



Clinical trial results:

The ASCEND Study: A Phase III, Multicenter, Double Blinded Vehicle Controlled Study of TMB-001 - with a Parallel Optional Maximal Use Arm - in the Treatment of RXLI (Xlinked) or ARCI Ichthyosis in Subjects Aged 6 Years

Summary

EudraCT number	2022-000459-35
Trial protocol	DE FR IT
Global end of trial date	23 September 2024

Results information

Result version number	v1 (current)
This version publication date	28 June 2025
First version publication date	28 June 2025

Trial information

Trial identification

Sponsor protocol code	TMB01-301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05295732
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Timber Pharmaceuticals, Inc
Sponsor organisation address	7 Giralda Farms, Madison, NJ, United States, 07940
Public contact	Clinical Disclosure, LEO Pharma A/S, 45 4494 5888, disclosure@leo-pharma.com
Scientific contact	Clinical Disclosure, LEO Pharma A/S, 45 4494 5888, disclosure@leo-pharma.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	24 February 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 June 2024
Global end of trial reached?	Yes
Global end of trial date	23 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To ascertain the efficacy of TMB-001 0.05% topical ointment as a treatment for congenital ichthyosis (CI) compared with Vehicle during a 12-week treatment.

Protection of trial subjects:

This study was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki (2013), CIOMS International Ethical Guidelines, applicable ICH GCP Guidelines, and other applicable laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 June 2022
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	France: 20
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	United States: 44
Worldwide total number of subjects	116
EEA total number of subjects	65

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)	24
Adolescents (12-17 years)	29

Adults (18-64 years)	58
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

34 sites across the United States, Canada, Germany, France, and Italy enrolled subjects, and 33 of these sites randomized subjects.

Pre-assignment

Screening details:

34 study centers recruited subjects.

Period 1

Period 1 title	double-blind period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	TMB-001 0.05%

Arm description:

In the first 3 weeks of the 12-week double-blind primary dosing period, subjects were randomized to TMB-001 0.05% QD with use of mandatory standardized bland emollient (Cetaphil™). For the last 9 weeks of the 12 week double-blind primary dosing period, the subjects continued with TMB-001 0.05% at the increased dosing frequency of BID. Mandatory bland emollient was discontinued.

Arm type	Experimental
Investigational medicinal product name	TMB-001 0.05%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use, Topical use

Dosage and administration details:

QD for 3 weeks in period 1 and then BID for 9 weeks in period 2

Arm title	Vehicle
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Arm description:

For the first 3 weeks of the 12-week double-blind primary dosing period, subjects were randomized to Vehicle QD treatment, with use of mandatory standardized bland emollient (Cetaphil™). For the last 9 weeks of the 12-week double-blind primary dosing period, the subjects continued with Vehicle at the increased dosing frequency of BID. Mandatory bland emollient was discontinued.

Arm type	Placebo
Investigational medicinal product name	Vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use

Dosage and administration details:

QD for 3 weeks in period 1 and then BID for 9 weeks in period 2

Number of subjects in period 1	TMB-001 0.05%	Vehicle
Started	78	38
Completed	65	36
Not completed	13	2
Various reasons	13	2

Period 2

Period 2 title	Open-label
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	TMB-001 0.05% QD

Arm description:

At Week 12, TMB-001 0.05% BID treatment responders (who had achieved a ≥ 1 -point reduction in IGA score from baseline) were re-randomized (1:1 ratio) to 12 weeks of open-label treatment with TMB-001 0.05% BID or TMB-001 0.05% QD. Subjects with less than a 1-point reduction in IGA score from baseline were discontinued from the study. Vehicle-treated subjects who achieved < 1 -point reduction in IGA score from baseline by week 12, were eligible to cross over to 12 weeks of open-label treatment with TMB-001 0.05% BID treatment. Subjects with a ≥ 1 -point reduction in IGA score from baseline on vehicle were discontinued from the study.

Arm type	Experimental
Investigational medicinal product name	TMB-001 0.05%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use, Topical use

Dosage and administration details:

TMB-001 0.05% QD for 12 weeks.

Arm title	TMB-001 0.05% BID
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Arm description:

At Week 12, TMB-001 0.05% BID treatment responders (who had achieved a ≥ 1 -point reduction in IGA score from baseline) were re-randomized (1:1 ratio) to 12 weeks of open-label treatment with TMB-001 0.05% BID or TMB-001 0.05% QD. Subjects with less than a 1-point reduction in IGA score from baseline were discontinued from the study. Vehicle-treated subjects who achieved < 1 -point reduction in IGA score from baseline by week 12, were eligible to cross over to 12 weeks of open-label treatment with TMB-001 0.05% BID treatment. Subjects with a ≥ 1 -point reduction in IGA score from baseline on vehicle were discontinued from the study.

