Clinical trial results:
A Randomized, Double-blind, Parallel-group, Placebo-controlled Study to Assess the Safety of REGN668 Administered Concomitantly with Topical Corticosteroids to Patients with Moderate-to-severe Atopic Dermatitis

Summary

EudraCT number	2012-000946-37
Trial protocol	HU DE
Global end of trial date	20 December 2012

Results information

Result version number	v1
This version publication date	09 May 2017
First version publication date	09 May 2017

Trial information

Trial identification

Sponsor protocol code	R668-AD-1121

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01639040
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Rd, Tarrytown, United States, 10591
Public contact	Clinical Trial Management, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com
Scientific contact	Clinical Trial Management, Regeneron Pharmaceuticals, Inc., 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	31 January 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 December 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the safety of repeated subcutaneous doses of Dupilumab (REGN668/SAR231893) administered concomitantly with topical corticosteroids (TCS) 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 Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy:

All subjects received concomitant, open-label, daily treatment for up to 28 days with Class 3 or 4 midpotency a topical corticosteroid (TCS) such as methylprednisolone aceponate 0.1%, mometasone furoate 0.1%, or betamethasone valerate 0.1%.

Evidence for comparator: -

Actual start date of recruitment	30 July 2012
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	Germany: 15
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Poland: 13
Worldwide total number of subjects	31
EEA total number of subjects	31

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)	30
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 38 subjects were screened in the study between 30 July 2012 and 20 December 2012.

Pre-assignment

Screening details:

Out of 38 subjects, 31 were randomized and treated in the study. Subjects were randomized in 2:1 ratio to receive Dupilumab 300 mg or Placebo.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo QW

Arm description:

Placebo (for Dupilumab) once weekly (QW) for 4 weeks by subcutaneous injection with the background therapy of potent topical corticosteroid (TCS) for up to 28 days

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:

Single subcutaneous injection in the abdomen or thigh.

Arm title	Dupilumab 300 mg QW

Arm description:

Dupilumab 300 mg once weekly (QW) for 4 weeks by subcutaneous injection with the background therapy of potent TCS for up to 28 days

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

Dosage and administration details:

Single subcutaneous injection in the abdomen or thigh.

Number of subjects in period 1	Placebo QW	Dupilumab 300 mg QW
Started	10	21
Completed	9	21
Not completed	1	0
Adverse event	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo QW
Reporting group description:	
Placebo (for Dupilumab) once weekly (QW) for 4 weeks by subcutaneous injection with the background therapy of potent topical corticosteroid (TCS) for up to 28 days	

Reporting group title	Dupilumab 300 mg QW
Reporting group description:	
Dupilumab 300 mg once weekly (QW) for 4 weeks by subcutaneous injection with the background therapy of potent TCS for up to 28 days	

Reporting group values	Placebo QW	Dupilumab 300 mg QW	Total
Number of subjects	10	21	31
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	37.8	36	
standard deviation	± 16.73	± 11.26	-
Gender categorical			
Units: Subjects			
Female	5	13	18
Male	5	8	13
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, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score range from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD.			
Units: units on a scale			
arithmetic mean	24.1	23.1	
standard deviation	± 12.7	± 12.35	-
Investigator’s Global Assessment (IGA) Score			
IGA was an assessment scale used to determine severity of AD and clinical response to treatment on a 6-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe; and 5 = very severe disease) based on erythema and papulation/infiltration. Therapeutic response was an IGA score of 0 (clear) or 1 (almost clear).			
Units: units on a scale			
arithmetic mean	3.4	3.4	
standard deviation	± 0.47	± 0.6	-
Pruritus Numerical Rating Scale (NRS) score			
Pruritus NRS was an assessment tool that was used to report intensity of subject’s pruritus (itch), both maximum and average intensity during a 24-hour recall period. Subjects were asked following question: how would a subject rate his itch at worst moment during previous 24 hours (for maximum itch intensity on a scale of 0–10 [0 = no itch; 10 = worst itch imaginable]).			
Units: units on a scale			
arithmetic mean	5	6.4	

standard deviation	± 1.39	± 2	-

End points

End points reporting groups

Reporting group title	Placebo QW

Reporting group description:

Placebo (for Dupilumab) once weekly (QW) for 4 weeks by subcutaneous injection with the background therapy of potent topical corticosteroid (TCS) for up to 28 days

Reporting group title	Dupilumab 300 mg QW

Reporting group description:

Dupilumab 300 mg once weekly (QW) for 4 weeks by subcutaneous injection with the background therapy of potent TCS for up to 28 days

Primary: Percentage of Participants With Treatment Emergent Adverse Events (TEAEs)

End point title	Percentage of Participants With Treatment Emergent Adverse Events (TEAEs)[1]

End point description:

Any untoward medical occurrence in a subject who received investigational medicinal product (IMP) was considered an AE without regard to possibility of causal relationship with this treatment. Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened or became serious during on-treatment period (from start of administration of first dose of study drug to the end of study [up to Day 78]). A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in any of following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included subjects with both serious and non-serious AEs. Safety population included all randomized subjects who received any study drug, based on treatment received.

End point type	Primary

End point timeframe:

Baseline up to the end of study (up to Day 78)

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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Placebo QW	Dupilumab 300 mg QW		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	21		
Units: percentage of participants				
number (not applicable)				
With at least one TEAE	70	57.1		
With study drug related TEAEs	40	28.6		
With serious TEAEs	10	0		
With TEAEs resulting in study discontinuation	10	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Participants Achieving Eczema Area and Severity Index (EASI) Score: Reduction of ≥50 at Day 29 - Censored Last Observation Carried Forward (LOCF)

End point title	Percentage of Participants Achieving Eczema Area and Severity Index (EASI) Score: Reduction of ≥50 at Day 29 - Censored Last Observation Carried Forward (LOCF)

End point description:

The EASI score was used to measure the severity and extent of atopic dermatitis (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 range from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. Efficacy data were set to missing after prohibited medication was used or after subject was discontinued from the study. All missing values were imputed by simple LOCF. Full analysis set (FAS) included all randomized subjects received at least 1 dose of study drug and had at least 1 post-baseline assessment, based on the treatment allocated (as randomized).

End point type	Other pre-specified

End point timeframe:

Day 29

End point values	Placebo QW	Dupilumab 300 mg QW		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	21		
Units: percentage of participants				
number (confidence interval 95%)	50 (18.7 to 81.3)	100 (83.9 to 100)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change in Pruritus Numerical Rating Scale (NRS) From Day 1 (Baseline) to Day 29 (Week 4)

End point title	Percent Change in Pruritus Numerical Rating Scale (NRS) From Day 1 (Baseline) to Day 29 (Week 4)

End point description:

Pruritus NRS was an assessment tool that was used to report the intensity of subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his 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]). FAS included all randomized subjects received at least 1 dose of study drug and had at least 1 post-baseline assessment, based on the treatment allocated (as randomized).

End point type	Other pre-specified

End point timeframe:

Baseline up to Day 29

End point values	Placebo QW	Dupilumab 300 mg QW		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	21		
Units: percent change				
arithmetic mean (standard deviation)	-24.7 (± 47.3)	-70.7 (± 21.45)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants Achieving an Investigator's Global Assessment (IGA) Score of "0" or "1" at Day 29

End point title	Number of Participants Achieving an Investigator's Global Assessment (IGA) Score of "0" or "1" at Day 29

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). FAS included all randomized subjects received at least 1 dose of study drug and had at least 1 post-baseline assessment, based on the treatment allocated (as randomized).

End point type	Other pre-specified

End point timeframe:

Day 29

End point values	Placebo QW	Dupilumab 300 mg QW		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	21		
Units: participants				
number (not applicable)	3	11		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change in Investigator's Global Assessment (IGA) Score From Day 1 (Baseline) to Day 29 (Week 4) - Censored LOCF

End point title	Percent Change in Investigator's Global Assessment (IGA) Score From Day 1 (Baseline) to Day 29 (Week 4) - Censored LOCF

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). The efficacy data were set to missing after prohibited medication was used or after the subject was discontinued from the study. Then, all missing values were imputed by simple LOCF. FAS included all randomized subjects received at least 1 dose of study drug and had at least 1 post-baseline assessment,

based on the treatment allocated (as randomized).

End point type	Other pre-specified

End point timeframe:

Baseline up to Day 29

End point values	Placebo QW	Dupilumab 300 mg QW		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	21		
Units: percent change				
arithmetic mean (standard deviation)	-30.6 (± 39)	-52.5 (± 21.44)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change in Eczema Area and Severity Index (EASI) Score From Day 1 (Baseline) to Day 29 (Week 4) - Censored LOCF

End point title	Percent Change in Eczema Area and Severity Index (EASI) Score From Day 1 (Baseline) to Day 29 (Week 4) - Censored LOCF

End point description:

EASI score was used to measure the severity and extent of atopic dermatitis (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. Efficacy data were set to missing after prohibited medication was used or after subject was discontinued from study. All missing values were imputed by simple LOCF. FAS included all randomized subjects received at least 1 dose of study drug and had at least 1 post-baseline assessment, based on the treatment allocated (as randomized).

End point type	Other pre-specified

End point timeframe:

Baseline up to Day 29

End point values	Placebo QW	Dupilumab 300 mg QW		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	21		
Units: Percent Change				
arithmetic mean (standard deviation)	-52.5 (± 39.53)	-75.6 (± 13.29)		

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 (Day 78) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that are AEs that developed/worsened during the 'on treatment period' (day from first dose of study drug to the end of study visit [up to Day 78]).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Placebo QW

Reporting group description:

Placebo (for Dupilumab) once weekly (QW) for 4 weeks by subcutaneous injection with the background therapy of potent topical corticosteroid (TCS) for up to 28 days

Reporting group title	Dupilumab 300 mg QW

Reporting group description:

Dupilumab 300 mg once weekly (QW) for 4 weeks by subcutaneous injection with the background therapy of potent TCS for up to 28 days

Serious adverse events	Placebo QW	Dupilumab 300 mg QW	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo QW	Dupilumab 300 mg QW	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)	8 / 21 (38.10%)	

Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 10 (10.00%)	3 / 21 (14.29%)	
occurrences (all)	6	8	
Loss of consciousness			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	0 / 10 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 10 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Oropharyngeal pain			
subjects affected / exposed	1 / 10 (10.00%)	3 / 21 (14.29%)	
occurrences (all)	1	4	
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal infection			

subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	0 / 10 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	2 / 10 (20.00%)	5 / 21 (23.81%)	
occurrences (all)	2	6	
Rhinitis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	3	
Sinusitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hyperlipidaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 April 2012	The purpose of the amendment was to indicate that collection of RNA samples (part of the research samples collected during the study) could have required separate informed consent, as required by local regulatory authorities.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

This was a small safety study that was not adequately powered to assess efficacy.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25006719