Clinical trial results:
A Randomized, Double-Blind, Phase 2, Placebo Controlled, 2 Arm Study To Evaluate Dupilumab In Patients With Bilateral Nasal Polyposis And Chronic Symptoms Of Sinusitis

Summary

EudraCT number	2013-001803-35
Trial protocol	BE SE ES
Global end of trial date	05 November 2014

Results information

Result version number	v1 (current)
This version publication date	06 April 2016
First version publication date	06 April 2016

Trial information

Trial identification

Sponsor protocol code	ACT12340

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01920893
WHO universal trial number (UTN)	U1111-1130-6475

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 & Developpement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Aventis Recherche & Developpement, 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	03 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the efficacy of dupilumab in the treatment of bilateral nasal polyp by assessment of the endoscopic nasal polyp score (NPS) in comparison to placebo.

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 is 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 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:

Mometasone furoate nasal spray (MFNS - 100 µg in each nostril twice daily) was administered during a 4-week run-in period and then continued throughout the study.

Evidence for comparator: -

Actual start date of recruitment	27 August 2013
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	Spain: 18
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	60
EEA total number of subjects	44

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)	60
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 14 sites in 4 countries. A total of 60 subjects were randomized between August 2013 and March 2014.

Pre-assignment

Screening details:

Randomization was stratified according to medical history of asthma (with/without asthma) and by nasal biopsy (biopsy performed Yes/No). Assignment to arms was done centrally using Interactive Voice/Web Response System in 1:1 ratio (dupilumab : placebo) after the 4-week run-in period on MFNS and confirmation of selection criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo (for dupilumab), 2 subcutaneous injections on Day 1 as a loading dose followed by a single injection every week from Week 1 to 15 in combination with MFNS.

Arm type	Placebo
Investigational medicinal product name	Placebo (for dupilumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection (2 mL) in the abdomen or upper thigh.

Arm title	Dupilumab

Arm description:

Dupilumab, 2 Subcutaneous injections on Day 1 as a loading dose for a total of 600 mg, followed by a single 300 mg injection every week from Week 1 to 15 in combination with MFNS.

Arm type	Experimental
Investigational medicinal product name	Dupilumab
Investigational medicinal product code	SAR231893, REGN668
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection (150 mg/mL) in the abdomen or upper thigh.

Number of subjects in period 1	Placebo	Dupilumab
Started	30	30
Treated (safety population)	30	30
Completed	23	28
Not completed	7	2
Adverse event	5	2
Lack of efficacy	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo (for dupilumab), 2 subcutaneous injections on Day 1 as a loading dose followed by a single injection every week from Week 1 to 15 in combination with MFNS.	
Reporting group title	Dupilumab
Reporting group description:	
Dupilumab, 2 Subcutaneous injections on Day 1 as a loading dose for a total of 600 mg, followed by a single 300 mg injection every week from Week 1 to 15 in combination with MFNS.	

Reporting group values	Placebo	Dupilumab	Total
Number of subjects	30	30	60
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	49.3	47.4	
standard deviation	± 9.1	± 9.8	-
Gender categorical Units: Subjects			
Female	14	12	26
Male	16	18	34
Number of subjects with asthma			
The diagnosis of asthma was based on subject history; subjects with asthma were required to have a forced expiratory volume in 1 second (FEV1) of more than 60% of predicted use, daily inhaled corticosteroids of no more than 1000 µg of fluticasone (or equivalent), and could not have had an asthma exacerbation requiring systemic corticosteroids or hospitalization within the prior 3 months.			
Units: Subjects			
Yes	19	16	35
No	11	14	25

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo (for dupilumab), 2 subcutaneous injections on Day 1 as a loading dose followed by a single injection every week from Week 1 to 15 in combination with MFNS.	
Reporting group title	Dupilumab
Reporting group description:	
Dupilumab, 2 Subcutaneous injections on Day 1 as a loading dose for a total of 600 mg, followed by a single 300 mg injection every week from Week 1 to 15 in combination with MFNS.	

Primary: Change From Baseline in Bilateral Endoscopic Nasal Polyp Score (NPS) at Week 16

End point title	Change From Baseline in Bilateral Endoscopic Nasal Polyp Score (NPS) at Week 16
End point description:	
NPS was the sum of the right and left nostril scores, as evaluated by means of nasal endoscopy. Total score ranges from 0 to 8 (scored 0 to 4 for each nostril), with a lower score indicating smaller-sized polyps. Analysis population = Intent-to-treat (ITT) population (ie. all randomized subjects analyzed according to the treatment group allocated by randomization). Here, 'n' signifies the number of subjects with available data for NPS.	
End point type	Primary
End point timeframe:	
Baseline, Week 16	

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=30, 30)	5.67 (± 0.88)	5.87 (± 1.01)		
Week 16 (n=23, 29)	5.39 (± 1.47)	3.97 (± 1.9)		
Change from baseline at Week 16 (n=23, 29)	-0.26 (± 1.32)	-1.9 (± 1.76)		

Statistical analyses

Statistical analysis title	Dupilumab vs Placebo
Statistical analysis description:	
Analysis was performed by a mixed model repeated measures (MMRM) model.	
Comparison groups	Dupilumab v Placebo

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0009
Method	Mixed models analysis
Parameter estimate	Least Square (LS) mean difference
Point estimate	-1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.43
upper limit	-0.67

Notes:

[1] - Threshold for significance at 0.05.

Secondary: Change from Baseline in Bilateral Endoscopic NPS at Week 16 in Subjects with Asthma

End point title	Change from Baseline in Bilateral Endoscopic NPS at Week 16 in Subjects with Asthma

End point description:

Analysis population = subjects of the ITT population with asthma and with available data at Week 16

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: score on a scale				
arithmetic mean (standard deviation)	0.27 (± 0.88)	-2.4 (± 2.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject Reported Symptoms of Sinusitis at Week 16

End point title	Change from Baseline in Subject Reported Symptoms of Sinusitis at Week 16

End point description:

Morning symptoms of sinusitis (nasal congestion/obstruction, anterior rhinorrhea [runny nose], posterior rhinorrhea [post nasal drip], and loss of sense of smell) were assessed using a 0-3 categorical scale where higher score indicates severe symptoms.

Severity of rhinosinusitis symptoms were assessed on a 0-10 Visual Analogue Scale (VAS) where higher score indicates worst thinkable troublesome.

Analysis population = ITT population.

Here, 'n' signifies the number of subjects with available data for individual symptom score.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: score on a scale				
arithmetic mean (standard deviation)				
Congestion/obstruction (n= 23, 29)	-0.26 (± 0.7)	-0.95 (± 0.86)		
Runny nose (n= 23, 29)	-0.1 (± 0.58)	-0.62 (± 0.9)		
Post nasal drip (23, 29)	-0.15 (± 0.59)	-0.49 (± 0.78)		
Loss of smell (23, 29)	-0.3 (± 0.6)	-1.36 (± 1.08)		
Rhinosinusitis symptoms severity (n=19, 28)	-1.84 (± 3.6)	-4.32 (± 2.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Nasal Peak Inspiratory Flow (NPIF) at Week 16

End point title	Change from Baseline in Nasal Peak Inspiratory Flow (NPIF) at Week 16

End point description:

NPIF evaluation represents a physiologic measure of the air flow through both nasal cavities during forced inspiration and/or expiration expressed in liter per minute.

Analysis population = subjects from ITT population with data available for NPIF at Week 16.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	29		
Units: Liter/minute				
arithmetic mean (standard deviation)				
NPIF-Morning	28.81 (± 34.26)	61.91 (± 43.39)		
NPIF-Evening	26.65 (± 34.31)	61.25 (± 45.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Smell Test (University of Pennsylvania Smell Identification Test [UPSIT]) at Week 16

End point title	Change from Baseline in Smell Test (University of Pennsylvania Smell Identification Test [UPSIT]) at Week 16

End point description:

UPSIT was a 40-item test to measure the individual's ability to detect odors. Total score ranges from 0-40; lower score indicates severe smell loss. Analysis population = subjects from ITT population with data available for UPSIT at Week 16.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	28		
Units: score on scale				
arithmetic mean (standard deviation)	-0.17 (± 5.1)	15.36 (± 9.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sinus Computed Tomography (CT) Scan Assessments at Week 16

End point title	Change from Baseline in Sinus Computed Tomography (CT) Scan Assessments at Week 16

End point description:

CT scan assessment included Lund-Mackay score and percent of the maxillary sinuses occupied by disease. The Lund-Mackay scoring system rates each of both the left and right frontal, maxillary, sphenoid, ostiomeatal complex, anterior ethmoid and posterior ethmoid sinuses. The total score ranges from 0-24; higher score indicates worse status. Analysis population = subjects from ITT population with CT scan data available at Week 16.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	29		
Units: specified in categories				
arithmetic mean (standard deviation)				
Lund-Mackay Score (Unit: score on scale)	-0.23 (± 3.74)	-9.24 (± 4.58)		
Area occupied by disease (unit: percent area)	-3.92 (± 20.54)	-35.66 (± 24.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Response in NPS: Kaplan-Meier Estimate at Week 16

End point title	Time to First Response in NPS: Kaplan-Meier Estimate at Week 16

End point description:

NPS response was defined as ≥1 point reduction from baseline. The probability of response at Week 16 is provided. Analysis population = ITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: Probability of response				
number (confidence interval 95%)	0.44 (0.242 to 0.638)	0.828 (0.69 to 0.965)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in 22-item Sinonasal Outcome Test (SNOT-22) at Week 16

End point title	Change from Baseline in 22-item Sinonasal Outcome Test (SNOT-22) at Week 16

End point description:

The SNOT-22 was a validated questionnaire to assess the impact of chronic rhinosinusitis on quality of life. The total score may range from 0-110, higher score represents worst quality of life; minimal

clinically important change ≥8.90. Analysis population = subjects from ITT population with SNOT-22 data available at Week 16

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	29		
Units: score on a scale				
arithmetic mean (standard deviation)	-8.26 (± 17.63)	-29.1 (± 19.9)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Change from Baseline in Nasal Total Symptoms Score (nTSS) at Week 16

End point title	Change from Baseline in Nasal Total Symptoms Score (nTSS) at Week 16

End point description:

nTSS was the sum of subject-assessed nasal symptom scores for nasal congestion/obstruction, decreased/loss of sense of smell, and rhinorrhea (anterior/posterior nasal discharge) using a 0-3 categorical scale. Total score ranges from 0 to 9. Higher score indicates severe symptoms. Analysis population =subjects from ITT population with nTSS data available at Week 16.

End point type	Post-hoc

End point timeframe:

Baseline, Week 16

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	29		
Units: score on a scale				
arithmetic mean (standard deviation)				
nTSS - Morning	-0.68 (± 1.44)	-2.87 (± 2.09)		
nTSS - Evening	-0.77 (± 1.48)	-2.9 (± 2.04)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 32) regardless of seriousness or relationship to investigational medicinal product (IMP).

Adverse event reporting additional description:

Reported AEs and deaths are treatment-emergent that is AEs that developed/worsened and deaths that occurred during the 'treatment emergent period' (from the first dose of the double-blind IMP injection up to the end of the 16 weeks post-treatment period).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects exposed to placebo (for dupilumab) in combination with MFNS (mean exposure of 96.2 days).

Reporting group title	Dupilumab

Reporting group description:

Subjects exposed to dupilumab in combination with MFNS (mean exposure of 108.6 days).

Serious adverse events	Placebo	Dupilumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 30 (13.33%)	2 / 30 (6.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine Cancer			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoaesthesia			

subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mononeuropathy			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal Polyps			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain In Extremity			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Herpes Zoster			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Dupilumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 30 (73.33%)	27 / 30 (90.00%)	
Investigations			
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 30 (3.33%)	3 / 30 (10.00%)	
occurrences (all)	1	7	
Headache			
subjects affected / exposed	5 / 30 (16.67%)	6 / 30 (20.00%)	
occurrences (all)	5	14	
Sinus Headache			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	8	3	
General disorders and administration site conditions			
Injection Site Reaction			
subjects affected / exposed	2 / 30 (6.67%)	12 / 30 (40.00%)	
occurrences (all)	3	50	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	
occurrences (all)	5	2	
Cough			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Epistaxis			

subjects affected / exposed	2 / 30 (6.67%)	7 / 30 (23.33%)	
occurrences (all)	2	8	
Nasal Polyps			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Oropharyngeal Pain			
subjects affected / exposed	2 / 30 (6.67%)	7 / 30 (23.33%)	
occurrences (all)	2	7	
Rhinalgia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Rhinitis Allergic			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Upper-Airway Cough Syndrome			
subjects affected / exposed	3 / 30 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	4	
Back Pain			
subjects affected / exposed	0 / 30 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 30 (13.33%)	1 / 30 (3.33%)	
occurrences (all)	4	1	
Nasopharyngitis			
subjects affected / exposed	10 / 30 (33.33%)	14 / 30 (46.67%)	
occurrences (all)	13	20	
Sinusitis			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	3	
Upper Respiratory Tract Infection			

subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	4 / 30 (13.33%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2013	Addition of a nasal secretion sampling at screening visit for the purpose of assay validation of biomarker in the unique biomatrix; Permitted concomitant medication was changed to provide more information on a potential effect of dupilumab on CYP450 and a list of CYP450 substrates with narrow therapeutic index to ensure monitoring and if needed dose adjustment following the initiation and stopping of dupilumab; Clinical Study Director was changed.
27 November 2013	Simplification of the protocol concerning tissue collection and processing of nasal polyp biopsies.
16 December 2013	Simplification of exclusion criteria (clarification for previous treatment with dupilumab, definition of wash-out periods after systematic corticosteroids, details concerning nasal surgeries); Correction of two errors in the Study Flow Chart of the protocol; Clarification for allergen immunotherapy in regards prohibited and permitted concomitant medication; Deletion of one sentence concerning IMP administration at home in the safety instructions as IMP was to be administered at the site only; Forced expiratory volume (FEV) threshold at screening in subjects with asthma was changed from FEV ≥60% to FEV >60% of predicted normal.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26836729