



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Nemolizumab (CD14152) in Subjects with Moderate-to-Severe Atopic Dermatitis

Summary

EudraCT number	2019-001887-31
Trial protocol	LV GB DE LT NL AT CZ PL
Global end of trial date	11 August 2022

Results information

Result version number	v1 (current)
This version publication date	02 October 2024
First version publication date	02 October 2024

Trial information

Trial identification

Sponsor protocol code	RD.06.SPR.118161
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03985943
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 117122

Notes:

Sponsors

Sponsor organisation name	Galderma S.A.
Sponsor organisation address	Zahlerweg 10, ZUG, Switzerland, 6300
Public contact	Clinical Trial Information Desk, Galderma S.A., CTA.Coordinator@galderma.com
Scientific contact	Clinical Trial Information Desk, Galderma S.A., CTA.Coordinator@galderma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001624-PIP01-14
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	11 August 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the efficacy and safety of Nemolizumab (CD14152) after a 16-week treatment period in adult and adolescent subjects with moderate-to-severe atopic dermatitis (AD) not adequately controlled with topical treatments.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulation.

Background therapy:

Subjects received topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) as background therapy.

Evidence for comparator: -

Actual start date of recruitment	27 June 2019
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	Netherlands: 7
Country: Number of subjects enrolled	Poland: 190
Country: Number of subjects enrolled	Spain: 46
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Austria: 29
Country: Number of subjects enrolled	Czechia: 64
Country: Number of subjects enrolled	Germany: 90
Country: Number of subjects enrolled	Latvia: 28
Country: Number of subjects enrolled	Lithuania: 10
Country: Number of subjects enrolled	Australia: 54
Country: Number of subjects enrolled	Canada: 102
Country: Number of subjects enrolled	New Zealand: 13
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 83
Country: Number of subjects enrolled	United States: 209
Worldwide total number of subjects	941
EEA total number of subjects	464

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)	134
Adults (18-64 years)	768
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 177 active sites in Australia, Austria, Canada, Czech Republic, Germany, Great Britain, Korea, Latvia, Lithuania, Netherlands, New Zealand, Poland, Spain and the United States from 27 June 2019 to 11 August 2022.

Pre-assignment

Screening details:

Total of 941 randomized 2:1 to receive either nemolizumab or placebo. At Week 16, 272 nemolizumab responders re-randomized to receive nemolizumab Q4W, nemolizumab Q8W, or placebo during Maintenance Period. 100 subjects received placebo in Initial Treatment, responded to placebo at Week 16, re-assigned to placebo and continued to receive placebo Q4W.

Period 1

Period 1 title	Initial Treatment(Day 1-Week 16 Predose)
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	Initial Treatment Period: Placebo

Arm description:

Subjects received placebo via 2 subcutaneous (SC) injections at Day 1, thereafter, every 4 weeks (Q4W) at Weeks 4, 8, and 12 by a single SC injection during Initial Treatment Period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Nemolizumab matched Placebo

Arm title	Initial Treatment Period: Nemolizumab 30 mg
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Arm description:

Subjects received nemolizumab 30 mg via 2 SC injections at Day 1, thereafter, Q4W at Weeks 4, 8, and 12 by a single SC injection during Initial Treatment Period.

Arm type	Experimental
Investigational medicinal product name	Nemolizumab
Investigational medicinal product code	
Other name	CD14152
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Nemolizumab 30 mg via 2 SC injections on Day 1 followed by single SC injection.

Number of subjects in period 1	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg
Started	321	620
Treated	321	620
Completed	296	560
Not completed	25	60
Physician decision	-	1
Subjects request	11	25
Adverse event, non-fatal	9	9
Randomized but not treated	-	4
Pregnancy	-	2
Lost to follow-up	-	10
Lack of efficacy	2	5
Protocol deviation	3	4

Period 2

Period 2 title	Maintenance Period (Week 16-Week 48)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Maintenance Period: Nemolizumab 30 mg Q4W to Q4W

Arm description:

Subjects who received nemolizumab, Q4W during Initial Treatment Period and were clinical responders (defined as subjects with an IGA of 0 (clear) or 1 (almost clear) or a $\geq 75\%$ improvement in EASI from Baseline) at Week 16 received nemolizumab 30 mg, every 4 weeks (Q4W) at Weeks 16, 20, 24, 28, 32, 36, 40, and 44 by a single SC injection during Maintenance Period.

Arm type	Experimental
Investigational medicinal product name	Nemolizumab
Investigational medicinal product code	
Other name	CD14152
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Nemolizumab 30 mg

Arm title	Maintenance Period: Nemolizumab 30 mg Q4W to Q8W
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Arm description:

Subjects who received nemolizumab, Q4W during Initial Treatment Period and were clinical responders (defined as subjects with an IGA of 0 (clear) or 1 (almost clear) or a $\geq 75\%$ improvement in EASI from Baseline) at Week 16 received nemolizumab 30 mg, Q8W at Weeks 16, 24, 32, and 40 by a single SC injection during Maintenance Period.

Arm type	Experimental
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Investigational medicinal product name	Nemolizumab
Investigational medicinal product code	
Other name	CD14152
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Nemolizumab 30 mg	
Arm title	Maintenance Period: Nemolizumab 30 mg Q4W to Placebo Q4W

Arm description:

Subjects who received nemolizumab, Q4W during Initial Treatment Period and were clinical responders (defined as subjects with an IGA of 0 [clear] or 1 [almost clear] or a $\geq 75\%$ improvement in EASI from Baseline) at Week 16 received placebo, Q4W at Weeks 16, 20, 24, 28, 32, 36, 40, and 44 by a single SC injection during Maintenance Period.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Nemolizumab matched Placebo

Arm title	Maintenance Period: Placebo Q4W Re-assigned to Placebo Q4W
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Arm description:

Subjects who received placebo, Q4W during Initial Treatment Period and were clinical responders (defined as subjects with an IGA of 0 [clear] or 1 [almost clear] or a $\geq 75\%$ improvement in EASI from Baseline) at Week 16 received placebo, Q4W at Weeks 16, 20, 24, 28, 32, 36, 40, and 44 by a single SC injection during Maintenance Period.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Nemolizumab matched Placebo

Number of subjects in period 2 ^[1]	Maintenance Period: Nemolizumab 30 mg Q4W to Q4W	Maintenance Period: Nemolizumab 30 mg Q4W to Q8W	Maintenance Period: Nemolizumab 30 mg Q4W to Placebo Q4W
Started	90	91	91
Completed	76	79	69
Not completed	14	12	22
Consent withdrawn by subject	6	4	5
Physician decision	2	1	1
Adverse event, non-fatal	1	3	1
Not specified	-	-	1
Lost to follow-up	-	1	1

Lack of efficacy	4	3	12
Protocol deviation	1	-	1

Number of subjects in period 2^[1]	Maintenance Period: Placebo Q4W Re- assigned to Placebo Q4W
Started	100
Completed	82
Not completed	18
Consent withdrawn by subject	9
Physician decision	2
Adverse event, non-fatal	1
Not specified	1
Lost to follow-up	1
Lack of efficacy	4
Protocol deviation	-

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: Subjects who received nemolizumab, Q4W during Initial Treatment Period and were clinical responders at Week 16 were rerandomized during Maintenance Period. Subjects who received placebo, Q4W during Initial Treatment Period and were clinical responders at Week 16, were re-assigned during Maintenance Period.

Baseline characteristics

Reporting groups

Reporting group title	Initial Treatment Period: Placebo
Reporting group description:	
Subjects received placebo via 2 subcutaneous (SC) injections at Day 1, thereafter, every 4 weeks (Q4W) at Weeks 4, 8, and 12 by a single SC injection during Initial Treatment Period.	
Reporting group title	Initial Treatment Period: Nemolizumab 30 mg
Reporting group description:	
Subjects received nemolizumab 30 mg via 2 SC injections at Day 1, thereafter, Q4W at Weeks 4, 8, and 12 by a single SC injection during Initial Treatment Period.	

Reporting group values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg	Total
Number of subjects	321	620	941
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	33.3	33.5	
standard deviation	± 15.61	± 15.93	-
Gender categorical Units: Subjects			
Female	144	297	441
Male	177	323	500
Ethnicity Units: Subjects			
Hispanic or Latino	32	64	96
Not Hispanic or Latino	288	552	840
Unknown or Not Reported	1	4	5
Race Units: Subjects			
Asian	51	117	168
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	18	36	54
White	244	451	695
More than one race	4	10	14
Unknown or Not Reported	1	3	4
American Indian or Alaska Native	3	2	5

End points

End points reporting groups

Reporting group title	Initial Treatment Period: Placebo
Reporting group description: Subjects received placebo via 2 subcutaneous (SC) injections at Day 1, thereafter, every 4 weeks (Q4W) at Weeks 4, 8, and 12 by a single SC injection during Initial Treatment Period.	
Reporting group title	Initial Treatment Period: Nemolizumab 30 mg
Reporting group description: Subjects received nemolizumab 30 mg via 2 SC injections at Day 1, thereafter, Q4W at Weeks 4, 8, and 12 by a single SC injection during Initial Treatment Period.	
Reporting group title	Maintenance Period: Nemolizumab 30 mg Q4W to Q4W
Reporting group description: Subjects who received nemolizumab, Q4W during Initial Treatment Period and were clinical responders (defined as subjects with an IGA of 0 (clear) or 1 (almost clear) or a $\geq 75\%$ improvement in EASI from Baseline) at Week 16 received nemolizumab 30 mg, every 4 weeks (Q4W) at Weeks 16, 20, 24, 28, 32, 36, 40, and 44 by a single SC injection during Maintenance Period.	
Reporting group title	Maintenance Period: Nemolizumab 30 mg Q4W to Q8W
Reporting group description: Subjects who received nemolizumab, Q4W during Initial Treatment Period and were clinical responders (defined as subjects with an IGA of 0 (clear) or 1 (almost clear) or a $\geq 75\%$ improvement in EASI from Baseline) at Week 16 received nemolizumab 30 mg, Q8W at Weeks 16, 24, 32, and 40 by a single SC injection during Maintenance Period.	
Reporting group title	Maintenance Period: Nemolizumab 30 mg Q4W to Placebo Q4W
Reporting group description: Subjects who received nemolizumab, Q4W during Initial Treatment Period and were clinical responders (defined as subjects with an IGA of 0 [clear] or 1 [almost clear] or a $\geq 75\%$ improvement in EASI from Baseline) at Week 16 received placebo, Q4W at Weeks 16, 20, 24, 28, 32, 36, 40, and 44 by a single SC injection during Maintenance Period.	
Reporting group title	Maintenance Period: Placebo Q4W Re-assigned to Placebo Q4W
Reporting group description: Subjects who received placebo, Q4W during Initial Treatment Period and were clinical responders (defined as subjects with an IGA of 0 [clear] or 1 [almost clear] or a $\geq 75\%$ improvement in EASI from Baseline) at Week 16 received placebo, Q4W at Weeks 16, 20, 24, 28, 32, 36, 40, and 44 by a single SC injection during Maintenance Period.	
Subject analysis set title	Initial Treatment Period: Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received placebo via 2 SC injections at Day 1, thereafter, Q4W at Weeks 4, 8, and 12 by a single SC injection during Initial Treatment Period.	
Subject analysis set title	Initial Treatment Period: Nemolizumab 30 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received nemolizumab 30 mg via 2 SC injections at Day 1, thereafter, Q4W at Weeks 4, 8, and 12 by a single SC injection during Initial Treatment Period.	

Primary: Percentage of Subjects With an Investigator's Global Assessment (IGA) Success (IGA of 0 or 1 and a More Than Equal to \geq 2-point Reduction): Intent-To-Treat (ITT) Population

End point title	Percentage of Subjects With an Investigator's Global Assessment (IGA) Success (IGA of 0 or 1 and a More Than Equal to \geq 2-point Reduction): Intent-To-Treat (ITT) Population
End point description: IGA success was defined as an IGA score of 0 (clear) or 1 (almost clear) and at least a 2-grade	

improvement from baseline to Week 16. The IGA is a 5-point scale ranging from 0 (clear) to 4 (severe) used by the Investigator or trained designee to evaluate the global severity of atopic dermatitis (AD) and the clinical response to treatment. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered treatment failure. Subjects with missing data at Week 16 were considered non-responders. The ITT population consisted of all randomised subjects. Data was planned to be collected and analysed for Initial Treatment Period.

End point type	Primary
End point timeframe:	
Week 16	

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	321	620		
Units: percentage of subjects				
number (not applicable)	24.6	35.6		

Statistical analyses

Statistical analysis title	Analysis 1
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Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level.

Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0003 ^[1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	11.5
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	4.7
upper limit	18.3

Notes:

[1] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe] and PP NRS [≥ 7 , < 7]).

Primary: Percentage of Subjects With an Investigator's Global Assessment (IGA) Success (IGA of 0 or 1 and a More Than Equal to [\geq] 2-point Reduction): Severe Pruritus Population

End point title	Percentage of Subjects With an Investigator's Global Assessment (IGA) Success (IGA of 0 or 1 and a More Than Equal to [\geq] 2-point Reduction): Severe Pruritus Population
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End point description:

IGA success was defined as an IGA score of 0 (clear) or 1 (almost clear) and at least a 2-grade improvement from baseline to Week 16. The IGA is a 5-point scale ranging from 0 (clear) to 4 (severe) used by the Investigator or trained designee to evaluate the global severity of AD and the clinical response to treatment. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered a treatment failure. Subjects with missing data at Week 16 are considered non-responders. Severe pruritus population consisted of all randomised subjects with a baseline PP NRS ≥ 7 . Data was planned to be collected and analysed for Initial Treatment Period.

End point type	Primary
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End point timeframe:

Week 16

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	406		
Units: percentage of subjects				
number (not applicable)	21.4	35.5		

Statistical analyses

Statistical analysis title	Analysis 1
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Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level.

Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0002 ^[2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	14.3
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	6.1
upper limit	22.5

Notes:

[2] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe]).

Primary: Percentage of Subjects With $\geq 75\%$ Improvement in Eczema Area and Severity Index (EASI-75) at Week 16: ITT Population

End point title	Percentage of Subjects With $\geq 75\%$ Improvement in Eczema Area and Severity Index (EASI-75) at Week 16: ITT Population
End point description:	
EASI-75 was defined as ≥ 75 percent (%) improvement in EASI from baseline to Week 16. EASI evaluates severity of subjects AD based on severity of AD clinical signs and % of body surface area (BSA) affected. Severity of clinical signs of AD (erythema, induration/papulation, excoriation and lichenification) scored separately for each of 4 body regions (head & neck, upper limbs, trunk & lower limbs) on 4-point scale: 0= absent; 1= mild; 2= moderate; 3= severe. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered a treatment failure. Subjects with missing data at Week 16 were considered non-responders. EASI total score is composite score ranging from 0 to 72. Higher scores represent greater severity of AD. The ITT population consisted of all randomised subjects.	
End point type	Primary
End point timeframe:	
Week 16	

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	321	620		
Units: percentage of subjects				
number (not applicable)	29.0	43.5		

Statistical analyses

Statistical analysis title	Analysis 1
Statistical analysis description:	
A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level.	
Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	14.9
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	7.8
upper limit	22

Notes:

[3] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe] and PP NRS [≥ 7 , < 7]).

Primary: Percentage of Subjects With $\geq 75\%$ Improvement in Eczema Area and Severity Index (EASI-75) at Week 16: Severe Pruritus Population

End point title	Percentage of Subjects With $\geq 75\%$ Improvement in Eczema Area and Severity Index (EASI-75) at Week 16: Severe Pruritus Population
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End point description:

EASI-75 was defined as ≥ 75 percent (%) improvement in EASI from baseline to Week 16. EASI evaluates severity of subjects AD based on severity of AD clinical signs and % of body surface area (BSA) affected. Severity of clinical signs of AD (erythema, induration/papulation, excoriation and lichenification) scored separately for each of 4 body regions (head & neck, upper limbs, trunk & lower limbs on 4-point scale: 0= absent; 1= mild; 2= moderate; 3= severe. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered a treatment failure. Subjects with missing data at Week 16 were considered non-responders. EASI total score is composite score ranging from 0 to 72. Higher scores represent greater severity of AD. The ITT population consisted of all randomised subjects.

End point type	Primary
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End point timeframe:

Week 16

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	406		
Units: percentage of subjects				
number (not applicable)	23.8	41.6		

Statistical analyses

Statistical analysis title	Analysis 1
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Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level.

Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	18.1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	9.6
upper limit	26.6

Notes:

[4] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe]).

Secondary: Percentage of Subjects With Improvement of ≥ 4 Points in Weekly Average Peak Pruritus Numeric Rating Scale (PP NRS) at Week 16: ITT Population

End point title	Percentage of Subjects With Improvement of ≥ 4 Points in Weekly Average Peak Pruritus Numeric Rating Scale (PP NRS) at Week 16: ITT Population
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End point description:

The PP NRS is a scale that was used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours on a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable'. Weekly average PP NRS score was calculated using 7 consecutive days diary data and set to missing if less than 4 days data available. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered treatment failure. The ITT population consisted of all randomised subjects. Data was planned to be collected and analysed for Initial Treatment Period.

End point type	Secondary
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End point timeframe:

Week 16

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	321	620		
Units: percentage of subjects				
number (not applicable)	17.8	42.7		

Statistical analyses

Statistical analysis title	Analysis 1
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Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level. Subjects with missing data are considered non-responders.

Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	24.9

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	18.4
upper limit	31.5

Notes:

[5] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe] and PP NRS [≥ 7 , < 7]).

Statistical analysis title	Analysis 2 - MI-MAR Method
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Statistical analysis description:

Nemolizumab 30 mg versus Placebo using multiple imputation (MI) with missing at random (MAR) assumption. The estimates are from 50 complete datasets by MI-MAR assumption.

Comparison groups	Initial Treatment Period: Nemolizumab 30 mg v Initial Treatment Period: Placebo
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	28.1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	22
upper limit	34.3

Notes:

[6] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe] and PP NRS [≥ 7 , < 7]).

Secondary: Percentage of Subjects With Improvement of ≥ 4 Points in Weekly Average Peak Pruritus Numeric Rating Scale (PP NRS) at Week 16: Severe Pruritus Population

End point title	Percentage of Subjects With Improvement of ≥ 4 Points in Weekly Average Peak Pruritus Numeric Rating Scale (PP NRS) at Week 16: Severe Pruritus Population
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End point description:

The PP NRS is a scale that was used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours on a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable'. Weekly average PP NRS score was calculated using 7 consecutive days diary data and set to missing if less than 4 days data available. If a subject received any rescue therapy, the data after receipt of rescue therapy is considered treatment failure. Severe pruritus population consisted of all randomised subjects with a baseline PP NRS ≥ 7 . Data was planned to be collected and analysed for Initial Treatment Period.

End point type	Secondary
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End point timeframe:

Week 16

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	406		
Units: percentage of subjects				
number (not applicable)	18.6	46.1		

Statistical analyses

Statistical analysis title	Analysis 1
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Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level. Subjects with missing data are considered non-responders.

Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	27.5
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	19.4
upper limit	35.7

Notes:

[7] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe]).

Statistical analysis title	Analysis 2: MI-MAR Method
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Statistical analysis description:

Nemolizumab 30 mg versus Placebo using MI-MAR assumption. The estimates are from 50 complete datasets by MI-MAR assumption.

Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	32.1

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	24.4
upper limit	39.8

Notes:

[8] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe]).

Secondary: Percentage of Subjects With <2 Points in Weekly Average PP NRS at Week 16: ITT Population

End point title	Percentage of Subjects With <2 Points in Weekly Average PP NRS at Week 16: ITT Population
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End point description:

The PP NRS is a scale that was used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours on a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable'. Weekly average PP NRS score was calculated using 7 consecutive days diary data and set to missing if less than 4 days data available. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered treatment failure. Subject with missing data were considered non-responders. The ITT population consisted of all randomised subjects. Data was planned to be collected and analysed for Initial Treatment Period.

End point type	Secondary
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End point timeframe:

Week 16

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	321	620		
Units: percentage of subjects				
number (not applicable)	11.2	30.6		

Statistical analyses

Statistical analysis title	Analysis 1
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Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level.

Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
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Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	19.5
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	13.7
upper limit	25.2

Notes:

[9] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe] and PP NRS [≥ 7 , < 7]).

