Clinical trial results:
A Phase 2b/3, Randomized, Double-Blind, Placebo-Controlled, 2-Arm, Efficacy and Safety Study in Prurigo Nodularis with Nalbuphine ER Tablets for Pruritus Relief Through Itch Scratch Modulation (PRISM Study)

Summary

EudraCT number	2018-001219-53
Trial protocol	DE FR AT
Global end of trial date	24 February 2023

Results information

Result version number	v1 (current)
This version publication date	08 March 2026
First version publication date	08 March 2026

Trial information

Trial identification

Sponsor protocol code	TR11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03497975
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Trevi Therapeutics, Inc.
Sponsor organisation address	195 Church St, 16th Floor, New Haven, United States, 06510
Public contact	Paula Buckley, Trevi Therapeutics, Inc., +1 203304 2499, paula.buckley@trevitherapeutics.com
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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 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the anti-pruritic efficacy and safety of Nalbuphine Extended Release (ER) (NAL ER) tablets in Prurigo Nodularis. Subjects were randomized to NAL ER (or matching placebo) with the primary endpoint evaluation at Week 14. During the open label extension, subjects who received NAL ER were continued on NAL ER and subjects who received placebo would then shift to NALER.

Protection of trial subjects:

An independent Data Safety Monitoring Board (DSMB) periodically reviewed safety data. Subjects were closely monitored for safety. AEs were continuously evaluated throughout the study. Vital signs, locally reviewed and central cardiac core laboratory-read ECGs, physical examinations and clinical laboratory testing were conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 August 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 97
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 96
Country: Number of subjects enrolled	United States: 146
Worldwide total number of subjects	353
EEA total number of subjects	207

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)	224
From 65 to 84 years	129
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 70 sites in Germany, Poland, Austria, France and the United States from 07 August 2018 to 24 February 2023.

Pre-assignment

Screening details:

A total of 608 subjects were screened, out of which 353 subjects were randomized, and 344 subjects were treated with NAL ER and/or placebo.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	NAL ER

Arm description:

During the double-blind (DB) period, subjects were titrated over 2 weeks to NAL ER 162 mg, orally, twice daily (BID), followed by 162 mg, orally, BID, for 12 weeks. During the open label extension (OLE) period, subjects received a titration period of 2 weeks, and continued to receive NAL ER 162 mg, orally, BID, for 38 weeks in total.

Arm type	Experimental
Investigational medicinal product name	Nalbuphine
Investigational medicinal product code	NAL ER
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were titrated over 2 weeks to NAL ER 162 mg, BID, followed by 162 mg, BID, for 12 weeks in DB period and 38 weeks in OLE period.

Arm title	Placebo

Arm description:

During the DB period, subjects received a titration period of 2 weeks during which they received placebo to match the active titration period, followed by placebo, orally, BID, for 12 weeks. During the OLE period, subjects were titrated over 2 weeks to NAL ER 162 mg, orally, BID, which they received for 38 weeks (including titration).

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

Dosage and administration details:

Subjects received a titration period of 2 weeks during which they received placebo to match the active titration period, followed by placebo, BID, for 12 weeks in DB period.

Investigational medicinal product name	Nalbuphine
Investigational medicinal product code	NAL ER
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Subjects were titrated over 2 weeks to NAL ER 162 mg, BID, followed by 162 mg, BID, for 38 weeks in OLE period.

Number of subjects in period 1	NAL ER	Placebo
Started	173	180
mITT Analysis Set	168	176
Subjects Who Entered the OLE Period	107	144
Completed	71	80
Not completed	102	100
Withdrew Consent	34	35
Physician decision	4	5
Discontinued	42	39
Lost to follow-up	7	7
Reason not specified	15	14

Baseline characteristics

Reporting groups	
Reporting group title	NAL ER

Reporting group description:

During the double-blind (DB) period, subjects were titrated over 2 weeks to NAL ER 162 mg, orally, twice daily (BID), followed by 162 mg, orally, BID, for 12 weeks. During the open label extension (OLE) period, subjects received a titration period of 2 weeks, and continued to receive NAL ER 162 mg, orally, BID, for 38 weeks in total.

Reporting group title	Placebo

Reporting group description:

During the DB period, subjects received a titration period of 2 weeks during which they received placebo to match the active titration period, followed by placebo, orally, BID, for 12 weeks. During the OLE period, subjects were titrated over 2 weeks to NAL ER 162 mg, orally, BID, which they received for 38 weeks (including titration).

Reporting group values	NAL ER	Placebo	Total
Number of subjects	173	180	353
Age categorical Units: Subjects			
18-64 years	98	126	224
65-84 years	75	54	129
85 years and above	0	0	0
Gender categorical Units: Subjects			
Female	104	114	218
Male	69	66	135
Worst Itch - Numerical Rating Scale (WI-NRS) Score			
NRS is a patient related outcome (PRO) instrument to quantify the intensity of worst itching experienced for 24-hour period and can be applied and validated either with reference to the average itch or to the absolute worst itch (WI-NRS). WI-NRS is a set of boxes, one for each number, from 0 (no itching) to 10 (worst possible itching). Higher scores indicate worst itching experience. Number of subjects indicates subjects with data available for analysis at a specified timepoint.			
Units: score on a scale arithmetic mean standard deviation	±	±	-

Subject analysis sets	
Subject analysis set title	NAL ER
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified Intent-to-treat (mITT) population included all randomized subjects who received at least a single dose of IP. During the DB period, subjects were titrated over 2 weeks to NAL ER 162 mg, orally, BID, followed by 162 mg, orally, BID, for 12 weeks. During the OLE period, subjects received a titration period of 2 weeks, and continued to receive NAL ER 162 mg, orally, BID, for 38 weeks in total.

Subject analysis set title	Placebo
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified Intent-to-treat (mITT) population included all randomized subjects who received at least a single dose of IP. During the DB period, subjects received a titration period of 2 weeks during which they received placebo to match the active titration period, followed by placebo, orally, BID, for 12 weeks. During the OLE period, subjects were titrated over 2 weeks to NAL ER 162 mg, orally, BID,

which they received for 38 weeks (including titration).

Reporting group values	NAL ER	Placebo	
Number of subjects	167	176	
Age categorical Units: Subjects			
18-64 years 65-84 years 85 years and above			
Gender categorical Units: Subjects			
Female Male			
Worst Itch - Numerical Rating Scale (WI-NRS) Score			
NRS is a patient related outcome (PRO) instrument to quantify the intensity of worst itching experienced for 24-hour period and can be applied and validated either with reference to the average itch or to the absolute worst itch (WI-NRS). WI-NRS is a set of boxes, one for each number, from 0 (no itching) to 10 (worst possible itching). Higher scores indicate worst itching experience. Number of subjects indicates subjects with data available for analysis at a specified timepoint.			
Units: score on a scale arithmetic mean standard deviation	 8.637 ± 0.9115	 8.650 ± 0.8902	

End points

End points reporting groups

Reporting group title	NAL ER

Reporting group description:

During the double-blind (DB) period, subjects were titrated over 2 weeks to NAL ER 162 mg, orally, twice daily (BID), followed by 162 mg, orally, BID, for 12 weeks. During the open label extension (OLE) period, subjects received a titration period of 2 weeks, and continued to receive NAL ER 162 mg, orally, BID, for 38 weeks in total.

Reporting group title	Placebo

Reporting group description:

During the DB period, subjects received a titration period of 2 weeks during which they received placebo to match the active titration period, followed by placebo, orally, BID, for 12 weeks. During the OLE period, subjects were titrated over 2 weeks to NAL ER 162 mg, orally, BID, which they received for 38 weeks (including titration).

Subject analysis set title	NAL ER
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified Intent-to-treat (mITT) population included all randomized subjects who received at least a single dose of IP. During the DB period, subjects were titrated over 2 weeks to NAL ER 162 mg, orally, BID, followed by 162 mg, orally, BID, for 12 weeks. During the OLE period, subjects received a titration period of 2 weeks, and continued to receive NAL ER 162 mg, orally, BID, for 38 weeks in total.

Subject analysis set title	Placebo
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified Intent-to-treat (mITT) population included all randomized subjects who received at least a single dose of IP. During the DB period, subjects received a titration period of 2 weeks during which they received placebo to match the active titration period, followed by placebo, orally, BID, for 12 weeks. During the OLE period, subjects were titrated over 2 weeks to NAL ER 162 mg, orally, BID, which they received for 38 weeks (including titration).

Primary: Percentage of Subjects With ≥ 4- Point Decrease in 7-day Average Worst Itch - Numerical Rating Scale (WI-NRS) up to Week 14

End point title	Percentage of Subjects With ≥ 4- Point Decrease in 7-day Average Worst Itch - Numerical Rating Scale (WI-NRS) up to Week 14

End point description:

The NRS is a patient related outcome (PRO) instrument, designed to quantify the intensity of worst itching experienced during a 24-hour period, and can be applied and validated either with reference to the average itch or to the absolute worst itch (WI-NRS) over that 24-hour period. WI-NRS is a set of boxes, one for each number, from 0 (no itching) to 10 (worst possible itching). Higher scores indicate worst itching experience. Responder was defined as a subject with a ≥4-point decrease in the 7-day average WI-NRS from baseline to Week 14. The mITT population included all randomized subjects who received at least a single dose of IP. Number of subjects analyzed indicates number of subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Week 14

End point values	NAL ER	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	131		
Units: percentage of subjects				
number (not applicable)	24.24	14.50		

Statistical analyses

Statistical analysis title	NAL ER vs Placebo Matched to NAL ER
Comparison groups	NAL ER v Placebo
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0309 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	4.13

Notes:

[1] - Logistic regression model includes WI-NRS baseline score as a covariate, treatment and the study site (with pooling) as a fixed effect.

Secondary: Change From Baseline in Itch-related Quality of Life (ItchyQoL) Total Score at Week 14

End point title	Change From Baseline in Itch-related Quality of Life (ItchyQoL) Total Score at Week 14

End point description:

The ItchyQoL consists of 22 pruritus-specific items measuring how pruritus affects subject's QoL in the area of symptoms related to the itch condition (6 questions), functional limitations (7 questions), and emotions (9 questions). The subject scored each question never = 1, rarely = 2, sometimes = 3, often = 4, all the time = 5. The ItchyQoL total score were obtained as the sum of the 22 items ranging from 22 to 110, with higher score indicating worsening of pruritus. A negative change from baseline indicated improvement in the pruritus-related difficulties. The mITT population included all randomized subjects who received at least a single dose of IP. Number of subjects analyzed indicates number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 14

End point values	NAL ER	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	127		
Units: score on a scale				
arithmetic mean (standard deviation)	-17.4 (± 18.01)	-8.8 (± 17.15)		

Statistical analyses

Statistical analysis title	NAL ER vs Placebo Matched to NAL ER
Comparison groups	NAL ER v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [2]
Method	Mixed Model for Repeated Measurements
Parameter estimate	Difference in LS Mean
Point estimate	-7.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.82
upper limit	-3.3
Variability estimate	Standard error of the mean
Dispersion value	1.91

Notes:

[2] - Repeated measures model with the fixed effects of treatment, visit, treatment by visit interaction and baseline ItchyQoL value. An unstructured covariance matrix is used.

Secondary: Change From Baseline in Prurigo Activity Score (PAS) Assessed by the Percentage of Subjects With 1-Category Improvement in the Percentage of Pruriginous Lesions With Excoriations/Crusts (Item 5a) at Week 14

End point title	Change From Baseline in Prurigo Activity Score (PAS) Assessed by the Percentage of Subjects With 1-Category Improvement in the Percentage of Pruriginous Lesions With Excoriations/Crusts (Item 5a) at Week 14

End point description:

PAS consists of 5 quantitative/qualitative measurements related to examination of skin:Type; number;distribution;quantitative number of lesions in a body part;activity.Prurigo lesion activity is recorded as a stage (0 to 4), based on percentage of overall lesions with relevant characteristic.Three types of PAS responders defined one for each of these items:Pruriginous lesions with excoriations/crusts (item 5a);Healed lesions (item 5b);Number of lesions (item 2).Pruriginous lesions with excoriations/crusts (item 5a) was recorded from 0 to 4;where 0=0-25%,1=26-50%,2=51-75%,3=76-90%,4=91-100%.Higher score=more number of pruriginous lesions with excoriations/crusts.A responder=a subject who has at least 1-category improvement in the relevant item from baseline to Week 14.Baseline=last non-missing evaluation (repeated,unscheduled assessment) taken prior to or on the date of first dose. Subjects from mITT population were included.Number analyzed=number

End point type	Secondary

End point timeframe:

Baseline, Week 14

End point values	NAL ER	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	146		
Units: percentage of subjects				
number (not applicable)	54.5	41.1		

Statistical analyses

Statistical analysis title	NAL ER vs Placebo Matched to NAL ER
Comparison groups	NAL ER v Placebo
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0179 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	3.07

Notes:

[3] - Logistic regression model includes PAS (Item 5a) baseline score as a covariate, treatment as a fixed effect and the study site (with pooling) as a fixed effect.

Secondary: Change From Baseline in Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance Short Form 8a at Week 14

End point title	Change From Baseline in Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance Short Form 8a at Week 14

End point description:

PROMIS Sleep Disturbance Short Form 8a questionnaire is a tool for assessing sleep with 8 questions which measures sleep in past 7 days.There is 1 broad sleep quality question with options:"very poor","poor","fair","good",and "very good".Left 7 questions are answered with:"not at all","a little bit","somewhat","quite a bit",and"very much".Lowest possible raw score=8;highest possible raw score=40.T-score rescales raw score into a standardized score with mean of 50,standard deviation of 10 derived from general population.Lowest possible T-score=28.9;highest possible T-score=76.6.Higher T-score=more of concept measured,higher T-Score=worse sleep disturbance.Scores <55=normal limits,55-60=mild,61-70=moderate,and >70=severe sleep disturbance.Baseline=last non-missing evaluation taken prior to or on the date of first dose of study medication.Negative change from baseline=better sleep.Subjects from mITT population were included.Number of subjects analyzed=subjects evaluable for this endpoint

End point type	Secondary

End point timeframe:

Baseline, Week 14

End point values	NAL ER	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	127		
Units: T-score				
arithmetic mean (standard deviation)	-9.5 (± 10.01)	-4.5 (± 8.44)		

Statistical analyses

Statistical analysis title	NAL ER vs Placebo Matched to NAL ER
Comparison groups	NAL ER v Placebo
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Mixed Model for Repeated Measurements
Parameter estimate	Difference in LS Mean
Point estimate	-4.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.55
upper limit	-2.31
Variability estimate	Standard error of the mean
Dispersion value	1.08

Notes:

[4] - Repeated measures model with the fixed effects of treatment, visit, treatment by visit interaction and baseline PROMIS value. An unstructured covariance matrix is used.

Secondary: Change From Baseline in 7-Day Average WI-NRS to Week 14

End point title	Change From Baseline in 7-Day Average WI-NRS to Week 14

End point description:

The NRS is a PRO instrument, designed to quantify the intensity of worst itching experienced during a 24-hour period, and can be applied and validated either with reference to the average itch or to the absolute worst itch (WI-NRS) over that 24-hour period. WI-NRS is a set of boxes, one for each number, from 0 (no itching) to 10 (worst possible itching). Higher scores indicate worst itching experience. Baseline WI-NRS value was calculated as the arithmetic mean of the WI-NRS values (minimum of 5 required) taken for eligibility review by site at the time of randomization. A negative change from baseline indicates improvement in symptoms. The mITT population included all randomized subjects who received at least a single dose of IP. Number of subjects analyzed indicates number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 14

End point values	NAL ER	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	131		
Units: score on a scale				
arithmetic mean (standard deviation)	-2.5 (± 2.36)	-1.6 (± 2.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PAS Assessed by the Percentage of Subjects With 1-Category Improvement in the Percentage of Healed Lesions (Item 5b) at Week 14

End point title	Change From Baseline in PAS Assessed by the Percentage of Subjects With 1-Category Improvement in the Percentage of Healed Lesions (Item 5b) at Week 14

End point description:

PAS consists of 5 quantitative/qualitative measurements related to skin-Type;number;distribution; quantitative number of lesions in body part;activity.Prurigo lesion activity is recorded as stage (0 to 4), based on percentage of overall lesions with relevant characteristic.Three types of PAS responders are defined:Pruriginous lesions with excoriations/crusts (item 5a);Healed lesions (item 5b);Number of lesions (item 2).Prurigo lesions (item 5b),where 0=100%,1=75-99%,2=50-74%,3=25-49%,4=0-24% healed pruriginous lesions.Lower score=more number of healed lesions.Responder=subject with at least 1-category improvement from baseline to Week 14.Baseline=the last non-missing evaluation (including repeated,unscheduled assessments) taken prior to or on the date of first dose of treatment.Negative change from baseline=higher number of healed lesions. The mITT population included all randomized subjects who received at least a single dose of IP.

End point type	Secondary

End point timeframe:

Baseline, Week 14

End point values	NAL ER	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	176		
Units: percentage of subjects				
number (not applicable)	39.3	34.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PAS Assessed by the Percentage of Subjects With 1-Category Improvement in the Percentage of Lesions (Item 2) at Week 14

End point title	Change From Baseline in PAS Assessed by the Percentage of Subjects With 1-Category Improvement in the Percentage of Lesions (Item 2) at Week 14

End point description:

PAS consists of 5 quantitative/qualitative measurements of skin-Type;number;distribution;quantitative number of lesions in body part;activity.Prurigo lesion activity is recorded as stage (0 to 4) based on percentage of overall lesions with relevant characteristic.Three types of PAS responders are defined:Pruriginous lesions with excoriations/crusts (item 5a);Healed lesions (item 5b);Number of lesions (item 2).Prurigo lesion activity is recorded as a stage (0-4),based on the percentage of overall lesions with the relevant characteristic.Lower score=less number of lesions.Responder=subject with at least 1-category improvement from baseline to Week 14.Baseline=last non-missing evaluation (including repeated,unscheduled assessment) taken prior to or on the date of first dose of study medication.Negative change from baseline=lower number of lesions. The mITT population included all randomized subjects who received at least a single dose of IP.

End point type	Secondary

End point timeframe:

Baseline, Week 14

End point values	NAL ER	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	176		
Units: percentage of subjects				
number (not applicable)	25.0	18.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Investigator Global Assessment-Prurigo Nodularis (IGA-PN) Assessed by the Percentage of Subjects With 1-Category Improvement in Activity at Week 14

End point title	Change From Baseline in Investigator Global Assessment-Prurigo Nodularis (IGA-PN) Assessed by the Percentage of Subjects With 1-Category Improvement in Activity at Week 14

End point description:

IGA-PN collects investigator global assessment status of PN skin lesions.It uses a 5-category scale (scoring 0-4) to describe the status of 2 aspects of disease:Activity (amount of excoriation and crusting associated with the prurigo lesions),Stage (the quantitative presence and proportion of flattening of the lesions).Excoriation/crusting activity on the surface (PN-Activity) considers number of PN lesion with excoriations and crusts on the top,0=clear (No nodules),1=small number,2=minority of nodules,3=most nodules,4=severe (vast majority of nodules). Higher number=severe status of PN skin lesions.IGA-PN responder for activity=subject with at a least 1-category improvement in the respective score from baseline to Week 14.Baseline=last non-missing evaluation (including repeated,unscheduled assessment) taken prior to or on the date of first dose.Subjects in the mITT population were included.Number of subjects analyzed=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 14

End point values	NAL ER	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	146		
Units: percentage of subjects				
number (not applicable)	57.1	41.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in IGA-PN Assessed by the Percentage of Subjects With 1-Category Improvement in Stage at Week 14

End point title	Change From Baseline in IGA-PN Assessed by the Percentage of Subjects With 1-Category Improvement in Stage at Week 14

End point description:

IGA-PN collects investigator global assessment status of PN skin lesions.IGA-PN uses a 5-category scale(scoring 0-4) to describe:Activity(amount of excoriation,crusting of prurigo lesions),Stage(quantitative presence,proportion of flattening of lesions),where 0=clear(No nodules),1=Rare,flattened lesions,with no more than single dome-shaped palpable nodules(1-5 nodules),2=Few,mostly flattened lesions,with small number of dome-shaped palpable nodules(6-19 nodules,3=Many lesions,partially flattened and dome-shaped palpable nodules (20-100 nodules),4=Abundant lesions,majority are dome-shaped palpable nodules(>100 nodules).Higher number=more lesions.Responder=subject with at least 1-category improvement from baseline to Week 14.Baseline=last non-missing evaluation(repeated,unscheduled assessments)taken prior to or on the date of first dose. Subjects in the mITT population were included. Number of subjects analyzed=subjects

End point type	Secondary

End point timeframe:

Baseline, Week 14

End point values	NAL ER	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	146		
Units: percentage of subjects				
number (not applicable)	43.8	32.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Having a Patient Benefit Index, Pruritus Version (PBI-P) Score of ≥1 at Week 14

End point title	Percentage of Subjects Having a Patient Benefit Index, Pruritus Version (PBI-P) Score of ≥1 at Week 14

End point description:

PBI-P is an instrument that measures subject-defined treatment objectives,benefits acquired during the treatment.During,after therapy, subject completes a matched “on-treatment” Treatment Benefits questionnaire and rates the extent to which the treatment objectives were achieved.It consists of 27

multiple choice questions that can be answered "not at all","somewhat","moderately","quite","very".Score is computed according to the score obtained for patient needs questionnaire (PNQ),patient benefit questionnaire(PBQ).Score may only be computed if the subject has provided valid data on PNQ,PBQ for at least 75% of the treatment goals i.e. for at least 21 of the 27 items.Total score=0-135. Higher score=more benefits received.Responses "does/did not apply","question answered" are considered valid values when counting the number of non-missing responses. Subjects in the mITT population were included. Number of subjects analyzed=subjects

End point type	Secondary

End point timeframe:

At Week 14

End point values	NAL ER	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	95		
Units: percentage of subjects				
number (not applicable)	100.0	100.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Experienced TEAEs, Serious TEAEs, and Discontinued From Study Drug Due to TEAEs in DB Period

End point title	Number of Subjects Who Experienced TEAEs, Serious TEAEs, and Discontinued From Study Drug Due to TEAEs in DB Period

End point description:

AE is untoward medical occurrence in subject who administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the study drug.AE can be any unfavorable,unintended sign, symptom,disease temporally associated with the use of a medicinal product,whether or not considered related to it.Serious adverse event (SAE) is any untoward medical occurrence that resulted in any of the following: death;life threatening;persistent/significant disability/incapacity;initial or prolonged inpatient hospitalization;congenital anomaly/birth defect or was otherwise considered medically important.DB period TEAEs=AEs that either start,worsen in severity on or after the first DB dose and prior to the first extension titration dose of study medication in the OLE period.TEAEs included both serious,non-serious TEAEs. The safety population included all randomized subjects who received at least a single dose of IP.

End point type	Secondary

End point timeframe:

Baseline up to Week 14

End point values	NAL ER	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	176		
Units: subjects				
Subjects with TEAEs	136	106		
Subjects with Serious TEAEs	9	8		
Subjects who Discontinued Study Drug Due to TEAEs	53	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Experienced TEAEs, Serious TEAEs, and Discontinued From Study Drug Due to TEAEs in OLE Period

End point title	Number of Subjects Who Experienced TEAEs, Serious TEAEs, and Discontinued From Study Drug Due to TEAEs in OLE Period

End point description:

AE is any untoward medical occurrence in subject who administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the study drug.AE can be any unfavorable,unintended sign, symptom,disease temporally associated with the use of a medicinal product, whether or not considered related to it.Serious adverse event (SAE) is any untoward medical occurrence that resulted in any of the following: death;life threatening;persistent/significant disability/incapacity;initial or prolonged inpatient hospitalization;congenital anomaly/birth defect or was otherwise considered medically important.OLE period TEAEs are defined as AEs that either start or worsen in severity on or after the first extension titration dose of study medication.TEAEs included both serious & non-serious TEAEs.Safety population included all randomized subjects who received at least a single dose of IP. Number of subjects analyzed=number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From Week 14 up to Week 56

End point values	NAL ER	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	144		
Units: subjects				
Subjects with TEAEs	84	116		
Subjects with Serious TEAEs	7	7		
Subjects Who Discontinued Study Drug Due to TEAEs	8	30		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
DB Period: Baseline up to Week 14; OLE Period: From Week 14 to Week 56	
Adverse event reporting additional description:	
The safety population included all randomized subjects who received at least a single dose of IP.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	NAL ER (DB Period)
Reporting group description:	
During the DB period, subjects were titrated over 2 weeks to NAL ER 162 mg orally BID, followed by 162 mg orally BID for 12 weeks.	
Reporting group title	Placebo (DB Period)
Reporting group description:	
During the DB period, subjects received a titration period of 2 weeks during which they received placebo to match the active titration period, followed by placebo, orally, BID, for 12 weeks.	
Reporting group title	Prior NAL ER (OLE Period)
Reporting group description:	
During the OLE period, subjects received a titration period of 2 weeks, and continued to receive NAL ER 162 mg, orally, BID, for 38 weeks in total.	
Reporting group title	Prior Placebo (OLE Period)
Reporting group description:	
During the OLE period, subjects were titrated over 2 weeks to NAL ER 162 mg, orally, BID, which they received for 38 weeks (including titration).	

Serious adverse events	NAL ER (DB Period)	Placebo (DB Period)	Prior NAL ER (OLE Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 168 (5.36%)	8 / 176 (4.55%)	7 / 107 (6.54%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serous cystadenocarcinoma ovary			

subjects affected / exposed	0 / 168 (0.00%)	1 / 176 (0.57%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 168 (0.00%)	1 / 176 (0.57%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dissociation			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
SARS-CoV-2 test positive			

subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 168 (0.60%)	0 / 176 (0.00%)	0 / 107 (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
Ligament rupture			
subjects affected / exposed	1 / 168 (0.60%)	0 / 176 (0.00%)	0 / 107 (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
Ligament sprain			
subjects affected / exposed	1 / 168 (0.60%)	0 / 176 (0.00%)	0 / 107 (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
Overdose			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 168 (0.00%)	1 / 176 (0.57%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypertensive heart disease			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 168 (0.60%)	0 / 176 (0.00%)	0 / 107 (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
Dysarthria			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine with aura			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	1 / 168 (0.60%)	0 / 176 (0.00%)	0 / 107 (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
Vision blurred			

subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurodermatitis			
subjects affected / exposed	1 / 168 (0.60%)	1 / 176 (0.57%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			
subjects affected / exposed	1 / 168 (0.60%)	1 / 176 (0.57%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 176 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			

subjects affected / exposed	1 / 168 (0.60%)	0 / 176 (0.00%)	0 / 107 (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
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 176 (0.00%)	0 / 107 (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
Sacroiliitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 176 (0.00%)	0 / 107 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 176 (0.57%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	1 / 168 (0.60%)	0 / 176 (0.00%)	0 / 107 (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
Erysipelas			
subjects affected / exposed	1 / 168 (0.60%)	0 / 176 (0.00%)	0 / 107 (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
Postoperative wound infection			
subjects affected / exposed	0 / 168 (0.00%)	1 / 176 (0.57%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 176 (0.00%)	0 / 107 (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

Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 168 (0.00%)	1 / 176 (0.57%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Prior Placebo (OLE Period)		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 144 (4.86%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Serous cystadenocarcinoma ovary			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			

Confusional state				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Disorientation				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dissociation				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
SARS-CoV-2 test positive				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Ankle fracture				
subjects affected / exposed	0 / 144 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament rupture				
subjects affected / exposed	0 / 144 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament sprain				
subjects affected / exposed	0 / 144 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Spinal compression fracture			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal fracture			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive heart disease			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dysarthria			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Migraine with aura			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vision blurred			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neurodermatitis			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pruritus			

subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ureterolithiasis			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sacroiliitis			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Empyema			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Postoperative wound infection			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 144 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	NAL ER (DB Period)	Placebo (DB Period)	Prior NAL ER (OLE Period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	112 / 168 (66.67%)	58 / 176 (32.95%)	49 / 107 (45.79%)
Injury, poisoning and procedural complications			
Medication error			
subjects affected / exposed	4 / 168 (2.38%)	6 / 176 (3.41%)	11 / 107 (10.28%)
occurrences (all)	4	6	12
Nervous system disorders			
Dizziness			
subjects affected / exposed	53 / 168 (31.55%)	6 / 176 (3.41%)	5 / 107 (4.67%)
occurrences (all)	73	9	5
Headache			
subjects affected / exposed	26 / 168 (15.48%)	14 / 176 (7.95%)	8 / 107 (7.48%)
occurrences (all)	46	17	10
Somnolence			
subjects affected / exposed	25 / 168 (14.88%)	6 / 176 (3.41%)	3 / 107 (2.80%)
occurrences (all)	30	10	3
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	23 / 168 (13.69%)	10 / 176 (5.68%)	5 / 107 (4.67%)
occurrences (all)	32	11	5
Treatment noncompliance			
subjects affected / exposed	4 / 168 (2.38%)	3 / 176 (1.70%)	8 / 107 (7.48%)
occurrences (all)	4	3	10
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	26 / 168 (15.48%)	7 / 176 (3.98%)	4 / 107 (3.74%)
occurrences (all)	32	7	4
Diarrhoea			
subjects affected / exposed	7 / 168 (4.17%)	5 / 176 (2.84%)	10 / 107 (9.35%)
occurrences (all)	7	5	10
Nausea			
subjects affected / exposed	52 / 168 (30.95%)	16 / 176 (9.09%)	13 / 107 (12.15%)
occurrences (all)	69	20	15
Vomiting			
subjects affected / exposed	19 / 168 (11.31%)	6 / 176 (3.41%)	3 / 107 (2.80%)
occurrences (all)	28	9	4
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	9 / 168 (5.36%)	0 / 176 (0.00%)	3 / 107 (2.80%)
occurrences (all)	9	0	3
Pruritus			
subjects affected / exposed	9 / 168 (5.36%)	9 / 176 (5.11%)	5 / 107 (4.67%)
occurrences (all)	11	10	8
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 168 (2.38%)	2 / 176 (1.14%)	6 / 107 (5.61%)
occurrences (all)	4	2	6

Non-serious adverse events	Prior Placebo (OLE Period)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	95 / 144 (65.97%)		
Injury, poisoning and procedural complications			

Medication error			
subjects affected / exposed	14 / 144 (9.72%)		
occurrences (all)	23		
Nervous system disorders			
Dizziness			
subjects affected / exposed	30 / 144 (20.83%)		
occurrences (all)	35		
Headache			
subjects affected / exposed	22 / 144 (15.28%)		
occurrences (all)	39		
Somnolence			
subjects affected / exposed	19 / 144 (13.19%)		
occurrences (all)	23		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 144 (12.50%)		
occurrences (all)	23		
Treatment noncompliance			
subjects affected / exposed	8 / 144 (5.56%)		
occurrences (all)	12		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	11 / 144 (7.64%)		
occurrences (all)	15		
Diarrhoea			
subjects affected / exposed	15 / 144 (10.42%)		
occurrences (all)	15		
Nausea			
subjects affected / exposed	44 / 144 (30.56%)		
occurrences (all)	60		
Vomiting			
subjects affected / exposed	20 / 144 (13.89%)		
occurrences (all)	22		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			

subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	5 / 144 (3.47%) 5 6 / 144 (4.17%) 8		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 3 / 144 (2.08%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 October 2018	The following changes were made as per amendment 1: • Addressed comments by Health Authority reviewers which identified items requiring further clarification or precision. • Incorporated suggestions from Investigators based on their experiences with practical implementation of the protocol. • Clarified study procedures. • Clarified ambiguities in the previous version. • Addressed ambiguities regarding safety procedures and safety assessments by clarifying the relevant safety definitions and assessments.
14 March 2019	The following changes were made as per amendment 2: • Addressed comments by Ethics Committees in Austria and Germany which proposed modification to the concomitant medication guidance for the study. • Incorporated suggestions from Investigators based on their experiences with practical implementation of the protocol. • Clarified study procedures. • Clarified ambiguities in the previous version. • Incorporated revised statistical methodology for consistency with statistical analysis plan in development based on additional statistical consultation.
22 January 2020	The following changes were made as per amendment 3: • Incorporated Administrative Clarification Memo dated 16 July, 2019 • Incorporated Administrative Clarification Memo dated 7 November, 2019 • Clarified the intention and/or execution of various study procedures. • Clarified procedural ambiguities in the previous version.

04 August 2020	The following changes were made as per amendment 4: • Updated the target enrolment of study subjects from 240 to 360, based on the DSMB recommendations after reviewing results from the pre-specified Sample Size Re-Estimation (SSRE). In that analysis, the Conditional Power fell within the 'promising zone' as defined in the reference Mehta and Pocock33 publication; the increase required in the 'promising zone' was pre-specified as 360. • Refined the exclusion criteria related to the ECG assessments of the QTcF based on advice from the consultant Cardiologist who is a recognized arrythmia expert. • Clarified text that washout during screening should be completed prior to the start of the WI- NRS collection. This has been the requirement throughout prior study conduct but the specific language has been confusing to sites. This confusion was primarily introduced by textual changes that inadvertently dropped the phrase 'WI-NRS collection' from the longer 'screening period WI-NRS collection" in earlier protocol revisions. • Clarified study procedures, and ambiguities noted across previous protocol versions, including ambiguity regarding the specifications for medication washout periods in relationship to the screening period and or the screening WI-NRS collection. • Formalized and integrated into the Study Protocol document the actual changes in the Operational implementation of the study that occurred due to the initial imposition of COVID- 19 Pandemic-related limitations on in-person study visits. These were previously documented and submitted to Health Authorities in real time as "COVID-19 Administrative Memorandum" numbers 1 and 2, dated April 1, 2020 and April 23, 2020, respectively.

05 March 2021	The following changes were made as per amendment 5: • Deleted exclusion criterion #18 to permit enrollment of subjects who have had prior exposure to dupilumab or nemolizumab. As per Exclusion Criterion #17, eligibility still requires a minimal period of 3 months with no exposure to either dupilumab or nemolizumab immediately prior to enrollment in TR11. • Enabled co-enrollment in TR11 for potential subjects who may also be participating in the long-term safety follow-up period of a COVID-19 vaccine study so long as: 1) they have completed the full vaccine series; 2) that specific vaccine has been approved via an Emergency Use Authorization or comparable relevant Health Authority assessment in the country where enrollment takes place; and 3) the concomitant vaccine safety follow-up study permits co-enrollment. • The additional text updates are all considered to be Operational clarifications in response to key questions from site staff and are described in the table below. • Corrected a typographic error in the body of the protocol for inclusion criterion #5. In the V5 version of the protocol the Synopsis text was updated correctly, but that update was accidentally omitted in Section 9.5.1 in the body of the protocol. The current change provides internal consistency between the Synopsis and Section 9.5.1. • Addition of clarifications regarding the eligibility check prior to randomization, and the specific instruction that the final WINRS score entry for confirming eligibility should be performed on the day of the baseline visit and prior to dosing. • Clarified the specific 'lesion healing' criterion to be used for assessing whether a subject is eligible to consider dose reduction at Weeks 28, 32 and 36 by specifically referencing the Prurigo Activity Score Item 5b.
21 July 2021	The following changes were made as per amendment 6: • Updated the inclusion criteria 6 to remove "non-sedating" so that it is consistent with the change allowing sedating antidepressants. Duration at stable dose also changes to coincide with allowed changes for sedating antidepressants. • Updated the exclusion criteria to eliminate systemic antihistamines as excluded and add that the subject must be on a stable dose. • Updated the exclusion criteria to eliminate sedating antidepressants as excluded. • Updated Table 3 to revise exclusion information for systemic antihistamines, sedating antidepressants, and for medicines with a known risk for Torsade de Pointes. • Provided clarification on the QTcF values to prevent exclusion of subjects who present with Right Bundle Branch block • Allowed drugs previously not allowed due to known risk for Torsade de Pointes as long as the subject has been on a stable dose for at least 4 weeks prior to screening. Elimination of exclusion criteria #34 as it is no longer required.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported