

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

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

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

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

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

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

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

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

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

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

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

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

7. I would keep using both skin care products

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

8. Both skin care products make my skin more hydrated

- ☐ Strongly agree

GALDERMA RESEARCH & DEVELOPMENT

Protocol N° RD.03.SPR.113322

version Final dated 10-FEB-2017

Page 101 of 106 CONFIDENTIAL

- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

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

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

10. Both skin care products are pleasant to use

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

C - Questions about the cosmetic product cleanser

1. The Cleanser left my skin with a clean healthy feeling:

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

2. The Cleanser provided deep cleansing without stripping the skin's moisture:

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

3. The Cleanser rinsed off easily:

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

4. The Cleanser did not make my skin feel tight or dry:

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

GALDERMA RESEARCH & DEVELOPMENT

Protocol N° RD.03.SPR.113322

version Final dated 10-FEB-2017

Page 104 of 106 CONFIDENTIAL

D - Questions about the cosmetic product Moisturizer

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

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

2. The Moisturizer improved my skin's texture:

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

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

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

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

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree or disagree
- ☐ Disagree
- ☐ Strongly disagree

GALDERMA RESEARCH & DEVELOPMENT

Protocol N° RD.03.SPR.113322

version Final dated 10-FEB-2017

Page 106 of 106 CONFIDENTIAL