Clinical trial results:
A randomized, double-blind, placebo controlled, multiple dose study to evaluate the safety, tolerability, and efficacy of intravenous administration of secukinumab (AIN457) in patients with asthma not adequately controlled with inhaled corticosteroids and long acting beta-agonists

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2011-003117-41
Trial protocol	GB DE BG
Global end of trial date	26 October 2014

Results information

Result version number	v1 (current)
This version publication date	29 April 2016
First version publication date	29 April 2016

Trial information

Trial identification

Sponsor protocol code	CAIN457D2204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01478360
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
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Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	26 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

to assess whether treatment with 10 mg/kg secukinumab versus placebo over 8 weeks, in individuals with asthma who were symptomatic despite treatment with high doses of ICS, leads to significant improvement in the severity of asthma as measured by change in the asthma control questionnaire (ACQ) score at Day 85

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 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: 25
Country: Number of subjects enrolled	United Kingdom: 21
Worldwide total number of subjects	46
EEA total number of subjects	46

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)	42
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 46 subjects were randomized into the study, of which the majority of subjects (n=41) completed the study as planned.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	AIN457

Arm description:

AIN457 10 mg/kg

Arm type	Experimental
Investigational medicinal product name	Secukinumab
Investigational medicinal product code	AIN457
Other name	
Pharmaceutical forms	Intravesical solution/solution for injection
Routes of administration	Intracavernous use

Dosage and administration details:

AIN457 10 mg/kg

Arm title	Placebo

Arm description:

Placebo intravenous injection

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

Dosage and administration details:

IV

Number of subjects in period 1	AIN457	Placebo
Started	31	15
PD (Pharmacodynamic) analysis set	31	15
PK (Pharmacokinetics) analysis set	31	0 [1]

Completed	29	12
Not completed	2	3
Adverse event, non-fatal	-	1
Administrative problems	1	2
Lost to follow-up	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: A total of 46 subjects were randomized into the study, of which the majority of subjects (n=41) completed the study as planned.

Baseline characteristics

Reporting groups	
Reporting group title	AIN457
Reporting group description: AIN457 10 mg/kg	
Reporting group title	Placebo
Reporting group description: Placebo intravenous injection	

Reporting group values	AIN457	Placebo	Total
Number of subjects	31	15	46
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)	27	15	42
From 65-84 years	4	0	4
85 years and over	0	0	0
Age Continuous | Units: Years			
arithmetic mean	49.8	46.2	
standard deviation	± 11.62	± 10.4	-
Gender, Male/Female Units: Participants			
Female	16	7	23
Male	15	8	23

End points

End points reporting groups	
Reporting group title	AIN457
Reporting group description: AIN457 10 mg/kg	
Reporting group title	Placebo
Reporting group description: Placebo intravenous injection	

Primary: Improvement in the severity of asthma as measured by change in the asthma control questionnaire (ACQ) score

End point title	Improvement in the severity of asthma as measured by change in the asthma control questionnaire (ACQ) score
End point description: The ACQ scores range from 0 to 6 with lower scores reflecting better asthma control. Without loss of generality, as Day 85 minus baseline (Visit 3) so that improvements in asthma control translate to negative change scores.	
End point type	Primary
End point timeframe: Baseline and 85 Days	

End point values	AIN457	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	13		
Units: Score				
least squares mean (confidence interval 90%)	-0.173 (-0.425 to 0.079)	-0.007 (-0.38 to 0.365)		

Statistical analyses

Statistical analysis title	Improvement in the severity of asthma
Comparison groups	Placebo v AIN457
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5392
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.166

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.617
upper limit	0.285

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	AIN457 10mg/kg
Reporting group description:	
AIN457 10mg/kg	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	AIN457 10mg/kg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 31 (3.23%)	2 / 15 (13.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
WRIST FRACTURE			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (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			
INTERVERTEBRAL DISC PROTRUSION			

subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
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	AIN457 10mg/kg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 31 (67.74%)	13 / 15 (86.67%)	
Investigations			
BODY TEMPERATURE INCREASED			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
WEIGHT INCREASED			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	1 / 31 (3.23%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
NAIL INJURY			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
PERIORBITAL CONTUSION			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	1 / 31 (3.23%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
HEADACHE			
subjects affected / exposed	3 / 31 (9.68%)	4 / 15 (26.67%)	
occurrences (all)	4	7	
General disorders and administration site conditions			

CHILLS			
subjects affected / exposed	1 / 31 (3.23%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
FATIGUE			
subjects affected / exposed	1 / 31 (3.23%)	1 / 15 (6.67%)	
occurrences (all)	1	5	
FEELING COLD			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
VESSEL PUNCTURE SITE BRUISE			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
TINNITUS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
ABDOMINAL RIGIDITY			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
CONSTIPATION			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
DIARRHOEA			
subjects affected / exposed	0 / 31 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
NAUSEA			
subjects affected / exposed	2 / 31 (6.45%)	4 / 15 (26.67%)	
occurrences (all)	3	6	
VOMITING			
subjects affected / exposed	1 / 31 (3.23%)	3 / 15 (20.00%)	
occurrences (all)	1	5	
Respiratory, thoracic and mediastinal disorders			

COUGH			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
DYSPNOEA			
subjects affected / exposed	3 / 31 (9.68%)	1 / 15 (6.67%)	
occurrences (all)	6	1	
ASTHMA			
subjects affected / exposed	7 / 31 (22.58%)	2 / 15 (13.33%)	
occurrences (all)	17	2	
HAEMOPTYSIS			
subjects affected / exposed	2 / 31 (6.45%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
OROPHARYNGEAL PAIN			
subjects affected / exposed	1 / 31 (3.23%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
RHINORRHOEA			
subjects affected / exposed	0 / 31 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	2 / 31 (6.45%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
MUSCLE SPASMS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Infections and infestations			
CYSTITIS			
subjects affected / exposed	2 / 31 (6.45%)	0 / 15 (0.00%)	
occurrences (all)	2	0	

LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 31 (9.68%)	2 / 15 (13.33%)	
occurrences (all)	4	2	
NASOPHARYNGITIS			
subjects affected / exposed	11 / 31 (35.48%)	6 / 15 (40.00%)	
occurrences (all)	19	11	
OTITIS EXTERNA			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
VIRAL INFECTION			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
IRON DEFICIENCY			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2011	To update the CTCAE (common terminology criteria for adverse events) version number, used for grading adverse events per FDA request. To avoid interference from bronchodilator medicines subjects were asked, where feasible, to withhold their normal morning asthma medications on days on which they attended the site for measurements of spirometry and FeNO until these measurements were complete. The eligibility criteria were amended to include only subjects with serum IgE <500 IU/mL.
14 March 2012	This protocol was amended in response to feedback from investigators. The amendment included some study restrictions such as avoiding nitrate rich foods prior to measurements of fractional exhaled nitric oxide (FeNO) and withholding long- and short-acting antihistamines prior to the skin prick testing. The requirement to avoid nitrate-rich food prior to measurement of FeNO was provided in a separate manual and the requirement to withhold antihistamines was included in the published guidelines that were referenced in the protocol.
03 September 2012	Feedback from investigators suggested that a significant proportion of the target population with uncontrolled asthma presented with Asthma Control Questionnaire (ACQ) scores between ≥ 1.5 and 2.0, and a significant proportion was between the age of 65 and 75 years. In order to allow this population to enter the trial, the eligibility criterion for baseline ACQ score will be changed from > 2.0 to ≥ 1.5 and the upper age limit will be increased from 65 years to 75 years.
09 May 2014	This protocol was amended primarily to increase the planned enrollment of the study to enable inclusion of a sufficient number of subjects for efficacy analyses in one or more subpopulations. The study enrollment was therefore increased to approximately 84 subjects randomized with an aim of at least 72 subjects completing the study. This expansion of the enrollment target ensured meaningful efficacy analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported