Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Parallel-group, 12-week Proof-of-Concept (PoC) Study to Assess the Efficacy, Safety, and Tolerability of SAR440340/REGN3500 and the Coadministration of SAR440340 and Dupilumab in Patients with Moderate-to-severe Asthma who are not well Controlled on Inhaled Corticosteroid (ICS) Plus Long-acting 2 Adrenergic Agonist (LABA) Therapy

Summary

EudraCT number	2017-003289-29
Trial protocol	PL
Global end of trial date	07 August 2019

Results information

Result version number	v1
This version publication date	21 August 2020
First version publication date	21 August 2020

Trial information

Trial identification

Sponsor protocol code	ACT15102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03387852
WHO universal trial number (UTN)	U1111-1194-2185

Notes:

Sponsors

Sponsor organisation name	Sanofi-aventis Recherche & Développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	07 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of SAR440340 with or without dupilumab, compared to placebo, on reducing the incidence of loss of asthma control (LOAC) events.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject was participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	12 March 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 37
Country: Number of subjects enrolled	Argentina: 16
Country: Number of subjects enrolled	Chile: 30
Country: Number of subjects enrolled	Mexico: 22
Country: Number of subjects enrolled	Russian Federation: 44
Country: Number of subjects enrolled	Turkey: 26
Country: Number of subjects enrolled	Ukraine: 63
Country: Number of subjects enrolled	United States: 58
Worldwide total number of subjects	296
EEA total number of subjects	37

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)	262
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted from 12-March-2018 to 7-August-2019. Subjects were screened at 70 centres across 8 countries, out of which 68 centres randomised at least 1 subject.

Pre-assignment

Screening details:

A total of 499 subjects were screened, out of which 296 subjects were enrolled and randomised to 1 of the 4 treatment groups.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received 2 subcutaneous (SC) injections of SAR440340 placebo along with 1 SC injection of dupilumab placebo once every 2 weeks (Q2W) for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Matching Placebo for SAR440340
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subject received 2 SC injections of matching placebo for SAR440340 Q2W for 12 weeks. SC injection sites were to alternate between the upper thighs, 4 quadrants of the abdomen, or the upper arms, so that the same site was not injected twice during 2 consecutive visits.

Investigational medicinal product name	Matching Placebo for Dupilumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subject received 1 SC injection of matching placebo for dupilumab Q2W for 12 weeks. SC injection sites were to alternate between the upper thighs, 4 quadrants of the abdomen, or the upper arms, so that the same site was not injected twice during 2 consecutive visits.

Arm title	SAR440340 300 mg

Arm description:

Subjects received 2 injections of SAR440340 300 milligram (mg) along with 1 injection of dupilumab placebo, SC Q2W for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	SAR440340
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subject received 2 SC injections of SAR440340 Q2W for 12 weeks. SC injection sites were to alternate between the upper thighs, 4 quadrants of the abdomen, or the upper arms, so that the same site was not injected twice during 2 consecutive visits.

Investigational medicinal product name	Matching Placebo for Dupilumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subject received 1 SC injection of matching placebo for dupilumab Q2W for 12 weeks. SC injection sites were to alternate between the upper thighs, 4 quadrants of the abdomen, or the upper arms, so that the same site was not injected twice during 2 consecutive visits.

Arm title	SAR440340 + Dupilumab

Arm description:

Subjects received 2 injections of SAR440340 300 mg along with 1 injection of dupilumab 300 mg, SC Q2W for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	SAR440340
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subject received 2 SC injections of SAR440340 Q2W for 12 weeks. SC injection sites were to alternate between the upper thighs, 4 quadrants of the abdomen, or the upper arms, so that the same site was not injected twice during 2 consecutive visits.

Investigational medicinal product name	Dupilumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subject received 1 SC injection of dupilumab 300 mg Q2W for 12 weeks. SC injection sites were to alternate between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site was not injected twice during 2 consecutive visits.

Arm title	Dupilumab 300 mg

Arm description:

Subjects received 1 injection of dupilumab 300 mg along with 2 injections of SAR440340 placebo, SC Q2W for 12 weeks.

Arm type	Active comparator
Investigational medicinal product name	Dupilumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subject received 1 SC injection of dupilumab 300 mg Q2W for 12 weeks. SC injection sites were to alternate between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site was not injected twice during 2 consecutive visits.

Investigational medicinal product name	Matching Placebo for SAR440340
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subject received 2 SC injections of matching placebo for SAR440340 Q2W for 12 weeks. SC injection sites were to alternate between the upper thighs, 4 quadrants of the abdomen, or the upper arms, so that the same site was not injected twice during 2 consecutive visits.

Number of subjects in period 1	Placebo	SAR440340 300 mg	SAR440340 + Dupilumab
Started	74	73	74
Treated	74	73	74
Completed	41	55	47
Not completed	33	18	27
Randomised and not treated	-	-	-
LOAC	28	16	20
Other- Unspecified	1	1	2
Poor compliance to protocol	-	-	-
Adverse event (AE)	3	-	2
Withdrawal by subject	1	1	3

Number of subjects in period 1	Dupilumab 300 mg
Started	75
Treated	74
Completed	56
Not completed	19
Randomised and not treated	1
LOAC	14
Other- Unspecified	1
Poor compliance to protocol	1
Adverse event (AE)	-
Withdrawal by subject	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received 2 subcutaneous (SC) injections of SAR440340 placebo along with 1 SC injection of dupilumab placebo once every 2 weeks (Q2W) for 12 weeks.	
Reporting group title	SAR440340 300 mg
Reporting group description:	
Subjects received 2 injections of SAR440340 300 milligram (mg) along with 1 injection of dupilumab placebo, SC Q2W for 12 weeks.	
Reporting group title	SAR440340 + Dupilumab
Reporting group description:	
Subjects received 2 injections of SAR440340 300 mg along with 1 injection of dupilumab 300 mg, SC Q2W for 12 weeks.	
Reporting group title	Dupilumab 300 mg
Reporting group description:	
Subjects received 1 injection of dupilumab 300 mg along with 2 injections of SAR440340 placebo, SC Q2W for 12 weeks.	

Reporting group values	Placebo	SAR440340 300 mg	SAR440340 + Dupilumab
Number of subjects	74	73	74
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	47.0	49.0	49.1
standard deviation	± 11.4	± 13.9	± 12.0
Gender categorical Units: Subjects			
Female	47	50	51
Male	27	23	23
Race Units: Subjects			
White	71	68	69
Black or African American	1	3	2
Asian	0	2	1
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	2	0	1
Multiple	0	0	1

Reporting group values	Dupilumab 300 mg	Total	
Number of subjects	75	296	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	51.3		
standard deviation	± 12.7	-	
Gender categorical Units: Subjects			
Female	41	189	
Male	34	107	
Race Units: Subjects			
White	73	281	
Black or African American	0	6	
Asian	1	4	
Native Hawaiian or Other Pacific Islander	0	0	
American Indian or Alaska Native	1	4	
Multiple	0	1	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received 2 subcutaneous (SC) injections of SAR440340 placebo along with 1 SC injection of dupilumab placebo once every 2 weeks (Q2W) for 12 weeks.	
Reporting group title	SAR440340 300 mg
Reporting group description:	
Subjects received 2 injections of SAR440340 300 milligram (mg) along with 1 injection of dupilumab placebo, SC Q2W for 12 weeks.	
Reporting group title	SAR440340 + Dupilumab
Reporting group description:	
Subjects received 2 injections of SAR440340 300 mg along with 1 injection of dupilumab 300 mg, SC Q2W for 12 weeks.	
Reporting group title	Dupilumab 300 mg
Reporting group description:	
Subjects received 1 injection of dupilumab 300 mg along with 2 injections of SAR440340 placebo, SC Q2W for 12 weeks.	

Primary: Percentage of Subjects With Loss of Asthma Control

End point title	Percentage of Subjects With Loss of Asthma Control
End point description:	
A LOAC event during the treatment period was a deterioration of asthma defined as any of the following: a) a 30 percent (%) or greater reduction from baseline in morning peak expiratory flow (PEF) on 2 consecutive days; b) greater than or equal to (≥) 6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared to baseline) on 2 consecutive days; c) increase in ICS ≥4 times the last prescribed ICS dose (or ≥50% of the prescribed ICS dose at Baseline if background therapy withdrawal completed); d) required use of systemic (oral and/or parenteral) steroid treatment; e) required hospitalisation or emergency room visit. The analysis was performed on modified intent-to-treat (mITT) population that included all randomised subjects who have received at least 1 dose of investigational medicinal product (IMP) analysed according to the treatment group allocated by randomisation.	
End point type	Primary
End point timeframe:	
From Baseline up to Week 12	

End point values	Placebo	SAR440340 300 mg	SAR440340 + Dupilumab	Dupilumab 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74	73	74	74
Units: percentage of subjects				
number (not applicable)	40.5	21.9	27	18.9

Statistical analyses

Statistical analysis title	SAR440340 300 mg versus Placebo

Statistical analysis description:

Odds ratio, 95% CI, and p-value derived from logistic regression with treatment, baseline eosinophil strata, region, background ICS dose level at randomisation and number of exacerbation events (defined as required use of systemic [oral and/or parenteral] steroid treatment, or required hospitalisation or emergency room visit) within 1 year prior to screening.

Comparison groups	SAR440340 300 mg v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0214
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.423
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.203
upper limit	0.88

Statistical analysis title	SAR440340+Dupilumab versus Placebo

Statistical analysis description:

Odds ratio, 95% CI, and p-value derived from logistic regression with treatment, baseline eosinophil strata, region, background ICS dose level at randomisation and number of exacerbation events (defined as required use of systemic [oral and/or parenteral] steroid treatment, or required hospitalisation or emergency room visit) within 1 year prior to screening.

Comparison groups	SAR440340 + Dupilumab v Placebo
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0709
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.256
upper limit	1.057

Secondary: Change From Baseline at Week 12 in Pre-bronchodilator Forced Expiratory Volume in 1 Second (FEV1)

End point title	Change From Baseline at Week 12 in Pre-bronchodilator Forced Expiratory Volume in 1 Second (FEV1)

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Pre-bronchodilator FEV1 refers to the spirometry performed after a wash period of

bronchodilators (i.e., not earlier than 6 hours) after the last dose of albuterol/salbutamol or levalbuterol/levosalbutamol from a primed meter dose inhaler and withholding the last dose of LABA for at least 12 hours, and prior to administration of study drug. Analysis was performed on mITT population. Here, "Number of subjects analysed" signifies subjects with available data for this end-point.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	SAR440340 300 mg	SAR440340 + Dupilumab	Dupilumab 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	58	49	56
Units: litres				
arithmetic mean (standard deviation)	0.06 (± 0.35)	0.11 (± 0.34)	0.06 (± 0.37)	0.14 (± 0.43)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 12 in Post-bronchodilator Forced Expiratory Volume in 1 Second

End point title	Change From Baseline at Week 12 in Post-bronchodilator Forced Expiratory Volume in 1 Second

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Post-bronchodilator FEV1 refers to the spirometry performed within 30 minutes after administration of bronchodilator. Analysis was performed on mITT population. Here, "Number of subjects analysed" signifies subjects with available data for this end-point.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	SAR440340 300 mg	SAR440340 + Dupilumab	Dupilumab 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	58	51	57
Units: litres				
arithmetic mean (standard deviation)	-0.02 (± 0.27)	-0.00 (± 0.33)	0.06 (± 0.41)	0.09 (± 0.42)

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 final visit (Week 32) regardless of seriousness or relationship to IMP.

Adverse event reporting additional description:

Reported AEs and death are treatment-emergent AEs (TEAE) that developed/worsened, and death that occurred during TEAE period (time from 1st to last administration of IMP + 154 days). Analysis was performed on safety population that included all enrolled subjects who received at least 1 dose of study drug, analysed as per actual treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received 2 SC injections of SAR440340 placebo along with 1 SC injection of dupilumab placebo Q2W for 12 weeks.

Reporting group title	SAR440340 300 mg

Reporting group description:

Subjects received 2 injections of SAR440340 300 mg along with 1 injection of dupilumab placebo, SC Q2W for 12 weeks.

Reporting group title	SAR440340 + Dupilumab

Reporting group description:

Subjects received 2 injections of SAR440340 300 mg along with 1 injection of dupilumab 300 mg, SC Q2W for 12 weeks.

Reporting group title	Dupilumab 300 mg

Reporting group description:

Subjects received 1 injection of dupilumab 300 mg along with 2 injections of SAR440340 placebo, SC Q2W for 12 weeks.

Serious adverse events	Placebo	SAR440340 300 mg	SAR440340 + Dupilumab
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 74 (4.05%)	3 / 73 (4.11%)	2 / 74 (2.70%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Alcohol Poisoning			
subjects affected / exposed	0 / 74 (0.00%)	0 / 73 (0.00%)	0 / 74 (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
Vascular disorders			
Aortic Aneurysm			
subjects affected / exposed	0 / 74 (0.00%)	0 / 73 (0.00%)	0 / 74 (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
Deep Vein Thrombosis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	0 / 74 (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
Cardiac disorders			
Aortic Valve Incompetence			
subjects affected / exposed	0 / 74 (0.00%)	0 / 73 (0.00%)	0 / 74 (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			
Vascular Encephalopathy			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	0 / 74 (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 / 74 (0.00%)	0 / 73 (0.00%)	0 / 74 (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
Asthma			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	0 / 74 (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
Nasal Polyps			

subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	0 / 74 (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
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	1 / 74 (1.35%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess Jaw			
subjects affected / exposed	0 / 74 (0.00%)	0 / 73 (0.00%)	0 / 74 (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
Pneumonia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Acute			
subjects affected / exposed	0 / 74 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dupilumab 300 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 74 (4.05%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Alcohol Poisoning			

subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Aortic Aneurysm			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deep Vein Thrombosis			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Aortic Valve Incompetence			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Vascular Encephalopathy			
subjects affected / exposed	0 / 74 (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	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nasal Polyps			

subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess Jaw			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis Acute			
subjects affected / exposed	0 / 74 (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	SAR440340 300 mg	SAR440340 + Dupilumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 74 (41.89%)	29 / 73 (39.73%)	26 / 74 (35.14%)
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 74 (9.46%)	6 / 73 (8.22%)	5 / 74 (6.76%)
occurrences (all)	7	7	9
General disorders and administration site conditions			
Injection Site Reaction			

subjects affected / exposed	4 / 74 (5.41%)	1 / 73 (1.37%)	5 / 74 (6.76%)
occurrences (all)	6	1	16
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 74 (2.70%)	4 / 73 (5.48%)	2 / 74 (2.70%)
occurrences (all)	4	4	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 74 (6.76%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	5	1	0
Rhinitis Allergic			
subjects affected / exposed	1 / 74 (1.35%)	3 / 73 (4.11%)	0 / 74 (0.00%)
occurrences (all)	1	4	0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 74 (1.35%)	4 / 73 (5.48%)	2 / 74 (2.70%)
occurrences (all)	1	4	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 74 (12.16%)	13 / 73 (17.81%)	8 / 74 (10.81%)
occurrences (all)	10	15	8
Upper Respiratory Tract Infection Bacterial			
subjects affected / exposed	2 / 74 (2.70%)	1 / 73 (1.37%)	4 / 74 (5.41%)
occurrences (all)	2	1	4
Urinary Tract Infection			
subjects affected / exposed	2 / 74 (2.70%)	1 / 73 (1.37%)	5 / 74 (6.76%)
occurrences (all)	3	1	7
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	5 / 74 (6.76%)	3 / 73 (4.11%)	5 / 74 (6.76%)
occurrences (all)	6	3	7

Non-serious adverse events	Dupilumab 300 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 74 (37.84%)		
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	10 / 74 (13.51%) 12		
General disorders and administration site conditions Injection Site Reaction subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 4		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	1 / 74 (1.35%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Rhinitis Allergic subjects affected / exposed occurrences (all)	1 / 74 (1.35%) 1 5 / 74 (6.76%) 6		
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all)	3 / 74 (4.05%) 3		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper Respiratory Tract Infection Bacterial subjects affected / exposed occurrences (all) Urinary Tract Infection subjects affected / exposed occurrences (all) Viral Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	9 / 74 (12.16%) 11 2 / 74 (2.70%) 2 3 / 74 (4.05%) 3 2 / 74 (2.70%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 September 2018	1. Clarified that the safety population was analysed based on the actual treatment received and not the treatment group allocated by randomisation. 2. Added baseline background ICS dose level and number of exacerbation events within 1 year prior to screening as covariates in the logistic regression model. 3. Clarified that the responsibility of the data monitoring committee was to evaluate all study data (i.e., not limited to safety data). 4. Clarified that half of the subjects enrolled were to be on a medium dose of ICS and half on a high ICS dose, in order to have a broad representation of background therapy in the study. 5. Excluded subjects diagnosed with pulmonary or systemic disease associated with elevated peripheral eosinophil counts, eg, eosinophilic granulomatosis with polyangiitis. 6. Excluded subjects who had been treated with commercially available dupilumab. 7. Excluded subjects with known allergy to doxycycline or related compounds, or a known allergy to SAR440340 excipients. 8. Allowed samples collected for pharmacokinetics at Week 4 to be used for anti-drug antibodies (ADA) (anti-SAR440340 or anti-dupilumab antibodies) analysis, when ADA samples tests were positive at Week 12 or at the first post-treatment time point analysed. 9. Removed intra-articular steroids from permitted concomitant therapy. 10. Clarified that serum (not plasma) was collected for testing pulmonary and activation-regulated chemokine. 11. Modified the definition of overdose with non-investigational medicinal product (NIMP) to "An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the subject and defined as at least twice the maximum daily dose as specified in a drug label, within the intended therapeutic interval".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported