Clinical trial results:
A randomized, double-blind, placebo controlled, parallel group, proof of concept study evaluating the efficacy,safety, pharmacokinetics and pharmacodynamics of QGE031 in the treatment of patients with moderate to severe atopic dermatitis

Summary

EudraCT number	2011-002112-84
Trial protocol	AT DE NL
Global end of trial date	28 August 2013

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	CQGE031X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01552629
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002 , Basel, Switzerland,
Public contact	Novartis Pharma AG, Novartis Pharma AG, +41 613241111,
Scientific contact	Novartis Pharma AG, 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	28 August 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 August 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of QGE031 relative to placebo at 12 weeks in patients with atopic dermatitis (AD) as assessed by Eczema Area and Severity Index (EASI)

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.
The use of topical rescue medication was allowed at all times during the trial but was restricted. Twice daily application of mild or moderate strength topical corticosteroids (using the European four category classification system of mild, moderate, potent and very potent) was allowed. These rescue medications were provided by the study site and used to control the patient's atopic dermatitis and the resulting symptoms not adequately controlled on study drug. The combination of allowed topical rescue medications that most closely approximates the patient's current regimen was dispensed at screening, and full tube weights obtained. The use of oral antihistamines as a rescue medication for itch not controlled by the study drug was allowed at all times during the trial; this medication was provided by the study site. Use of rescue medication was required to be recorded in the eCRF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 January 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	Austria: 14
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	22
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 30 patients were planned to be randomly assigned to one of three treatment groups conducted in parallel. Based upon the results of the first interim analysis, the study was terminated after 22 patients were enrolled.

Pre-assignment

Screening details:

The study consisted of up to a 28-day screening period (Day -28 to Day -1), a treatment period of 12 weeks, a follow-up period of 12 weeks, and an End of Study (EoS) evaluation.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	QGE031

Arm description:

QGE031 will be administered as a subcutaneous dose every two weeks (q2)

Arm type	Experimental
Investigational medicinal product name	QGE031
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

subcutaneous injection, which was administered 280 mg once every two weeks

Arm title	Placebo

Arm description:

A QGE031 matched placebo will be administered as a subcutaneous dose q2 weeks

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

Dosage and administration details:

subcutaneous injection, which was administered once every two weeks

Arm title	Cyclosporine A

Arm description:

Cyclosporine A will be administered (as per label) for atopic dermatitis.
2.5 – 5.0 mg/kg BID

Arm type	Experimental

Investigational medicinal product name	Cyclosporine A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

2.5 – 5.0 mg/kg oral daily dose split twice a day

Number of subjects in period 1	QGE031	Placebo	Cyclosporine A
Started	10	10	2
Randomized	10	10	2
Completed	7	9	1
Not completed	3	1	1
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	1	-	1
Administrative problems	-	1	-
Lost to follow-up	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	QGE031
Reporting group description:	
QGE031 will be administered as a subcutaneous dose every two weeks (q2)	

Reporting group title	Placebo
Reporting group description:	
A QGE031 matched placebo will be administered as a subcutaneous dose q2 weeks	

Reporting group title	Cyclosporine A
Reporting group description:	
Cyclosporine A will be administered (as per label) for atopic dermatitis. 2.5 – 5.0 mg/kg BID	

Reporting group values	QGE031	Placebo	Cyclosporine A
Number of subjects	10	10	2
Age categorical Units: Subjects			
Adults (18-64 years)	10	10	2
Age continuous Units: years			
arithmetic mean	35	32.4	52.5
standard deviation	± 12.6	± 10.1	± 7.8
Gender categorical Units: Subjects			
Female	5	5	1
Male	5	5	1

Reporting group values	Total		
Number of subjects	22		
Age categorical Units: Subjects			
Adults (18-64 years)	22		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	11		
Male	11		

End points

End points reporting groups

Reporting group title	QGE031

Reporting group description:

QGE031 will be administered as a subcutaneous dose every two weeks (q2)

Reporting group title	Placebo

Reporting group description:

A QGE031 matched placebo will be administered as a subcutaneous dose q2 weeks

Reporting group title	Cyclosporine A

Reporting group description:

Cyclosporine A will be administered (as per label) for atopic dermatitis.
2.5 – 5.0 mg/kg BID

Primary: Change in Eczema Area and Severity Index (EASI) from baseline to week 12

End point title	Change in Eczema Area and Severity Index (EASI) from baseline to week 12[1]

End point description:

The EASI was used to make an assessment of the extent and severity of each patient's atopic dermatitis. Erythema, induration/papulation, excoriation and lichenification were scored in each of four body areas, head/neck (H), upper limbs (UL), trunk (T), and lower limbs (LL) assigned proportionate body surface areas of 10% (H), 20% (UL), 30% (T), and 40% (LL). The severity for each sign was scored on a scale from 0-3 (none, mild, moderate and severe)
where half-points were allowed. The area within each body region with the key signs of inflammation was estimated as a percentage of the total area of that particular body region.

End point type	Primary

End point timeframe:

Baseline and Week 12

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: No statistical analysis has been performed for this endpoint.

End point values	QGE031	Placebo	Cyclosporine A	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[2]	10[3]	2[4]	
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline	25.37 (± 9.624)	24.73 (± 4.514)	22.95 (± 7.566)	
Week 12 (n = 9, 10, 2)	19.82 (± 10.932)	18.4 (± 7.281)	1.18 (± 0.813)	
Change from baseline (n = 9, 10, 2)	-7.48 (± 10.995)	-6.33 (± 5.296)	-21.78 (± 6.753)	

Notes:

[2] - Subjects with any available EASI PD data for a minimum of 4 weeks and no major protocol deviations
[3] - Subjects with any available EASI PD data for a minimum of 4 weeks and no major protocol deviations

[4] - Subjects with any available EASI PD data for a minimum of 4 weeks and no major protocol deviations

Statistical analyses

No statistical analyses for this end point

Primary: Combined EASI50 responders

End point title	Combined EASI50 responders[5]

End point description:

Combined EASI50 responders are defined as those with 50% decrease from baseline in Eczema Area and Severity Index (EASI) plus no more than a 25% increase in topical rescue medication use.

End point type	Primary

End point timeframe:

Week 12

Notes:

[5] - 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: No statistical analysis has been performed for this endpoint.

End point values	QGE031	Placebo	Cyclosporine A	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[6]	10[7]	2[8]	
Units: percent				
number (not applicable)	11	10	100	

Notes:

[6] - Subjects with any available EASI PD data for a minimum of 4 weeks and no major protocol deviations
[7] - Subjects with any available EASI PD data for a minimum of 4 weeks and no major protocol deviations
[8] - Subjects with any available EASI PD data for a minimum of 4 weeks and no major protocol deviations

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Investigator Global Assessment (IGA) for atopic dermatitis

End point title	Change in Investigator Global Assessment (IGA) for atopic dermatitis

End point description:

Participants dermatitis will be visually assessed and an IGA score will be determined by the Investigator using a prespecified evaluation criteria. The number of patients reported as per their IGA score. Majority of cases were reported as mild, moderate or severe. There were very few cases reported as clear or almost clear during the study.

End point type	Secondary

End point timeframe:

Weeks 6, 12

End point values	QGE031	Placebo	Cyclosporine A	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[9]	10[10]	2[11]	
Units: percent				
number (not applicable)				
Week 0 - Clear	0	0	0	
Week 0 - Almost clear	0	0	0	
Week 0 - Mild	0	0	0	
Week 0 - Moderate	60	50	50	
Week 0 - Severe	40	40	50	
Week 0 - Very severe	0	10	0	
Week 6 - Clear	0	0	0	
Week 6 - Almost clear	0	0	50	
Week 6 - Mild	0	10	50	
Week 6 - Moderate	70	50	0	
Week 6 - Severe	30	40	0	
Week 6 - Very severe	0	0	0	
Week 12 - Clear	0	0	0	
Week 12 - Almost clear	0	0	100	
Week 12 - Mild	20	20	0	
Week 12 - Moderate	50	60	0	
Week 12 - Severe	10	10	0	
Week 12 - Very severe	10	10	0	

Notes:

[9] - Subjects with any available EASI PD data for a minimum of 4 weeks and no major protocol deviations

[10] - Subjects with any available EASI PD data for a minimum of 4 weeks and no major protocol deviations

[11] - Subjects with any available EASI PD data for a minimum of 4 weeks and no major protocol deviations

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events

End point title	Number of participants with adverse events

End point description:

Adverse events will be determined by observation and non-leading questioning of patients, and by measuring safety parameters (electrocardiograms, clinical laboratory, blood pressure)

End point type	Secondary

End point timeframe:

Week 24

End point values	QGE031	Placebo	Cyclosporine A	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[12]	10[13]	2[14]	
Units: percent				
number (not applicable)	90	90	100	

Notes:

[12] - All patients that received at least one dose of study drug

[13] - All patients that received at least one dose of study drug

[14] - All patients that received at least one dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: QGE031 plasma concentrations

End point title	QGE031 plasma concentrations[15]

End point description:

Blood samples will be collected for determination of QGE031 serum levels

End point type	Secondary

End point timeframe:

24 weeks

Notes:

[15] - 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 plasma concentrations were reported for the compound QGE031.

End point values	QGE031			
Subject group type	Reporting group			
Number of subjects analysed	10[16]			
Units: µg/mL				
arithmetic mean (standard deviation)				
Day 1 n=10	0.12 (± 0.379)			
Day 15 n=10	11 (± 4.51)			
Day 29 n=9	14 (± 5.58)			
Day 43 n=10	16.7 (± 6.54)			
Day 57 n=10	18 (± 7.54)			
Day 71 n=10	18.1 (± 7.28)			
Day 85 n=9	17.8 (± 7.78)			
Day 99 n=8	10.4 (± 5.71)			
Day 113 n=8	4.72 (± 2.79)			
Day 127 n=7	3.05 (± 2.12)			
Day 141 n=7	1.74 (± 1.46)			
Day 155 n=5	0.91 (± 1.07)			
Day 169 n=9	1.16 (± 1.42)			

Notes:

[16] - Patients with evaluable (or complete) PK parameter data.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All other adverse events are monitored from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	QGE031
Reporting group description:	
QGE031	
Reporting group title	Cyclosporine
Reporting group description:	
Cyclosporine	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	QGE031	Cyclosporine	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 10 (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

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

Non-serious adverse events	QGE031	Cyclosporine	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 10 (90.00%)	2 / 2 (100.00%)	9 / 10 (90.00%)
Investigations			
White blood cell count increased			

subjects affected / exposed	0 / 10 (0.00%)	1 / 2 (50.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Post procedural complication			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	11
Syncope			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Injury associated with device			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 2 (50.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Eyelids pruritus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Conjunctivitis			

subjects affected / exposed	1 / 10 (10.00%)	1 / 2 (50.00%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Lip blister			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Duodenogastric reflux			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			

Dermatitis atopic			
subjects affected / exposed	0 / 10 (0.00%)	1 / 2 (50.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Urticaria			
subjects affected / exposed	2 / 10 (20.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Fracture pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Herpes simplex			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Groin abscess			
subjects affected / exposed	0 / 10 (0.00%)	1 / 2 (50.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Folliculitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 2 (50.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	4 / 10 (40.00%)	0 / 2 (0.00%)	2 / 10 (20.00%)
occurrences (all)	5	0	2

Molluscum contagiosum			
subjects affected / exposed	0 / 10 (0.00%)	1 / 2 (50.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Rhinitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Postoperative wound infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Otitis externa			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2011	The purpose of Amendment 1 was to clarify, and correct, certain criteria and procedures in the protocol and to make the length of the QGE031/placebo and cyclosporine treatment periods consistent.
22 November 2011	Amendment 2 of the protocol was made to add an exclusion criterion: Patients with a history of schistosomiasis, or stool examination positive for ova or parasites at Screening, or travel to an area endemic with schistosomiasis (in the six months prior to Screening).
23 January 2012	Amendment 3 of the protocol was made to address concerns of the potential for QGE031 to cause thrombocytopenia. Thrombocytopenia has been observed in pre-clinical studies with omalizumab, an anti-IgE monoclonal antibody with a related mechanism of action, although it has not emerged as a safety concern in man for this drug. Thrombocytopenia has thus far not been observed with QGE031 in the conducted toxicology studies in non-human primates or in man.
14 May 2012	Amendment 4 of the protocol :As new clinical data from other studies became available, these new data were incorporated into the protocol. In addition, it was requested that study endpoints be specified in the protocol.
19 June 2012	The protocol allowed some flexibility to replace patients whose atopic dermatitis was not stable and thus worsened shortly after starting study treatment. As this caused concern that it would lead to replacement of patients showing a clear lack of efficacy, which would bias the estimation of efficacy, this flexibility has been removed from the protocol. After a request to change study eligibility criteria to include a population more closely reflecting that of the cyclosporine label, it was decided to stop the cyclosporine arm instead.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 April 2013	Decision to terminate study.	-

Notes:

Limitations and caveats

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

In April 2013, Novartis informed the Health Authorities about its decision to terminate the study. Any ongoing patients enrolled at the time of termination were allowed to complete the study according to the approved protocol. The last follow-up vi

Notes: