



Clinical trial results:

A randomized, subject and investigator blinded, placebo controlled, multi-center study in parallel groups to assess the efficacy and safety of LYS006 in patients with moderate to severe inflammatory acne

Summary

EudraCT number	2017-003191-30
Trial protocol	NL DE HU CZ FR
Global end of trial date	09 March 2022

Results information

Result version number	v1 (current)
This version publication date	02 June 2023
First version publication date	02 June 2023

Trial information

Trial identification

Sponsor protocol code	CLYS006X2201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03497897
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG , 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG , 41 613241111, Novartis.email@Novartis.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	09 March 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of LYS006 versus placebo on facial inflammatory lesion counts in subjects with moderate to severe inflammatory acne

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 September 2018
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	Czechia: 1
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	United States: 28
Worldwide total number of subjects	66
EEA total number of subjects	38

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)	66
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 18 investigative sites in 6 countries.

Pre-assignment

Screening details:

There was an initial screening period of up to 4 weeks.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	LYS006 20 mg BID
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Arm description:

LYS006, 20 mg, orally, twice daily (BID), for 12 weeks

Arm type	Experimental
Investigational medicinal product name	LYS006
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg, BID, for 12 weeks

Arm title	LYS006 2 mg BID
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Arm description:

LYS006, 2 mg, orally, BID, for 12 weeks

Arm type	Experimental
Investigational medicinal product name	LYS006
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 mg, BID, for 12 weeks

Arm title	Placebo BID
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Arm description:

Matching placebo, orally, BID, for 12 weeks

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

Dosage and administration details:
Matching placebo, BID, for 12 weeks

Number of subjects in period 1	LYS006 20 mg BID	LYS006 2 mg BID	Placebo BID
Started	26	11	29
Completed Treatment Period	23	9	24
Pharmacodynamic (PD) Analysis Set	24	11	28
Completed	20	9	23
Not completed	6	2	6
Physician decision	1	-	-
Adverse Event	1	1	1
Subject/Guardian Decision	2	1	3
Lost to follow-up	2	-	2

Baseline characteristics

Reporting groups

Reporting group title	LYS006 20 mg BID
Reporting group description:	
LYS006, 20 mg, orally, twice daily (BID), for 12 weeks	
Reporting group title	LYS006 2 mg BID
Reporting group description:	
LYS006, 2 mg, orally, BID, for 12 weeks	
Reporting group title	Placebo BID
Reporting group description:	
Matching placebo, orally, BID, for 12 weeks	

Reporting group values	LYS006 20 mg BID	LYS006 2 mg BID	Placebo BID
Number of subjects	26	11	29
Age Categorical			
Units:			
Between 18 and 65 years	26	11	29
Age Continuous			
Units: years			
arithmetic mean	23.2	24.5	25.0
standard deviation	± 6.89	± 6.23	± 5.40
Sex: Female, Male			
Units: participants			
Female	16	8	22
Male	10	3	7
Race/Ethnicity, Customized			
Units: Subjects			
Asian	1	1	1
Black or African American	2	1	6
Other	2	1	6
White	21	8	16

Reporting group values	Total		
Number of subjects	66		
Age Categorical			
Units:			
Between 18 and 65 years	66		
Age Continuous			
Units: years			
arithmetic mean	-		
standard deviation	-		
Sex: Female, Male			
Units: participants			
Female	46		
Male	20		

Race/Ethnicity, Customized Units: Subjects			
Asian	3		
Black or African American	9		
Other	9		
White	45		

End points

End points reporting groups

Reporting group title	LYS006 20 mg BID
Reporting group description: LYS006, 20 mg, orally, twice daily (BID), for 12 weeks	
Reporting group title	LYS006 2 mg BID
Reporting group description: LYS006, 2 mg, orally, BID, for 12 weeks	
Reporting group title	Placebo BID
Reporting group description: Matching placebo, orally, BID, for 12 weeks	

Primary: Total inflammatory lesion count

End point title	Total inflammatory lesion count
End point description: Inflammatory facial lesion count included papules, pustules, and nodules. The natural log transformed inflammatory facial lesion count up to Week 12 was analyzed using a Bayesian mixed effect model for repeated measurements (MMRM). Values estimated from the model at Week 12 are presented in the table. Posterior geometric mean and 90% credible intervals in each group are presented.	
End point type	Primary
End point timeframe: Week 12	

End point values	LYS006 20 mg BID	LYS006 2 mg BID	Placebo BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	9	23	
Units: lesions				
geometric mean (confidence interval 90%)	18.55 (14.16 to 24.32)	24.51 (16.35 to 36.94)	20.04 (15.42 to 26.13)	

Statistical analyses

Statistical analysis title	Analysis of total inflammatory lesion count
Statistical analysis description: The effects included in the model are: log transformed baseline inflammatory facial lesion count, treatment group, visit, treatment group by visit interaction, log transformed baseline inflammatory facial lesion count by visit interaction and type of center. 90% credible intervals are reported on the geometric means ratio.	
Comparison groups	LYS006 20 mg BID v Placebo BID

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.637 ^[1]
Method	Bayesian analysis
Parameter estimate	Posterior geometric means ratio
Point estimate	0.93
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.64
upper limit	1.34

Notes:

[1] - The posterior probability of geometric mean ratio <1 is presented in the P-Value field.

Statistical analysis title	Analysis of total inflammatory lesion count
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Statistical analysis description:

The effects included in the model are: log transformed baseline inflammatory facial lesion count, treatment group, visit, treatment group by visit interaction, log transformed baseline inflammatory facial lesion count by visit interaction and type of center.

Posterior probability on geometric mean ratio is reported.

Comparison groups	LYS006 20 mg BID v Placebo BID
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.171 ^[2]
Method	Bayesian analysis
Parameter estimate	Posterior geometric mean ratio
Point estimate	0.93
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.64
upper limit	1.34

Notes:

[2] - The posterior probability of geometric mean ratio <0.75 is presented in the P-Value field.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 128 days

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	LYS006 20 mg BID
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Reporting group description:

LYS006, 20 mg, orally, twice daily (BID), for 12 weeks

Reporting group title	Total
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Reporting group description:

Total

Reporting group title	Placebo BID
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Reporting group description:

Matching placebo, orally, BID, for 12 weeks

Reporting group title	LYS006 2 mg BID
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Reporting group description:

LYS006, 2 mg, orally, BID, for 12 weeks

Serious adverse events	LYS006 20 mg BID	Total	Placebo BID
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 66 (0.00%)	0 / 29 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	LYS006 2 mg BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	LYS006 20 mg BID	Total	Placebo BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 26 (38.46%)	34 / 66 (51.52%)	16 / 29 (55.17%)
Investigations			
Albumin urine present			
subjects affected / exposed	1 / 26 (3.85%)	1 / 66 (1.52%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 26 (3.85%)	1 / 66 (1.52%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Bacterial test positive			
subjects affected / exposed	1 / 26 (3.85%)	1 / 66 (1.52%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 26 (7.69%)	6 / 66 (9.09%)	3 / 29 (10.34%)
occurrences (all)	2	6	3
Blood creatinine increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 66 (1.52%)	1 / 29 (3.45%)
occurrences (all)	0	1	1
Blood urine present			
subjects affected / exposed	1 / 26 (3.85%)	1 / 66 (1.52%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Creatinine urine increased			
subjects affected / exposed	1 / 26 (3.85%)	1 / 66 (1.52%)	0 / 29 (0.00%)
occurrences (all)	2	2	0
Crystal urine present			
subjects affected / exposed	2 / 26 (7.69%)	6 / 66 (9.09%)	4 / 29 (13.79%)
occurrences (all)	3	7	4
Haematocrit increased			
subjects affected / exposed	1 / 26 (3.85%)	2 / 66 (3.03%)	1 / 29 (3.45%)
occurrences (all)	1	2	1
Haemoglobin increased			
subjects affected / exposed	0 / 26 (0.00%)	2 / 66 (3.03%)	2 / 29 (6.90%)
occurrences (all)	0	2	2
Lipase increased			

subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	1 / 29 (3.45%) 1
Neutrophil count increased subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	1 / 29 (3.45%) 1
Protein urine present subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 2	2 / 66 (3.03%) 3	1 / 29 (3.45%) 1
Urine protein/creatinine ratio increased subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	4 / 66 (6.06%) 4	1 / 29 (3.45%) 1
White blood cell count increased subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	1 / 29 (3.45%) 1
White blood cells urine positive subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Injury, poisoning and procedural complications			
Muscle strain subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	1 / 29 (3.45%) 1
Procedural pain subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Skin abrasion subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Sunburn subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	1 / 29 (3.45%) 1
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	5 / 66 (7.58%) 5	3 / 29 (10.34%) 3
Blood and lymphatic system disorders			

Haemoglobinaemia subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Polycythaemia subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
General disorders and administration site conditions			
Influenza like illness subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	1 / 29 (3.45%) 1
Oedema subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 2	1 / 66 (1.52%) 2	0 / 29 (0.00%) 0
Ear and labyrinth disorders			
Tinnitus subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	2 / 66 (3.03%) 4	0 / 29 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	2 / 66 (3.03%) 2	1 / 29 (3.45%) 1
Constipation subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	2 / 66 (3.03%) 2	1 / 29 (3.45%) 1
Diarrhoea subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	3 / 66 (4.55%) 4	1 / 29 (3.45%) 2

Flatulence subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	3 / 66 (4.55%) 4	2 / 29 (6.90%) 3
Respiratory, thoracic and mediastinal disorders			
Epistaxis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	2 / 66 (3.03%) 2	0 / 29 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Tonsillar hypertrophy subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Dermatitis contact subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	1 / 29 (3.45%) 1
Pruritus subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Rash papular subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 2	1 / 66 (1.52%) 2	0 / 29 (0.00%) 0
Urticaria aquagenic subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	1 / 29 (3.45%) 1
Psychiatric disorders			

Insomnia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	1 / 29 (3.45%) 1
Renal and urinary disorders Micturition urgency subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Infections and infestations Acarodermatitis subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
COVID-19 subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Bronchitis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	1 / 29 (3.45%) 1
Cystitis subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Gastrointestinal infection subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Genital infection fungal subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Gingivitis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 66 (1.52%) 1	1 / 29 (3.45%) 1
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3	9 / 66 (13.64%) 12	3 / 29 (10.34%) 4
Otitis media subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 66 (1.52%) 1	0 / 29 (0.00%) 0
Urethritis			

subjects affected / exposed	1 / 26 (3.85%)	1 / 66 (1.52%)	0 / 29 (0.00%)
occurrences (all)	2	2	0
Sinusitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 66 (1.52%)	1 / 29 (3.45%)
occurrences (all)	0	1	1
Urinary tract infection			
subjects affected / exposed	0 / 26 (0.00%)	4 / 66 (6.06%)	2 / 29 (6.90%)
occurrences (all)	0	4	2
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 66 (1.52%)	1 / 29 (3.45%)
occurrences (all)	0	1	1

Non-serious adverse events	LYS006 2 mg BID		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 11 (72.73%)		
Investigations			
Albumin urine present			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Bacterial test positive			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Blood urine present			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Creatinine urine increased			

subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Crystal urine present			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Haematocrit increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Haemoglobin increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Lipase increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Neutrophil count increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Protein urine present			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Urine protein/creatinine ratio increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
White blood cell count increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
White blood cells urine positive			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Procedural pain			

subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Skin abrasion			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Sunburn			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Haemoglobinaemia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Polycythaemia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Oedema			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	4		
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Tonsillar hypertrophy			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Dermatitis contact			

subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Rash papular			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Urticaria aquagenic			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
COVID-19			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Gastrointestinal infection			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Genital infection fungal			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Gingivitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	5		
Otitis media			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Urethritis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2018	The main purpose of this amendment was to define study population used for primary, secondary and exploratory statistical analyses.
22 June 2018	The main purpose of this amendment was to align the clinical outcome assessments (COAs) with the comments from the Dutch Ethics Committee (Beoordeling Ethiek Biomedisch Onderzoek) following the review of the initial Clinical Trial Application. Acne-QoL was removed from the COAs. The preliminary assessment for futility at the planned IA1 was removed, and only preliminary safety and efficacy assessment for potential sample size revision was proposed. This amendment clarified the data privacy rights related to the European Economic Area General Data Protection Regulation (EEA GDPR) in force since 25 May 2018. The withdrawal of informed consent section was aligned with the EEA GDPR, in order to correctly inform the EEA based subjects on their data privacy rights when recruitment started.
20 May 2019	The main purpose of this amendment was to integrate FDA comments received after initiation of the study, mainly pertaining to the eligibility criteria and endpoints. In particular, a minimal threshold for facial non-inflammatory lesions (>10 at baseline) was implemented in the inclusion criteria to comply with FDA recommendations.
10 January 2020	The main purpose of this amendment was to reduce the sample size of the study in order to limit exposure to the 2 mg BID arm (low dose), while keeping the power to detect efficacy of the 20 mg BID arm (high dose). The planned number of subjects to be enrolled was decreased from 75 to 56 subjects. The randomization ratio 3:1:3 for first 35 patients was extended to 56 patients. In addition, the assessment schedule was revised in order to simplify further the protocol. Visit 102 (Week 1) was removed and the time window for Visit 103 (Week 2) was extended. The number and timing of interim analysis was updated. The wash-out period for systemic retinoids was reduced from 6 months to 3 months prior to baseline. This amendment also included country specific request from Health Authorities in Czech Republic to use highly effective or double barrier methods of contraception in the Czech investigation sites.
23 March 2021	The main purpose of this amendment was to implement learnings from an interim analysis (IA) conducted on 32 randomized and treated subject's data. A higher-than-expected drop-out rate was observed (approximately 28% instead of 20% assumed). Thus, a replacement policy was set up for subjects who discontinued from the study treatment before completion of Week 12 assessments in order to ensure a sufficient number of evaluable subjects at Week 12 at time of final analysis. The results from IA were encouraging, therefore, the sponsor proposed to drop the central reader as one of the requirements for inclusion as central reader is not a common practice in clinical trials. The central reader would continue to assess pictures collected during the trials but would not constitute a criterion for eligibility anymore. A few additional changes and corrections were done, such as clarification of exclusion criteria, biomarkers and analysis of the primary endpoint. The exclusion criteria #16 was slightly updated, as the data on safety in subjects from interim analysis did not indicate an increased risk in particular for urinary crystals, which could be seen in healthy volunteers due to specific food consumptions. Due to the closure of one site, interested in imaging [and in particular in reflectance confocal microscopy (RCM)], this endpoint was no more conducted. Based on a request from HA, double barrier method of contraception was withdrawn.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported