Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Efficacy and Safety of REGN3500 Monotherapy and Combination of REGN3500 Plus Dupilumab in Adult Patients With Moderate-to-Severe Atopic Dermatitis

Summary

EudraCT number	2018-001543-30
Trial protocol	DE BE ES NL
Global end of trial date	28 July 2020

Results information

Result version number	v1 (current)
This version publication date	08 August 2021
First version publication date	08 August 2021

Trial information

Trial identification

Sponsor protocol code	R3500-AD-1798

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03736967
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Road, Tarrytown, NY, United States, 10591
Public contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., 001 844-734-6643, clinicaltrials@regeneron.com
Scientific contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., 001 844-734-6643, clinicaltrials@regeneron.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 July 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of REGN3500 monotherapy compared with placebo treatment in adult subjects with moderate-to-severe atopic dermatitis (AD).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 November 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: 33
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Korea, Republic of: 54
Country: Number of subjects enrolled	United States: 46
Country: Number of subjects enrolled	Czechia: 28
Worldwide total number of subjects	206
EEA total number of subjects	106

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)	194
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 299 subjects were screened at sites in Republic of Korea, United States of America, Germany, Poland, Czech Republic, Belgium, and Spain. Out of 299 subjects, 206 subjects met eligibility criteria and randomized in this study.

Pre-assignment

Screening details:

Subjects were randomized in a 1:1:1:1 ratio to 1 of the 4 treatment groups: Placebo every 2 weeks (Q2W); REGN3500 300 milligrams (mg) Q2W; Dupilumab 300 mg Q2W and combination of REGN3500 300 mg and Dupilumab 300 mg Q2W.

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, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Q2W

Arm description:

Subjects received 2 subcutaneous (SC) injections of placebo matched to REGN3500 and 2 SC injections of placebo matched to Dupilumab (loading dose) on Day 1 and then 2 SC injections of placebo matched to REGN3500 and 1 SC injection of placebo matched to Dupilumab Q2W up to Week 14.

Arm type	Placebo
Investigational medicinal product name	Placebo matched to REGN3500
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection of placebo matched to REGN3500 on different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site was not injected for 2 consecutive administrations.

Investigational medicinal product name	Placebo matched to Dupilumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection of placebo matched to dupilumab on different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site was not injected for 2 consecutive administrations.

Arm title	REGN3500 300 mg Q2W

Arm description:

Subjects received 2 SC injections of REGN3500 at a dose of 150 mg (300 mg loading dose) and 2 SC injections of placebo matched to Dupilumab (loading dose) on Day 1 and then 2 SC injections of REGN3500 at a dose of 150 mg (300 mg loading dose) and 1 SC injection of placebo matched to Dupilumab Q2W up to Week 14.

Arm type	Experimental

Investigational medicinal product name	Placebo matched to Dupilumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection of placebo matched to dupilumab on different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site was not injected for 2 consecutive administrations.

Investigational medicinal product name	REGN3500
Investigational medicinal product code	
Other name	Itepekimab
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection of REGN3500 on different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site was not injected for 2 consecutive administrations.

Arm title	Dupilumab 300 mg Q2W

Arm description:

Subjects received 2 SC injections of Dupilumab at a dose of 300 mg (600 mg loading dose) and 2 SC injections of placebo matched to REGN3500 on Day 1 and then 1 SC injection of Dupilumab at a dose 300 mg and 2 SC injections of placebo matched to REGN3500 Q2W up to Week 14.

Arm type	Experimental
Investigational medicinal product name	Placebo matched to REGN3500
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection of placebo matched to REGN3500 on different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site was not injected for 2 consecutive administrations.

Investigational medicinal product name	Dupilumab
Investigational medicinal product code	REGN668
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection of Dupilumab on different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site was not injected for 2 consecutive administrations.

Arm title	REGN3500 300 mg + Dupilumab 300 mg Q2W

Arm description:

Subjects received 2 SC injections of REGN3500 at a dose of 150 mg (300 mg loading dose) and 2 SC injections of Dupilumab at a dose of 300 mg (600 mg loading dose) on Day 1 and then 2 SC injections of REGN3500 at a dose of 150 mg and 1 SC injection of Dupilumab at a dose of 300 mg Q2W up to Week 14.

Arm type	Experimental
Investigational medicinal product name	REGN3500
Investigational medicinal product code	REGN3500
Other name	Itepekimab
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection of REGN3500 on different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site was not injected for 2 consecutive administrations.

Investigational medicinal product name	Dupilumab
Investigational medicinal product code	REGN668
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection of Dupilumab on different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site was not injected for 2 consecutive administrations.

Number of subjects in period 1	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W
Started	51	52	51
Completed	20	24	27
Not completed	31	28	24
Adverse event, serious fatal	-	-	-
Physician decision	1	-	-
Consent withdrawn by subject	26	25	23
Adverse event, non-fatal	-	1	-
Death	-	-	-
Randomized but never treated	1	-	-
Lost to follow-up	3	2	1

Number of subjects in period 1	REGN3500 300 mg + Dupilumab 300 mg Q2W
Started	52
Completed	22
Not completed	30
Adverse event, serious fatal	1
Physician decision	1
Consent withdrawn by subject	26
Adverse event, non-fatal	-
Death	1
Randomized but never treated	-
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo Q2W
Reporting group description:	
Subjects received 2 subcutaneous (SC) injections of placebo matched to REGN3500 and 2 SC injections of placebo matched to Dupilumab (loading dose) on Day 1 and then 2 SC injections of placebo matched to REGN3500 and 1 SC injection of placebo matched to Dupilumab Q2W up to Week 14.	
Reporting group title	REGN3500 300 mg Q2W
Reporting group description:	
Subjects received 2 SC injections of REGN3500 at a dose of 150 mg (300 mg loading dose) and 2 SC injections of placebo matched to Dupilumab (loading dose) on Day 1 and then 2 SC injections of REGN3500 at a dose of 150 mg (300 mg loading dose) and 1 SC injection of placebo matched to Dupilumab Q2W up to Week 14.	
Reporting group title	Dupilumab 300 mg Q2W
Reporting group description:	
Subjects received 2 SC injections of Dupilumab at a dose of 300 mg (600 mg loading dose) and 2 SC injections of placebo matched to REGN3500 on Day 1 and then 1 SC injection of Dupilumab at a dose 300 mg and 2 SC injections of placebo matched to REGN3500 Q2W up to Week 14.	
Reporting group title	REGN3500 300 mg + Dupilumab 300 mg Q2W
Reporting group description:	
Subjects received 2 SC injections of REGN3500 at a dose of 150 mg (300 mg loading dose) and 2 SC injections of Dupilumab at a dose of 300 mg (600 mg loading dose) on Day 1 and then 2 SC injections of REGN3500 at a dose of 150 mg and 1 SC injection of Dupilumab at a dose of 300 mg Q2W up to Week 14.	

Reporting group values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W
Number of subjects	51	52	51
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	47	51	46
From 65-84 years	4	1	5
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	34.9	33.3	38.4
standard deviation	± 14.04	± 12.19	± 15.89
Gender Categorical Units: Subjects			
Female	19	16	23
Male	32	36	28
Race, Customized Units: Subjects			
White	26	29	38

Black or African American	1	6	3
Asian	24	16	10
Other	0	1	0
Ethnicity (NIH/OMB) Units: Subjects			
Not Hispanic or Latino	51	48	50
Hispanic or Latino	0	2	1
Not reported/unknown	0	2	0
Eczema Area and Severity Index (EASI) Score			
The EASI score was used to measure the severity and extent of atopic dermatitis (AD) and measures erythema, induration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. Full Analysis Set (FAS) includes all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analysed" signifies those subjects who were evaluable at baseline. Here N= 50 for "Placebo Q2W" arm.			
Units: Scores on a Scale			
arithmetic mean	28.2	29.9	30.6
standard deviation	± 9.537	± 13.02	± 13.86

Reporting group values	REGN3500 300 mg + Dupilumab 300 mg Q2W	Total	
Number of subjects	52	206	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	50	194	
From 65-84 years	2	12	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	32.1		
standard deviation	± 12.10	-	
Gender Categorical Units: Subjects			
Female	22	80	
Male	30	126	
Race, Customized Units: Subjects			
White	31	124	
Black or African American	2	12	
Asian	19	69	
Other	0	1	
Ethnicity (NIH/OMB) Units: Subjects			
Not Hispanic or Latino	50	199	

Hispanic or Latino	1	4	
Not reported/unknown	1	3	

Eczema Area and Severity Index (EASI) Score			
The EASI score was used to measure the severity and extent of atopic dermatitis (AD) and measures erythema, induration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. Full Analysis Set (FAS) includes all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analysed" signifies those subjects who were evaluable at baseline. Here N= 50 for "Placebo Q2W" arm.			
Units: Scores on a Scale			
arithmetic mean	29.0		
standard deviation	± 10.74	-	

End points

End points reporting groups

Reporting group title	Placebo Q2W
Reporting group description:	
Subjects received 2 subcutaneous (SC) injections of placebo matched to REGN3500 and 2 SC injections of placebo matched to Dupilumab (loading dose) on Day 1 and then 2 SC injections of placebo matched to REGN3500 and 1 SC injection of placebo matched to Dupilumab Q2W up to Week 14.	
Reporting group title	REGN3500 300 mg Q2W
Reporting group description:	
Subjects received 2 SC injections of REGN3500 at a dose of 150 mg (300 mg loading dose) and 2 SC injections of placebo matched to Dupilumab (loading dose) on Day 1 and then 2 SC injections of REGN3500 at a dose of 150 mg (300 mg loading dose) and 1 SC injection of placebo matched to Dupilumab Q2W up to Week 14.	
Reporting group title	Dupilumab 300 mg Q2W
Reporting group description:	
Subjects received 2 SC injections of Dupilumab at a dose of 300 mg (600 mg loading dose) and 2 SC injections of placebo matched to REGN3500 on Day 1 and then 1 SC injection of Dupilumab at a dose 300 mg and 2 SC injections of placebo matched to REGN3500 Q2W up to Week 14.	
Reporting group title	REGN3500 300 mg + Dupilumab 300 mg Q2W
Reporting group description:	
Subjects received 2 SC injections of REGN3500 at a dose of 150 mg (300 mg loading dose) and 2 SC injections of Dupilumab at a dose of 300 mg (600 mg loading dose) on Day 1 and then 2 SC injections of REGN3500 at a dose of 150 mg and 1 SC injection of Dupilumab at a dose of 300 mg Q2W up to Week 14.	