Secondary: Percentage of Subjects With <2 Points in Weekly Average PP NRS at Week 16: Severe Pruritus Population

End point title	Percentage of Subjects With <2 Points in Weekly Average PP NRS at Week 16: Severe Pruritus Population
-----------------	---

End point description:

The PP NRS is a scale that was used by the subject to report the intensity of their pruritus (itch) during the last 24 hours on a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable'. Weekly average PP NRS score was calculated using 7 consecutive days diary data and set to missing if less than 4 days data available. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered treatment failure. Subjects with missing data were considered non-responders. Severe pruritus population consisted of all randomised subjects with a baseline PP NRS ≥ 7 . Data was planned to be collected and analysed for Initial Treatment Period.

End point type	Secondary
End point timeframe:	
Week 16	

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	406		
Units: percentage of subjects				
number (not applicable)	7.6	27.8		

Statistical analyses

Statistical analysis title	Analysis 1
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Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level.

Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	20.3
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	13.8
upper limit	26.8

Notes:

[10] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe]).

Secondary: Percentage of Subjects With an Improvement of Sleep Disturbance Numeric Rating Scale (SD NRS) ≥ 4 at Week 16: ITT Population

End point title	Percentage of Subjects With an Improvement of Sleep Disturbance Numeric Rating Scale (SD NRS) ≥ 4 at Week 16: ITT Population
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End point description:

The sleep disturbance NRS is a scale used by the subjects to report the degree of their sleep loss related to AD. Subjects were asked the following question in their local language: how would you rate your sleep last night? On a scale of 0 to 10, with 0 being 'no sleep loss related to signs/symptoms of AD' and 10 being 'I cannot sleep at all due to the signs/symptoms of AD'. Weekly average SD NRS score was calculated using 7 consecutive days diary data and set to missing if less than 4 days data available. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered treatment failure. Subjects with missing data were considered non-responders. The ITT population consisted of all randomised subjects.

End point type	Secondary
End point timeframe:	
Week 16	

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	321	620		
Units: percentage of subjects				
number (not applicable)	19.9	37.9		

Statistical analyses

Statistical analysis title	Analysis 1
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Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level.

Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	17.9
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	11.3
upper limit	24.5

Notes:

[11] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe] and PP NRS [≥ 7 , < 7]).

Secondary: Percentage of Subjects With an Improvement of Sleep Disturbance Numeric Rating Scale (SD NRS) ≥ 4 at Week 16: Severe Pruritus Population

End point title	Percentage of Subjects With an Improvement of Sleep Disturbance Numeric Rating Scale (SD NRS) ≥ 4 at Week 16: Severe Pruritus Population
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End point description:

The sleep disturbance NRS is a scale used by the subjects to report the degree of their sleep loss related to AD. Subjects were asked the following question in their local language: how would you rate your sleep last night? On a scale of 0 to 10, with 0 being 'no sleep loss related to signs/symptoms of AD' and 10 being 'I cannot sleep at all due to the signs/symptoms of AD'. Weekly average SD NRS score was calculated using 7 consecutive days diary data and set to missing if less than 4 days data available. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered treatment failure. Subjects with missing data were considered non-responders. Severe pruritus population consisted of all randomised subjects with a baseline PP NRS ≥ 7 .

End point type	Secondary
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End point timeframe:

Week 16

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	406		
Units: percentage of subjects				
number (not applicable)	22.4	42.1		

Statistical analyses

Statistical analysis title	Analysis 1
Statistical analysis description: A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level.	
Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	11.2
upper limit	28.2

Notes:

[12] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe]).

Secondary: Percentage of Subjects With Improvement of ≥ 4 Points in Weekly Average Peak Pruritus Numeric Rating Scale (PP NRS) at Week 4: ITT Population

End point title	Percentage of Subjects With Improvement of ≥ 4 Points in Weekly Average Peak Pruritus Numeric Rating Scale (PP NRS) at Week 4: ITT Population
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End point description:

The PP NRS is a scale that was used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours on a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable'. Weekly average PP NRS score was calculated using 7 consecutive days diary data and set to missing if less than 4 days data available. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered treatment failure. Subjects with missing data were considered non-responders. The ITT population consisted of all randomised subjects. Data was planned to be collected and analysed for Initial Treatment Period.

End point type	Secondary
End point timeframe: Week 4	

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	321	620		
Units: percentage of subjects				
number (not applicable)	6.5	27.4		

Statistical analyses

Statistical analysis title	Analysis 1
Statistical analysis description: A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level.	
Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	20.9
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	15.8
upper limit	26

Notes:

[13] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe] and PP NRS [≥ 7 , < 7]).

Secondary: Percentage of Subjects With Improvement of ≥ 4 Points in Weekly Average Peak Pruritus Numeric Rating Scale (PP NRS) at Week 4: Severe Pruritus Population

End point title	Percentage of Subjects With Improvement of ≥ 4 Points in Weekly Average Peak Pruritus Numeric Rating Scale (PP NRS) at Week 4: Severe Pruritus Population
-----------------	--

End point description:

The PP NRS is a scale that was used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours on a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable'. Weekly average PP NRS score was calculated using 7 consecutive days diary data and set to missing if less than 4 days data available. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered treatment failure. Subjects with missing data were considered non-responders. Severe pruritus population consisted of all randomised subjects with a baseline PP NRS ≥ 7 . Data was planned to be collected and analysed for Initial Treatment Period.

End point type	Secondary
End point timeframe:	
Week 4	

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	406		
Units: percentage of subjects				
number (not applicable)	7.1	28.3		

Statistical analyses

Statistical analysis title	Analysis 1
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Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level.

Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	21.2
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	14.8
upper limit	27.6

Notes:

[14] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe]).

Secondary: Percentage of Subjects With Peak Pruritus Numeric Rating Scale (PP NRS) <2 at Week 4: ITT Population

End point title	Percentage of Subjects With Peak Pruritus Numeric Rating Scale (PP NRS) <2 at Week 4: ITT Population
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End point description:

The PP NRS is a scale that was used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours on a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable'. Weekly average PP NRS score was calculated using 7 consecutive days diary data and set to missing if less than 4 days data available. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered treatment failure. Subjects with missing data were considered non-responders. The ITT population consisted of all randomised subjects. Data was planned to be collected and analysed for Initial Treatment Period.

End point type	Secondary
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End point timeframe:

Week 4

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	321	620		
Units: percentage of subjects				
number (not applicable)	3.7	16		

Statistical analyses

Statistical analysis title	Analysis 1
Statistical analysis description:	
A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level.	
Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[15]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	12.2
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	8.2
upper limit	16.3

Notes:

[15] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe] and PP NRS [≥ 7 , < 7]).

Secondary: Percentage of Subjects With Peak Pruritus Numeric Rating Scale (PP NRS) <2 at Week 4: Severe Pruritus Population

End point title	Percentage of Subjects With Peak Pruritus Numeric Rating Scale (PP NRS) <2 at Week 4: Severe Pruritus Population
End point description:	
The PP NRS is a scale that was used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours on a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable'. Weekly average PP NRS score was calculated using 7 consecutive days diary data and set to missing if less than 4 days data available. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered treatment failure. Subjects with missing data were considered non-responders. Severe pruritus population consisted of all randomised subjects with a baseline PP NRS ≥ 7 . Data was planned to be collected and analysed for Initial Treatment Period.	
End point type	Secondary

End point timeframe:

Week 4

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	406		
Units: percentage of subjects				
number (not applicable)	2.9	12.6		

Statistical analyses

Statistical analysis title	Analysis 1
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Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level.

Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	9.7
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	5.2
upper limit	14.2

Notes:

[16] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe]).

Secondary: Percentage of Subjects With Improvement of ≥ 4 Points in Weekly Average Peak Pruritus Numeric Rating Scale (PP NRS) at Week 2: ITT Population

End point title	Percentage of Subjects With Improvement of ≥ 4 Points in Weekly Average Peak Pruritus Numeric Rating Scale (PP NRS) at Week 2: ITT Population
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End point description:

The PP NRS is a scale that was used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours on a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable'. Weekly average PP NRS score was calculated using 7 consecutive days diary data and set to missing if less than 4 days data available. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered treatment failure. Subjects with missing data were considered non-responders. The ITT population consisted of all randomised subjects. Data was planned to be collected and analysed

for Initial Treatment Period.

End point type	Secondary
End point timeframe:	
Week 2	

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	321	620		
Units: percentage of subjects				
number (not applicable)	3.1	17.7		

Statistical analyses

Statistical analysis title	Analysis 1
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Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level.

Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[17]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	14.6
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	10.6
upper limit	18.7

Notes:

[17] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe] and PP NRS [≥ 7 , < 7]).

Secondary: Percentage of Subjects With Improvement of ≥ 4 Points in Weekly Average Peak Pruritus Numeric Rating Scale (PP NRS) at Week 2: Severe Pruritus Population

End point title	Percentage of Subjects With Improvement of ≥ 4 Points in Weekly Average Peak Pruritus Numeric Rating Scale (PP NRS) at Week 2: Severe Pruritus Population
-----------------	--

End point description:

The PP NRS is a scale that was used by the subjects to report the intensity of their pruritus (itch) during

the last 24 hours on a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable'. Weekly average PP NRS score was calculated using 7 consecutive days diary data and set to missing if less than 4 days data available. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered treatment failure. Subjects with missing data were considered non-responders. Severe pruritus population consisted of all randomised subjects with a baseline PP NRS ≥ 7 . Data was planned to be collected and analysed for Initial Treatment Period.

End point type	Secondary
End point timeframe:	
Week 2	

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	406		
Units: percentage of subjects				
number (not applicable)	3.8	20.7		

Statistical analyses

Statistical analysis title	Analysis 1
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Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level.

Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	16.9
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	11.5
upper limit	22.3

Notes:

[18] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe]).

Secondary: Percentage of Subjects With Improvement of ≥ 4 Points in Weekly Average Peak Pruritus Numeric Rating Scale (PP NRS) at Week 1: ITT Population

End point title	Percentage of Subjects With Improvement of ≥ 4 Points in Weekly Average Peak Pruritus Numeric Rating Scale (PP NRS)
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End point description:

The PP NRS is a scale that was used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours on a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable'. Weekly average PP NRS score was calculated using 7 consecutive days diary data and set to missing if less than 4 days data available. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered treatment failure. Subjects with missing data were considered non-responders. The ITT population consisted of all randomised subjects. Data was planned to be collected and analysed for Initial Treatment Period.

End point type

Secondary

End point timeframe:

Week 1

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	321	620		
Units: percentage of subjects				
number (not applicable)	1.2	4.5		

Statistical analyses

Statistical analysis title

Analysis 1

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level.

Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0064 ^[19]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	3.4
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	1.1
upper limit	5.8

Notes:

[19] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe] and PP NRS [≥ 7 , <7]).

Secondary: Percentage of Subjects With Improvement of ≥ 4 Points in Weekly Average Peak Pruritus Numeric Rating Scale: Severe Pruritus Population

End point title	Percentage of Subjects With Improvement of ≥ 4 Points in Weekly Average Peak Pruritus Numeric Rating Scale: Severe Pruritus Population
-----------------	---

End point description:

The PP NRS is a scale that was used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours on a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable'. Weekly average PP NRS score was calculated using 7 consecutive days diary data and set to missing if less than 4 days data available. If a subject received any rescue therapy, the data after receipt of rescue therapy was considered treatment failure. Subjects with missing data were considered non-responders. Severe pruritus population consisted of all randomised subjects with a baseline PP NRS ≥ 7 . Data was planned to be collected and analysed for Initial Treatment Period.

End point type	Secondary
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End point timeframe:

Week 1

End point values	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	406		
Units: percentage of subjects				
number (not applicable)	1.9	6.2		

Statistical analyses

Statistical analysis title	Analysis 1
----------------------------	------------

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. Testing was performed sequentially in order the endpoints were reported and continued when the test for preceding endpoint was statistically significant at two-sided 2.5% significance level.

Comparison groups	Initial Treatment Period: Placebo v Initial Treatment Period: Nemolizumab 30 mg
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0177 [20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Strata-adjusted percentage difference
Point estimate	4.3
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.9
upper limit	7.7

Notes:

[20] - Strata-adjusted p-values were calculated from Cochran-Mantel-Haenszel test adjusting randomised stratification variables (IGA severity [3=moderate, 4=severe]).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Initial Treatment Period: From baseline to Week 16 pre-dose; Maintenance Period: From end of Initial Treatment Period to Week 48

Adverse event reporting additional description:

The safety population comprised all subjects who received at least 1 dose of study drug. One subject was re-randomized to Nemolizumab Q8W for Maintenance Period, but erroneously received Nemolizumab three times consecutively and thus counted in Nemolizumab 30 mg Q4W to Q4W for safety analysis.

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	Initial Treatment Period: Placebo
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Reporting group description:

Subjects received placebo via 2 subcutaneous (SC) injections at Day 1, thereafter, every 4 weeks (Q4W), at Weeks 4, 8, and 12 by a single SC injection during Initial Treatment Period.

Reporting group title	Initial Treatment Period: Nemolizumab 30 mg
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Reporting group description:

Subjects received nemolizumab 30 mg via 2 SC injections at Day 1, thereafter, Q4W at Weeks 4, 8, and 12 by a single SC injection during Initial Treatment Period.

Reporting group title	Maintenance Period: Nemolizumab 30 mg Q4W to Q4W
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Reporting group description:

Subjects who received nemolizumab, Q4W during Initial Treatment Period and were clinical responders at Week 16 received nemolizumab 30 mg, Q4W at Weeks 16, 20, 24, 28, 32, 36, 40, and 44 by a single SC injection during Maintenance Period.

Reporting group title	Maintenance Period: Nemolizumab 30 mg Q4W to Q8W
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Reporting group description:

Subjects who received nemolizumab, Q4W during Initial Treatment Period and were clinical responders at Week 16 received nemolizumab 30 mg, Q8W at Weeks 16, 24, 32, and 40 by a single SC injection during Maintenance Period.

Reporting group title	Maintenance Period: Nemolizumab 30 mg Q4W to Placebo Q8W
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Reporting group description:

Subjects who received nemolizumab, Q4W during Initial Treatment Period and were clinical responders at Week 16 received placebo, Q4W at Weeks 16, 20, 24, 28, 32, 36, 40, and 44 by a single SC injection during Maintenance Period.

Reporting group title	Maintenance Period: Placebo Q4W Re-assigned to Placebo Q4W
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Reporting group description:

Subjects who received placebo, Q4W during Initial Treatment Period and were clinical responders at Week 16 received placebo, Q4W at Weeks 16, 20, 24, 28, 32, 36, 40, and 44 by a single SC injection during Maintenance Period.

Serious adverse events	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg	Maintenance Period: Nemolizumab 30 mg Q4W to Q4W
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 321 (1.25%)	6 / 616 (0.97%)	4 / 91 (4.40%)

number of deaths (all causes) number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Plasmablastic lymphoma subjects affected / exposed	0 / 321 (0.00%)	0 / 616 (0.00%)	0 / 91 (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
Salivary gland cancer subjects affected / exposed	0 / 321 (0.00%)	1 / 616 (0.16%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma subjects affected / exposed	0 / 321 (0.00%)	1 / 616 (0.16%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications Meniscus injury subjects affected / exposed	0 / 321 (0.00%)	0 / 616 (0.00%)	0 / 91 (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
Splenic injury subjects affected / exposed	0 / 321 (0.00%)	0 / 616 (0.00%)	0 / 91 (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 Lumbar radiculopathy subjects affected / exposed	0 / 321 (0.00%)	1 / 616 (0.16%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders Dermatitis atopic subjects affected / exposed	3 / 321 (0.93%)	2 / 616 (0.32%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 321 (0.00%)	0 / 616 (0.00%)	0 / 91 (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
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 321 (0.00%)	1 / 616 (0.16%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 321 (0.00%)	0 / 616 (0.00%)	0 / 91 (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
Musculoskeletal and connective tissue disorders			
Dupuytren's contracture			
subjects affected / exposed	0 / 321 (0.00%)	0 / 616 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periarthritis			
subjects affected / exposed	0 / 321 (0.00%)	0 / 616 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 321 (0.00%)	0 / 616 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 321 (0.00%)	0 / 616 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			

subjects affected / exposed	1 / 321 (0.31%)	0 / 616 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 321 (0.00%)	0 / 616 (0.00%)	0 / 91 (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
Erysipelas			
subjects affected / exposed	0 / 321 (0.00%)	0 / 616 (0.00%)	0 / 91 (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

Serious adverse events	Maintenance Period: Nemolizumab 30 mg Q4W to Q8W	Maintenance Period: Nemolizumab 30 mg Q4W to Placebo Q8W	Maintenance Period: Placebo Q4W Re- assigned to Placebo Q4W
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 90 (3.33%)	2 / 91 (2.20%)	1 / 100 (1.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasmablastic lymphoma			
subjects affected / exposed	0 / 90 (0.00%)	1 / 91 (1.10%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland cancer			
subjects affected / exposed	0 / 90 (0.00%)	0 / 91 (0.00%)	0 / 100 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 90 (0.00%)	0 / 91 (0.00%)	0 / 100 (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			
Meniscus injury			

subjects affected / exposed	0 / 90 (0.00%)	0 / 91 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic injury			
subjects affected / exposed	1 / 90 (1.11%)	0 / 91 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Lumbar radiculopathy			
subjects affected / exposed	0 / 90 (0.00%)	0 / 91 (0.00%)	0 / 100 (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 atopic			
subjects affected / exposed	0 / 90 (0.00%)	0 / 91 (0.00%)	0 / 100 (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			
Anxiety			
subjects affected / exposed	1 / 90 (1.11%)	0 / 91 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 90 (0.00%)	0 / 91 (0.00%)	0 / 100 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 90 (0.00%)	1 / 91 (1.10%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Dupuytren's contracture			

subjects affected / exposed	0 / 90 (0.00%)	0 / 91 (0.00%)	0 / 100 (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
Periarthritis			
subjects affected / exposed	0 / 90 (0.00%)	0 / 91 (0.00%)	0 / 100 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 90 (0.00%)	0 / 91 (0.00%)	0 / 100 (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
COVID-19			
subjects affected / exposed	0 / 90 (0.00%)	0 / 91 (0.00%)	0 / 100 (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
COVID-19 pneumonia			
subjects affected / exposed	0 / 90 (0.00%)	0 / 91 (0.00%)	0 / 100 (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
Cellulitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 91 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 90 (0.00%)	1 / 91 (1.10%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	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	Initial Treatment Period: Placebo	Initial Treatment Period: Nemolizumab 30 mg	Maintenance Period: Nemolizumab 30 mg Q4W to Q4W
Total subjects affected by non-serious adverse events subjects affected / exposed	67 / 321 (20.87%)	144 / 616 (23.38%)	27 / 91 (29.67%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	11 / 321 (3.43%) 12	28 / 616 (4.55%) 37	5 / 91 (5.49%) 7
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	13 / 321 (4.05%) 14	33 / 616 (5.36%) 33	3 / 91 (3.30%) 3
Skin and subcutaneous tissue disorders Dermatitis atopic subjects affected / exposed occurrences (all)	33 / 321 (10.28%) 39	73 / 616 (11.85%) 92	7 / 91 (7.69%) 8
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	6 / 321 (1.87%) 6 8 / 321 (2.49%) 8 14 / 321 (4.36%) 14	10 / 616 (1.62%) 10 9 / 616 (1.46%) 9 9 / 616 (1.46%) 9	9 / 91 (9.89%) 9 7 / 91 (7.69%) 10 3 / 91 (3.30%) 3

Non-serious adverse events	Maintenance Period: Nemolizumab 30 mg Q4W to Q8W	Maintenance Period: Nemolizumab 30 mg Q4W to Placebo Q8W	Maintenance Period: Placebo Q4W Re-assigned to Placebo Q4W
Total subjects affected by non-serious adverse events subjects affected / exposed	28 / 90 (31.11%)	33 / 91 (36.26%)	35 / 100 (35.00%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	5 / 90 (5.56%) 10	3 / 91 (3.30%) 4	1 / 100 (1.00%) 1
Respiratory, thoracic and mediastinal disorders			

Asthma subjects affected / exposed occurrences (all)	6 / 90 (6.67%) 6	5 / 91 (5.49%) 5	5 / 100 (5.00%) 8
Skin and subcutaneous tissue disorders Dermatitis atopic subjects affected / exposed occurrences (all)	8 / 90 (8.89%) 8	12 / 91 (13.19%) 15	10 / 100 (10.00%) 11
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	9 / 90 (10.00%) 9	6 / 91 (6.59%) 7	10 / 100 (10.00%) 10
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 90 (5.56%) 6	7 / 91 (7.69%) 9	6 / 100 (6.00%) 6
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 90 (3.33%) 3	5 / 91 (5.49%) 5	9 / 100 (9.00%) 11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported