Clinical trial results:
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

Summary

EudraCT number	2017-000157-40
Trial protocol	HU DE CZ PL
Global end of trial date	08 February 2018

Results information

Result version number	v1 (current)
This version publication date	11 March 2021
First version publication date	11 March 2021

Trial information

Trial identification

Sponsor protocol code	RD.03.SPR.113322

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03075891
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GALDERMA R&D SNC
Sponsor organisation address	Les Templiers, 2400 Route des Colles, Biot, France, 06410
Public contact	CTA Coordinator, GALDERMA R&D SNC, +33 (0)493 95 70 85, cta.coordinator@galderma.com
Scientific contact	CTA Coordinator, GALDERMA R&D SNC, +33 (0)493 95 70 85, cta.coordinator@galderma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy of Ivermectin 1% topical cream associated with Doxycycline 40 mg Modified release (DMR) capsules versus IVM monotherapy in the treatment of severe rosacea.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles from the Declaration of Helsinki revised version (Somerset West, 1996), the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and in compliance with local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 July 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 57
Country: Number of subjects enrolled	Czech Republic: 44
Country: Number of subjects enrolled	Hungary: 60
Country: Number of subjects enrolled	Denmark: 41
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	United States: 54
Worldwide total number of subjects	273
EEA total number of subjects	202

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	219
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 39 sites in Canada, Czech Republic, Germany, Hungary, Poland, and United States of America between 05 July 2017 to 08 February 2018.

Pre-assignment

Screening details:

A total of 273 subjects were randomized and treated, out of which 251 subjects completed the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind[1]
Roles blinded	Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules

Arm description:

Ivermectin 1 percent (%) 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 for 12 weeks.

Doxycycline 40 milligram (mg) Modified Release (MR) (30 mg Immediate Release & 10 mg Delayed Release beads) capsules: 1 capsule once-daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Ivermectin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

Subjects applied ivermectin 1% cream topically once a day for 12 weeks.

Investigational medicinal product name	Doxycycline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received doxycycline 40 mg MR (30 mg immediate release & 10 mg delayed release beads) capsule orally once-daily for 12 weeks.

Arm title	Ivermectin 1% Cream + Oral Placebo Capsules

Arm description:

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 for 12 weeks.

Oral placebo capsules: 1 capsule once-daily for 12 weeks.

Arm type	Experimental

Investigational medicinal product name	Ivermectin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

Subjects applied ivermectin 1% cream topically once a day for 12 weeks.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo capsule matching to doxycycline 40 mg MR orally once-daily for 12 weeks.

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: This study was designed as investigator-blinded.

Number of subjects in period 1	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules
Started	135	138
Completed	126	125
Not completed	9	13
Consent withdrawn by subject	3	6
Adverse event, non-fatal	1	4
Pregnancy	3	1
Patient requiring study withdrawal	-	1
Lost to follow-up	1	-
visits not performed (no time)	1	-
Drug abuse relapse issue	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules
Reporting group description:	
Ivermectin 1 percent (%) 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 for 12 weeks. Doxycycline 40 milligram (mg) Modified Release (MR) (30 mg Immediate Release & 10 mg Delayed Release beads) capsules: 1 capsule once-daily for 12 weeks.	
Reporting group title	Ivermectin 1% Cream + Oral Placebo Capsules
Reporting group description:	
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 for 12 weeks. Oral placebo capsules: 1 capsule once-daily for 12 weeks.	

Reporting group values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules	Total
Number of subjects	135	138	273
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	109	110	219
From 65-84 years	26	28	54
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	52.4	51.6	
standard deviation	± 13.5	± 13.3	-
Gender categorical Units: Subjects			
Female	75	80	155
Male	60	58	118
Skin Phototype			
Fitzpatrick skin phototype is a system used to describe a person's skin type. It ranges from skin phototype I to VI. Where, skin phototype I = pale white skin, always burns easily, never tans; skin phototype II = fair skin, always burns easily, tans minimally and with difficulty; skin phototype III = darker white skin, burns minimally, tans gradually and uniformly; skin phototype IV = light brown skin, burns minimally, always tans well; skin phototype V = brown skin, rarely burns, tans profusely; skin phototype VI = dark brown or black skin, never burns, tans profusely.			
Units: Subjects			
Skin phototype I	5	11	16
Skin phototype II	82	83	165
Skin phototype III	37	38	75

Skin phototype IV	8	6	14
Skin phototype V	1	0	1
Skin phototype VI	2	0	2

End points

End points reporting groups

Reporting group title	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules

Reporting group description:

Ivermectin 1 percent (%) 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 for 12 weeks.

Doxycycline 40 milligram (mg) Modified Release (MR) (30 mg Immediate Release & 10 mg Delayed Release beads) capsules: 1 capsule once-daily for 12 weeks.

Reporting group title	Ivermectin 1% Cream + Oral Placebo Capsules

Reporting group description:

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 for 12 weeks.

Oral placebo capsules: 1 capsule once-daily for 12 weeks.

Primary: Percent Change From Baseline in Inflammatory Lesion Count at Week 12

End point title	Percent Change From Baseline in Inflammatory Lesion Count at Week 12

End point description:

Percent change from baseline in inflammatory lesion count at week 12 was reported. Inflammatory lesions included facial inflammatory lesions of rosacea (that is [i.e.] papules and pustules) which were defined as follows: Papule – a small, solid elevation less than 1.0 centimeter (cm) in diameter; and Pustule – a small, circumscribed elevation of the skin, which contains yellow white exudates. Papules and pustules were counted separately on each of the 5 facial regions (forehead, chin, nose, right cheek and left cheek). Notably, nodules (i.e. circumscribed, elevated, solid lesions more than 1.0 cm in diameter with palpable depth) were not included in the count of inflammatory lesions. Intent-to-treat (ITT) population consisted of the entire population enrolled and randomized. The last observation carried forward (LOCF) method was used to impute missing values for inflammatory lesion count.

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	138		
Units: Percent change				
arithmetic mean (standard deviation)	-80.29 (± 21.65)	-73.56 (± 30.52)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules v

	Ivermectin 1% Cream + Oral Placebo Capsules
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032
Method	Cochran-Mantel-Haenszel

Secondary: Percent Change From Baseline in Inflammatory Lesion Count at Weeks 4 and 8

End point title	Percent Change From Baseline in Inflammatory Lesion Count at Weeks 4 and 8

End point description:

Percent change from baseline in inflammatory lesion count at Weeks 4 and 8 was reported. Inflammatory lesions included facial inflammatory lesions of rosacea (i.e. papules and pustules) which were defined as follows: Papule – a small, solid elevation less than 1.0 centimeter in diameter. Pustule – a small, circumscribed elevation of the skin, which contains yellow white exudates. Papules and pustules were counted separately on each of the 5 facial regions (forehead, chin, nose, right cheek and left cheek). Notably, nodules (i.e. circumscribed, elevated, solid lesions more than 1.0 cm in diameter with palpable depth) were not included in the count of inflammatory lesions. ITT population consisted of the entire population enrolled and randomized. The LOCF method was used to impute missing values for inflammatory lesion count.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4 and 8

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	138		
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 4	-48.15 (± 26.71)	-39.27 (± 27.93)		
Week 8	-69.14 (± 24.10)	-61.44 (± 28.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Clear Inflammatory Lesions at Week 12

End point title	Percentage of Subjects with Clear Inflammatory Lesions at Week 12

End point description:

Percentage of subjects with clear inflammatory lesions at week 12 was reported. Inflammatory lesions included facial inflammatory lesions of rosacea (i.e. papules and pustules) which were defined as

follows: Papule – a small, solid elevation less than 1.0 cm in diameter. Pustule – a small, circumscribed elevation of the skin, which contains yellow white exudates. Papules and pustules were counted separately on each of the 5 facial regions (forehead, chin, nose, right cheek and left cheek). Notably, nodules (i.e. circumscribed, elevated, solid lesions more than 1.0 cm in diameter with palpable depth) were not included in the count of inflammatory lesions. ITT population consisted of the entire population enrolled and randomized. The LOCF method was used to impute missing values for inflammatory lesion count.

End point type	Secondary

End point timeframe:

Week 12

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	138		
Units: Percentage of subjects				
number (not applicable)	17.8	7.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With 100 Percent (%) Reduction in Inflammatory Lesions at Weeks 4, 8 and 12

End point title	Percentage of Subjects With 100 Percent (%) Reduction in Inflammatory Lesions at Weeks 4, 8 and 12

End point description:

Percentage of subjects with 100% reduction in inflammatory lesions at Weeks 4, 8 and 12 was reported. Inflammatory lesions included facial inflammatory lesions of rosacea (i.e. papules and pustules) which were defined as follows: Papule – a small, solid elevation less than 1.0 centimeter in diameter. Pustule – a small, circumscribed elevation of the skin, which contains yellow white exudates. Papules and pustules were counted separately on each of the 5 facial regions (forehead, chin, nose, right cheek and left cheek). Notably, nodules (i.e. circumscribed, elevated, solid lesions more than 1.0 cm in diameter with palpable depth) were not included in the count of inflammatory lesions. ITT population consisted of the entire population enrolled and randomized. The LOCF method was used to impute missing values for inflammatory lesion count.

End point type	Secondary

End point timeframe:

Weeks 4, 8 and 12

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	138		
Units: Percentage of Subjects				
number (not applicable)				
Week 4: Yes	1.5	0.0		
Week 4: No	98.5	100.0		
Week 8: Yes	5.2	2.9		
Week 8: No	94.8	97.1		
Week 12: Yes	17.8	7.2		
Week 12: No	82.2	92.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinician's Erythema Assessment (CEA) Total Score at Weeks 4, 8 and 12

End point title	Clinician's Erythema Assessment (CEA) Total Score at Weeks 4, 8 and 12

End point description:

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 centimeter (cm) using CEA scale, at each visit. CEA is a 5 point scale where 0 = clear (clear skin with no signs of erythema); 1 = almost clear (almost clear; slight redness); 2 = mild (mild erythema; definite redness); 3 = moderate (moderate erythema; marked redness); 4 = severe (severe erythema; fiery redness). A higher score than baseline indicates a worse outcome. ITT population consisted of the entire population enrolled and randomized. The LOCF method was used to impute missing values.

End point type	Secondary

End point timeframe:

Weeks 4, 8 and 12

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	138		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4	2.47 (± 0.94)	2.56 (± 0.94)		
Week 8	1.85 (± 0.95)	1.97 (± 0.94)		
Week 12	1.51 (± 1.02)	1.58 (± 0.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Each Clinician's Erythema Assessment Score Category at Weeks 4, 8 and 12

End point title	Percentage of Subjects in Each Clinician's Erythema Assessment Score Category at Weeks 4, 8 and 12

End point description:

The percentage of subjects in each clinician’s erythema assessment score category was reported. 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 centimeter (cm) using CEA scale, at each visit. CEA is a 5 point scale where 0 = clear (clear skin with no signs of erythema); 1 = almost clear (almost clear; slight redness); 2 = mild (mild erythema; definite redness); 3 = moderate (moderate erythema; marked redness); 4 = severe (severe erythema; fiery redness). A higher score than baseline indicates a worse outcome. ITT population consisted of the entire population enrolled and randomized. The LOCF method was used to impute missing values.

End point type	Secondary

End point timeframe:

Weeks 4, 8 and 12

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	138		
Units: Percentage of Subjects				
number (not applicable)				
Week 4 (0= Clear skin)	0.7	0.7		
Week 4 (1= Almost clear)	16.3	12.3		
Week 4 (2= Mild erythema)	31.9	34.1		
Week 4 (3= Moderate erythema)	37.8	36.2		
Week 4 (4= Severe erythema)	13.3	16.7		
Week 8 (0= Clear skin)	5.2	1.4		
Week 8 (1= Almost clear)	31.1	33.3		
Week 8 (2= Mild erythema)	43.7	39.1		
Week 8 (3= Moderate erythema)	13.3	18.8		
Week 8 (4= Severe erythema)	6.7	7.2		
Week 12 (0= Clear skin)	14.1	7.2		
Week 12 (1= Almost clear)	41.5	47.8		
Week 12 (2= Mild erythema)	28.1	29.7		
Week 12 (3= Moderate erythema)	11.9	10.1		
Week 12 (4= Severe erythema)	4.4	5.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator's Global Assessment (IGA) Total Score at Weeks 4, 8 and 12

End point title	Investigator's Global Assessment (IGA) Total Score at Weeks 4, 8 and 12

End point description:

The evaluator assessed the subject's rosacea by performing a static ("snap shot") evaluation, at a social distance of approximately 50 cm, using the IGA score. IGA is a 5 point scale where, 0 = clear (no inflammatory lesions present, no erythema); 1 = almost clear (very small papules/pustules, very mild erythema present); 2 = mild (few small papules/pustules, mild erythema); 3 = moderate (severe small or large papules/pustules, moderate erythema); 4 = severe (numerous small and/or large papules/pustules, severe erythema). ITT population consisted of the entire population enrolled and randomized. The LOCF method was used to impute missing values.

End point type	Secondary

End point timeframe:

Weeks 4, 8 and 12

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	138		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4	2.59 (± 0.88)	2.84 (± 0.83)		
Week 8	1.78 (± 0.83)	2.04 (± 0.93)		
Week 12	1.34 (± 0.89)	1.57 (± 0.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Each Investigator's Global Assessment Score Category at Weeks 4, 8 and 12

End point title	Percentage of Subjects in Each Investigator's Global Assessment Score Category at Weeks 4, 8 and 12

End point description:

The percentage of subjects in each Investigator's Global Assessment (IGA) score category was reported. The evaluator assessed the subject's rosacea by performing a static ("snap shot") evaluation, at a social distance of approximately 50 cm, using the IGA score. IGA is a 5 point scale where, 0 = clear (no inflammatory lesions present, no erythema); 1 = almost clear (very small papules/pustules, very mild erythema present); 2 = mild (few small papules/pustules, mild erythema); 3 = moderate (severe small or large papules/pustules, moderate erythema); 4 = severe (numerous small and/or large papules/pustules, severe erythema). ITT population consisted of the entire population enrolled and randomized. The LOCF method was used to impute missing values.

End point type	Secondary

End point timeframe:

Weeks 4, 8 and 12

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	138		
Units: Percentage of Subject				
number (not applicable)				
Week 4 (0 - Clear)	1.5	0.7		
Week 4 (1 - Almost clear)	11.1	5.1		
Week 4 (2- Mild)	25.2	23.9		
Week 4 (3 - Moderate)	51.9	50.0		
Week 4 (4 - Severe)	10.4	20.3		
Week 8 (0 - Clear)	3.0	3.6		
Week 8 (1 - Almost clear)	34.8	22.5		
Week 8 (2 - Mild)	48.1	47.8		
Week 8 (3 - Moderate)	9.6	18.1		
Week 8 (4 - Severe)	4.4	8.0		
Week 12 (0 - Clear)	11.9	5.1		
Week 12 (1 - Almost clear)	54.8	54.3		
Week 12 (2 - Mild)	24.4	26.1		
Week 12 (3 - Moderate)	5.2	8.0		
Week 12 (4 - Severe)	3.7	6.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Stinging/Burning Severity Score at at Weeks 4, 8 and 12

End point title	Stinging/Burning Severity Score at at Weeks 4, 8 and 12

End point description:

The evaluator recorded the severity of the subject’s facial stinging/burning sensation during the last 24 hours according to the stinging/burning scale. Stinging/burning scale is a 4 point scale where, 0 = none (No stinging/burning); 1 = mild (slight warm, tingling/stinging sensation, not really bothersome); 2 = moderate (definite warm, tingling/stinging sensation that is somewhat bothersome); 3 = severe (hot, tingling/stinging sensation that has caused definite discomfort). ITT population consisted of the entire population enrolled and randomized. The LOCF method was used to impute missing values.

End point type	Secondary

End point timeframe:

Weeks 4, 8 and 12

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	138		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4	0.73 (± 0.79)	0.65 (± 0.75)		
Week 8	0.41 (± 0.64)	0.44 (± 0.67)		
Week 12	0.31 (± 0.55)	0.33 (± 0.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Each Stinging/Burning Severity Score Category at Weeks 4, 8 and 12

End point title	Percentage of Subjects in Each Stinging/Burning Severity Score Category at Weeks 4, 8 and 12

End point description:

The percentage of subjects in each stinging/burning severity score category was reported. The evaluator recorded the severity of the subject's facial stinging/burning sensation during the last 24 hours according to the stinging/burning scale. Stinging/burning scale is a 4 point scale where, 0 = none (No stinging/burning); 1 = mild (slight warm, tingling/stinging sensation, not really bothersome); 2 = moderate (definite warm, tingling/stinging sensation that is somewhat bothersome); 3 = severe (hot, tingling/stinging sensation that has caused definite discomfort). ITT population consisted of the entire population enrolled and randomized. The LOCF method was used to impute missing values

End point type	Secondary

End point timeframe:

Weeks 4, 8 and 12

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	138		
Units: Percentage of Subjects				
number (not applicable)				
Week 4 (0 - None)	47.4	50.0		
Week 4 (1 - Mild)	32.6	36.2		
Week 4 (2 - Moderate)	19.3	12.3		
Week 4 (3 - Severe)	0.7	1.4		
Week 8 (0 - None)	67.4	64.5		
Week 8 (1 - Mild)	24.4	28.3		
Week 8 (2 - Moderate)	8.1	5.8		
Week 8 (3 - Severe)	0.0	1.4		
Week 12 (0 - None)	73.3	75.4		

Week 12 (1 - Mild)	22.2	17.4		
Week 12 (2 - Moderate)	4.4	6.5		
Week 12 (3 - Severe)	0.0	0.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Global Improvement Total Score at Week 12 (Last Visit/Early Termination)

End point title	Global Improvement Total Score at Week 12 (Last Visit/Early Termination)

End point description:

Subjects were evaluated for his/her improvement in rosacea compared to his/her rosacea condition before study, using global Improvement scale. It is a 7 item scale where, 0=complete improvement (all signs and symptoms of disease have resolved [100% improvement]); 1=excellent improvement (nearly all signs and symptoms cleared [90% improvement]. Only minimal residual signs and symptoms remain); 2=very good improvement (majority of the signs and symptoms have resolved [about 75% improvement]); 3=good improvement (significant improvement, but many signs and symptoms remain [about 50% improvement]); 4=minimal improvement (slight overall improvement, but not clinically significant [about 25% improvement]); 5=no change (overall severity similar to baseline); 6=worse (worse than baseline). ITT population consisted of the entire population enrolled and randomized. Here 'N' (subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 12 (last visit/early termination)

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	129		
Units: Units on a scale				
arithmetic mean (standard deviation)	1.79 (± 1.20)	1.81 (± 1.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Each Global Improvement Score Category at Week 12 (Last Visit/Early Termination)

End point title	Percentage of Subjects in Each Global Improvement Score Category at Week 12 (Last Visit/Early Termination)

End point description:

Subjects were to evaluated for his/her improvement in rosacea compared to his/her rosacea condition before study, using global Improvement scale. it is a 7 item scale where, 0=complete improvement (all signs and symptoms of disease have resolved [100% improvement]); 1=excellent improvement (nearly

all signs and symptoms cleared [90% improvement]. Only minimal residual signs and symptoms remain); 2=very good improvement (majority of the signs and symptoms have resolved [about 75% improvement]); 3=good improvement (significant improvement, but many signs and symptoms remain [about 50% improvement]); 4=minimal improvement (slight overall improvement, but not clinically significant [about 25% improvement]); 5=no change (overall severity similar to baseline); 6=worse (worse than baseline). ITT population consisted of the entire population enrolled and randomized. Here 'N' (subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 12 (last visit/early termination)

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	129		
Units: Percentage of Subjects				
number (not applicable)				
0 - Complete improvement	7.9	6.2		
1 - Excellent improvement	39.7	44.2		
2 - Very good improvement	31.7	25.6		
3 - Good improvement	11.9	15.5		
4 - Minimal improvement	4.0	3.9		
5 - No change	4.0	3.9		
6 - Worse	0.8	0.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was 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. A SAE was any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Safety population (all patients treated [APT]) – consisted of the ITT population, after exclusion of subjects who never used the treatment with certainty based on monitoring report.

End point type	Secondary

End point timeframe:

From the signing of the informed consent form (ICF) up to Week 12

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	138		
Units: Subjects				
AEs	27	50		
SAEs	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Dermatology Life Quality Index (DLQI) Questionnaire Total Score at Week 12 (Last Visit/Early Termination Visit)

End point title	Dermatology Life Quality Index (DLQI) Questionnaire Total Score at Week 12 (Last Visit/Early Termination Visit)

End point description:

DLQI focuses on impact of dermatological diseases on quality of life. It is a 10-item validated quality-of-life questionnaire specific to dermatological conditions. 1) how itchy, sore, painful, stinging, 2) how embarrassed/self-conscious, 3) interfere shopping or looking after home or garden, 4) Influence clothes, 5) affect social/leisure activity, 6) difficult to do sport, 7) prevent from working/studying or If no, problem at work/studying, 8) problem with partner or close friend, 9) cause sexual difficulties, 10) problem caused by treatment. Total score ranged from 0-30,where,0-1=no effect at all on life;2-5=small effect on life; 6-10=moderate effect on life;11-20=very large effect on life;21-30=extremely large effect on life. A higher score indicates a low quality of life due to more severe disease. ITT population consisted of the entire population enrolled and randomised.Here 'N' (subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 12 (last visit/early termination)

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	129		
Units: Units on a scale				
arithmetic mean (standard deviation)	1.4 (± 2.2)	2.2 (± 4.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Each Dermatology Life Quality Index (DLQI) Questionnaire Score Category

End point title	Percentage of Subjects in Each Dermatology Life Quality Index (DLQI) Questionnaire Score Category

End point description:

DLQI focuses on impact of dermatological diseases on quality of life. It is a 10-item validated quality-of-life questionnaire specific to dermatological conditions. 1) how itchy, sore, painful, stinging, 2) how embarrassed/self-conscious, 3) interfere shopping or looking after home or garden, 4) Influence clothes, 5) affect social/leisure activity, 6) difficult to do sport, 7) prevent from working/studying or If no, problem at work/studying, 8) problem with partner or close friend, 9) cause sexual difficulties, 10) problem caused by treatment. Total score ranged from 0-30,where,0-1=no effect at all on life;2-5=small effect on life; 6-10=moderate effect on life;11-20=very large effect on life;21-30=extremely large effect on life. A higher score indicates a low quality of life due to more severe disease. ITT population consisted of the entire population enrolled and randomised. Here 'n' (number analyzed) signifies number of subject evaluable for specified categories.

End point type	Secondary

End point timeframe:

Baseline, Week 12 (last visit/early termination)

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	138		
Units: Percentage of Subjects				
number (not applicable)				
Baseline: 0-1 (n=135,138)	17.8	18.8		
Baseline: 2-5 (n=135,138)	37.8	33.3		
Baseline: 6-10 (n=135,138)	27.4	32.6		
Baseline: 11-20 (n=135,138)	14.8	12.3		
Baseline: 21-30 (n=135,138)	2.2	2.9		
Last visit: 0-1 (n=125,129)	68.0	65.1		
Last visit: 2-5 (n=125,129)	26.4	24.0		
Last visit: 6-10 (n=125,129)	4.8	7.0		
Last visit: 11-20 (n=125,129)	0.8	3.1		
Last visit: 21-30 (n=125,129)	0.0	0.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Dermatology Life Quality Index Questionnaire Total Score at Week 12 (Last Visit/ Early Termination)

End point title	Percent Change From Baseline in Dermatology Life Quality Index Questionnaire Total Score at Week 12 (Last Visit/ Early Termination)

End point description:

DLQI focuses on impact of dermatological diseases on quality of life. It is a 10-item validated quality-of-life questionnaire specific to dermatological conditions. 1) how itchy, sore, painful, stinging, 2) how embarrassed/self-conscious, 3) interfere shopping or looking after home or garden, 4) Influence clothes, 5) affect social/leisure activity, 6) difficult to do sport, 7) prevent from working/studying or If no, problem at work/studying, 8) problem with partner or close friend, 9) cause sexual difficulties, 10) problem caused by treatment. Total score ranged from 0-30,where,0-1=no effect at all on life;2-5=small effect on life; 6-10=moderate effect on life;11-20=very large effect on life;21-30=extremely large effect on life. A higher score indicates a low quality of life due to more severe disease. ITT population consisted of the entire population enrolled and randomised.Here 'N' (subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12 (last visit/early termination)

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	126		
Units: Percent change				
arithmetic mean (standard deviation)	-59.5 (± 66.3)	-59.2 (± 70.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQol-5 Dimension-5 Level (EQ-5D-5L) Questionnaire at Week 12 (Last Visit/Early Termination Visit)

End point title	EuroQol-5 Dimension-5 Level (EQ-5D-5L) Questionnaire at Week 12 (Last Visit/Early Termination Visit)

End point description:

EQ-5D-5L is a 5-level, 5-dimensional format standardized instrument for use as a measure of health outcome used to assess the impact of study treatments on subject's quality of life as follows: 1) mobility; 2) self-care; 3) usual activities; 4) pain/discomfort; 5) anxiety/depression. Each dimension comprises 5 levels with corresponding numeric scores, where 1 indicates no problems, and 5 indicates extreme problems. An increase in the EQ-5D-5L total score indicates improvement. ITT population consisted of the entire population enrolled and randomised. Here 'N' (subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 12/Last visit or early termination visit

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	129		
Units: Units on a scale				
arithmetic mean (standard deviation)	83.5 (± 16.2)	83.0 (± 15.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Each EuroQol-5 Dimension-5 Level Questionnaire Questions at Baseline and Week 12 (last visit/early termination)

End point title	Percentage of Subjects in Each EuroQol-5 Dimension-5 Level Questionnaire Questions at Baseline and Week 12 (last visit/early termination)

End point description:

EQ-5D-5L is a 5-level, 5-dimensional format standardized instrument for use as a measure of health outcome used to assess the impact of study treatments on subject's quality of life as follows: 1) mobility; 2) self-care; 3) usual activities; 4) pain/discomfort; 5) anxiety/depression. Each dimension comprises 5 levels with corresponding numeric scores, where 1 indicates no problems, and 5 indicates extreme problems. An increase in the EQ-5D-5L total score indicates improvement. ITT population consisted of the entire population enrolled and randomised. Here 'n' (number analyzed) signifies number of subject evaluable for specified categories.

End point type	Secondary

End point timeframe:

Baseline and Week 12 (last visit/early termination)

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	138		
Units: Percentage of Subjects				
number (not applicable)				
Baseline: Mobility (n=135,138)	80	84.1		
Baseline: Self-care (n=135,138)	96.3	97.8		
Baseline: Usual activities (n=135,138)	85.9	89.1		
Baseline: Pain/discomfort (n=135,138)	55.6	57.2		
Baseline: Anxiety/depression (n=135,138)	65.9	69.6		
Last visit: Mobility (n=125,129)	80.0	83.7		
Last visit: Self-care (n=125,129)	94.4	96.9		
Last visit: Usual activities (n=125,129)	89.6	90.7		
Last visit: Pain/discomfort (n=125,129)	68.0	79.1		
Last visit: Anxiety/depression (n=125,129)	77.6	82.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reported Work Productivity and Activity Impairment: General Health (WPAI:GH) Questionnaire for Currently Employed Question at Week 12 (Last Visit/Early Termination Visit)

End point title	Percentage of Subjects Reported Work Productivity and Activity Impairment: General Health (WPAI:GH) Questionnaire for Currently Employed Question at Week 12 (Last Visit/Early Termination Visit)

End point description:

WPAI:GH questionnaire was 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. Low scores indicate little or no impact of health problems on work and activities, and a negative change in the WPAI score indicates improvement. Currently Employed question was assessed in this outcome measure. ITT population consisted of the entire population enrolled and randomised. Here 'N' (subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 12 (Last visit/early termination visit)

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	128		
Units: percentage of subjects				
number (not applicable)				
Yes	65.9	65.2		
No	34.1	34.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Work Productivity and Activity Impairment: General Health (WPAI:GH) Questionnaire at Week 12 (Last Visit/Early Termination Visit)

End point title	Work Productivity and Activity Impairment: General Health (WPAI:GH) Questionnaire at Week 12 (Last Visit/Early Termination Visit)

End point description:

WPAI:GH questionnaire is an instrument to measure impairment in both paid and unpaid work during the past week including questions: missed hours from work because of rosacea?, missed hours from work because of other reason?, number of Working hours. It measures absenteeism, presenteeism as well as the impairments in unpaid activity because of health problem during the past seven days. Low scores indicate little or no impact of health problems on work and activities, and a negative change in the WPAI score indicates improvement. ITT population consisted of the entire population enrolled and randomised. Here 'n' (number analyzed) signifies number of subject evaluable for specified categories.

End point type	Secondary

End point timeframe:

Week 12 (Last visit/Early termination visit)

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	82		
Units: hours				
arithmetic mean (standard deviation)				
Missed hours from work because of rosacea	0.1 (± 0.9)	0.0 (± 0.0)		
Missed hours from work because of other reason	4.2 (± 10.9)	2.9 (± 9.6)		
Number of Working hours	36.3 (± 17.7)	38.2 (± 14.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Work Productivity and Activity Impairment: General Health (WPAI:GH) Questionnaire (How Much Rosacea Affect Productivity at Work, How Much Rosacea Affect Daily Activity) at Week 12 (Last Visit/Early Termination Visit)

End point title	Work Productivity and Activity Impairment: General Health (WPAI:GH) Questionnaire (How Much Rosacea Affect Productivity at Work, How Much Rosacea Affect Daily Activity) at Week 12 (Last Visit/Early Termination Visit)

End point description:

WPAI:GH questionnaire is an instrument to measure impairment in both paid and unpaid work during the past week including questions: 5)how much rosacea affect productivity at work?; 6) how much rosacea affect daily activity?. It measures absenteeism, presenteeism as well as the impairments in unpaid activity because of health problem during the past seven days. Low scores indicate little or no impact of health problems on work and activities, and a negative change in the WPAI score indicates improvement. ITT population consisted of the entire population enrolled and randomized. Here 'N' (subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 12 (Last visit/Early termination visit)

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	128		
Units: units on a scale				
arithmetic mean (standard deviation)				
How much rosacea affect productivity at work	0.6 (± 1.5)	0.5 (± 1.2)		
How much rosacea affect daily activity	0.5 (± 1.3)	0.7 (± 1.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reported Satisfied for Subject Satisfaction Questionnaire at Week 12 (Last Visit/Early Termination Visit): Part A

End point title	Percentage of Subjects Reported Satisfied for Subject Satisfaction Questionnaire at Week 12 (Last Visit/Early Termination Visit): Part A

End point description:

Subject’s satisfaction questionnaire was used to specifically collect the subjects feedback on the treatment, the level of satisfaction and future usage. Questionnaire consisted of 4 parts: Part A, B, C and D. where Part A consisted of following 12 questions (Q) about study drugs: 1-Time the study regimen took to work, 2-Improvement of facial lesions, 3-Improvement of facial redness, 4-Improvement of ocular symptoms, 5-Improvement of flushing episodes, 6-How bothered by side effects, 7-Your face looks, 8-You feel, 9-Easy to incorporate in daily routine, 10-Using the study regimen again, 11-Overall satisfaction, 12-Compared to last treatment. Satisfied score of questionnaire meant as subjects responded as Very satisfied (Q -1,2,3,4,5,11), Not bothered at all (Q-6),A lot better (Q-7,8,12), yes (Q-10), strongly agree (Q-9). ITT population consisted of the entire population enrolled and randomised. Here 'N' (subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 12 (Last visit/early termination visit)

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	129		
Units: percentage of subjects				
number (not applicable)				
1.Time the study regimen took to work	48.0	45.0		
2.Improvement of facial lesions	48.0	46.5		
3.Improvement of facial redness	45.6	41.1		
4.Improvement of ocular symptoms	25.6	26.4		
5.Improvement of flushing episodes	41.6	38.0		
6.How bothered by side effects	84.0	76.7		

7.Your face looks	70.4	65.9		
8.You feel	61.6	55.0		
9.Easy to incorporate in daily routine	62.4	58.9		
10.Using the study regimen again	86.4	82.9		
11.Overall satisfaction	54.4	52.7		
12.Compared to last treatment	42.4	41.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reported Strongly Agree for Subject Satisfaction Questionnaire at Week 12 (Last Visit/Early Termination Visit): Part B

End point title	Percentage of Subjects Reported Strongly Agree for Subject Satisfaction Questionnaire at Week 12 (Last Visit/Early Termination Visit): Part B

End point description:

Part B of Questionnaire consisted of following 10 questions about both provided skin care products cleanser and moisturizer: 1-Easy to incorporate into a daily routine, 2-Recommend to my family or friends, 3-Help my skin look healthier, 4-More confident with rosacea, 5-More confident with skin appearance, 6-Positive difference in the
appearance, 7-Keep using both skin care products, 8-Make my skin more hydrated, 9-Improve the texture of my skin, 10-Pleasant to use. ITT population consisted of the entire population enrolled and randomised. Here 'N' (subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 12 (Last visit/early termination visit)

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	129		
Units: percentage of subjects				
number (not applicable)				
1.Easy to incorporate into a daily routine	68.5	70.5		
2.Recommend to my family or friends	60.5	52.7		
3.Help my skin look healthier	58.1	50.4		
4.More confident with rosacea	33.1	32.6		
5.More confident with skin appearance	37.9	36.4		
6.Positive difference in the appearance	47.6	44.2		
7.Keep using both skin care products	52.4	48.8		
8.Make my skin more hydrated	42.7	38.8		
9.Improve the texture of my skin	35.5	34.9		
10.Pleasant to use	54.0	50.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reported Strongly Agree for Subject Satisfaction Questionnaire at Week 12 (Last Visit/Early Termination Visit): Part C

End point title	Percentage of Subjects Reported Strongly Agree for Subject Satisfaction Questionnaire at Week 12 (Last Visit/Early Termination Visit): Part C

End point description:

Part C subject satisfaction questionnaire consisted of following 4 questions about the cosmetic product cleanser: 1- Clean healthy skin feeling, 2-Deep cleansing without stripping moisture, 3-Rinsed off easily, 4-Not make my skin feel tight or dry. ITT population consisted of the entire population enrolled and randomised. Here 'N' (subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 12 (Last visit or early termination visit)

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	129		
Units: percentage of subjects				
number (not applicable)				
1.Clean healthy skin feeling	49.2	46.5		
2.Deep cleansing without stripping moisture	41.1	40.3		
3.Rinsed off easily	54.0	48.8		
4.Not make my skin feel tight or dry	59.7	50.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reported Strongly Agree for Subject Satisfaction Questionnaire at Week 12 (Last Visit/Early Termination Visit): Part D

End point title	Percentage of Subjects Reported Strongly Agree for Subject Satisfaction Questionnaire at Week 12 (Last Visit/Early Termination Visit): Part D

End point description:

Part D of subject satisfaction questionnaire consisted of following 4 questions about the cosmetic

product moisturizer: 1-Skin feel soft and smooth, 2-Improve my skin moisture, 3-Leave my skin hydrated and protected, 4-Provide comforting sensation.

End point type	Secondary

End point timeframe:

Week 12 (Last visit/early termination visit)

End point values	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	129		
Units: percentage of subjects				
number (not applicable)				
1.Skin feel soft and smooth	48.0	35.7		
2.Improve my skin moisture	38.2	34.1		
3.Leave my skin hydrated and protected	42.3	38.0		
4.Provide comforting sensation	43.9	37.2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signing of the informed consent form (ICF) up to week 12

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules

Reporting group description:

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 for 12 weeks.

Doxycycline 40 mg MR (30 mg Immediate Release & 10 mg Delayed Release beads) capsules: 1 Capsule once-daily for 12 weeks.

Reporting group title	Ivermectin 1% Cream + Oral Placebo Capsules

Reporting group description:

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 for 12 weeks.

Oral placebo capsules: 1 Capsule once-daily for 12 weeks.

Serious adverse events	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 135 (0.74%)	1 / 138 (0.72%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Hepatobiliary disorders			
Cholezystolithiasis			
subjects affected / exposed	0 / 135 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Multilevel discopathy in the cervical spine			
subjects affected / exposed	1 / 135 (0.74%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Ivermectin 1% Cream + Doxycycline 40 mg MR Capsules	Ivermectin 1% Cream + Oral Placebo Capsules	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 135 (12.59%)	33 / 138 (23.91%)	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 135 (2.22%)	3 / 138 (2.17%)	
occurrences (all)	3	4	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 135 (0.74%)	6 / 138 (4.35%)	
occurrences (all)	1	6	
Nausea			
subjects affected / exposed	0 / 135 (0.00%)	2 / 138 (1.45%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	2 / 135 (1.48%)	1 / 138 (0.72%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
Rosacea			
subjects affected / exposed	1 / 135 (0.74%)	2 / 138 (1.45%)	
occurrences (all)	1	2	
Skin irritation			
subjects affected / exposed	0 / 135 (0.00%)	2 / 138 (1.45%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	2 / 135 (1.48%)	0 / 138 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 135 (0.00%)	3 / 138 (2.17%)	
occurrences (all)	0	3	

Nasopharyngitis			
subjects affected / exposed	6 / 135 (4.44%)	10 / 138 (7.25%)	
occurrences (all)	6	10	
Rhinitis			
subjects affected / exposed	0 / 135 (0.00%)	2 / 138 (1.45%)	
occurrences (all)	0	2	
Upper respiratory tract infection			
subjects affected / exposed	2 / 135 (1.48%)	2 / 138 (1.45%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported