Clinical trial results:
A Randomized, Placebo-Controlled, Phase IIb Dose-Finding Study of CYT003-QbG10, a TLR9-Agonist, in Patients with Moderate to Severe Allergic Asthma not Sufficiently Controlled on Current Standard Therapy (GINA Steps 3+4)

Summary

EudraCT number	2012-003070-39
Trial protocol	HU DE CZ PL
Global end of trial date	14 April 2014

Results information

Result version number	v2 (current)
This version publication date	17 July 2016
First version publication date	25 February 2015
Version creation reason	• Correction of full data set correction needed due to EudraCT downtime between Jul-2015 and Jan 2016
Summary attachment (see zip file)	Study report (CYT003_CSR_140811_HA3_12_Study Report_Final.pdf) Appendix 16.1.5 Signatures (QbG10_CSR_140811_HA3_12_Appendix 16.1.5 Signatures.pdf) Addendum 17.1 Safety (QbG10_CSR_140811_TL1_12_Addendum_17_1_Safety_Final.pdf) Addendum 17.2 Efficacy (CYT003_CSR_140811_WJ1_12_Addendum_17_2_Efficacy_Final.pdf)

Trial information

Trial identification

Sponsor protocol code	CYT003-QbG1012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01673672
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cytos Biotechnology AG
Sponsor organisation address	Wagistrasse 25, Schlieren, Switzerland, 8952
Public contact	Information Desk, Cytos Biotechnology AG, 0041 447334747, info@cytos.com
Scientific contact	Information Desk, Cytos Biotechnology AG, 0041 447334747, info@cytos.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	14 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 April 2014
Global end of trial reached?	Yes
Global end of trial date	14 April 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the therapeutic potential and safety/tolerability of CYT003-QbG10 at 3 dose levels versus placebo in patients with persistent moderate to severe allergic asthma not sufficiently controlled on current standard therapy

Protection of trial subjects:

Usual standard of care; study drug as add-on therapy

Background therapy:

Current standard inhaled corticosteroids (ICS) with or without long-acting β2 agonist (±LABA) therapy (Global Initiative for Asthma [GINA] steps 3 and 4)

Evidence for comparator:

No comparator used

Actual start date of recruitment	14 October 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	Poland: 34
Country: Number of subjects enrolled	Czech Republic: 22
Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	Hungary: 39
Country: Number of subjects enrolled	United States: 115
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	Ukraine: 74

Worldwide total number of subjects	365
EEA total number of subjects	139

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)	365
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient first visit: 14-Oct-2012; Last patient last visit: 24-Jan-2014. Patient assessments performed at Investigator sites.

Pre-assignment

Screening details:

606 patients have been screened; 241 patients were screening failures; 365 patients have been included and dosed.

Period 1

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

Blinding implementation details:

Study was kept double-blind until study report was finalized

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo (buffer)

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

Dosage and administration details:

7 subcutaneous injections of 1 ml over 10 weeks

Arm title	0.3 mg

Arm description:

0.3 mg CYT003

Arm type	Experimental
Investigational medicinal product name	0.3 mg CYT003
Investigational medicinal product code	0.3 mg CYT003
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

7 subcutaneous injections of 1 ml over 10 weeks

Arm title	1.0 mg

Arm description:

1.0 mg CYT003

Arm type	Experimental

Investigational medicinal product name	1.0 mg CYT003
Investigational medicinal product code	1.0 mg CYT003
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

7 subcutaneous injections of 1 ml over 10 weeks

Arm title	2.0 mg

Arm description:

2.0 mg CYT003

Arm type	Experimental
Investigational medicinal product name	2.0 mg CYT003
Investigational medicinal product code	2.0 mg CYT003
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

7 subcutaneous injections of 1 ml over 10 weeks

Number of subjects in period 1	Placebo	0.3 mg	1.0 mg
Started	89	91	94
Completed	87	88	90
Not completed	2	3	4
Consent withdrawn by subject	2	3	4

Number of subjects in period 1	2.0 mg
Started	91
Completed	89
Not completed	2
Consent withdrawn by subject	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo (buffer)	
Reporting group title	0.3 mg
Reporting group description: 0.3 mg CYT003	
Reporting group title	1.0 mg
Reporting group description: 1.0 mg CYT003	
Reporting group title	2.0 mg
Reporting group description: 2.0 mg CYT003	

Reporting group values	Placebo	0.3 mg	1.0 mg
Number of subjects	89	91	94
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)	89	91	94
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	47.5	47.2	47.3
standard deviation	± 12.37	± 11.94	± 12.39
Gender categorical Units: Subjects			
Female	52	56	58
Male	37	35	36
Asthma Control Questionnaire (ACQ) Units: ACQ score			
arithmetic mean	2.63	2.57	2.62
standard deviation	± 0.61	± 0.61	± 0.65

Reporting group values	2.0 mg	Total	
Number of subjects	91	365	
Age categorical Units: Subjects			
In utero	0	0	

Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	91	365	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	48		
standard deviation	± 12.05	-	
Gender categorical			
Units: Subjects			
Female	57	223	
Male	34	142	
Asthma Control Questionnaire (ACQ)			
Units: ACQ score			
arithmetic mean	2.56		
standard deviation	± 0.69	-	

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

FAS was analyzed according to Intent to Treat principle and a last Obesrvation Carried Forward procedure was adopted.

Reporting group values	Full Analysis Set (FAS)		
Number of subjects	365		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	365		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	47.5		
standard deviation	± 12.15		

Gender categorical Units: Subjects			
Female	223		
Male	142		
Asthma Control Questionnaire (ACQ) Units: ACQ score arithmetic mean standard deviation	 ±		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo (buffer)	
Reporting group title	0.3 mg
Reporting group description: 0.3 mg CYT003	
Reporting group title	1.0 mg
Reporting group description: 1.0 mg CYT003	
Reporting group title	2.0 mg
Reporting group description: 2.0 mg CYT003	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: FAS was analyzed according to Intent to Treat principle and a last Obesrvation Carried Forward procedure was adopted.	

Primary: ACQ score - Change from Baseline at week 12

End point title	ACQ score - Change from Baseline at week 12
End point description: Change in Asthma Controm Questionnaire Score at week 12 compared to Baseline score	
End point type	Primary
End point timeframe: 12 weeks treatment period for each patient	

End point values	Placebo	0.3 mg	1.0 mg	2.0 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	89	91	94	91
Units: Delta ACQ score				
arithmetic mean (standard deviation)	-0.649 (± 0.7631)	-0.641 (± 0.8799)	-0.546 (± 0.8176)	-0.544 (± 0.7147)

Statistical analyses

Statistical analysis title	Primary Efficacy Analysis 0.3 mg
Statistical analysis description: The treatment effect was evaluated as a contrast of each active treatment versus placebo.	
Comparison groups	0.3 mg v Placebo

Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.818 [2]
Method	ANCOVA

Notes:

[1] - ANCOVA

[2] - Hochberg procedure to control for multiple comparisons.

Statistical analysis title	Primary Efficacy Analysis 1.0 mg

Statistical analysis description:

The treatment effect was evaluated as a contrast of each active treatment versus placebo.

Comparison groups	1.0 mg v Placebo
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.4025 [4]
Method	ANCOVA

Notes:

[3] - ANCOVA

[4] - Hochberg procedure to control for multiple comparisons.

Statistical analysis title	Primary Efficacy Analysis 2.0 mg

Statistical analysis description:

The treatment effect was evaluated as a contrast of each active treatment versus placebo.

Comparison groups	2.0 mg v Placebo
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.4883 [6]
Method	ANCOVA

Notes:

[5] - ANCOVA

[6] - Hochberg procedure to control for multiple comparisons.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
12 weeks	
Adverse event reporting additional description:	
Treatment phase	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo buffer	
Reporting group title	1.0 mg
Reporting group description:	
1.0 mg CYT003	
Reporting group title	2.0 mg
Reporting group description:	
2.0 mg CYT003	
Reporting group title	0.3 mg
Reporting group description:	
0.3 mg CYT003	

Serious adverse events	Placebo	1.0 mg	2.0 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 89 (0.00%)	1 / 94 (1.06%)	0 / 91 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma exacerbation			
subjects affected / exposed	0 / 89 (0.00%)	1 / 94 (1.06%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	0.3 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 91 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Respiratory, thoracic and mediastinal disorders			
Asthma exacerbation			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Placebo	1.0 mg	2.0 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 89 (40.45%)	62 / 94 (65.96%)	61 / 91 (67.03%)
Investigations			
blood creatinkinase increased			
subjects affected / exposed	0 / 89 (0.00%)	1 / 94 (1.06%)	0 / 91 (0.00%)
occurrences (all)	36	62	61
Body temperature increased			
subjects affected / exposed	0 / 89 (0.00%)	0 / 94 (0.00%)	4 / 91 (4.40%)
occurrences (all)	36	62	61
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 89 (6.74%)	3 / 94 (3.19%)	7 / 91 (7.69%)
occurrences (all)	36	62	61
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 89 (0.00%)	24 / 94 (25.53%)	27 / 91 (29.67%)
occurrences (all)	36	62	61
Injection site swelling			
subjects affected / exposed	0 / 89 (0.00%)	27 / 94 (28.72%)	23 / 91 (25.27%)
occurrences (all)	36	62	61
Injection site pruritus			
subjects affected / exposed	2 / 89 (2.25%)	19 / 94 (20.21%)	11 / 91 (12.09%)
occurrences (all)	36	62	61
Injection site pain			
subjects affected / exposed	1 / 89 (1.12%)	12 / 94 (12.77%)	16 / 91 (17.58%)
occurrences (all)	36	62	61
Injection site induration			

subjects affected / exposed	0 / 89 (0.00%)	2 / 94 (2.13%)	4 / 91 (4.40%)
occurrences (all)	36	62	61
Injection site reaction			
subjects affected / exposed	0 / 89 (0.00%)	3 / 94 (3.19%)	1 / 91 (1.10%)
occurrences (all)	36	62	61
Influenza like illness			
subjects affected / exposed	2 / 89 (2.25%)	7 / 94 (7.45%)	3 / 91 (3.30%)
occurrences (all)	36	62	61
Pyrexia			
subjects affected / exposed	2 / 89 (2.25%)	2 / 94 (2.13%)	5 / 91 (5.49%)
occurrences (all)	36	62	61
Fatigue			
subjects affected / exposed	0 / 89 (0.00%)	0 / 94 (0.00%)	0 / 91 (0.00%)
occurrences (all)	36	62	61
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 89 (2.25%)	4 / 94 (4.26%)	2 / 91 (2.20%)
occurrences (all)	36	62	61
Wheezing			
subjects affected / exposed	1 / 89 (1.12%)	1 / 94 (1.06%)	3 / 91 (3.30%)
occurrences (all)	36	62	61
Oropharyngeal pain			
subjects affected / exposed	0 / 89 (0.00%)	3 / 94 (3.19%)	0 / 91 (0.00%)
occurrences (all)	36	62	61
Rhinitis allergic			
subjects affected / exposed	0 / 89 (0.00%)	0 / 94 (0.00%)	1 / 91 (1.10%)
occurrences (all)	36	62	61
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 89 (4.49%)	5 / 94 (5.32%)	6 / 91 (6.59%)
occurrences (all)	36	62	61
Bronchitis			
subjects affected / exposed	1 / 89 (1.12%)	1 / 94 (1.06%)	2 / 91 (2.20%)
occurrences (all)	36	62	61
Upper respiratory tract infection			

subjects affected / exposed	1 / 89 (1.12%)	4 / 94 (4.26%)	4 / 91 (4.40%)
occurrences (all)	36	62	61
Acute sinusitis			
subjects affected / exposed	0 / 89 (0.00%)	3 / 94 (3.19%)	0 / 91 (0.00%)
occurrences (all)	36	62	61
Respiratory tract infection viral			
subjects affected / exposed	3 / 89 (3.37%)	0 / 94 (0.00%)	0 / 91 (0.00%)
occurrences (all)	36	62	61

Non-serious adverse events	0.3 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 91 (58.24%)		
Investigations			
blood creatinkinase increased			
subjects affected / exposed	3 / 91 (3.30%)		
occurrences (all)	53		
Body temperature increased			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences (all)	53		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 91 (6.59%)		
occurrences (all)	53		
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	20 / 91 (21.98%)		
occurrences (all)	53		
Injection site swelling			
subjects affected / exposed	20 / 91 (21.98%)		
occurrences (all)	53		
Injection site pruritus			
subjects affected / exposed	11 / 91 (12.09%)		
occurrences (all)	53		
Injection site pain			
subjects affected / exposed	10 / 91 (10.99%)		
occurrences (all)	53		
Injection site induration			

subjects affected / exposed	3 / 91 (3.30%)		
occurrences (all)	53		
Injection site reaction			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences (all)	53		
Influenza like illness			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences (all)	53		
Pyrexia			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences (all)	53		
Fatigue			
subjects affected / exposed	3 / 91 (3.30%)		
occurrences (all)	53		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 91 (2.20%)		
occurrences (all)	53		
Wheezing			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences (all)	53		
Oropharyngeal pain			
subjects affected / exposed	2 / 91 (2.20%)		
occurrences (all)	53		
Rhinitis allergic			
subjects affected / exposed	3 / 91 (3.30%)		
occurrences (all)	53		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 91 (5.49%)		
occurrences (all)	53		
Bronchitis			
subjects affected / exposed	5 / 91 (5.49%)		
occurrences (all)	53		
Upper respiratory tract infection			

subjects affected / exposed	0 / 91 (0.00%)		
occurrences (all)	53		
Acute sinusitis			
subjects affected / exposed	2 / 91 (2.20%)		
occurrences (all)	53		
Respiratory tract infection viral			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences (all)	53		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2013	Global amendment 1: Several minor changes such as additional details on analysis populations
20 December 2013	Global amendment 2: several minor changes such as biomarkers

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 January 2013	Delay in study drug availability	15 May 2013

Notes:

Limitations and caveats

None reported