Arm type	Experimental
Investigational medicinal product name	TMB-001 0.05%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use, Topical use

Number of subjects in period 2^[1]	TMB-001 0.05% QD	TMB-001 0.05% BID
Started	28	38
Completed	28	37
Not completed	0	1
Discontinued IMP before week 12	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: TMB-001 0.05% treated subjects with less than a 1-point reduction in IGA score from baseline were discontinued from the study.

Vehicle-treated subjects with a ≥ 1 -point reduction in IGA score from baseline were discontinued from the study.

Baseline characteristics

Reporting groups

Reporting group title	TMB-001 0.05%
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Reporting group description:

In the first 3 weeks of the 12-week double-blind primary dosing period, subjects were randomized to TMB-001 0.05% QD with use of mandatory standardized bland emollient (Cetaphil™). For the last 9 weeks of the 12 week double-blind primary dosing period, the subjects continued with TMB-001 0.05% at the increased dosing frequency of BID. Mandatory bland emollient was discontinued.

Reporting group title	Vehicle
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Reporting group description:

For the first 3 weeks of the 12-week double-blind primary dosing period, subjects were randomized to Vehicle QD treatment, with use of mandatory standardized bland emollient (Cetaphil™). For the last 9 weeks of the 12-week double-blind primary dosing period, the subjects continued with Vehicle at the increased dosing frequency of BID. Mandatory bland emollient was discontinued.

Reporting group values	TMB-001 0.05%	Vehicle	Total
Number of subjects	78	38	116
Age categorical			
Units: Subjects			
6-11 years	16	8	24
12-16 years	19	8	27
>=17 years	43	22	65
Gender categorical			
Units: Subjects			
Female	29	15	44
Male	49	23	72
Race			
Units: Subjects			
White	57	25	82
Black or African American	2	5	7
Asian	3	2	5
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	1	1
Other	1	0	1
Missing	15	5	20
Ethnicity			
Units: Subjects			
Hispanic or Latino	2	2	4
Not Hispanic or Latino	28	19	47
Unknown/Missing	48	17	65
BMI			
BMI=Body Mass Index			
Units: kg/m2			
arithmetic mean	22.903	24.092	
standard deviation	± 5.4218	± 7.6000	-

Subject analysis sets

Subject analysis set title	Maximal Use
Subject analysis set type	Safety analysis

Subject analysis set description:

The optional maximal use arm part of the trial was conducted under the same protocol number for operational reasons, but with separate design, objective, and patients. Adult and pediatric subjects, at a subset of preselected centers, were enrolled in an open-label Optional Maximal Use Arm to evaluate the systemic exposure and safety of TMB-001 0.05% for the treatment of congenital ichthyosis under maximal use conditions. Initially, adult and pediatric subjects with congenital ichthyosis were dosed for 14 days with TMB-001 0.05% BID. Following an interim pharmacokinetic (PK) analysis and based on the exposure data for subjects aged ≥ 12 years, pediatric subjects aged 6 to 11 years began dosing with TMB-001 0.05% BID for 14 days. Following the 14-day PK assessment period, subjects received TMB-001 0.05% BID treatment for 10 weeks to provide additional safety and limited efficacy data.

Reporting group values	Maximal Use		
Number of subjects	34		
Age categorical			
Units: Subjects			
6-11 years	9		
12-16 years	7		
≥ 17 years	18		
Gender categorical			
Units: Subjects			
Female	16		
Male	18		
Race			
Units: Subjects			
White	21		
Black or African American	7		
Asian	3		
American Indian or Alaska Native	1		
Native Hawaiian or Other Pacific Islander	0		
Other	1		
Missing	1		
Ethnicity			
Units: Subjects			
Hispanic or Latino	2		
Not Hispanic or Latino	25		
Unknown/Missing	7		
BMI			
BMI=Body Mass Index			
Units: kg/m ²			
arithmetic mean	24.468		
standard deviation	± 8.6960		

End points

End points reporting groups

Reporting group title	TMB-001 0.05%
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Reporting group description:

In the first 3 weeks of the 12-week double-blind primary dosing period, subjects were randomized to TMB-001 0.05% QD with use of mandatory standardized bland emollient (Cetaphil™). For the last 9 weeks of the 12-week double-blind primary dosing period, the subjects continued with TMB-001 0.05% at the increased dosing frequency of BID. Mandatory bland emollient was discontinued.

Reporting group title	Vehicle
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Reporting group description:

For the first 3 weeks of the 12-week double-blind primary dosing period, subjects were randomized to Vehicle QD treatment, with use of mandatory standardized bland emollient (Cetaphil™). For the last 9 weeks of the 12-week double-blind primary dosing period, the subjects continued with Vehicle at the increased dosing frequency of BID. Mandatory bland emollient was discontinued.

Reporting group title	TMB-001 0.05% QD
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Reporting group description:

At Week 12, TMB-001 0.05% BID treatment responders (who had achieved a ≥ 1 -point reduction in IGA score from baseline) were re-randomized (1:1 ratio) to 12 weeks of open-label treatment with TMB-001 0.05% BID or TMB-001 0.05% QD. Subjects with less than a 1-point reduction in IGA score from baseline were discontinued from the study. Vehicle-treated subjects who achieved < 1 -point reduction in IGA score from baseline by week 12, were eligible to cross over to 12 weeks of open-label treatment with TMB-001 0.05% BID treatment. Subjects with a ≥ 1 -point reduction in IGA score from baseline on vehicle were discontinued from the study.

Reporting group title	TMB-001 0.05% BID
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Reporting group description:

At Week 12, TMB-001 0.05% BID treatment responders (who had achieved a ≥ 1 -point reduction in IGA score from baseline) were re-randomized (1:1 ratio) to 12 weeks of open-label treatment with TMB-001 0.05% BID or TMB-001 0.05% QD. Subjects with less than a 1-point reduction in IGA score from baseline were discontinued from the study. Vehicle-treated subjects who achieved < 1 -point reduction in IGA score from baseline by week 12, were eligible to cross over to 12 weeks of open-label treatment with TMB-001 0.05% BID treatment. Subjects with a ≥ 1 -point reduction in IGA score from baseline on vehicle were discontinued from the study.

Subject analysis set title	Maximal Use
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The optional maximal use arm part of the trial was conducted under the same protocol number for operational reasons, but with separate design, objective, and patients. Adult and pediatric subjects, at a subset of preselected centers, were enrolled in an open-label Optional Maximal Use Arm to evaluate the systemic exposure and safety of TMB-001 0.05% for the treatment of congenital ichthyosis under maximal use conditions. Initially, adult and pediatric subjects with congenital ichthyosis were dosed for 14 days with TMB-001 0.05% BID. Following an interim pharmacokinetic (PK) analysis and based on the exposure data for subjects aged ≥ 12 years, pediatric subjects aged 6 to 11 years began dosing with TMB-001 0.05% BID for 14 days. Following the 14-day PK assessment period, subjects received TMB-001 0.05% BID treatment for 10 weeks to provide additional safety and limited efficacy data.

Primary: Change in Investigator Global Assessment (IGA) Score

End point title	Change in Investigator Global Assessment (IGA) Score
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End point description:

Comparison of proportions of subjects with ≥ 2 -point changes from Baseline in Investigator Global Assessment (IGA)-scaling and fissuring scores in the Treatment Area at Week 12 between TMB-001 0.05% and vehicle-treated subjects. Investigator's Global Assessment Score is a 0-4 scale, where 0 is clear and 4 is severe.

End point type	Primary
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End point timeframe:

12 weeks

End point values	TMB-001 0.05%	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	38		
Units: percentage of responders				
number (not applicable)	41.4	44.9		

Statistical analyses

Statistical analysis title	statistical analysis 1
Comparison groups	TMB-001 0.05% v Vehicle
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39
Method	Cochran-Mantel-Haenszel
Parameter estimate	treatment difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.4
upper limit	16.5

Secondary: Number of Subjects With IGA Scores

End point title	Number of Subjects With IGA Scores
End point description:	
Comparison of proportion of subjects with IGA scores of clear or almost clear at Week 12 between TMB-001 0.05% and vehicle-treated subjects. Investigator's Global Assessment Score is a 0-4 scale, where 0 is clear and 4 is severe.	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	TMB-001 0.05%	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	38		
Units: percentage of responders				
number (not applicable)	35.8	38.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in IGA-scaling Severity Sub-score

End point title	Change in IGA-scaling Severity Sub-score
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End point description:

Comparison of proportion of subjects who achieve IGA-scaling severity sub-score improvement ≥ 2 -points from Baseline to Week 12 between TMB-001 0.05% and vehicle-treated subjects. Investigator's Global Assessment Score is a 0-4 scale, where 0 is clear and 4 is severe.

End point type	Secondary
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End point timeframe:

12 weeks

End point values	TMB-001 0.05%	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	36		
Units: percentage of responders				
number (not applicable)	40.4	36.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Worst Itch-Quality of Life (QoL) Scores

End point title	Change in Worst Itch-Quality of Life (QoL) Scores
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End point description:

Comparison of proportion of subjects with ≥ 4 -point improvement from baseline in Worst Itch-QoL scores at Week 12 in subjects with baseline WI-NRS of ≥ 7 between TMB-001 0.05% and vehicle-treated subjects. Itch-Numeric Rating Scale (I-NRS) and Worst Itch-Numeric Rating Scale (WI-NRS) is an 0-10 scale where 0 is "no itching" and 10 is "worst itch imaginable".

End point type	Secondary
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End point timeframe:

12 weeks

End point values	TMB-001 0.05%	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	9		
Units: percentage of responders				
number (not applicable)	54.4	68.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Visual Index of Ichthyosis Severity (VIIS) Score

End point title	Change in Visual Index of Ichthyosis Severity (VIIS) Score
End point description: Comparison of proportion of subjects who achieve 50% reduction from Baseline in VIIS-scaling scores at Week 12 in all areas with Baseline VIIS score ≥ 3 between TMB-001 0.05% and vehicle-treated subjects. Visual Index for Ichthyosis Severity Score is a 0-4 scale where 0 is clear and 4 is severe.	
End point type	Secondary
End point timeframe: 12 weeks	

End point values	TMB-001 0.05%	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	38		
Units: percentage of responders				
number (not applicable)	47.2	42.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in VIIS Score

End point title	Change in VIIS Score
End point description: Comparison of proportion of subjects who achieve 25% reduction from Baseline in VIIS-scaling scores at Week 12 in all areas with Baseline VIIS score ≥ 3 between TMB-001 0.05% and vehicle-treated subjects. Visual Index for Ichthyosis Severity Score is a 0-4 scale where 0 is clear and 4 is severe.	
End point type	Secondary
End point timeframe: 12 weeks	

End point values	TMB-001 0.05%	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	38		
Units: percentage of responders				
number (not applicable)	71.3	64.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in IGA-fissuring Severity Sub-scores

End point title	Change in IGA-fissuring Severity Sub-scores
End point description: Comparison of proportion of subjects achieving ≥ 2 point improvement in IGA-fissuring severity sub-scores from Baseline to Week 12 between TMB-001 0.05% and vehicle-treated subjects. Investigator's Global Assessment Score is a 0-4 scale, where 0 is clear and 4 is severe.	
End point type	Secondary
End point timeframe: 12 weeks	

End point values	TMB-001 0.05%	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	17		
Units: percentage of responders				
number (not applicable)	54.1	57.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in IGA Score

End point title	Change in IGA Score
End point description: Comparison of proportions of subjects achieving ≥ 2 -point improvement from Baseline in IGA scores at Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing. Investigator's Global Assessment Score is a 0-4 scale, where 0 is clear and 4 is severe.	
End point type	Secondary
End point timeframe: 24 weeks	

End point values	TMB-001 0.05% QD	TMB-001 0.05% BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	27		
Units: percentage (%) of responders				
number (confidence interval 95%)	57.1 (38.8 to 75.5)	85.2 (71.8 to 98.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in VIIS Score

End point title	Change in VIIS Score
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End point description:

Comparison of proportion of subjects who achieve 50% reduction from Baseline in VIIS-scaling scores at Week 24 in all areas with Baseline VIIS score ≥ 3 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing. Visual Index for Ichthyosis Severity Score is a 0-4 scale where 0 is clear and 4 is severe.

End point type	Secondary
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End point timeframe:

24 weeks

End point values	TMB-001 0.05% QD	TMB-001 0.05% BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	27		
Units: percentage of responders				
number (confidence interval 95%)	63.0 (44.7 to 81.2)	85.2 (71.8 to 98.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Ichthyosis Quality of Life (IQoL)-32 Scores

End point title	Change in Ichthyosis Quality of Life (IQoL)-32 Scores
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End point description:

Comparison of proportions of subjects with ≥ 11 -point changes from Baseline in IQoL-32 scores at Week 12 between TMB-001 0.05% and vehicle-treated subjects. The IQoL-32 is a questionnaire containing 32, each scored from 0 to 4 ('not applicable', 'not at all', 'a little', 'a lot', 'tremendously') for a total score that varies between 0 and 128. A higher score, the higher impact on quality of life.

End point type	Secondary
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End point timeframe:

12 weeks

End point values	TMB-001 0.05%	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	21		
Units: percentage of responders				
number (not applicable)	47.1	9.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI) Scores

End point title	Change in Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI) Scores
End point description: Comparison of proportion of subjects with reduction from Baseline in DLQI or CDLQI ≥ 4 points at Week 12 between TMB-001 0.05% and vehicle-treated subjects in adult subjects with Baseline scores ≥ 11 and pediatric subjects with Baseline scores of ≥ 13 . The age-appropriate questionnaire contains 10 questions scored from 0 (no impact of skin disease on QoL) to 30 (maximum impact on QoL).	
End point type	Secondary
End point timeframe: 12 weeks	

End point values	TMB-001 0.05%	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	8		
Units: percentage of responders				
number (not applicable)				
DLQI, n=15, 8	86.7	37.5		
CDLQI, n=5, 0	80.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Itch-Quality of Life Scores - WI-NRS

End point title	Change in Itch-Quality of Life Scores - WI-NRS
End point description: Comparison of proportions of subjects with WI-NRS improvement ≥ 4 points from Baseline in Itch-QoL scores (in subjects with Baseline WI-NRS ≥ 7) at Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing.	

End point type	Secondary
End point timeframe:	
24 weeks	

End point values	TMB-001 0.05% QD	TMB-001 0.05% BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: percentage of responders				
number (confidence interval 95%)	66.7 (0.00 to 100.0)	75.0 (19.2 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in DLQI or CDLQI Scores

End point title	Change in DLQI or CDLQI Scores
End point description:	
Comparison of changes from Baseline in DLQI or CDLQI at Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing in adult subjects with Baseline scores ≥ 11 and pediatric subjects with Baseline scores of ≥ 13 . The age-appropriate questionnaire contains 10 questions scored from 0 (no impact of skin disease on QoL) to 30 (maximum impact on QoL).	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	TMB-001 0.05% QD	TMB-001 0.05% BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: percentage of responders				
number (confidence interval 95%)				
DLQI, n=4, 4	75.0 (32.6 to 100.0)	100 (100.0 to 100.0)		
CDLQI, n=1, 3	100 (100.0 to 100.0)	100 (100.0 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in IQoL-32 Scores

End point title	Change in IQoL-32 Scores
End point description: Proportions of subjects with ≥ 11 -point change from Baseline in IQoL-32 at Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing in adult subjects. The IQoL-32 is a questionnaire containing 32, each scored from 0 to 4 ('not applicable', 'not at all', 'a little', 'a lot', 'tremendously') for a total score that varies between 0 and 128. A higher score, the higher impact on quality of life.	
End point type	Secondary
End point timeframe: 24 weeks	

End point values	TMB-001 0.05% QD	TMB-001 0.05% BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: percentage of responders				
number (confidence interval 95%)	40.0 (9.6 to 70.4)	60.0 (29.6 to 90.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: To Investigate the Proportion of Subjects Experiencing Local Skin Reactions (LSRs) With Topically Applied TMB-001 0.05% Ointment

End point title	To Investigate the Proportion of Subjects Experiencing Local Skin Reactions (LSRs) With Topically Applied TMB-001 0.05% Ointment
End point description: Comparison of proportion of subjects experiencing LSRs through Week 12 between TMB-001 0.05% and vehicle-treated subjects.	
End point type	Secondary
End point timeframe: 12 weeks	

End point values	TMB-001 0.05%	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	38		
Units: percentage of participants				
number (confidence interval 95%)	64.1 (52.4 to 74.7)	36.8 (21.8 to 54.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: To Investigate the Proportion of Subjects Experiencing Treatment-emergent Adverse Events (TEAEs)

End point title	To Investigate the Proportion of Subjects Experiencing Treatment-emergent Adverse Events (TEAEs)
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End point description:

Comparison of proportion of subjects experiencing TEAEs through Week 12 between TMB-001 0.05% and vehicle-treated subjects.

End point type	Secondary
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End point timeframe:

12 weeks

End point values	TMB-001 0.05%	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	38		
Units: percentage of participants				
number (not applicable)	76.9	63.2		

Statistical analyses

No statistical analyses for this end point

Secondary: To Investigate the Proportion of Subjects Experiencing LSRs With Topically Applied TMB-001 0.05% Ointment.

End point title	To Investigate the Proportion of Subjects Experiencing LSRs With Topically Applied TMB-001 0.05% Ointment.
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End point description:

Comparison of proportion of subjects experiencing LSRs through Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing.

End point type	Secondary
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End point timeframe:

24 weeks

End point values	TMB-001 0.05% QD	TMB-001 0.05% BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	27		
Units: percentage of participants				
number (confidence interval 95%)	32.1 (15.9 to 52.4)	40.7 (22.4 to 61.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: To Investigate the Proportion of Subjects Experiencing TEAEs

End point title To Investigate the Proportion of Subjects Experiencing TEAEs

End point description:

Comparison of proportion of subjects experiencing TEAEs through Week 24.

End point type Secondary

End point timeframe:

24 weeks

End point values	TMB-001 0.05% QD	TMB-001 0.05% BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	27		
Units: percentage of participants				
number (confidence interval 95%)	53.6 (33.9 to 72.5)	48.1 (28.7 to 68.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: To Investigate the Proportion of Subjects Demonstrating Clinically Confirmed Allergic Contact Dermatitis

End point title To Investigate the Proportion of Subjects Demonstrating Clinically Confirmed Allergic Contact Dermatitis

End point description:

Comparison of proportion of subjects demonstrating clinically confirmed allergic contact dermatitis by patch testing through Week 12 between TMB-001 0.05% and vehicle-treated subjects.

End point type Secondary

End point timeframe:

during week 12

End point values	TMB-001 0.05%	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	38		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximal Use Arm: Isotretinoin, Tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin - Cmax After Multiple Dosing - Adults

End point title	Maximal Use Arm: Isotretinoin, Tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin - Cmax After Multiple Dosing - Adults
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End point description:

maximal observed plasma concentration. Assessment of concentrations of isotretinoin, tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin. Mean values are presented.

End point type	Secondary
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End point timeframe:

14 days

End point values	Maximal Use			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: ng/mL				
number (not applicable)				
Isotretinoin	4.13			
4-oxo-isotretinoin	16.7			
Tretinoin	0.04			
4-oxo-tretinoin	0.00			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximal Use Arm: Isotretinoin, Tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin - Cmax After Multiple Dosing - Adolescents

End point title	Maximal Use Arm: Isotretinoin, Tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin - Cmax After Multiple Dosing - Adolescents
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End point description:

maximal observed plasma concentration. Assessment of concentrations of isotretinoin, tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin. Mean values are presented.

End point type	Secondary
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End point timeframe:

14 days

End point values	Maximal Use			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: ng/mL				
number (not applicable)				
Isotretinoin	7.7			
4-oxo-isotretinoin	25.44			
Tretinoin	4.52			
4-oxo-tretinoin	3.60			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximal Use Arm: Isotretinoin, Tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin - AUC0-24 After Multiple Dosing - Adults

End point title	Maximal Use Arm: Isotretinoin, Tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin - AUC0-24 After Multiple Dosing - Adults
End point description:	
AUC0-24 = area under the curve over the first 24 hours post dose. Assessment of concentrations of isotretinoin, tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin. Mean values are presented.	
End point type	Secondary
End point timeframe:	
14 days	

End point values	Maximal Use			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: hr*ng/mL				
number (not applicable)				
Isotretinoin	78.44			
4-Oxo-Isotretinoin	352.95			
Tretinoin	0.17			
4-oxo-tretinoin	0.00			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximal Use Arm: Isotretinoin, Tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin - AUC0-24 After Multiple Dosing - Adolescents

End point title	Maximal Use Arm: Isotretinoin, Tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin - AUC0-24 After Multiple Dosing - Adolescents
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End point description:

AUC0-24 = area under the curve over the first 24 hours post dose. Assessment of concentrations of isotretinoin, tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin. Mean values are presented.

End point type	Secondary
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End point timeframe:

14 days

End point values	Maximal Use			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: hr*ng/mL				
number (not applicable)				
Isotretinoin	101.34			
4-oxo-isotretinoin	432.96			
Tretinoin	13.74			
4-oxo-tretinoin	10.15			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximal Use Arm: Isotretinoin, Tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin - Tmax After Multiple Dosing - Adults

End point title	Maximal Use Arm: Isotretinoin, Tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin - Tmax After Multiple Dosing - Adults
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End point description:

Tmax = time to maximal plasma concentration. Assessment of concentrations of isotretinoin, tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin. Median values are presented.

End point type	Secondary
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End point timeframe:

14 days

End point values	Maximal Use			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: hours				
number (not applicable)				
Isotretinoin	1.5			
4-oxo-isotretinoin	5			
Tretinoin	0.00			
4-oxo-tretinoin	0.00			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximal Use Arm: Isotretinoin, Tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin - Tmax After Multiple Dosing - Adolescents

End point title	Maximal Use Arm: Isotretinoin, Tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin - Tmax After Multiple Dosing - Adolescents
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End point description:

Tmax = time to maximal plasma concentration. Assessment of concentrations of isotretinoin, tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin. Median values are presented.

End point type	Secondary
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End point timeframe:

14 days

End point values	Maximal Use			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: hours				
number (not applicable)				
Isotretinoin	14			
4-oxo-isotretinoin	18			
Tretinoin	2.00			
4-oxo-tretinoin	1.00			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximal Use Arm: Isotretinoin, Tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin - Steady State Concentration After Multiple Dosing - Children

End point title	Maximal Use Arm: Isotretinoin, Tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin - Steady State Concentration After Multiple Dosing - Children
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End point description:

Assessment of concentrations of isotretinoin, tretinoin, 4-oxo-tretinoin and 4-oxo-isotretinoin. Values for the metabolites 4-Oxo-Isotretinoin, Tretinoin and 4-oxo-tretinoin could not be plotted due to the sparse sampling schedule.

End point type	Secondary
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End point timeframe:

14 days

End point values	Maximal Use			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: ng/mL				
arithmetic mean (standard deviation)				
Isotretinoin	1.27 (± 1.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximal Use Arm: Assessment of the Exposure of TMB-001 and Oral Isotretinoin - Cmax

End point title	Maximal Use Arm: Assessment of the Exposure of TMB-001 and Oral Isotretinoin - Cmax
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End point description:

Cmax: maximal observed plasma concentration. The exposure levels observed for TMB-001 0.05% topical ointment after multiple dosing were compared with the cross-trial for PK parameters obtained for oral isotretinoin (single dose 80 mg) in healthy volunteers.

End point type	Secondary
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End point timeframe:

14 days

End point values	Maximal Use			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: ng/mL				
number (not applicable)				
Oral 80 mg Isotretinoin, single dose	1110.00			
TMB-001 0.05% topical, multiple dose, adolescents	7.70			
TMB-001 0.05% topical, multiple dose, adults	4.13			
ratio (oral/topical) - adolescents	144			
ratio (oral/topical) - adults	269			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximal Use Arm: Assessment of the Exposure of TMB-001 and Oral

Isotretinoin - AUC0-24

End point title	Maximal Use Arm: Assessment of the Exposure of TMB-001 and Oral Isotretinoin - AUC0-24
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End point description:

AUC0-24: area under the curve over the first 24 hours post dose The exposure levels observed for TMB-001 0.05% topical ointment after multiple dosing were compared with the cross-trial for PK parameters obtained for oral isotretinoin (single dose 80 mg) in healthy volunteers.

End point type	Secondary
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End point timeframe:

14 days

End point values	Maximal Use			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: h*ng/mL				
number (not applicable)				
Oral 80 mg Isotretinoin, single dose	10700.00			
TMB-001 0.05% topical, multiple dose, adolescents	101.34			
TMB-001 0.05% topical, multiple dose, adults	78.44			
ratio (oral/topical) - adolescents	106			
ratio (oral/topical) - adults	136			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximal Use Arm: Safety and Tolerability - LSRs

End point title	Maximal Use Arm: Safety and Tolerability - LSRs
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End point description:

Local skin reactions (burnings/stinging, erythema, erosions and edema) are reported as LSRs.

End point type	Secondary
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End point timeframe:

12 weeks

End point values	Maximal Use			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: events				
Erythema	16			
Erosions	7			
Edema	2			
Burning/stinging	17			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximal Use Arm: Safety and Tolerability - TEAEs

End point title	Maximal Use Arm: Safety and Tolerability - TEAEs
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End point description:

Local safety are reported as severe TEAEs related to treatment area.

End point type	Secondary
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End point timeframe:

12 weeks

End point values	Maximal Use			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: events				
Pruritus	2			
Administration site reactions	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Itch-Quality of Life scores - I-NRS

End point title	Change in Itch-Quality of Life scores - I-NRS
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End point description:

Comparison of proportions of subjects with I-NRS improvement ≥ 4 points from Baseline in Itch-QoL scores (in subjects with Baseline I-NRS ≥ 7) at Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing.

End point type	Secondary
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End point timeframe:

24 weeks

End point values	TMB-001 0.05% QD	TMB-001 0.05% BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[1]	1		
Units: percentage of responders				
number (confidence interval 95%)	(to)	100 (100.0 to 100.0)		

Notes:

[1] - No data available.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 weeks for the phase 3 trial part (TMB-001 0.005% and vehicle arms) and 12 weeks for the Maximal use arm

Adverse event reporting additional description:

TEAEs. An AE is defined as treatment emergent if the AE start on or after treatment start until 30 days after treatment end date.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	TMB-001 0.05%
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Reporting group description:

Safety Population = all subjects randomly assigned to study treatment and who received at least 1 dose of study medication.

Reporting group title	Vehicle
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Reporting group description:

Safety Population = all subjects randomly assigned to study treatment and who received at least 1 dose of study medication.

Reporting group title	Maximal Use
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Reporting group description:

Safety population = all subjects enrolled in the maximal use arm who received at least 1 dose of study medication.

Serious adverse events	TMB-001 0.05%	Vehicle	Maximal Use
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 78 (1.28%)	0 / 38 (0.00%)	0 / 34 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Viral rash			
subjects affected / exposed	1 / 78 (1.28%)	0 / 38 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	TMB-001 0.05%	Vehicle	Maximal Use
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 78 (67.95%)	20 / 38 (52.63%)	22 / 34 (64.71%)
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 78 (10.26%)	1 / 38 (2.63%)	1 / 34 (2.94%)
occurrences (all)	10	4	1
General disorders and administration site conditions			
Application site dermatitis			
subjects affected / exposed	2 / 78 (2.56%)	2 / 38 (5.26%)	1 / 34 (2.94%)
occurrences (all)	2	2	1
Application site erosion			
subjects affected / exposed	14 / 78 (17.95%)	4 / 38 (10.53%)	7 / 34 (20.59%)
occurrences (all)	21	7	7
Application site erythema			
subjects affected / exposed	31 / 78 (39.74%)	6 / 38 (15.79%)	11 / 34 (32.35%)
occurrences (all)	55	9	16
Application site oedema			
subjects affected / exposed	7 / 78 (8.97%)	1 / 38 (2.63%)	2 / 34 (5.88%)
occurrences (all)	8	1	2
Application site pain			
subjects affected / exposed	29 / 78 (37.18%)	5 / 38 (13.16%)	13 / 34 (38.24%)
occurrences (all)	56	6	17
Application site pruritus			
subjects affected / exposed	13 / 78 (16.67%)	3 / 38 (7.89%)	5 / 34 (14.71%)
occurrences (all)	17	4	7
Pyrexia			
subjects affected / exposed	4 / 78 (5.13%)	1 / 38 (2.63%)	2 / 34 (5.88%)
occurrences (all)	4	1	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 78 (5.13%)	1 / 38 (2.63%)	0 / 34 (0.00%)
occurrences (all)	4	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 78 (0.00%)	2 / 38 (5.26%)	0 / 34 (0.00%)
occurrences (all)	0	2	0

Skin and subcutaneous tissue disorders	Erythema			
	subjects affected / exposed	6 / 78 (7.69%)	0 / 38 (0.00%)	0 / 34 (0.00%)
	occurrences (all)	6	0	0
	Pruritus			
	subjects affected / exposed	31 / 78 (39.74%)	2 / 38 (5.26%)	2 / 34 (5.88%)
	occurrences (all)	3	2	2
Infections and infestations	Folliculitis			
	subjects affected / exposed	0 / 78 (0.00%)	2 / 38 (5.26%)	0 / 34 (0.00%)
	occurrences (all)	0	2	0
	Gastroenteritis			
	subjects affected / exposed	2 / 78 (2.56%)	2 / 38 (5.26%)	0 / 34 (0.00%)
	occurrences (all)	4	2	0
	Influenza			
	subjects affected / exposed	4 / 78 (5.13%)	1 / 38 (2.63%)	0 / 34 (0.00%)
	occurrences (all)	4	1	0
	Nasopharyngitis			
	subjects affected / exposed	6 / 78 (7.69%)	4 / 38 (10.53%)	1 / 34 (2.94%)
	occurrences (all)	8	4	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2022	Monthly UPT, INRS daily, Risk section

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported