Clinical trial results:
A randomized double-blind multiple-dose placebo controlled trial to establish the efficacy of QBX258 (combination of VAK694 and QAX576) in asthma that is inadequately 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	2011-003066-32
Trial protocol	GB DE
Global end of trial date	27 February 2015

Results information

Result version number	v1 (current)
This version publication date	01 June 2016
First version publication date	01 June 2016

Trial information

Trial identification

Sponsor protocol code	CQBX258X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01479595
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,

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	27 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether treatment with QBX258 versus placebo over a 12–week period, in individuals with moderate to severe asthma that is inadequately controlled, 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	14 February 2012
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	Germany: 14
Country: Number of subjects enrolled	United States: 48
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	65
EEA total number of subjects	17

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)	64

From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were assigned to either QBX258 or placebo in a 2:1 ratio. Randomization was done by stratification of Q576R.

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	QBX258

Arm description:

Participants received QBX258 intravenous (iv) infusion every 4 weeks for up to 4 doses total.

Arm type	Experimental
Investigational medicinal product name	QBX258
Investigational medicinal product code	QBX258
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received QBX258 (combination of VAK696, 3mg/kg, and QAX576, 6mg/kg) intravenous (iv) infusion every 4 weeks for up to 4 doses.

Arm title	Placebo

Arm description:

Participants received placebo to QBX258 iv infusion every 4 weeks for up to 4 doses total.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received placebo (equal volume of 5% dextrose to QBX258) iv infusion every 4 weeks for up to 4 doses total.

Number of subjects in period 1	QBX258	Placebo
Started	44	21
PK analysis set	42	0 [1]
Per protocol analysis set	41 [2]	20
Completed	42	19
Not completed	2	2
Adverse event, non-fatal	2	1
Protocol deviation	-	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: The number of subjects for the PK analysis set and Per Protocol analysis set is correct.

[2] - 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: The number of subjects for the PK analysis set and Per Protocol analysis set is correct.

Baseline characteristics

Reporting groups	
Reporting group title	QBX258
Reporting group description:	
Participants received QBX258 intravenous (iv) infusion every 4 weeks for up to 4 doses total.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo to QBX258 iv infusion every 4 weeks for up to 4 doses total.	

Reporting group values	QBX258	Placebo	Total
Number of subjects	44	21	65
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)	43	21	64
From 65-84 years	1	0	1
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	42.5	42.8	
standard deviation	± 11.71	± 13.54	-
Gender, Male/Female Units: Participants			
Female	23	11	34
Male	21	10	31

End points

End points reporting groups

Reporting group title	QBX258
Reporting group description:	
Participants received QBX258 intravenous (iv) infusion every 4 weeks for up to 4 doses total.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo to QBX258 iv infusion every 4 weeks for up to 4 doses total.	

Primary: Change from baseline in Asthma Control Questionnaire (ACQ) score

End point title	Change from baseline in Asthma Control Questionnaire (ACQ) score
End point description:	
The ACQ consists of 7 questions assessing symptoms, rescue medication use and lung function. Except for lung function (FEV1), each question was scored on a 7-point scale where 0 = no impairment and 6 = maximum impairment. Scores ranged between 0 totally controlled to 6 (severely uncontrolled). Participants with a score below 1.0 are considered to have adequately controlled asthma. Participants with a score above 1.0 were considered not to be well controlled. A negative change from baseline indicates improvement.	
End point type	Primary
End point timeframe:	
Baseline and 12 weeks	

End point values	QBX258	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	19		
Units: score on a scale				
least squares mean (standard error)	-0.513 (± 0.097)	0.001 (± 0.1487)		

Statistical analyses

Statistical analysis title	Change from baseline in ACQ score
Comparison groups	QBX258 v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.005
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.514

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.811
upper limit	-0.217

Secondary: Change in Forced Expiratory Volume in one second (FEV1)

End point title	Change in Forced Expiratory Volume in one second (FEV1)

End point description:

FEV1 was assessed using central spirometry according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	QBX258	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	19		
Units: Liters				
least squares mean (standard error)	0.076 (± 0.0528)	0.05 (± 0.077)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Asthma Quality of Life Questionnaire (AQLQ) score

End point title	Change in Asthma Quality of Life Questionnaire (AQLQ) score

End point description:

The AQLQ is a 32-item disease specific questionnaire designed to measure functional impairments that are most important to patients with asthma. It consists of 4 domains: symptoms, emotions., exposure to environmental stimuli and activity limitation. Patients were asked to recall their experiences during the previous 2 weeks and to score each item on a 7-point scale. The scale ranges from 1 to 7. The overall AQLQ score was the mean response to all 32 questions. Higher scores represent better outcomes.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	QBX258	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	19		
Units: score on a scale				
least squares mean (standard error)	0.58 (± 0.1294)	0.468 (± 0.1878)		

Statistical analyses

No statistical analyses for this end point

Secondary: Morning and evening peak expiratory flow (PEF) rate

End point title	Morning and evening peak expiratory flow (PEF) rate

End point description:

Morning and evening PEFs were recorded on an electronic diary (e-diary). PEF was assessed twice daily approximately 12 hours apart and the measurements were recorded in the e-diary.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	QBX258	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: Liters				

Notes:

[1] - This outcome was not analyzed due to high variability in the data.

[2] - This outcome was not analyzed due to high variability in the data.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in maximum expiratory flow

End point title	Change from baseline in maximum expiratory flow

End point description:

Maximum expiratory flow was assessed using central spirometry according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	QBX258	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	19		
Units: L/sec				
arithmetic mean (standard deviation)	0.099 (± 0.427)	0.025 (± 0.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with anti-QAX576 antibodies or anti-VAK694 antibodies

End point title	Number of participants with anti-QAX576 antibodies or anti-VAK694 antibodies

End point description:

Anti-QAX576 and anti-VAK694 antibodies in serum were analyzed.

End point type	Secondary

End point timeframe:

12 weeks

End point values	QBX258	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	21		
Units: Participants	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Observed maximum plasma concentration following drug administration at steady state (Cmax,ss) of the QAX576 analyte

End point title	Observed maximum plasma concentration following drug administration at steady state (Cmax,ss) of the QAX576 analyte[3]

End point description:

Blood samples were obtained to measure Cmax,ss.

End point type	Secondary

End point timeframe:

days 1 (pre-dose and 2 hours post-dose), 15, 29 (pre-dose and 2 hours post-dose), 43, 57 (pre-dose and 2 hours post-dose), 71, 85 (pre-dose and 2 hours post-dose), 99, 113, 141, 183

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the 3 arms presented are applicable to this end point.

End point values	QBX258			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: ng/mL				
arithmetic mean (standard deviation)				
Q576R SNP stratum: QQ (n=21)	169000 (± 47000)			
Q576R SNP stratum: RR/QR (n=19)	184000 (± 85000)			
QBX258 (n=40)	176000 (± 67300)			

Statistical analyses

No statistical analyses for this end point

Secondary: Observed maximum plasma concentration following drug administration at steady state (Cmax,ss) of the VAK694 analyte

End point title	Observed maximum plasma concentration following drug administration at steady state (Cmax,ss) of the VAK694 analyte[4]

End point description:

Blood samples were obtained to measure Cmax,ss.

End point type	Secondary

End point timeframe:

days 1 (pre-dose and 2 hours post-dose), 15, 29 (pre-dose and 2 hours post-dose), 43, 57 (pre-dose and 2 hours post-dose), 71, 85 (pre-dose and 2 hours post-dose), 99, 113, 141, 183

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the 3 arms presented are applicable to this end point.

End point values	QBX258			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: ug/mL				
arithmetic mean (standard deviation)				
Q576R SNP stratum: QQ (n=21)	56.7 (± 8.9)			
Q576R SNP stratum: RR/QR (n=19)	58.6 (± 14.9)			
QBX258 (n=40)	57.6 (± 12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Lowest plasma concentration observed during a dosing interval at steady state (Cmin,ss) of the QAX576 analyte

End point title	Lowest plasma concentration observed during a dosing interval at steady state (Cmin,ss) of the QAX576 analyte[5]

End point description:

Blood samples were obtained to measure Cmin,ss.

End point type	Secondary

End point timeframe:

days 1 (pre-dose and 2 hours post-dose), 15, 29 (pre-dose and 2 hours post-dose), 43, 57 (pre-dose and 2 hours post-dose), 71, 85 (pre-dose and 2 hours post-dose), 99, 113, 141, 183

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the 3 arms presented are applicable to this end point.

End point values	QBX258			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: ng/mL				
arithmetic mean (standard deviation)				
Q576R SNP stratum: QQ (n=21)	37500 (± 11900)			
Q576R SNP stratum: RR/QR (n=19)	32200 (± 9930)			
QBX258 (n=40)	35000 (± 11200)			

Statistical analyses

No statistical analyses for this end point

Secondary: Lowest plasma concentration observed during a dosing interval at steady state (Cmin,ss) of the VAK694 analyte

End point title	Lowest plasma concentration observed during a dosing interval at steady state (Cmin,ss) of the VAK694 analyte[6]

End point description:

Blood samples were obtained to measure Cmin,ss.

End point type	Secondary

End point timeframe:

days 1 (pre-dose and 2 hours post-dose), 15, 29 (pre-dose and 2 hours post-dose), 43, 57 (pre-dose and 2 hours post-dose), 71, 85 (pre-dose and 2 hours post-dose), 99, 113, 141, 183

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the 3 arms presented are applicable to this end point.

End point values	QBX258			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: ug/mL				
arithmetic mean (standard deviation)				
Q576R SNP stratum: QQ (n=21)	10.7 (± 2.69)			
Q576R SNP stratum: RR/QR (n=19)	9.83 (± 2.94)			
QBX258 (n=40)	10.3 (± 2.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in fractional exhaled nitric oxide (FeNO)

End point title	Change from baseline in fractional exhaled nitric oxide (FeNO)

End point description:

FeNO was assessed as a measure of airway inflammation. An FeNO machine was used to obtain the FeNO measurements. FeNO measurements were obtained prior to the spirometry assessments.

End point type	Secondary

End point timeframe:

baseline, 12 weeks

End point values	QBX258	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	15		
Units: parts per billion (ppb)				
least squares mean (standard error)	-3.67 (± 3.58)	2.21 (± 5.393)		

Statistical analyses

No statistical analyses for this end point

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	QBX258
Reporting group description:	
QBX258	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	QBX258	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 44 (2.27%)	1 / 21 (4.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
ABORTION			
subjects affected / exposed	0 / 44 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
LARYNGEAL OEDEMA			
subjects affected / exposed	1 / 44 (2.27%)	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	QBX258	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 44 (29.55%)	7 / 21 (33.33%)	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	5 / 44 (11.36%)	1 / 21 (4.76%)	
occurrences (all)	6	1	
Gastrointestinal disorders			
NAUSEA			
subjects affected / exposed	3 / 44 (6.82%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
VOMITING			
subjects affected / exposed	3 / 44 (6.82%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	3 / 44 (6.82%)	3 / 21 (14.29%)	
occurrences (all)	3	3	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	4 / 44 (9.09%)	2 / 21 (9.52%)	
occurrences (all)	5	2	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 44 (4.55%)	2 / 21 (9.52%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2011	Amendment 1 introduced the following changes as requested from the health authority: clarified the period of time following dosing during which women of child-bearing potential were to use highly effective contraception; and introduced a requirement for males to use contraception to minimize potential risk of exposure to the fetus.
16 November 2011	Amendment 2 introduced the following changes: revised the blood volumes to reflect accurate volumes for the central laboratory. The overall blood volume taken during the study was reduced from 559.4 mL to 523.4 mL; and revised inclusion criterion 6 to require a peripheral blood eosinophil count > 140/µL combined with serum IgE > 100 IU/mL.
16 January 2012	Amendment 3 introduced the following changes: included a blood sample for Serum IgE to be taken at Screening in order for patients to be eligible as per Inclusion Criterion 6 (introduced at Amendment 2 but requirement for sample to be taken was missed); added a requirement for women of child bearing potential to have a negative pregnancy test result up to 14 days prior to the methacholine challenge (as per the package insert for methacholine); and revised inclusion criterion 7 to note that patients taking antihistamine therapy should withhold their medication prior to skin prick testing.
15 February 2013	Amendment 4 introduced the following changes: revised inclusion criterion 6 to require peripheral blood eosinophil count ≥ 140/µL and serum IgE ≥ 100 IU/mL at Screening, or IgE ≥ 400 IU/mL at Screening regardless of eosinophil count (change made to enrich the study population with individuals whose asthma was more likely to be characterized by Th2-type inflammation and therefore were more likely to respond to therapy targeting IL-4 and IL-13); clarified ACQ measurements were to be performed at Visit 3 and added a spirometry measurement (integral to measurement of ACQ) at Visit 3; added body weight measurement to Visit 4 (prior to dosing); revised the first Baseline visit from Days -14 to -4 to Days -14 to -3, to allow all Baseline assessments to be performed on Day -3, where logistically possible; revised dispensing of the eDiary to allow the eDiary to be dispensed at the Screening visit while screening results were obtained; revised exclusion criterion 17 to clarify that travel was restricted not to all of Southeast and Southwest Asia, South America, and Africa, but only to those parts that were endemic for schistosomiasis; revised the study stopping rules for clarification that "study-related SAE" referred to a study drug-related or study procedure-related SAE; added windows for early collection of PK assessment and performance of other study procedures; added more details for the withholding of asthma medications prior to spirometry, FeNOand the methacholine challenge; clarified that local spirometers, as opposed to central spirometry, may have been used for safety monitoring of lung function during induced sputum procedures; and added restriction of nitrate-rich foods and allowed for the consumption of water prior to measurements of FeNO.
19 June 2013	Amendment 5 introduced the following changes: removed the requirement for the methacholine challenge, sputum collection for biomarker assessments, and Elispot PBMC biomarker collection; shortened the Screening period and Run-in period to minimize study durations; clarified the definition of positive stool sample for ova and parasites; revised exclusion criterion 14 to include a more specific value of ≤ 12mg/dL; clarified the early withdrawal assessments and procedures for individual patient withdrawal; and revised the analysis of placebo treated patients in the additional explorative analysis onthe impact of the Q576R SNP on the QBX258 treatment. Placebo treated patients were not to be pooled but analyzed by their Q576R SNP status.

11 December 2013	Amendment 6 introduced the following changes as requested by the Paul- Ehrlich Institute: included a specific futility analysis in the planned interim analysis, and the definition of change from baseline was updated to the current reporting standard; and added Germany-specific requirements for contraception, to recommend against the use of spermicidals and condoms in this country.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported