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.

NCT Number: NCT03075891

Date: 12 Apr 2018

STATISTICAL ANALYSIS PLAN FOR RD.03.SPR.113322

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.

APPROVALS

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GALDERMA PHASE IV

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GALDERMA PHASE IV

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Original: GALDERMA RESEARCH & DEVELOPMENT Archives, Sophia-Antipolis site

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1. LIST OF ABBREVIATIONS

List all abbreviations used in the document e.g.:

AE	Adverse event
APT	All Patients Treated (Safety Population)
ATC	Anatomical-therapeutic-chemical classification of drugs
CEA	Clinician's Erythema Assessment
CMH	Cochran-Mantel-Haenszel
DLQI	Dermatology Life Quality Index
DOXY	Doxycycline
eCRF	electronic Case Report Form
EQ-5D-5L	EuroQol-5 Dimensional-5 Level
GH	General Health
IGA	Investigator's Global Assessment
ITT	Intention To Treat
IVM	Ivermectin
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MR	Modified Release
PP	Per Protocol
PRO	Patient Reported Outcomes
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
WPAI	Work Productivity and Activity Impairment

2. STUDY OBJECTIVES

The main objective of this study was to evaluate the efficacy of Ivermectin 1% topical cream (IVM) associated with Doxycycline (Doxy) 40 mg Modified release (MR) capsules versus Ivermectine 1% topical cream associated with Placebo in the treatment of severe rosacea. The Safety and Patient Reported Outcomes (PRO) were also be evaluated.

3. INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN

This study was to be conducted as a multi-center, randomized, investigator-blind, vehicle-controlled and parallel-group comparison trial, involving subjects of any gender or race, aged 18 years or older, with severe rosacea characterized by persistent diffuse facial erythema and inflammatory lesions (papules and pustules), and meeting specific inclusion/exclusion criteria.

A total of 270 subjects (135 in each group) were to be enrolled at approximately 50 sites in the United States of America, Canada and Europe (Germany, Czech Republic, Hungary and Poland). Subjects were to be enrolled at baseline and, depending on randomization scheme, were to be treated for 12 weeks as follows:

IVM/Doxy:

- Ivermectin 1% cream: one small pea size amount per facial region (forehead, chin, nose, and each cheek) once a day in the evening for 12 weeks.
- Doxycycline 40 mg MR (30 mg Immediate Release & 10 mg Delayed Release beads): 1 capsule once-daily in the morning on an empty stomach for 12 weeks.

IVM/Placebo:

- Ivermectin 1% cream: one small pea size amount per facial region (forehead, chin, nose, and each cheek) once a day in the evening for 12 weeks.
- CD2475-101 placebo: 1 capsule once-daily in the morning on an empty stomach for 12 weeks.

There were up to 5 study visits: screening/baseline, week 4, week 8 and week 12.

3.2 SAMPLE SIZE CONSIDERATION

3.2.1 Historical data and assumptions

No previous study exists associating Ivermectin 1% cream and Doxycycline MR. Therefore, this sample size was calculated using the results of previous studies on subjects treated with Ivermectin 1% cream alone and Doxycycline MR alone.
With Ivermectin 1% cream alone, for % change from baseline in inflammatory lesion counts at week 12, results showed a standard deviation (SD) between 25.4% to 39.9% with a mean around 35%.
With Doxycycline MR alone, results showed a minimum difference of 26% at Week 12 versus Placebo.

Using this historical data, we assumed that the difference between the association (Ivermectin + Doxy) and (Ivermectin + Placebo) was at least of 15% with a SD of 35%.

3.2.2 Sample size calculation

With the assumptions mentioned above, a total of 114 evaluable subjects per group were to 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) were to be enrolled.

4. ANALYZED VARIABLES

4.1 EFFICACY VARIABLES

4.1.1 Primary efficacy variable

- *Percent change from Baseline in inflammatory lesion (IL) count at Week 12:* The evaluator performed inflammatory lesion count on facial papules and pustules of rosacea.

4.1.2 Secondary efficacy variables

- *Percent change from Baseline in IL count at each intermediate visit:* (week 4 and week 8).

- *Percent of subject clear inflammatory lesions at each post-baseline visit:* % of subject with 100% reduction of IL

- *Clinical Erythema Assessment (CEA) at each visit*: % of subject across score. The evaluator assessed 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.

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

- *Investigator's Global Assessment (IGA) at each post-baseline visit*: % of subject across score. The evaluator assessed 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 was to be made.

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,

- *Stinging/Burning at each post-baseline visit*: % of subject across score. The evaluator recorded the severity of subject's facial stinging/burning sensation (a prickling pain sensation) during the last 24h at each visit.

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

- *Subject's Global Improvement in Rosacea at week 12/early termination visit*: % of subject across score. The subject evaluated his/her improvement in rosacea at last visit compared with his/her rosacea condition before the study

Complete Improvement	0	All signs and symptoms of disease have resolved (**100% improvement from Baseline**)
Excellent Improvement	1	Nearly all signs and symptoms cleared (**90% improvement from Baseline**)
Very good Improvement	2	Majority of the signs and symptoms have resolved (**about 75% improvement from Baseline**)
Good Improvement	3	Significant improvement, but many signs and symptoms remain (**about 50% improvement from Baseline**)
Minimal Improvement	4	Slight overall improvement, but many signs and symptoms remain (**about 25% improvement from Baseline**)
No Change	5	Overall severity **similar** from Baseline
Worse	6	**Worse** than Baseline

4.1.3 Exploratory efficacy variables

- *Global assessment of ocular signs and symptoms at each post-baseline visit*: % of subject across score. The evaluator recorded the severity of the ocular signs and symptoms after discussion with the subject.

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

- *Percent change from baseline (medical history) in terms of flushing count per week:* At baseline the investigator recorded in medical history the frequency of flushing as reported by subject for the previous week before baseline visit. During the study, the number of weekly flushing was reported in the eCRF by the investigator or designee based on the flushing episodes recorded daily by the subject in the diary.

- *Change from baseline (medical history) in mean score severity per week:* At baseline the investigator recorded in medical history the average severity of flushing by grading as mild, moderate or severe. (severity from the previous week before baseline visit). During the study, the average severity was reported in the eCRF by the investigator or designee based on the severity recorded daily by the subject in the diary.

- *Change from baseline in Facial redness colorimetric measurements (CEI) at each post-baseline visit*: In selected investigational sites, the investigator assessed the colorimetry using a Chromameter that converts colors perceived by the human eye into a digital code composed of the following parameters: L*: for clarity (from dark to light), a*: for the green-to-red component, b*: for the blue-to-yellow component.

  When evaluating an erythema, the a* parameter is of highest importance. The decrease in luminance L* can also be considered useful because it reflects the darkest character of an erythema. The CEI (Colormetric Erythema Index) is the reflection of these two parameters. It is calculated on the zone treated with the tested product and the blank formulation zone according to the following formula: $CEI = (\Delta L^{*2} + \Delta a^{*2})1/2$

  ΔL^*: variation in the skin luminosity under the effect of the erythema
  Δa^*: variation in the skin color on the green-to-red axis under the effect of the erythema.

4.2 PATIENT-REPORTED OUTCOMES VARIABLES

- *Dermatology Life Quality Index (DLQI) at week12/early termination*: % of subject across Total score at baseline and last visit; and the % change from baseline.

Grade	Description
0-1	No effect at all on patient's life
2-5	Small effect on patient's life
6-10	Moderate effect on patient's life
11-20	Very large effect on patient's life
21-30	Extremely large effect on patient's life

- *EQ-5D questionnaire at week12/early termination*: % of subjects across score of questions at baseline and last visit.

- *Work Productivity and Activity Impairment Questionnaire at week 12/early termination*: General Health (WPAI: GH) modified for Rosacea. % of subjects across score of questions at baseline and last visit.

- *Subject's satisfaction questionnaire at week12/early termination*: % of subjects across score of questions at last visit.

4.3 SAFETY VARIABLES

- *Adverse events*: Incidence of adverse events - All clinical medical events, whether observed by the investigator or reported by the subject and whether or not thought to be study product -related were to be considered adverse events.

5. POPULATIONS ANALYZED

The definition of the populations and the pooling center will be finalized after a blind data review meeting, during which the distribution of subjects per site will be reviewed.

5.1 INTENT TO TREAT POPULATION (ITT)

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

5.2 PER PROTOCOL POPULATION (PP)

The PP Population is defined as comprising the ITT subjects who have no major protocol deviations that will be refined during a blind review. The primary efficacy endpoint will be analysed based on this population.

5.3 SAFETY POPULATION (ALL SUBJECT TREATED (APT))

This population consists of the ITT 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)

5.4 MISSING VALUES

In order to evaluate the effect of major deviations or of data exclusions, the last observation carried forward (LOCF) method will be used to impute missing values for inflammatory lesion count and IGA. If no post-baseline data are available, baseline will be carried forward. Thus, the number of subjects will not vary at each visit. The other missing values will not be replaced (observed data).

5.5 POOLING OF CENTERS

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.

6. STATISTICAL METHODS AND DATA CONSIDERATIONS

SAS version 9.3 will be used for all analyses. All tests will be two-sided and significance will be declared at a 0.05 level.

6.1 DATA PRESENTATION

All continuous data will be summarized at each visit 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 parallel group and by visit (when applicable).

The adverse events will be descriptively summarized (n, %). All summaries are based on the safety population (APT). The adverse events will be descriptively summarized (n, %) by relationship to study 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 event, SOC and preferred term. Deaths and serious adverse events will be reported as well as withdrawals due to adverse events. A subject will be counted once per System Organ Class (SOC) and 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 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).

6.2 STUDY SUBJECTS

6.2.1 Subject disposition

Normal completion as well as early discontinuation will be described on the ITT population. Reasons for withdrawals and normal completions will be summarized using frequency distribution (n, %). All withdrawals will be detailed in a subject-by-subject listing.

6.2.2 Protocol deviation

Major protocol deviations will be summarized using frequency distribution (n, %) detailed in a subject-by-subject listing.

6.2.3 Data sets analyzed

Number of subjects included in each efficacy analyses (PP, ITT) and number of patients included in the safety analysis (APT) will be presented by parallel group and overall.

6.2.4 Demographic data

Demographic data collected at baseline will be descriptively summarized for ITT population by parallel group and overall.

6.2.5 Rosacea co-morbidities and Medical history

Rosacea co-mobordities and medical history defined as the relevant or major illnesses not previously reported as co-mobordities present before the baseline visit will be presented separately by System Organ Class and preferred term (MedDRA).

6.2.6 Medical history of acute rosacea (worsening)

Facial rosacea duration will be descriptively summarized on the ITT population, by duration classes, study group and overall.
History of flushing or worsening of erythema will be descriptively summarized on the ITT population using frequency distribution (n, %), by type of stimuli triggers, study group and overall.

6.2.7 Previous and concomitant drug and procedure therapies

Previous drugs/procedures therapies are defined as drugs/procedures stopped on or before the baseline visit. Concomitant drugs/procedures are defined as drugs/procedures occurred between the baseline visit and the last visit. Previous and Concomitant drugs/procedures will be descriptively summarized on the ITT population, by Anatomical-therapeutic-chemical (ATC) text level 5 and drug name for drugs and by SOC and preferred term for procedures, by study group and overall. Frequency distribution of subjects with at least one previous drug/ procedure at baseline and/or with at least one concomitant drug/procedure will be tabulated (n, %).

6.2.8 Compliance

Compliance of investigational products (oral and topical) will be calculated from the data captured at every visit and will be summarized by group in terms of frequency counts and percentages by products and for the association of investigational products. The compliance will be calculated as follows:

$$Compliance = \frac{((Date\ of\ last\ visit - Date\ of\ baseline) - total\ number\ of\ missing\ applications) * 100}{(Date\ of\ last\ visit - Date\ of\ baseline).}$$

Compliance of the moisturizer will be also calculated as follows:

$$Moisturizer\ compliance = \frac{Total\ number\ of\ days\ where\ the\ moisturizer\ was\ used\ * 100}{(Date\ of\ last\ visit - Date\ of\ baseline)}$$

6.2.9 Baseline disease characteristics

The characteristics of the disease collected at baseline will be descriptively summarized on ITT population by parallel group and overall.

6.3 EFFICACY ANALYSES

6.3.1 Primary efficacy analyses

The primary objective of this study was to demonstrate the superiority of the IVM/Doxy compared to IVM/Placebo, in terms of percent change from baseline in 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 ridit 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.

6.3.2 Secondary and other efficacy analyses

The variables will be analyzed similarly as primary analyses on ITT/LOCF population at each post-baseline evaluation time on appropriate population.

6.4 PATIENT-REPORTED OUTCOMES ANALYSES

DLQI, EQ-5D-5L, WPAI-GH and subject satisfaction questionnaires will be statistically analyzed similarly as primary analyses on ITT population at each post-baseline evaluation time.

6.5 SAFETY ANALYSES

6.5.1 Extent of exposure

6.5.1.1 Treatment duration

Treatment duration will be calculated as the number of days between the date of first use and the date of the last use of each study treatment (oral and topical). In case of missing data of last use, the last visit will be taken into account.

6.5.2 Adverse Events

The adverse events will be summarized (n, %) for APT population by parallel group. Deaths and serious adverse events will be reported as well as withdrawals due to adverse events.
In case of worsening of rosacea, a specific questionnaire was filled on and the results will be listed.

7. CHANGES FROM THE PROTOCOL ANALYSIS PLAN

The Percent of subject clear inflammatory lesions (100% reduction of IL) at each post-baseline visit will be analyzed.

APPENDIX 1: LIST AND FORMAT OF TABLES

GENERAL FEATURES

- Margins for portrait orientation
    - Top = 3.71 cm
    - Bottom = 3.17 cm
    - Left = 3 cm
    - Right = 1.4 cm
    - Heading = 2.41 cm
    - Footnote = 2.16 cm

- Margins for landscape orientation
    - Top = 3 cm
    - Bottom = 1.4 cm
    - Left = 3.17 cm
    - Right = 3.71 cm
    - Heading = 2.16 cm
    - Footnote = 1.25 cm

8. TABLE SHELLS

14.1. Study Subjects

14.1.1. Conduct of the study

Table 1. Enrolment by analysis center and investigational site (ITT)

	IVM + Doxycycline (N=xxx)	IVM + Vehicle (N=xxx)	Total (N=xxx)
Analysis-Center 1 (n,%) Center 1 (n,%) ….. Analysis-Center 2 (n,%) ….			

Table 2.1. Subjects who discontinued study and reason for discontinuation (ITT)

	IVM + Doxycycline (N=xxx)	IVM + Vehicle (N=xxx)	Total (N=xxx)
Randomized Normal study completion n (%) Premature discontinuation n (%) Lack of efficacy n (%) Adverse event n (%) …..			

Table 2.2. Listing of subjects who discontinued treatment and reason for discontinuation (ITT)
(Include : treatment, investigator number, subject number and reason for discontinuation)

Table 3. Adherence to the visit schedule in days (ITT)

	IVM + Doxycycline	IVM + Vehicle	Total
Nb of days between baseline visit and week 4 visit N Mean±SD Median (Min,Max)			
...			
Nb of days between baseline visit and week 12 visit N Mean±SD Median (Min,Max)			
Nb of days between baseline visit and last visit N Mean±SD Median (Min,Max)			

Table 4.1. Major protocol deviations (ITT)

	IVM + Doxycycline		IVM + Vehicle		Total	
eg:	N.	% subj.	N	% subj.	N	% subj.
AT LEAST ONE MAJOR DEVIATION No post-Baseline data No study medication dispensed …						

A subject may have several major protocol deviations
Numbers in columns cannot be added because a given subject may have reported more than one deviation.

Table 4.2. Listing of subjects with Major protocol deviations (ITT)
(Include : treatment, investigator number, subject number, reason and detail of deviations)

Table 5. Data sets analyzed

	IVM + Doxycycline	IVM + Vehicle	Total
Intent to treat population (ITT) n(%)			
Per Protocol population (PP) n(%)*			
Safety population (APT) n(%)*			

* Denominator is the number of subjects in the Intent to treat population

14.1.2. Subject characteristics

Table 6. Demographic data (ITT)

	IVM + Doxycycline	IVM + Vehicle	Total
Gender N Male n(%) Female n(%)			
Age N 18-65 years >= 65 years Mean ±SD Median Min,Max			
Race N White n (%) Black n (%) …			
Ethnicity* N Hispanic or Latino n (%) Not hispanic or Latino n (%) …			
Phototype N I n (%) II n (%) ….			

* Ethnicity is optional for Canada and Europe

Table 7. Rosacea co-morbidities (ITT)

	IVM + Doxycycline (N=xxx)	IVM + Vehicle (N=xxx)	Total (N=xxx)
Subjects reporting at least one co-morbidity ***List all co-morbidities by SOC and preferred term***			

The numbers in the columns cannot be added because a given subject could report more than one co-morbidity

Table 8. Medical history other than co-morbidities (ITT)

	IVM + Doxycycline (N=xxx)	IVM + Vehicle (N=xxx)	Total (N=xxx)
Subjects reporting at least one medical history ***List all medical histories by SOC and preferred term***			

The numbers in the columns cannot be added because a given subject could report more than one medical history

Table 9. Medical history of rosacea (ITT)

	IVM + Doxycycline	IVM + Vehicle	Total
For rosacea: duration in year N Less than 1 year n(%) Between 1 and 5 year n(%) More than 5 years n(%) Mean ±SD Median Min,Max			
History of flushing or worsening of erythema N No n(%) Yes n(%)			
Stimuli triggers Spicy food n(%) ….			

Table 10. Previous drug therapies within the previous 6 months, by ATC text and drug name (ITT)

	IVM + Doxycycline (N=xxx)	IVM + Vehicle (N=xxx)	Total (N=xxx)
Subjects reporting at least one previous therapy ***List all previous drugs by ATC and drug name.***			

The numbers in the columns cannot be added because a given subject could report more than one previous therapy

Table 11. Previous procedure therapies within the previous 6 months, by System Organ class and Preferred Term (ITT)

	IVM + Doxycycline (N=xxx)	IVM + Vehicle (N=xxx)	Total (N=xxx)
Subjects reporting at least one previous procedure ***List all previous procedures by SOC and preferred term***			

The numbers in the columns cannot be added because a given subject could report more than one previous procedure.

Table 12. Concomitant drug therapies by ATC text and drug name (ITT)

	IVM + Doxycycline (N=xxx)	IVM + Vehicle (N=xxx)	Total (N=xxx)
Subjects with at least one concomitant medication ***List all concomitant drugs by ATC and drug name***			

The numbers in the columns cannot be added because a given subject could report more than one concomitant therapy.

Table 13. Concomitant procedure therapies by System Organ Class and Preferred Term (ITT)

	IVM + Doxycycline (N=xxx)	IVM + Vehicle (N=xxx)	Total (N=xxx)
Subjects with at least one concomitant procedure ***List all concomitant procedures by SOC and preferred term***			

The numbers in the columns cannot be added because a given subject could report more than one concomitant procedure.

Table 14. Baseline disease characteristics (ITT)

	IVM + Doxycycline (N=xxx)	IVM + Vehicle (N=xxx)	Total (N=xxx)
Facial inflammatory lesion counts N Mean ±SD Median Min,Max			
Clinician's Erythema Assessment N 3: Moderate n (%) 4: Severe n (%) Mean ±SD Median Min,Max			
Investigator's Global Assessment N 4: Severe n (%) Mean ±SD Median Min,Max			
Severity Score of Stinging/Burning N 0: None n (%) 1: Mild n (%) 2: Moderate n (%) 3: Severe n (%) Mean ±SD Median Min,Max			
Ocular Signs and Symptoms N 0: None n (%) 1: Mild n (%) 2: Mild-Moderate n (%) 3: Moderate-Severe n (%) 4: Severe n (%) Mean ±SD Median Min,Max			
Number of flushing during the last week before baseline N Mean ±SD Median Min,Max			
Average severity of flushing during the last week before baseline N Mild n(%) Moderate n(%) Severe n(%)			

14.2. Efficacy analyses

14.2.1. Primary efficacy analyses

Table 15. Inflammatory lesions: % change from baseline at week 12 (ITT/LOCF)

	IVM + Doxycycline	IVM + Vehicle	p-value (1)
Week 12 (ITT/LOCF) N Mean ±SD Median Min,Max			xxx
Week 12 (PP) …..			xxx

(1) p-value of CMH test based on ridit scores stratified by analysis-center.

14.2.2. Secondary efficacy analyses

14.2.2.1. Inflammatory lesions

Table 16. Inflammatory lesions: % change from baseline at other post-baseline visit (ITT/LOCF)

	IVM + Doxycycline	IVM + Vehicle	p-value (1)
Week 4 (ITT/LOCF) N Mean ±SD Median Min,Max			xxx
Week 8 (ITT/LOCF) …..			xxx

(1) p-value of CMH test based on ridit scores stratified by analysis-center.

Table 17. Inflammatory lesions: 100% reduction from baseline at each post-baseline visit (ITT/LOCF)

	IVM + Doxycycline	IVM + Vehicle	p-value (1)
Week 4 (ITT/LOCF) N No (n,%) Yes(n,%)			xxx
Week 8 (ITT/LOCF) …			xxx
Week 12 (ITT/LOCF) …..			xxx

(1) p-value of CMH test based on ridit scores stratified by analysis-center.

Table 18. Inflammatory lesions: Count at each visit - Descriptive (ITT/LOCF)

	IVM + Doxycycline	IVM + Vehicle
Baseline N Mean ±SD Median Min,Max		
…..		
Week 12 (ITT/LOCF) …..		

14.2.2.2. Clinician's Erythema Assessment

Table 19. Clinician's Erythema Assessment: Raw value at each visit (ITT/LOCF)

	IVM + Doxycycline	IVM + Vehicle	p-value (1)
Baseline …..			NA
Week 4 (ITT/LOCF) N 0: Clear n (%) 1: Almost clear n (%) 2: Mild n (%) 3: Moderate n (%) 4: Severe n (%) Mean ±SD Median Min,Max			xxx
…..			
Week 12 (ITT/LOCF) …..			xxx

(1) p-value by CMH test based on ridit scores stratified by analysis-center.

14.2.2.3. Investigator's Global Assessment

Table 20. Investigator's Global Assessment full scale at each visit (ITT/LOCF)

	IVM + Doxycycline	IVM + Vehicle	p-value (1)
Baseline N 0: Clear n (%) 1: Almost clear n (%) 2: Mild n (%) 3: Moderate n (%) 4: Severe n (%) Mean ±SD Median Min,Max			NA
…..			
Week 12 (ITT/LOCF) ……			xxx

(1) p-value by CMH test based on ridit scores stratified by analysis-center.

14.2.2.4. Stinging/Burning severity score

Table 21. Stinging/Burning at each visit (ITT/LOCF)

	IVM + Doxycycline	IVM + Vehicle	p-value (1)
Baseline N 0: None n (%) 1: Mild n (%) 2: Moderate n (%) 3: Severe n (%) Mean ±SD Median Min,Max			NA
…			
Week 12 (ITT/LOCF) ...			xxx

(1) p-value by CMH test based on ridit scores stratified by analysis-center.

14.2.2.5. Subject's Global Improvement

Table 22. Subject's Global Improvement at last visit (ITT)

	IVM + Doxycycline	IVM + Vehicle	p-value (1)
N 0: Complete Improvement n (%) 1: Excellent Improvement n (%) 2: Very good Improvement n (%) 3: Good Improvement n (%) 4: Minimal Improvement n (%) 5: No Change n(%) 6: Worse n (%) Mean ±SD Median Min,Max			xxx

(1) p-value for between treatment difference, by CMH test based on ridit scores stratified by analysis-center.

14.2.3. Exploratory efficacy analyses

14.2.3.1. Ocular signs

Table 23. Ocular signs and symptoms at each visit (ITT)

	IVM + Doxycycline	IVM + Vehicle	p-value (1)
Baseline N 0: None n (%) 1: Mild n (%) 2: Mild-Moderate n (%) 3: Moderate-Severe n (%) 4: Severe n (%) Mean ±SD Median Min,Max			NA
…			
Week 12 (ITT) ...			xxx

(1) p-value by CMH test based on ridit scores stratified by analysis-center.

14.2.3.2. Flushing

Table 24. Number of flushing per week: % change from baseline (ITT)

	IVM + Doxycycline	IVM + Vehicle	p-value (1)
Week1 N Mean ±SD Median Min,Max			xxx
…			
Week 12 …..			xxx

(1) p-value of CMH test based on ridit scores stratified by analysis-center.

Table 25. Number of flushing per week: Count at each visit - Descriptive (ITT)

	IVM + Doxycycline	IVM + Vehicle
Baseline N Mean ±SD Median Min,Max		
…..		
Week 12 …..		

Table 26. Mean score severity of flushing per week: change from baseline (ITT)

	IVM + Doxycycline	IVM + Vehicle	p-value (1)
Week1 2 grades less n (%) 1 grade less n (%) 0: No change n (%) 1 grade more n (%) 2 grades more n (%)			xxx
…			
Week 12 …..			xxx

(1) p-value of CMH test based on ridit scores stratified by analysis-center.

Table 27. Mean score severity of flushing per week: Count at each visit - Descriptive (ITT)

	IVM + Doxycycline	IVM + Vehicle
Baseline N 1-Mild 2-Moderate 3-Severe Mean ±SD Median Min,Max		
…..		
Week 12 …..		

14.2.3.3. Colorimetry

Table 28. Colorimetry CEI: % change from baseline (ITT)

	IVM + Doxycycline	IVM + Vehicle	p-value (1)
Week4 N Mean ±SD Median Min,Max			xxx
…			
Week 12 …..			xxx

(1) p-value of CMH test based on ridit scores stratified by analysis-center.

14.2.4. Patient reported outcomes

14.2.4.1. Dermatology Life Quality Index

Table 29. DLQI at baseline - Descriptive (ITT)

	IVM + Doxycycline	IVM + Vehicle
1. DLQI itch, sore, painful, stinging? N 0: Not at all 1: A little 2: A lot 3: Very much		
……		
10. DLQI problem caused by treatment? N 0: Not at all 0: Not relevant 1: A little 2: A lot 3: Very much		

Table 30. DLQI at last visit - Descriptive (ITT)

Table 31. DLQI: Total score at each visit and percent change from baseline (ITT)

	IVM + Doxycycline	IVM + Vehicle	p-value
Baseline (Total score) N 0-1: No effect at all on patient's life 2-5: Small effect on patient's life 6-10: Moderate effect on patient's life Mean±SD Median (Min,Max)			NA
Last visit (Total score) …			xxx
Last visit (% change from Baseline) N Mean±SD Median (Min,Max)			xxx

(1) p-value by CMH test based on ridit scores stratified by analysis-center.

14.2.4.2. EQ-5D-5L questionnaire

Table 32. EQ-5D-5L questionnaire at baseline - Descriptive (ITT)

	IVM + Doxycycline	IVM + Vehicle
Mobility N I have no problems walking I have slight problems walking I have moderate problems walking I have severe problems walking I have unable to walk		
Self-Care …		
Usual Activities …		
Pain/Discomfort …		
Anxiety/Depression …		
Health State Today N Mean ±SD Median Min,Max		

Table 33. EQ-5D-5L questionnaire at last visit (ITT)

	IVM + Doxycycline	IVM + Vehicle	p-value (1)
Mobility N I have no problems in walking about I have slight problems in walking about I have moderate problems in walking about I have severe problems in walking about I have unable to walk about			xxx
Self-Care ….			xxx
Usual Activities …			xxx
Pain/Discomfort …			xxx
Anxiety/Depression …			xxx
Health State Today N Mean ±SD Median Min,Max			xxx

(1) p-value by CMH test based on ridit scores stratified by analysis-center.

14.2.4.3. Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH)

Table 34. WPAI :GH questionnaire at baseline - Descriptive (ITT)

	IVM + Doxycycline	IVM + Vehicle
Currently employed N No Yes		
Missed hours from work because of rosacea? N Mean ±SD Median Min,Max		
Missed hours from work because of other reason? …		
Number of Working hours …		
How much rosacea affect productivity at work? …		
How much rosacea affect daily activity? N Mean ±SD Median Min,Max		

Table 35. WPAI :GH questionnaire at last visit (ITT)

	IVM + Doxycycline	IVM + Vehicle	p-value (1)
Currently employed N No Yes			xxx
Missed hours from work because of rosacea? N Mean ±SD Median Min,Max			xxx
Missed hours from work because of other reason? …			xxx
Number of Working hours …			xxx
How much rosacea affect productivity at work? …			xxx
How much rosacea affect daily activity? N Mean ±SD Median Min,Max			xxx

(1) p-value by CMH test based on ridit scores stratified by analysis-center.

14.2.4.4. Subject's satisfaction questionnaire

Table 36. Subject's satisfaction questionnaire – Part A at last visit (ITT)

Questions about study drugs	IVM + Doxycycline	IVM + Vehicle	p-value (1)
1. How satisfied are you with the amount of time the study regimen took to work? N Very satisfied Satisfied Somewhat satisfied Not satisfied			xxx
…..			
12. How did you find the study regimen compared to your last treatment? N A lot better Better Similar Worse Never treated with a previous treatment			xxx

(1) p-value by CMH test based on ridit scores stratified by analysis-center.

Table 37. Subject's satisfaction questionnaire – Part B at last visit (ITT)

Questions about skin care products Cleanser and Moisturizer	IVM + Doxycycline	IVM + Vehicle	p-value (1)
1. Both skin care products easy to incorporate into a daily routine N Strongly agree Agree Neither agree or disagree Disagree Strongly disagree			xxx
…..			
10. Both skin care products are pleasant to use? N Strongly agree Agree Neither agree or disagree Disagree Strongly disagree			xxx

(1) p-value by CMH test based on ridit scores stratified by analysis-center.

Table 38. Subject's satisfaction questionnaire – Part C at last visit (ITT)

Questions about the cosmetic product cleanser	IVM + Doxycycline	IVM + Vehicle	p-value (1)
1. The Cleanser left my skin with a clean healthy feeling N Strongly agree Agree Neither agree or disagree Disagree Strongly disagree			xxx
…..			
4. The Cleanser did not make my skin feel tight or dry N Strongly agree Agree Neither agree or disagree Disagree Strongly disagree			xxx

(1) p-value by CMH test based on ridit scores stratified by analysis-center.

Table 39. Subject's satisfaction questionnaire – Part D at last visit (ITT)

Questions about the cosmetic product Moisturizer	IVM + Doxycycline	IVM + Vehicle	p-value (1)
1. The Moisturizer made my skin feel soft and smooth N Strongly agree Agree Neither agree or disagree Disagree Strongly disagree			xxx
…..			
4. The Moisturizer provided a conforting sensation on the skin N Strongly agree Agree Neither agree or disagree Disagree Strongly disagree			xxx

(1) p-value by CMH test based on ridit scores stratified by analysis-center.

14.3 Safety analyses

14.3.1. Extent of Exposure

Table 40. Quantity of topical treatment in gram (1) used during the study (APT)

	IVM + Doxycycline	IVM + Vehicle
N		
Mean±SD		
Median		
Min,Max		

(1) Assumes non-returned products were used in the same way as returned products.

Table 41. Extent of exposure (days) (APT)

	IVM + Doxycycline	IVM + Vehicle
Oral treatment		
N		
Mean±SD		
Median		
Min,Max		
Topical treatment		
N		
Mean±SD		
Median		
Min,Max		

Treatment duration will be calculated as the number of days between the date of first use and the date of the last use of each study treatment (oral and topical). In case of missing data of last use, the last visit will be taken into account.

Table 42. Compliance for investigational products (APT)

	IVM + Doxycycline	IVM + Vehicle
Compliance for oral treatment N <25% of compliance [25%;50%[of compliance [50%;75%[of compliance >=75% of compliance Mean±SD Median Min,Max		
Compliance for topical treatment N <25% of compliance [25%;50%[of compliance [50%;75%[of compliance >=75% of compliance Mean±SD Median Min,Max		
Overall compliance of investigational product N <25% of compliance [25%;50%[of compliance [50%;75%[of compliance >=75% of compliance Mean±SD Median Min,Max		

Compliance= ((Date of last visit - Date of baseline) - total number of corresponding missing applications)*100/ (Date of last visit - Date of baseline).
Overall compliance is the mean of each compliance.

Table 43. Compliance for the Moisturizer (APT)

	IVM + Doxycycline	IVM + Vehicle
N <25% of compliance [25%;50%[of compliance [50%;75%[of compliance >=75% of compliance Mean±SD Median Min,Max		

Moisturizer compliance = total number of days where the moisturizer was used *100/ (Date of last visit – Date of baseline)

14.3.2. Adverse events

Table 44. Overview of adverse events by group (APT)

	IVM + Doxycycline (N=xxx)		IVM + Vehicle (N=xxx)	
	Event	Subject* n(%)	Event	Subject* n(%)
All AEs				
All dermatologic AEs				
All worsening of rosacea AEs				
All severe AEs				
All serious AEs				
Deaths				
All AEs leading to discontinuation				
Related AEs				
Related dermatologic AEs				
Related worsening of rosacea AEs				
Related severe AEs				
Related serious AEs				
Related AEs leading to discontinuation				

* Subjects with at least one event. Numbers in columns cannot be added because a given subject may have reported more than one AE.

Table 45. Frequency of all adverse events by preferred term (APT)

e.g.	IVM + Doxycycline (N=xxx)		IVM + Vehicle (N=xxx)	
Abdominal pain nos	Event	Subject* n(%)	Event	Subject* n(%)
Diarrhoea nos				
Peptic ulcer				
….				

* Subjects with at least one event.
Numbers in columns cannot be added because a given subject may have reported more than one AE.

Table 46. Frequency of all adverse events (except SAE) by preferred term (APT)

Table 47. Frequency of related adverse events by preferred term (APT)

Table 48: Frequency of all adverse events by SOC and preferred term (APT)

e.g.	IVM + Doxycycline (N=xxx)		IVM + Vehicle (N=xxx)	
ANY ADVERSE EVENT	Event	Subject* n(%)	Event	Subject* n(%)
GASTROINTESTINAL DISORDERS				
Abdominal pain nos				
Diarrhoea nos				
Peptic ulcer				
Vomiting nos				
IMMUNE SYSTEM DISORDERS				
Allergic sinusitis				
Conjunctivitis allergic				
….				

*Subjects with at least one event. Numbers in columns cannot be added because a given subject may have reported more than one AE.
A subject was counted once per SOC and once per preferred term even if more than one occurrence of an event was reported within a SOC or preferred term.

Table 49. Frequency of related adverse by SOC and preferred term (APT)

Table 50. Subject incidence by severity of all adverse events by SOC and preferred term (APT)

e.g.	IVM + Doxycycline (N=xxx)			IVM + Vehicle (N=xxx)		
	Mild n(%)	Moderate n(%)	Severe n(%)	Mild n(%)	Moderate n(%)	Severe n(%)
ANY ADVERSE EVENT						
GASTROINTESTINAL DISORDERS Abdominal pain nos Diarrhoea nos Peptic ulcer Vomiting nos …..						
IMMUNE SYSTEM DISORDERS Allergic sinusitis Conjunctivitis allergic						
….						

*Subjects with at least one event.
Numbers in columns cannot be added because a given subject may have reported more than one AE.
A subject was counted once per SOC (highest intensity whatever the AE within the SOC) and once per preferred term (highest intensity if more than one occurrence of an event is reported)

Table 51. Subject incidence by severity of related adverse events by SOC and preferred term (APT)

Table 52. Incidence of subject with serious adverse events by SOC and preferred term (APT)

e.g.	IVM + Doxycycline (N=xxx)		IVM + Vehicle (N=xxx)	
	Event	Subject* n(%)	Event	Subject* n(%)
ANY SERIOUS ADVERSE EVENT				
GASTROINTESTINAL DISORDERS Abdominal pain nos ….				

*Subjects with at least one event. Numbers in columns cannot be added because a given subject may have reported more than one AE.
A subject was counted once per SOC and once per preferred term even if more than one occurrence of an event was reported within a SOC or preferred term.

(A listing can be provided with the information of the AE form if too few SAE)
Table 52. Listing of subjects with serious adverse events (APT)
(Include : subject number, treatment group, SOC, preferred term, date of onset, severity, subject discontinued, outcome, date of resolution and relationship

Table 53. Incidence of subject with adverse events leading to discontinuation of treatment by SOC and preferred term (APT)

e.g.	IVM + Doxycycline (N=xxx)		IVM + Vehicle (N=xxx)	
	Event	Subject* n(%)	Event	Subject* n(%)
ANY SERIOUS ADVERSE EVENT				
GASTROINTESTINAL DISORDERS Abdominal pain nos ….				

*Subjects with at least one event. Numbers in columns cannot be added because a given subject may have reported more than one AE.
A subject was counted once per SOC and once per preferred term even if more than one occurrence of an event was reported within a SOC or preferred term.

(A listing can be provided with the information of the AE form if too few subjects with adverse events leading to discontinuation of treatment)
Table 53. Listing of subjects with adverse events leading to discontinuation of treatment (APT)
(Include : subject number, treatment group, SOC, preferred term, date of onset, severity, SAE, outcome, date of resolution and relationship)

Table 54. List of worsening of rosacea AEs (APT)