Primary: Percent Change From Baseline in Eczema Area and Severity Index (EASI) Score Based on Observed Values Set to Missing After Rescue Treatment at Week 16

End point title	Percent Change From Baseline in Eczema Area and Severity Index (EASI) Score Based on Observed Values Set to Missing After Rescue Treatment at Week 16[1]
End point description:	
The EASI score was used to measure the severity and extent of AD and measures erythema, induration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. Percent change from baseline in EASI score at Week 16 based on observed values set to missing after rescue treatment was reported. Values after first rescue treatment were set to missing and subjects with missing EASI score at Week 16 were counted as non-responders. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analysed" signifies those subjects who were evaluable for this endpoint.	
End point type	Primary
End point timeframe:	
Week 16	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the premature discontinuation of the study, all analyses were change from hypothesis testing to descriptive.

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	14	22	20
Units: Percentage of Change				
arithmetic mean (standard deviation)	-52.4 (± 31.86)	-66.6 (± 22.46)	-77.8 (± 23.73)	-76.9 (± 20.79)

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change From Baseline in Eczema Area and Severity Index (EASI) Score Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point title	Percent Change From Baseline in Eczema Area and Severity Index (EASI) Score Based on All Observed Values Regardless of Rescue Treatment at Week 16[2]

End point description:

The EASI score was used to measure the severity and extent of AD and measures erythema, induration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. Percent change from baseline in EASI score at Week 16 based on all observed values regardless of rescue treatment was reported. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Week 16

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the premature discontinuation of the study, all analyses were change from hypothesis testing to descriptive.

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	26	24
Units: Percentage of Change				
arithmetic mean (standard deviation)	-46.6 (± 36.58)	-58.0 (± 29.69)	-77.4 (± 22.59)	-75.8 (± 19.66)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Eczema Area and Severity Index-50 (EASI-50) (Greater Than or Equal to [≥] 50 Percent (%) Improvement From Baseline) Based on Observed Values Set to Missing After Rescue Treatment at Week

16

End point title	Percentage of Subjects Who Achieved Eczema Area and Severity Index- 50 (EASI-50) (Greater Than or Equal to [≥] 50 Percent (%) Improvement From Baseline) Based on Observed Values Set to Missing After Rescue Treatment at Week 16

End point description:

The EASI score was used to measure the severity and extent of AD and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. Percentage of subjects who achieved EASI-50 (≥ 50% Improvement from baseline) at Week 16 based on observed values set to missing after rescue treatment were reported. Values after first rescue treatment were set to missing and subjects with missing EASI score at Week 16 were counted as non-responders. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	14	22	20
Units: Percentage of Subjects				
number (not applicable)	57.9	78.6	95.5	85.0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Eczema Area and Severity Index-50 (EASI-50) ≥ 50% Improvement From Baseline Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point title	Percentage of Subjects Who Achieved Eczema Area and Severity Index- 50 (EASI-50) ≥ 50% Improvement From Baseline Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point description:

The EASI score was used to measure the severity and extent of AD and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. Percentage of subjects who achieved EASI-50 (≥ 50% Improvement from baseline) at Week 16 based on all observed values regardless of rescue treatment were reported. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	26	24
Units: Percentage of Subjects				
number (not applicable)	52.2	65.2	96.2	87.5

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Eczema Area and Severity Index-75 (EASI-75) ≥ 75% Improvement From Baseline Based on Observed Values Set to Missing After Rescue Treatment at Week 16

End point title	Percentage of Subjects Who Achieved Eczema Area and Severity Index- 75 (EASI-75) ≥ 75% Improvement From Baseline Based on Observed Values Set to Missing After Rescue Treatment at Week 16

End point description:

The EASI score was used to measure the severity and extent of AD and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. Percentage of subjects who achieved EASI-75 (≥ 75% Improvement from baseline) at Week 16 based on observed values set to missing after rescue treatment were reported. Values after first rescue treatment were set to missing and subjects with missing EASI score at Week 16 were counted as non-responders. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	14	22	20
Units: Percentage of Subjects				
number (not applicable)	31.6	35.7	63.6	60.0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Eczema Area and Severity Index-75 (EASI-75) ≥75% Improvement From Baseline Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point title	Percentage of Subjects Who Achieved Eczema Area and Severity Index- 75 (EASI-75) ≥75% Improvement From Baseline Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point description:

The EASI score was used to measure the severity and extent of AD and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. Percentage of subjects who achieved EASI-75 (≥75% Improvement from baseline) at Week 16 based on all observed values regardless of rescue treatment were reported. FAS included all randomized subjects and it was based on the treatment allocated (as randomized). Here, "Number of Subjects Analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	26	24
Units: Percentage of Subjects				
number (not applicable)	26.1	30.4	61.5	58.3

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Eczema Area and Severity Index-90 (EASI-90) ≥90% Improvement From Baseline Based on Observed Values Set to Missing After Rescue Treatment at Week 16

End point title	Percentage of Subjects Who Achieved Eczema Area and Severity Index- 90 (EASI-90) ≥90% Improvement From Baseline Based on Observed Values Set to Missing After Rescue Treatment at Week 16

End point description:

The EASI score was used to measure the severity and extent of AD and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. Percentage of subjects who achieved EASI-90 (≥90% Improvement from baseline) at Week 16 based on observed values set to missing after rescue treatment were reported. Values after first rescue treatment were set to missing and subjects with missing EASI score at Week 16 were counted as non-responders. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	14	22	20
Units: Percentage of Subjects				
number (not applicable)	10.5	28.6	40.9	35.0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Eczema Area and Severity Index-90 (EASI-90) ≥90% Improvement From Baseline Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point title	Percentage of Subjects Who Achieved Eczema Area and Severity Index- 90 (EASI-90) ≥90% Improvement From Baseline Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point description:

The EASI score was used to measure the severity and extent of AD and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. Percentage of subjects who achieved EASI-90 (≥90% Improvement from baseline) at Week 16 based on all observed values regardless of rescue treatment were reported. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	26	24
Units: Percentage of Subjects				
number (not applicable)	8.7	17.4	38.5	29.2

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Eczema Area and Severity Index (EASI) Score Based on Observed Values Set to Missing After Rescue Treatment at Week 16

End point title	Absolute Change From Baseline in Eczema Area and Severity Index (EASI) Score Based on Observed Values Set to Missing After Rescue Treatment at Week 16

End point description:

The EASI score was used to measure the severity and extent of AD and measures erythema, induration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. Absolute change from baseline in EASI score at Week 16 was reported. Values after first rescue treatment were set to missing and subjects with missing EASI score at Week 16 were counted as non-responders. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	14	22	20
Units: Scores on a Scale				
arithmetic mean (standard deviation)	-13.25 (± 8.073)	-18.94 (± 9.383)	-25.40 (± 15.769)	-23.28 (± 9.177)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Eczema Area and Severity Index (EASI) Score Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point title	Absolute Change From Baseline in Eczema Area and Severity Index (EASI) Score Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point description:

The EASI score was used to measure the severity and extent of AD and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. Absolute change from baseline in EASI score at Week 16 based on all observed values regardless of rescue treatment was reported. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	26	24
Units: Scores on a Scale				
arithmetic mean (standard deviation)	-12.18 (± 9.819)	-16.46 (± 10.002)	-24.06 (± 14.825)	-21.82 (± 9.008)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Both Investigator Global Assessment (IGA) Score 0 or 1 (on the 0 to 5 IGA Scale) and a Reduction From Baseline of ≥2 Points Based on Observed Values Set to Missing After Rescue Treatment at Week 16

End point title	Percentage of Subjects With Both Investigator Global Assessment (IGA) Score 0 or 1 (on the 0 to 5 IGA Scale) and a Reduction From Baseline of ≥2 Points Based on Observed Values Set to Missing After Rescue Treatment at Week 16

End point description:

IGA was an assessment scale used to determine severity of AD and clinical response to treatment on a 5 point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/infiltration. Therapeutic response was an IGA score of 0 (clear) or 1 (almost clear). Subjects with both IGA score of "0" or "1"and a reduction from baseline of ≥2 points at Week 16 based on observed values set to missing after rescue treatment were reported. Values after first rescue treatment were set to missing and subjects with missing IGA score at Week 16 were counted as non-responders. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	14	22	20
Units: Percentage of Subjects				
number (not applicable)	21.1	28.6	36.4	35.0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Both Investigator Global Assessment (IGA) Score 0 or 1 (on the 0 to 5 IGA Scale) and a Reduction From Baseline of ≥2 Points Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point title	Percentage of Subjects With Both Investigator Global Assessment (IGA) Score 0 or 1 (on the 0 to 5 IGA Scale) and a Reduction From Baseline of ≥2 Points Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point description:

IGA was an assessment scale used to determine severity of AD and clinical response to treatment on a 5 point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/infiltration. Therapeutic response was an IGA score of 0 (clear) or 1 (almost clear). Subjects with both IGA score of "0" or "1" and a reduction from baseline of ≥2 points at Week 16 based on all observed values regardless of rescue treatment were reported. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	23	26	24
Units: Percentage of Subjects				
number (not applicable)	17.4	21.7	38.5	29.2

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Weekly Average of Daily Peak Pruritus Numerical Rating Scale (NRS) Score Based on Observed Values Set to Missing After Rescue Treatment at Week 16

End point title	Absolute Change From Baseline in Weekly Average of Daily Peak Pruritus Numerical Rating Scale (NRS) Score Based on Observed Values Set to Missing After Rescue Treatment at Week 16

End point description:

Pruritus NRS was an assessment tool used to report the intensity of a subject’s pruritus (itch), both maximum and average intensity, using an electronic questionnaire (e-diary). Subjects were asked the following question: how would you rate your itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 - 10 [0 = no itch; 10 = worst itch imaginable]). Absolute change from baseline in weekly average of daily peak pruritus NRS score at Week 16 based on observed values set to missing after rescue treatment was reported. Values after first rescue treatment were set to missing and subjects with missing NRS score at Week 16 were counted as non-responders. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	12	17	14
Units: Scores on a Scale				
arithmetic mean (standard deviation)	-2.08 (± 2.825)	-2.90 (± 1.781)	-3.16 (± 2.607)	-3.92 (± 2.433)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Weekly Average of Daily Peak Pruritus NRS Score Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point title	Absolute Change From Baseline in Weekly Average of Daily Peak Pruritus NRS Score Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point description:

Pruritus NRS was an assessment tool used to report the intensity of a subject’s pruritus (itch), both maximum and average intensity, using an electronic questionnaire (e-diary). Subjects were asked the following question: how would you rate your itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 - 10 [0 = no itch; 10 = worst itch imaginable]). Absolute change from baseline in weekly average of daily peak pruritus NRS score at Week 16 based on all observed values regardless of rescue treatment was reported. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	15	18	17
Units: Scores on a Scale				
arithmetic mean (standard deviation)	-2.11 (± 2.651)	-2.87 (± 1.743)	-3.19 (± 2.532)	-3.64 (± 2.326)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Weekly Average of Daily Peak Pruritus NRS Score Based on Observed Values Set to Missing After Rescue Treatment at Week 16

End point title	Percent Change From Baseline in Weekly Average of Daily Peak Pruritus NRS Score Based on Observed Values Set to Missing After Rescue Treatment at Week 16

End point description:

Pruritus NRS was an assessment tool used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, using an electronic questionnaire (e-diary). Subjects were asked the following question: how would you rate your itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 - 10 [0 = no itch; 10 = worst itch imaginable]). Percent change from baseline in weekly average of daily peak pruritus NRS score at Week 16 based on observed values set to missing after rescue treatment was reported. Values after first rescue treatment were set to missing and subjects with missing NRS score at Week 16 were counted as non-responders. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	12	17	14
Units: Percentage of Change				
arithmetic mean (standard deviation)	-26.6 (± 36.71)	-38.0 (± 22.94)	-44.9 (± 35.73)	-60.2 (± 34.87)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Weekly Average of Daily Peak Pruritus NRS Score Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point title	Percent Change From Baseline in Weekly Average of Daily Peak Pruritus NRS Score Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point description:

Pruritus NRS was an assessment tool used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, using an electronic questionnaire (e-diary). Subjects were asked the following question: how would you rate your itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 - 10 [0 = no itch; 10 = worst itch imaginable]). Absolute change from baseline in weekly average of daily peak pruritus NRS score at Week 16 based on all observed values regardless of rescue treatment was reported. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	15	18	17
Units: Percentage of Change				
arithmetic mean (standard deviation)	-27.6 (± 35.04)	-37.8 (± 21.88)	-45.1 (± 34.68)	-55.7 (± 34.22)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Improvement (Reduction from Baseline) of Weekly Average of Peak Daily Pruritus NRS ≥4 Based on Observed Values Set to Missing After Rescue Treatment at Week 16

End point title	Percentage of Subjects With Improvement (Reduction from Baseline) of Weekly Average of Peak Daily Pruritus NRS ≥4 Based on Observed Values Set to Missing After Rescue Treatment at Week 16

End point description:

Pruritus NRS was an assessment tool used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, using an electronic questionnaire (e-diary). Subjects were asked the following question: how would you rate your itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 - 10 [0 = no itch; 10 = worst itch imaginable]). Percentage of subjects with improvement of weekly average of daily peak pruritus NRS from baseline to Week 16 based on observed values set to missing after rescue treatment were reported. Values after first rescue treatment were set to missing and subjects with missing NRS score at Week 16 were counted as non-responders. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	12	17	14
Units: Percentage of Subjects				
number (not applicable)	26.7	16.7	35.3	50.0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Improvement (Reduction from Baseline) of Weekly Average of Peak Daily Pruritus NRS ≥4 Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point title	Percentage of Subjects With Improvement (Reduction from Baseline) of Weekly Average of Peak Daily Pruritus NRS ≥4 Based on All Observed Values Regardless of Rescue Treatment at Week 16

End point description:

Pruritus NRS was an assessment tool used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, using an electronic questionnaire (e-diary). Subjects were asked the following question: how would you rate your itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 - 10 [0 = no itch; 10 = worst itch imaginable]). Percentage of subjects with improvement of weekly average of daily peak pruritus NRS from baseline to Week 16 based on all observed values regardless of rescue treatment were reported. FAS included all randomized subjects and was based on the treatment allocated (as randomized). Here, "Number of Subjects Analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	15	18	17
Units: Percentage of Subjects				
number (not applicable)	27.8	20.0	33.3	41.2

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Effect on Pruritus (≥4-point reduction of weekly average of daily peak Pruritus NRS from baseline)

End point title	Time to Onset of Effect on Pruritus (≥4-point reduction of weekly average of daily peak Pruritus NRS from baseline)

End point description:

Peak Pruritus NRS is an assessment tool used by subjects to report intensity of pruritus (itch) during a 24-hour recall period. Subjects were asked the following question: For maximum itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable,' how would you rate your

itch at the worst moment during the previous 24 hours?"

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51[3]	52[4]	51[5]	52[6]
Units: Hours				
median (full range (min-max))	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)

Notes:

[3] - Due to premature discontinuation, all analyses were changed to descriptive and were not summarized

[4] - Due to premature discontinuation, all analyses were changed to descriptive and were not summarized

[5] - Due to premature discontinuation, all analyses were changed to descriptive and were not summarized

[6] - Due to premature discontinuation, all analyses were changed to descriptive and were not summarized

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in SCORing Atopic Dermatitis (SCORAD) at Week 16

End point title	Percent Change From Baseline in SCORing Atopic Dermatitis (SCORAD) at Week 16

End point description:

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51[7]	52[8]	51[9]	52[10]
Units: Percentage of change				
arithmetic mean (standard deviation)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

Notes:

[7] - Due to premature discontinuation, all analyses were changed to descriptive and were not summarized

[8] - Due to premature discontinuation, all analyses were changed to descriptive and were not summarized
[9] - Due to premature discontinuation, all analyses were changed to descriptive and were not summarized
[10] - Due to premature discontinuation, all analyses were changed to descriptive and were not summarized

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Percent Body Surface Area (BSA) of Atopic Dermatitis (AD) Involvement at Week 16

End point title	Absolute Change From Baseline in Percent Body Surface Area (BSA) of Atopic Dermatitis (AD) Involvement at Week 16

End point description:

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51[11]	52[12]	51[13]	52[14]
Units: Score on a scale				
arithmetic mean (standard deviation)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

Notes:

[11] - Due to premature discontinuation, all analyses were changed to descriptive and were not summarized
[12] - Due to premature discontinuation, all analyses were changed to descriptive and were not summarized
[13] - Due to premature discontinuation, all analyses were changed to descriptive and were not summarized
[14] - Due to premature discontinuation, all analyses were changed to descriptive and were not summarized

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs and Adverse Events of Special Interest (AESIs) From Baseline up to Week 16

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs and Adverse Events of Special Interest (AESIs) From Baseline up to Week 16

End point description:

AE: any untoward medical occurrence in a subject administered a study drug which may/may not have a causal relationship with study drug. Serious AE: any untoward medical occurrence that resulted in any of following outcomes: death, life-threatening, required initial/prolonged in-subject hospitalization, persistent/significant disability/incapacity, congenital anomaly/birth defect/considered as medically

important event. TEAE was defined as AEs starting/worsening after first intake of the study drug. TEAEs included: SAEs and Non-SAEs. AESI included: Anaphylactic reactions; Systemic/severe hypersensitivity reactions; Malignancy; Helminthic infections; Suicide-related events; Severe injection site reactions; Mycosis fungoides/other forms of cutaneous T-cell lymphoma; Conjunctivitis and significant ALT elevation. Safety analysis set (SAF) included all randomized subjects who received any study drug and was based on the treatment received (as treated).

End point type	Secondary

End point timeframe:

Up to Week 16

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	52	51	52
Units: Subjects				
number (not applicable)				
Subjects with TEAEs	25	24	29	22
Subjects with Serious TEAEs	1	0	1	1
Subjects with AESIs	2	0	1	2

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs and Adverse Events of Special Interest (AESIs) From Baseline up to Week 36

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs and Adverse Events of Special Interest (AESIs) From Baseline up to Week 36

End point description:

AE: any untoward medical occurrence in a subject administered a study drug which may/may not have a causal relationship with study drug. Serious AE: any untoward medical occurrence that resulted in any of following outcomes: death, life-threatening, required initial/prolonged in-subject hospitalization, persistent/significant disability/incapacity, congenital anomaly/birth defect/considered as medically important event. TEAE was defined as AEs starting/worsening after first intake of the study drug. TEAEs included: SAEs and Non-SAEs. AESI included: Anaphylactic reactions; Systemic/severe hypersensitivity reactions; Malignancy; Helminthic infections; Suicide-related events; Severe injection site reactions; Mycosis fungoides/other forms of cutaneous T-cell lymphoma; Conjunctivitis and significant ALT elevation. SAF included all randomized subjects who received any study drug and was based on the treatment received (as treated).

End point type	Secondary

End point timeframe:

Up to week 36

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	52	51	52
Units: Subjects				
number (not applicable)				
Subjects with TEAEs	27	26	35	28
Subjects with Serious TEAEs	1	1	2	1
Subjects with AESIs	2	0	1	2

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Changes From Baseline in Laboratory Parameters

End point title	Number of Subjects With Clinically Significant Changes From Baseline in Laboratory Parameters

End point description:

The laboratory measurements included hematology, blood chemistry, urinalysis and pregnancy testing. Number of subjects with clinically significant changes from baseline in laboratory parameters were reported. Clinical significance was decided by investigator. SAF included all randomized subjects who received any study drug and was based on the treatment received (as treated).

End point type	Secondary

End point timeframe:

Up to week 36

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	52	51	52
Units: Subjects				
number (not applicable)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Changes From Baseline in Vital Signs

End point title	Number of Subjects With Clinically Significant Changes From Baseline in Vital Signs

End point description:

Vital sign assessment included blood pressure, heart rate, body temperature and respiration rate. Number of subjects with clinically significant changes form baseline in vital signs were reported. Clinical significance was decided by Investigator. SAF included all randomized subjects who received any study drug and was based on the treatment received (as treated).

End point type	Secondary

End point timeframe:

Up to week 36

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	52	51	52
Units: Subjects				
number (not applicable)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Changes From Baseline in 12-lead Electrocardiogram (ECG)

End point title	Number of Subjects With Clinically Significant Changes From Baseline in 12-lead Electrocardiogram (ECG)

End point description:

ECG recordings included ventricular heart rate, PR interval, QRS interval, corrected QT interval. Number of subjects with clinically significant changes from baseline in ECG were reported. Clinical significance was decided by Investigator. SAF included all randomized subjects who received any study drug and was based on the treatment received (as treated).

End point type	Secondary

End point timeframe:

Up to week 36

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	52	51	52
Units: Subjects				
number (not applicable)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Changes From Baseline in Physical Examination Findings

End point title	Number of Subjects With Clinically Significant Changes From Baseline in Physical Examination Findings

End point description:

Number of subjects with clinically significant changes from baseline in physical examination findings were reported. Clinical significance was decided by Investigator. SAF included all randomized subjects who received any study drug and was based on the treatment received (as treated).

End point type	Secondary

End point timeframe:

Up to week 36

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	52	51	52
Units: Subjects				
number (not applicable)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Positive Treatment-Emergent Anti-drug Antibodies (ADA) to REGN3500 and Dupilumab

End point title	Number of Subjects With Positive Treatment-Emergent Anti-drug Antibodies (ADA) to REGN3500 and Dupilumab

End point description:

Treatment-Emergent (TE) ADA: any positive post baseline assay response when baseline results were negative/missing. TE ADA responses were further classified as: - persistent (treatment-emergent positive ADA response detected in at least 2 consecutive post baseline samples separated by at least a 16-week post baseline period [based on nominal sampling time], with no ADA-negative samples in-between, regardless of any missing samples or a positive response at the last ADA sampling time point),- indeterminate (a positive assay response at the last collection time point only, regardless of any missing samples), - transient (not persistent/indeterminate, regardless of any missing samples). The ADA analysis set (AAS) included all subjects who received any study drug and had at least 1 non-missing ADA result in the respective ADA assays, after the first dose of the study drug. Here, “Number of Subjects Analysed” signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to week 36

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	48	44	46
Units: Subjects				
number (not applicable)				
Treatment-Emergent Response	0	0	3	6

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Functional REGN3500

End point title	Serum Concentration of Functional REGN3500

End point description:

Serum Concentration of Functional REGN3500 was reported. Pharmacokinetic (PK) analysis set included all randomized subjects who received any study drug (active or placebo [safety analysis set]) and who had at least 1 non-missing study drug concentration result following the first dose of study drug. Here, "n" signifies those subjects who were evaluable at given time points.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32 and 36

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[15]	52	0[16]	52
Units: Milligrams per Liter (mg/L)				
arithmetic mean (standard deviation)				
Week 0: (n = 52, 52)	()	0 (± 0)	()	0.00373 (± 0.0269)
Week 2: (n = 52, 51)	()	22.8 (± 9.06)	()	25.2 (± 9.58)
Week 4: (n = 48, 46)	()	41.6 (± 14.8)	()	41.9 (± 16.4)
Week 8: (n = 39, 43)	()	58.8 (± 20.5)	()	63.0 (± 22.8)
Week 12: (n = 30, 36)	()	67.4 (± 26.7)	()	74.5 (± 25.7)
Week 16: (n = 16, 21)	()	73.9 (± 31.4)	()	82.4 (± 33.5)
Week 20: (n = 9, 15)	()	33.3 (± 21.9)	()	45.1 (± 24.2)
Week 24: (n = 8, 11)	()	13.1 (± 11.9)	()	23.3 (± 14.4)
Week 28: (n = 5, 11)	()	7.31 (± 5.49)	()	12.3 (± 12.5)
Week 32: (n = 6, 10)	()	4.61 (± 4.48)	()	5.43 (± 4.12)
Week 36: (n = 7, 11)	()	2.42 (± 2.70)	()	2.79 (± 2.48)

Notes:

[15] - Data was reported for REGN3500 300 mg Q2W and REGN3500 300 mg + Dupilumab 300 mg Q2W arms only

[16] - Data was reported for REGN3500 300 mg Q2W and REGN3500 300 mg + Dupilumab 300 mg

Q2W arms only

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Functional Dupilumab

End point title	Serum Concentration of Functional Dupilumab

End point description:

Serum Concentration of Functional Dupilumab was reported. PK analysis set included all randomized subjects who received any study drug (active or placebo [safety analysis set]) and who had at least 1 non-missing study drug concentration result following the first dose of study drug. Here, "n" signifies those subjects who were evaluable at given time points.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32 and 36

End point values	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W	REGN3500 300 mg + Dupilumab 300 mg Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[17]	0[18]	51	52
Units: mg/L				
arithmetic mean (standard deviation)				
Week 0: (n = 51, 52)	()	()	0 (± 0)	0.00219 (± 0.0158)
Week 2: (n = 50, 51)	()	()	51.4 (± 19.0)	50.6 (± 19.0)
Week 4: (n = 47, 46)	()	()	51.5 (± 23.6)	57.6 (± 26.1)
Week 8: (n = 40, 43)	()	()	63.0 (± 32.5)	64.9 (± 26.3)
Week 12: (n = 37, 36)	()	()	70.4 (± 37.8)	69.6 (± 29.2)
Week 16: (n = 23, 21)	()	()	73.4 (± 39.2)	71.6 (± 30.9)
Week 20: (n = 15, 15)	()	()	25.8 (± 26.9)	28.0 (± 24.8)
Week 24: (n = 14, 11)	()	()	4.36 (± 8.97)	6.50 (± 12.5)
Week 28: (n = 14, 11)	()	()	1.47 (± 3.86)	2.39 (± 7.93)
Week 32: (n = 14, 10)	()	()	0.0227 (± 0.0850)	0 (± 0)
Week 36: (n = 11, 11)	()	()	0 (± 0)	0 (± 0)

Notes:

[17] - Data was reported for Dupilumab 300 mg Q2W and REGN3500 300 mg + Dupilumab 300 mg Q2W arms only

[18] - Data was reported for Dupilumab 300 mg Q2W and REGN3500 300 mg + Dupilumab 300 mg Q2W arms only

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the end of study (Week 36) regardless of seriousness or relationship to investigational product (IP).

Adverse event reporting additional description:

SAF included all randomized subjects who received any study drug and was based on the treatment received (as treated).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Placebo Q2W

Reporting group description:

Subjects received 2 subcutaneous (SC) injections of placebo matched to REGN3500 and 2 SC injections of placebo matched to Dupilumab (loading dose) on Day 1 and then 2 SC injections of placebo matched to REGN3500 and 1 SC injection of placebo matched to Dupilumab Q2W up to Week 14.

Reporting group title	REGN3500 300 mg Q2W

Reporting group description:

Subjects received 2 SC injections of REGN3500 at a dose of 150 mg (300 mg loading dose) and 2 SC injections of placebo matched to Dupilumab (loading dose) on Day 1 and then 2 SC injections of REGN3500 at a dose of 150 mg (300 mg loading dose) and 1 SC injection of placebo matched to Dupilumab Q2W up to Week 14.

Reporting group title	Dupilumab 300 mg Q2W

Reporting group description:

Subjects received 2 SC injections of REGN3500 at a dose of 150 mg (300 mg loading dose) and 2 SC injections of placebo matched to Dupilumab (loading dose) on Day 1 and then 2 SC injections of REGN3500 at a dose of 150 mg (300 mg loading dose) and 1 SC injection of placebo matched to Dupilumab Q2W up to Week 14.

Reporting group title	REGN3500 300 mg and Dupilumab 300 mg Q2W

Reporting group description:

Subjects received 2 SC injections of REGN3500 at a dose of 150 mg (300 mg loading dose) and 2 SC injections of Dupilumab at a dose of 300 mg (600 mg loading dose) on Day 1 and then 2 SC injections of REGN3500 at a dose of 150 mg and 1 SC injection of Dupilumab at a dose of 300 mg Q2W up to Week 14.

Serious adverse events	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 50 (2.00%)	1 / 52 (1.92%)	2 / 51 (3.92%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	0 / 51 (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

Encephalopathy			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	0 / 51 (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
Intracranial aneurysm			
subjects affected / exposed	0 / 50 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ruptured cerebral aneurysm			
subjects affected / exposed	0 / 50 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	0 / 51 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	0 / 51 (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
Renal and urinary disorders			
Goodpasture's syndrome			
subjects affected / exposed	0 / 50 (0.00%)	0 / 52 (0.00%)	0 / 51 (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			
Sepsis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 52 (0.00%)	0 / 51 (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
Tracheobronchitis			

subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	0 / 51 (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	REGN3500 300 mg and Dupilumab 300 mg Q2W		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 52 (1.92%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intracranial aneurysm			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ruptured cerebral aneurysm			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	0 / 52 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Goodpasture's syndrome			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheobronchitis			
subjects affected / exposed	0 / 52 (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	Placebo Q2W	REGN3500 300 mg Q2W	Dupilumab 300 mg Q2W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 50 (34.00%)	15 / 52 (28.85%)	25 / 51 (49.02%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 50 (4.00%)	1 / 52 (1.92%)	3 / 51 (5.88%)
occurrences (all)	2	1	4
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	2 / 51 (3.92%)
occurrences (all)	0	1	3
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	2 / 50 (4.00%)	1 / 52 (1.92%)	3 / 51 (5.88%)
occurrences (all)	2	2	3

Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	7 / 50 (14.00%)	7 / 52 (13.46%)	8 / 51 (15.69%)
occurrences (all)	9	8	11
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 50 (16.00%)	5 / 52 (9.62%)	11 / 51 (21.57%)
occurrences (all)	9	5	14
Upper respiratory tract infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	2 / 51 (3.92%)
occurrences (all)	2	0	2
Conjunctivitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	6 / 51 (11.76%)
occurrences (all)	1	0	6
Oral herpes			
subjects affected / exposed	0 / 50 (0.00%)	0 / 52 (0.00%)	4 / 51 (7.84%)
occurrences (all)	0	0	4
Urinary tract infection			
subjects affected / exposed	0 / 50 (0.00%)	3 / 52 (5.77%)	1 / 51 (1.96%)
occurrences (all)	0	3	1

Non-serious adverse events	REGN3500 300 mg and Dupilumab 300 mg Q2W		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 52 (38.46%)		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			

Dermatitis atopic subjects affected / exposed occurrences (all)	10 / 52 (19.23%) 11		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 52 (11.54%) 6		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 4		
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Oral herpes subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 September 2018	• Modified exclusion criterion #4 to decrease the length of the washout period from 12 weeks or 5 half-lives • Added an inclusion criteria of an Investigator's Global Assessment (IGA) score ≥3 (on the 0 to 4 IGA scale, in which 3 was moderate and 4 was severe) at screening and baseline visits • Updated the randomization to include stratification by baseline disease severity (moderate [IGA=3] vs. severe [IGA=4] AD) • As per FDA comments, subject sample was positive in the REGN3500 ADA assay at Week 16 or the first time point analyzed, the Week 4 pharmacokinetic (PK) sample may be analyzed in the anti-drug antibody (ADA) assay • As per FDA request, physical examination added at Week 16
10 December 2018	• Revised text regarding onsite monitoring after each administration of study drug to indicate that the minimum 30 minutes monitoring may be extended to up to 2 hours as per country-specific requirements • Revised Inclusion Criterion number 1 to add an upper age limit of 75 years • Added text in Exclusion Criterion number 12 to specify that patients with a positive tuberculosis (TB) QuantiFERON test result will be excluded from the study • Added myocardial infarction, unstable arterial hypertension, unstable angina, and cerebrovascular accident as examples of uncontrolled cerebrocardiovascular conditions that will exclude a subject from the study
23 January 2019	• Added secondary safety and pharmacokinetic (PK) endpoints
17 July 2019	• The secondary safety endpoints were updated to include "incidence of treatment-emergent anti-drug antibodies (ADA) to REGN3500 and dupilumab over time" to reflect that this endpoint will be analyzed and to align with other ongoing studies in the REGN3500 clinical program • The neutrophil count qualifying for permanent discontinuation of study drug was changed from "≤0.5×10^3 per microliter (mcl)" to "≤1.0×10^3/mcl" • The exclusion criteria were updated to more broadly exclude subjects who have previously participated in any anti-IL-33 antibody class • Language was added to clarify that for the primary endpoint, the analysis will be comparing the REGN3500 300 mg every 2 weeks (Q2W) monotherapy treatment group to the placebo group

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 February 2020	The decision was made by the sponsor to terminate the study on 12 Feb 2020 due to lack of efficacy. Study enrollment was not complete at that time, therefore planned sample sizes were not met. Subjects discontinued study drug and transitioned into the post-treatment follow-up period.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

As a result of the decision to terminate the study, all statistical analyses were descriptive and no hypothesis testing was performed.

Notes: