CLINICAL STUDY REPORT

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)

Trial Number:	**CYT003-QbG10 12**	
EudraCT number:	2012-003070-39	
Study Dates:	FPFV: 14 Oct 2012 Screening: 14 Oct 2012 1st injection: 28 May 2013	LPLV (Week 12): 24 Jan 2014 Premature Study Termination: 14 Apr 2014
Investigational Product:	CYT003-QbG10 (CYT003)	
Indication Studied:	Persistent Allergic Asthma	
Development Phase:	Phase IIb	
Study Design:	Randomized, placebo-controlled, parallel-group, multicenter, dose-finding, efficacy, pharmacodynamic and safety study	
Sponsor:	Cytos Biotechnology AG, Wagistrasse 25 CH-8952 Schlieren, Switzerland	
Legal representative in EU:	Clinical Technology Center (International) Limited, Granta Park, Great Abington, Cambridge Cambridgeshire CB21 6GQ, United Kingdom	
Principal Investigator:	Thomas B Casale, MD Department of Internal Medicine Division of Allergy and Immunology University of South Florida 12901 Bruce B Downs Blvd, MDC19, Tampa, FL 33612 USA	
CRO:	PPD Development 929 North Front Street, Wilmington, NC 28401, USA	
Biostatistics:	Tony Wu, Ph.D. Lead Biostatistician, Biostatistics, PPD	
Authors:	J. Willers, A. Hammann, L. Trokan, M. Zimmermann, J. Klisic, P. Martin, C. Lassen Cytos Biotechnology AG, CH-8952 Schlieren, Switzerland	
GCP Statement:	This study was performed in compliance with ICH-GCP guidelines.	
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1 Title Page

2 Synopsis

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NAME OF ACTIVE INGREDIENT CYT003-QbG10 (CYT003)	Report No.: Volume:	

Title of Study:	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)

Investigators and Study Centers*:

USA:

101 Bernstein David, Bernstein Clinical Research Center, Inc., Cincinnati, USA
102 Binker Josefa, Community Research Foundation, Miami, USA
103 Bridges Tracy, Georgia Pollens Clinical Research Centers, Albany, USA
104 Casale Thomas, Creighton University Medical Center, Omaha, USA, after Oct-13 University of South Florida, Tampa, USA
105 Cole Jeremy, Integrity People Services Research Company, Oklahoma City, USA
106 Condemi John, AAIR Research Center, Rochester, USA
107 Daul Carolyn, Clinical Research Specialists, Metairie, USA
108 Diaz Joseph, Allergy & Asthma Center, PA, San Antonio, USA
109 Fogarty Charles, Spartanburg Medical Research, Spartanburg, USA
110 Ford Linda, The Asthma and Allergy Center, Pc, Bellevue, USA
115 Harris James, South Bend Clinic, South Bend, USA
116 Harper, III Thomas, Asthma & Allergy Consultants, LLP, Summerville, USA
117 Hill David, Waterbury Pulmonary Associates, Waterbury, USA
118 Jacobs Joshua, Allergy & Asthma Clinical Research Inc., Walnut Creek, USA
119 Friesen Jason, Allergy & Asthma Research Group, Eugene, USA
120 Kerwin Edward, Clinical Research Institute of Southern Oregon, PC, Medford, USA
121 Korenblat Phillip, The Clinical Research Center, L.L.C., St. Louis, USA
123 Ostrom Nancy, Allergy & Asthma Medical Group and Research Center APC, San Diego, USA
124 Patel Amit, Integrated Research Group Inc., Riverside, USA
126 Pham David, Allianz Medical and Research Center, Fountain Valley, USA
128 Raphael Gordon, Private Practice, Bethesda, USA
130 Saff Ronald, Allergy and Asthma Dtc, Tallahassee, USA
131 Settipane Robert, Asthma, Nasal Disease And Allergy Research Center, Providence, USA
132 Shapero Paul, Private Practice, Bangor, USA
133 Sitz Karl, Little Rock Allergy & Asthma Clinical Research Center, Little Rock, USA
134 Soteres Daniel, Asthma And Allergy Associates, P.C., Pueblo, USA
135 Spector Sheldon, California Allergy & Asthma Medical Group, Inc., Los Angeles, USA
136 Weinstein Steven, Allergy & Asthma Specialists Medical Group, Huntington Beach, USA
137 Goldsobel Alan, Allergy & Asthma Associates of Santa Clara Valley, San Jose, USA
138 Zwetchkenbaum John, Asthma & Allergy Physicians of Rhode Island Clinical Research Institute (AAPRI CRI), Warwick, USA

139 Call Robert, Clinical Research Partners LLC, Henrico, USA
140 Katial Rohit, National Jewish Medical & Research Center, Denver, USA
141 Mello Curtis, Infinity Medical Research Inc., North Dartmouth, USA

Czech Republic:
201 Bystron Jaromir, Fakultni Nemocnice Olomouc, Olomouc, Czech Republic
202 Chlumsky Jan, Thomayerova nemocnice, Praha 4, Czech Republic
203 Kasl Milan, KASMED s.r.o., Tabor, Czech Republic
206 Kolman Petr, Nemocnice Kyjov, prispevkova organizace, Kyjov, Czech Republic
207 Krcmova Irena, Fakultni nemocnice Hradec Kralove, Hradec Kralove, Czech Republic
208 Malkusova Ivana, Fakultni nemocnice Plzen, Plzen - Lochotin, Czech Republic
209 Rohovsky Tomas, HORNMED s.r.o., Brno, Czech Republic

Germany:
301 Kornmann Marc Oliver, IKF Pneumologie, Frankfurt am Main, Germany
302 Eckhardt Gerald, Aeskulap GmbH/ MVZ Dr. Eckhardt - Dr. Deckelmann, Delitzsch, Germany
304 Westerhausen Ulrike, Privatpraxis Westerhausen, Berlin, Germany
305 von Versen Lutz, Praxis Dr. med. Lutz von Versen, Berlin, Germany
306 Beck Ekkehard, IFG-Institut für Gesundheitsförderung GmbH, Rüdersdorf, Germany
307 Junggeburth Josef, Praxis Dr. med. Junggeburth, Bad Wörishofen, Germany
308 Geßner Christian, POIS Leipzig GbR, Leipzig, Germany
309 Illies Gabriele, SMO.MD GmbH, Magdeburg, Germany

Hungary:
402 Böcskei Csaba, Szent Borbála Kórház, Tatabánya, Hungary
403 Cseke Zsuzsanna, Vas Megyei Markusovszky Lajos Kórház, Szombathely, Hungary
404 Czompó Márta, Dr. Czompó Márta Tüdögyógyászati Rendelés, Györ, Hungary
405 Juhász Gábor, Csornai Margit Korhaz, Csorna, Hungary
406 Mohácsi Edit, Szent János Kórház és Észak-Budai Egyesített Kórházak, Budapest, Hungary
407 Póczi Magdolna, Dr. Kenessey Albert Kórház-Rendelöintézet, Balassagyarmat, Hungary
408 Radeczky Eva, FARMAKONTROLL Bt., Százhalombatta, Hungary
409 Schlezák Judit, Selye János Kórház és Rendelöintézet, Komárom, Hungary

Israel:
501 Fink Gershon, Kaplan Medical Center, Rehovot, Israel
502 Kramer Mordechai, Rabin Medical Center, Petach Tikva, Israel
503 Segel Michael, The Chaim Sheba Medical Center, Ramat Gan, Israel
505 Yigla Mordechai, Rambam Health Care Campus, Haifa, Israel
506 Breuer Raphael, Hadassah University Hospital Ein Kerem, Jerusalem, Israel
507 Vilayi-Weiler Zeev, Barzilai Medical Center, Ashkelon, Israel
509 Izbicki Gabriel, Shaare Zedek Medical Center, Jerusalem, Israel
510 Adir Yochai, The Lady Davis Carmel Medical Center, Haifa, Israel
511 Stav David, Assaf Harofe Medical Center, Zerifin, Israel

Poland:
601 Kuna Piotr, SPZOZ Uniwersytecki Szpital Kliniczny nr 1 im. Norberta Barlickiego Uniwersytetu Medycznego w Lodzi, Lodz, Poland
603 Majorek-Olechowska Bernadetta, Alergo-Med Specjalistyczna Przychodnia Lekarska, Tarnow, Poland
605 Pisarczyk-Bogacka Ewa, Dobrostan - Gabinety Lekarskie, Wroclaw, Poland
607 Springer Ewa, SNZOZ Alergologia Plus, Poznan, Poland

608	Wytrychowski Krzysztof, NZOZ Lekarze Specjalisci J. Malolepszy i Partnerzy, Wroclaw, Poland
610	Garbicz Slawomir, NZOZ Poradnia Chorob Pluc i Alergologii, Slupsk, Poland
611	Damps-Konstanska Iwona, Uniwersyteckie Centrum Kliniczne, Gdańsk, Poland
613	Zurowska-Gebala Malgorzata, CenterMed Sp. z o.o., Tarnow, Poland

Russia:

701	Bukreeva Ekaterina, Siberian State Medical University of Roszdrav, Tomsk, Russia
702	Emelyanov Alexander, St. Petersburg State Institution of Healthcare «City Outpatient Clinic #94», St. Petersburg, Russia
705	Klimko Nikolay, St. Petersburg Medical Academy of Postgraduate Education, St. Petersburg, Russia
706	Kudelya Lubov, Novosibirsk State Regional Clinical Hospital, Novosibirsk, Russia
707	Leshchenko Igor, Ural State Medical Academy, Ekaterinburg, Russia
708	Punin Alexander, Clinical Hospital #1, Smolensk, Russia
709	Reutskaya Elena, Regional Clinical Hospital, Barnaul, Russia

Ukraine:

802	Blazhko Viktor, Municipal Institution of Health Care "Kharkiv City Clinical Hospital #13", Kharkiv, Ukraine
803	Dziublyk Oleksandr, SI "National Institute of Phthisiology and Pulmonology n.a. F.G.Yanovsky" under NAMS of Ukraine, Kyiv, Ukraine
805	Gavrysyuk Volodymyr, SI "National Institute of Phthisiology and Pulmonology n.a. F.G.Yanovsky" under NAMS of Ukraine, Kyiv, Ukraine
806	Knopyk Liubov, State Institution "Road Clinical Hospital #2 of Kyiv station DTGO “Southwest Railway”, Kyiv, Ukraine
807	Kovalenko – Ratushniak Svitlana, Regional Municipal Institution "Chernivtsi Regional Clinical Hospital", Chernivtsi, Ukraine
808	Kraydashenko Oleg, Municipal Institution "City Clinical Hospital #6", Zaporizhzhya, Ukraine
810	Melnyk Vasyl, Kyiv City Tuberculosis Hospital #1 with dispensary, Kyiv, Ukraine
811	Molodtsov Valeriy, City Hospital #1, Mykolayiv, Ukraine
812	Monogarova Nadiya, ME MMPI Donetsk Regional Clinical Territorial Medical Association, Donetsk, Ukraine
813	Moskalenko Liubov, Municipal Institution of Health Care “Kharkiv City Clinical Hospital #27”, Kharkiv, Ukraine
814	Mostovoy Yuriy, City Clinical Hospital #1, Vinnytsya, Ukraine
815	Ostrovskyy Mykola, Regional Centre of Phthisiology and Pulmonology, Ivano-Frankivsk, Ukraine

* All sites that participated in screening of patients are listed.

Publication (Reference):	None	
Studied Period:	FPFV: 14 Oct 2012 Screening: 14 Oct 2012 1st injection: 28 May 2013	LPLV (week 12): 24 Jan 2014 Premature Study Termination: 14 Apr 2014
Phase of Development:	Phase IIb	

Objectives:

The primary objective of this study was to assess the therapeutic potential and safety/tolerability of CYT003 at 3 dose levels versus placebo in patients with persistent moderate to severe allergic asthma not sufficiently controlled (Asthma Control Questionnaire 7 items [ACQ] score ≥ 1.5) on current standard inhaled glucocorticosteroids (ICS) with or without long-acting β2-agonists (±LABA) therapy (Global Initiative for Asthma [GINA] Steps 3 and 4)

Methodology:

This was a randomized, placebo-controlled, double-blind, parallel-group, multicenter, dose finding study of 7 sc injections of CYT003 versus placebo in 365 patients (0.3mg = 91 patients, 1.0mg = 94 patients, 2.0 mg = 91 patients, placebo = 89 patients) with persistent allergic asthma not sufficiently controlled (ACQ ≥1.5) on current standard controller therapy. Patients enrolled were insufficiently controlled on medium/high dose ICS with or without LABA (GINA Step 3 and 4).

The study consisted of 3 distinct phases, i.e., Screening/Run-in, treatment and follow-up phase, involving a total of 15 visits per patient from the screening visit to the end of the study.

Premature Study Termination:

The study was prematurely terminated on 14-Apr-2014. The primary efficacy endpoint (change from baseline in asthma control as measured by the ACQ) after 12 weeks did not show any difference for all dose levels compared with that of placebo, and no other substantiating evidence or signal of effectiveness for other secondary endpoints or subgroup analyses were observed.

Number of Subjects:

365 patients were enrolled into the treatment phase of the study. 91 patients were randomized to the 0.3mg CYT003 treatment group, 94 patients to the 1.0mg treatment group, 91 patients to the 2.0mg treatment group, and 89 patients to the placebo group.

Diagnosis and Main Criteria for Inclusion:

- Persistent asthma with all of the following:
  - Present for at least 6 months according to GINA 2011 guidelines at Step 3 or 4 of treatment
  - Stable doses of controller therapy for at least 4 weeks prior to signing the informed consent form (ICF)
  - Symptoms not sufficiently controlled with medium to high doses of ICS (>250 to ≤1000 µg/day fluticasone or equivalent) in combination with or without LABA
  - ACQ score ≥1.5
- Positive skin prick test (SPT) or radioallergosorbent test (RAST) to at least 1 aero-allergen during the screening visit
- Forced expiratory volume in 1 second (FEV1) ≥40% to ≤90% of predicted value
- Reversibility of airway obstruction as demonstrated by:
  - FEV1 improvement of ≥12%, and
  - FEV1 improvement of ≥200 mL after inhaled β2-agonist (400 µg salbutamol or equivalent)

Test Product, Dose, Duration, Mode of Administration, and Batch Number:

7 sc injections of CYT003 of either of 3 doses (0.3mg, 1.0mg or 2.0mg or placebo were administered at equal volumes of 1 mL per injection over 10 weeks. Injections were given at baseline, week 1 and 2 (at intervals of 1 week) and then at week 4, 6, 8 and 10 (at intervals of 2 weeks).

CYT003: Batch numbers for 0.3mg, 1.0mg and 2.0mg were BAG 130802, 130803 and 130804, respectively.

Placebo: Batch number was BAG 130801.

Reference Product, Dose, Duration, Mode of Administration, and Batch Number: Not applicable

Criteria for Efficacy Evaluation:

Primary Efficacy

- Asthma Control Questionnaire 7 items (ACQ) composite score

Secondary Efficacy

- FEV1 pre- and post-bronchodilator
- The Mini Asthma Quality of Life Questionnaire (MiniAQLQ)
- Daytime/nighttime symptoms, use of reliever medication (SABA) and morning and evening PEF rate as self-reported by patients in e-diaries*) (the data was collected but the statistical analysis has not been performed)*
  - Number of and time to asthma exacerbations
  - Moderate asthma exacerbation: need for systemic steroids for at least 3 days.
  - Severe asthma exacerbation: need for systemic steroids for at least 3 days and either emergency room treatment or hospitalization (overnight or for a longer period)

- Additional exploratory analyses *(the data was collected but the statistical analysis has not been performed)*
    - An increase in the use of SABA defined as at least a doubling of the number of puffs from baseline (baseline was defined as the average puffs per day over the last 10 days prior to the baseline visit [BL/T1]), or as an increase to 8 or more puffs of SABA over a 24-hour period
    - A 30% decrease from baseline (baseline was defined as the average of best morning PEF values over the last 10 days prior to the baseline visit [BL/T1]) in PEF provided that the decrease persists for 2 or more consecutive days

Safety and Tolerability:

Safety Assessments:

- Demographics and Medical history
- Adverse events (AEs) and concomitant medications
- Physical examination and electrocardiogram (ECG)
- SPT or RAST
- Routine hematology, blood chemistry, urinalyses, C-reactive protein , antinuclear antibody (ANA), anti-double stranded deoxyribonucleic acid (anti-ds-DNA), HIV, HBV, HCV
- Vital signs (blood pressure, heart rate, body temperature)
- Injection sites are inspected by the investigator 1 hour after injection and at the following visit
- Diaries for local reactions were filled-in by the patients for 4 days after each injection *(not analyzed)*
- Urine pregnancy test

Immunogenicity and Pharmacodynamic Assessments:

Fraction of nitric oxide in exhaled air (FeNO), biomarker periostin, total IgG, total IgE, anti-Qb IgG, eosinophils in peripheral blood were planned to be measured during the study. Due to premature study termination, only data for FeNO, total IgG, total IgE and eosinophils in peripheral blood were measured and evaluated.

Statistical Methods:

A treatment phase analysis was performed when all randomized patients had completed the Week 12 visit. The study was prematurely terminated after the results of these data were presented. Limited follow-up data, as was available at the time of premature termination of the study, were analyzed descriptively.

Efficacy:

The primary efficacy analysis was performed on the Full Analysis Set (FAS). The FAS consisted of those patients in the Safety Set who had at least 1 post baseline assessment. The primary efficacy endpoint was change from baseline in ACQ score at Week 12 which was assessed using analysis of covariance (ANCOVA) with the baseline value as a covariate. Missing values were imputed using the last observation carried forward (LOCF) method.

Secondary efficacy endpoints were analyzed analogous to the primary efficacy endpoint, using the ANCOVA model. For each endpoint, the baseline value was used as a continuous covariate in the ANCOVA model. Unless otherwise stated, only observed values were used with no imputation of missing values.

Pharmacodynamic endpoints (FeNO, total IgG, total IgE, and eosinophils in peripheral blood) were summarized by time point and by treatment using descriptive statistics and graphical presentations. Changes from baseline visit to each post-baseline time point was assessed.

Safety:

The safety population (SAF) consisted of all patients who received at least 1 injection of study medication. The SAF and FAS populations are identical. Pulmonary function measurements, vital signs (blood pressure, heart rate, and body temperature), ECG, and safety laboratory data (hematology, serum chemistry,) were summarized by treatment group. Change from baseline in these parameters was summarized by treatment group. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities Version 12.1 or higher. Analysis of the incidence of AEs (% of patients), are

presented as overall, by system organ class, and by preferred term. Incidences of AEs (% of patients) by severity and relationship to study drug are presented. Adverse events resulting in discontinuation from the study and the incidence of serious AEs are summarized. SAEs during the treatment phase are presented.

Blood hematology and chemistry laboratory results were summarized descriptively for each treatment group by visit for the observed value as well as for the change from baseline value. In addition, laboratory shift tables are provided for laboratory parameters with low/normal/high or abnormal/normal status.

SUMMARY – CONCLUSIONS

Efficacy Results:

- The primary endpoint of the study defined as the change from baseline in ACQ score at week 12 did not show any statistically significant difference between the active treatment groups (0.3mg, 1.0mg, 2.0mg CYT003) compared with that of placebo.
- Secondary endpoints:
    - All other ACQ score analyses including changes from baseline at all time points and the responder analyses revealed no significant differences between active treatment groups compared with that of placebo.
    - All FEV1 change from baseline including absolute values, % changes and % predicted values and the responder analyses did not show any significant differences between active treatment groups compared with that of placebo.
    - The MiniAQLQ score change from baseline at all time points as well as eosinophil counts and FeNO measurements did not reveal any statistically significant difference between the active treatment groups compared with that of placebo.
- All subgroup analyses (i.e. ICS dose, eosinophil counts or FeNO measurement at baseline, age of asthma onset, baseline BMI, or study region) performed for the outcome parameters ACQ, FEV1, MiniAQLQ, eosinophils, and FeNO showed no significant difference for the change from baseline between the active treatment groups compared with that of placebo.
- There was no dose response observed between the 0.3mg, 1.0mg, and 2.0mg treatment groups.
- A strong and persistent placebo effect was observed for the change from baseline in ACQ scores at all time points.

Safety Results:

- This clinical study report presents the safety data during the treatment phase (up to 30 days after the last injection). As the study was prematurely terminated, the data collected during the follow-up phase of the study are discussed in a separate document (Addendum to the Clinical Study Report).
- In summary, 58% of all enrolled patients experienced at least one treatment-emergent adverse Event (TEAE). The majority of these TEAEs were injection site reactions (63%). Most of the AEs were mild (64%) in intensity, followed by moderate (29%) and severe (7%).
- Except for the injection site reactions which are an expected TEAE for CYT003, there was no pattern that would indicate any higher rate of specific AEs in the active treatment groups compared to that of placebo.
- There was no suspected unexpected serious adverse drug reactions during the trial (SUSAR).
- There was one SAE reported during the treatment phase of the study.
- Of the 15 patients that discontinued the study due to an AE, the majority discontinued due to injection site reactions (0% in placebo group, 1% in 0.3mg group, 6% in 1.0mg and 8% in 2.0mg group).
- Local injection site reactions as recorded in the patient e-diaries have not been analyzed
- Due to the premature termination of the study it was not meaningful to perform any analysis of the asthma exacerbations during this period.
- Systemic AEs (headache, pyrexia, body temperature increased, fatigue, and influenza-like illness) were not different to that reported in previous studies.
- Changes blood laboratory examinations (hematology, chemistry, and ANA titer/dsDNA) values as well as evaluation of vital signs, ECGs, and physical examinations did not show any safety concern and were not different to that reported in previous studies.

Conclusions:

- CYT003 as add-on therapy to patients with insufficiently controlled moderate to severe allergic asthma did not show clinical efficacy in any assessed endpoints when compared to those of placebo treated patients.
- Due to the lack of efficacy this clinical trial was prematurely terminated after the analysis of the 12-week data.
- CYT003 was generally well tolerated. No suspected serious adverse events were reported. The most reported adverse events were injection site reactions.
- Overall, the TLR9 agonist, CYT003 has a good safety profile but did not show efficacy compared with that of placebo in moderate to severe allergic asthma patients.

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4 List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	adverse event
ANA	antinuclear antibody
ANCOVA	analysis of covariance
anti-ds-DNA	anti-double stranded deoxyribonucleic acid
ACQ	Asthma Control Questionnaire 7 items
AQLQ	Asthma Quality of Life Questionnaire
ASMS	Average Symptoms and Medication Score
AST	aspartate aminotransferase
ALT	alanine aminotransferase
ATS	American Thoracic Society
BL	Base line
BMI	Body Mass Index
CI	Confidence Interval
CLIA	chemiluminescent immunoassay
CpG	DNA-containing non-methylated CG motif
CPMP	Council for Proprietary Medicinal Products
CPK	creatine phosphokinase
CRA	clinical research associates
CRO	contract research organization
CRP	C-reactive protein
CTL	cytotoxic T lymphocyte
CYT003	bacteriophage capsid Qb packaged with the immunostimulatory oligonucleotide G10 (QbG10)
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
ERC	Ethics Review Committee
ERS	European Respiratory Society
FAS	Full Analysis Set
FDA	Food and Drug Administration
FeNO	fraction of nitric oxide in exhaled air
FEV_1	forced expiratory volume in 1 second
FPFV	First Patient First Visit
FSH	follicle-stimulating hormone
FU	follow-up visit

Abbreviation	Definition
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GGT	gamma-glutamyltransferase
Ha	alternative hypothesis
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
Ho	null hypothesis
ICF	informed consent form
ICH	International Conference on Harmonisation
ICS	inhaled glucocorticosteroids
IEC	independent ethics committee
IFN	interferon
IgE	immunoglobulin E
IgG	immunoglobulin G
IL	interleukin
ITT	intent-to-treat
IRB	institutional review board
ISR	injection site reaction
IVRS	interactive voice response system
LABA	long-acting β2-agonists
LDH	lactate dehydrogenase
LOCF	last observation carried forward
LPLV	Last Patient Last Visit
LS	Least square of the mean
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MiniAQLQ	Mini Asthma Quality of Life Questionnaire
mg	milligram
MPV	mean platelet volume
NO	nitric oxide
PD	protocol deviation
pDCs	plasmacytoid dendritic cells
PEF	peak expiratory flow

Abbreviation	Definition
PEI	Paul Ehrlich Institut
PP	per protocol
PTEAE	pretreatment-emergent adversee
pts	patients
PVG	pharmacovigilance
Qb	recombinantly expressed viral capsid shell
RAST	radioallergosorbent test
RBC	red blood cells
RNP	ribonucleoprotein
SABA	short-acting β2-agonists
SAE	serious adverse event
SAP	statistical analysis plan
SEM	Standard error of the mean
sc	subcutaneous
SD	Standard deviation
SIT	specific allergen immunotherapy
SOC	System Organ Class (MedDRA)
SPT	skin prick test
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TLR9	Toll-like receptor 9
Th2	T-cell helper 2
TMF	trial master file
ULN	upper laboratory norm
VLP	virus-like particle
WHO	World Health Organization

5 Ethics

5.1 Independent Ethics Committee (IEC) / Institutional Review Board (IRB)

The protocol, revised protocols, informed consent forms (ICFs), and revised ICFs were reviewed by local Independent Ethics Committee/Ethics Review Committees (IEC/ERC) and notified by local health authorities (HA) prior to study initiation in the USA, Czech Republic, Germany, Hungary, Israel, Russia, Poland and Ukraine.

All relevant approvals can be found in Appendix 16.1.3 and the TMF.

5.2 Ethical Conduct of the Study

This study was conducted in accordance with the ICH-GCP Guidelines (Directive CPMP/ICH/135/95) and the Declaration of Helsinki (1964) and subsequent revisions.

5.3 Patient Information and Consent

Subjects were informed by the investigators and were required to read the patient information and sign an ICF before screening. The patient information summarized in non-technical terms the purpose of the study, the procedures to be carried out, and the potential hazards. Appendix 16.1.3 contains a representative version of the information for patient and informed consent forms as used in the study in the respective language.

6 Investigators and Study Administrative Structure

Co-ordinating Investigator

Prof. Thomas Casale, MD (*after October 2013):*Department of Internal Medicine, University of South Florida, 12901 Bruce B Downs Blvd, MDC19, Tampa, FL 33612, USA

Investigators at the Trial Sites

In total, 92 trial sites participated and screened patients in the study: 33 in the USA, 7 in Czech Republic, 8 in Germany, 8 in Hungary, 9 in Israel, 8 in Poland, 7 in Russia and 12 in the Ukraine.

Appendix 16.1.4 contains the list of site investigators including contact details. Curriculum vitae of site investigators can be found in the TMF.

API Manufacturer

Cytos Biotechnology AG, Wagistrasse 25, CH -8952 Schlieren, Switzerland

IMP Manufacturer

Biologische Analysensystem GmbH (BAG), Amtsgerichtsstr. 1-5, D-35423 Lich, Germany

Clinical Supply

Global Clinical Supplies (GCS), PPD Brussels, Kleine Kloosterstraat, 23, 1932 Sint Stevens Woluwe, Belgium

Patient eDiaries and Spirometry

eResearchTechnology GmbH, Sieboldstrasse 3, Estenfeld D-97230, Germany

Clinical Central Laboratory (Safety)

Steve Lobel, PPD, 2 Tesseneer Drive, Highland Heights, KY 41076-9167, USA (North America) and Cluster Park, Kleine Kloosterstraat 19, B-1932 Zaventem, Belgium (Europe and Middle East). ANA/dsDNA measurements (screening tests LIAISON DiaSorin) were performed in central laboratory Cluster Park, Kleine Kloosterstraat 19, B-1932 Zaventem, Belgium for all study participants.

ANA titer and IFA panel: Cleveland Clinic Laboratories 2119 E. 93rd St. Cleveland, OH 44106, USA

Immunoassays

Not applicable due to premature termination of the study

CRO

PPD Development, 929 North Front Street, Wilmington, NC 28401, USA

Data Management & Biostatistics

Tony Wu, Ph.D. Lead Biostatistician, Biostatistics, PPD

7 Introduction

7.1 Allergic Asthma

The Global Initiative for Asthma (GINA 2012) defines asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment.

Common risk factors for asthma include exposure to allergens (e.g. those from house dust mites, animals with fur, cockroaches, pollens, and molds), occupational irritants, tobacco smoke, respiratory (viral) infections, exercise, strong emotional expressions, chemical irritants, and drugs. Allergy is a predominant risk factor for developing asthma. The chemical mediators released upon an allergic reaction can cause inflammatory responses which have been linked to asthma signs and symptoms. The pathogenesis is largely promoted by type 2 T-helper cells (Th2), which are found in the airways of asthmatics. Upregulation of the Th2-mediated immune response provokes not only an increase in IgE levels, but also secretion of Th2 cytokines, which inhibit the differentiation of counterbalancing Th1 cells. Moreover, secretion of Th2 cytokines such as interleukin-5 (IL-5) and eotaxin can directly be linked to the underlying allergic airway inflammation (Cohn *et al*, 2004). Interleukin-13, another Th2 cytokine, is responsible for excessive mucus production in airways.

7.2 Current Treatment Modalities

Three general approaches are currently being pursued to relieve the clinical manifestations of allergies including allergic asthma: i) avoidance of the allergen, ii) symptomatic therapies to alleviate acute consequences of allergen exposure or chronic consequences of inflammatory processes, and iii) treatments with a disease-modifying long-term effect.

Asthma severity is by current consensus classified on the basis of the intensity of treatment required to achieve good asthma control. Assessment of asthma control includes not only control of the clinical manifestations but also control of expected future risk to the patient such as exacerbations, instability, accelerated decline in lung function, and side effects of treatment.

According to the GINA guidelines, a stepwise approach to pharmacological treatment is recommended in order to achieve and maintain control of asthma. Inhaled and oral corticosteroids, leukotriene modifiers, theophylline, anti-immunoglobulin E (IgE) and specific allergen immunotherapy (SIT) are well-established treatments for asthma (Bateman *et al*, 2008). Medications to treat asthma can be classified as controllers (e.g., inhaled glucocorticosteroids [ICS], long-acting β2-agonists [LABA]) or relievers (e.g., short-acting β2-agonists [SABA]). The recommend stepwise (reliever alone followed by combination of reliever and one or more controller) treatment for control of asthma; for example, if asthma is not controlled on the current treatment regimen, treatment should be stepped up. If control has been maintained for at least 3 months, treatment can be stepped down. However, despite treatment with ICS or combined therapy with ICS plus LABA, many patients with asthma remain symptomatic and fail to achieve asthma control (Bateman *et al*, 2004; Gruenberg &

Busse, 2010). Hence, there remains an unmet therapeutic need for asthmatics who fail to achieve symptom control on ICS alone or in combination with LABA.

Anti-inflammatory drugs and bronchodilating agents are symptomatic treatments and do not address the underlying allergic disposition. New treatment approaches targeting the underlying inflammatory nature of asthma are currently under evaluation.

7.3 CYT003-QbG10 (CYT003)

Cytos Biotechnology has developed CYT003 which is a bacteriophage capsid filled with immune stimulatory oligonucleotides (G10), that are A-type CpGs acting as toll-like receptor-9 (TLR9) agonists, postulated to inhibit T-cell mediated inflammation of the airways in asthma.

7.3.1 CpGs as TLR9 Agonists

Toll-like receptors (TLRs) are a key set of sensors for pathogens, recognizing so-called pathogen-associated molecular patterns (PAMPs). The DNA containing non methylated CG motifs; CpGs, are overrepresented in bacterial and viral genomes and are recognized by TLR9. G10 is a synthetic A-type CpG oligonucleotide acting as a TLR9 agonist. Stimulation of TLR9 induces a cytokine pattern that favors a Th1 response. TLR9 agonists have been introduced into first clinical trials in patients with allergic asthma. Inhalation as well as subcutaneous injection of CpG oligonucleotides was found to be safe and well tolerated. Both applications had a beneficial impact on inflammatory processes (Casale & Stokes, 2008).

7.3.2 Bacteriophage Qbeta Capsids

The presentation of an antigen in a highly ordered, repetitive array normally provokes strong antibody responses whereas the same antigen presented as a monomer is non-immunogenic (Bachmann *et al*, 1993). Examples of such repetitive antigenic arrays are the protein shells or coats of certain viruses. The repetitive and ordered characteristics of virus shells can be mimicked by virus-like particles or capsids which spontaneously form during recombinant expression of certain coat proteins of the virus or bacteriophage. Unlike whole viruses or bacteriophages, capsids do not carry any replicative genetic information and are thus non-infectious. They are typically non-toxic and very immunogenic and induce strong humoral and/or cellular immune responses.

The coat protein of the bacteriophage Qbeta is another example of a protein that assembles into capsids. These capsids - called Qb - have been clinically used as carriers for therapeutic vaccines for the development of the treatment of hypertension, smoking cessation, and Alzheimer's disease and were shown to induce strong antibody responses against various therapeutic targets (Ambuhl *et al*, 2007; Cornuz *et al*, 2008; Kundig *et al*, 2006; Maurer *et al*, 2005; Tissot *et al*, 2010; Winblad *et al*, 2012).

7.3.3 Postulated Mode of Action

Since A-type CpG oligonucleotides are rapidly degraded *in vivo* by deoxyribose nucleases, Cytos Biotechnology has encapsulated the A-type CpG G10 into bacteriophage Qbeta derived capsids to generate CYT003. The capsid protects the CpG from degradation and facilitates its uptake by cells the immune system.

The postulated mechanism of action after subcutaneous (sc) injection includes efficient uptake and transport of the CYT003 by plasmacytoid dendritic cells (pDCs) into the lymph node. The capsids are degenerated in the endosomes where the CpG is released and acts as a TLR9 agonist. CYT003 induces production of type I interferons in pDCs, which are key cytokines for the development of Th1 responses.

Several aspects of CYT003 are thought to contribute to its activity: Antigenic determinants of Qb are presented on the cell surface of antigen-presenting cells in association with major histocompatibility complex molecules and cytokines such as IFNα and IL-12 are released. Naïve T cells recognize the appropriate antigen/major histocompatibility complexes with their T-cell receptor, become activated and differentiate into Qb-specific effector T-helper cells secreting IFNγ. Moreover pDCs and B-cells which express TLR9 are activated by the A-type CpG to produce Th1-type cytokines, chemokines, and induce immunoglobulin G (IgG) class switching. As a consequence of CYT003 administration, the immune system of an allergy/asthma patient may respond in a number of ways. A local Th1-biased environment may be evoked which could suppress the Th2 mediated allergic response. Also, IFNα, which is induced by CYT003, can reportedly reverse Th2-commitment in human peripheral blood mononuclear cells in vitro (Huber *et al*, 2010).

In addition, the synthesis of IgE antibodies could be inhibited. Furthermore, a number of allergic effector cells (mast cells, basophils and eosinophils) were recently reported to express TLR9 in humans (Fransson *et al*, 2007) and could be positively influenced.

7.4 Previous Clinical Trial Experience with CYT003 prior to the commencement of study CYT003-QbG10 12

Clinical trials have been conducted with CYT003 as a monotherapy (CYT003-QbG10 program) and in combination with allergen extracts with the aim to enhance efficacy of specific immunotherapy (CYT005-AllQbG10 program). The CYT003 capsid carrier has also been used as a carrier for a tumor-specific peptide vaccine (CYT004-MelQbG10 program) aiming to induce a cytotoxic T lymphocyte (CTL) response in melanoma patients.

Excluding the current study CYT003-QbG10 12, a total of 456 subjects (healthy subjects, patients with perennial rhino conjunctivitis due to house dust allergy or cat allergy, patients with seasonal grass pollen allergy, patients with atopic dermatitis and allergic asthma) were exposed in these trials to CYT003, and another 268 patients received placebo or an allergen extract without CYT003. The 43 patients with melanoma received the cancer vaccine CYT004-MelQbG10 containing the same capsid carrier.

There was no suspected unexpected serious adverse reaction (SUSAR) in any of the clinical trials with CYT003, CYT003 + allergen or CYT004-MelQbG10 (i.e. CYT003-QbG10 02, 03, 08, 09, 11; CYT005-AllQbG10 01, 02, 03, 04; CYT004-MelQbG10 01, 02, 03, 04).

The majority of the Treatment Emergent Adverse Events with suspected relationship to study treatment represent local reactions at the injection site such as pain, itching, erythema, swelling, and induration. The injection site reactions were recorded as adverse events if they had not disappeared on the occasion of the next visit, or when they required some therapeutic intervention additionally, in study 12 also if patient reported reaction as severe according to the criteria per protocol. In the pooled analysis of CYT003-QbG10 program with CYT003 as a monotherapy (Studies CYT003-QbG10 08, 09 and 11) the term “local reaction” appeared in

6.2% of patients after CYT003, other local symptoms like erythema, pain and pruritus in 4-5% of patients. Although reported as AEs, these events were mostly mild (72%) or moderate (23%). Therapeutic intervention consisted e.g., of local antihistaminic gel and oral antihistamines. No oral analgesics were required for treating local pain.

The incidence of symptoms of systemic reactogenicity such as fever/pyrexia or influenza-like illness in performed clinical trials was generally low and slightly more frequent after CYT003 than after placebo. In the pooled analysis on 442 patients from CYT003-QbG10 program with CYT003 (Studies CYT003-QbG10 08, 09 and 11) symptoms that were reported in both treatment groups included headache, pyrexia, and influenza-like illness. Fatigue, chills, malaise, and asthenia occurred in the CYT003 treatment group only but the incidence was low.

7.5 Study Rationale

Treatment options for patients with severe allergic asthma include increase in the ICS dose, add-on therapy with leukotriene antagonists, and anti-IgE. Hence, there remains an unmet therapeutic need for asthmatics who fail to achieve symptom control on ICS alone, and treatments which potentially address the underlying allergic condition would be highly desirable.

A favorable risk-benefit assessment for the proposed CYT003 monotherapy can be forecast since the magnitude of the medical need for an efficient causative therapy of allergic asthma and other allergic conditions is high. Other factors include the potential of the proposed CYT003 treatment to induce a modulation of the system's immune responsiveness within a few weeks, the allergen-independent mode of action devoid of allergen-specific risks, and the promising results in patients with mild-moderate asthma under a condition of ICS withdrawal. Initial studies of CYT003 used as a monotherapy have shown efficacy; however, formal dose-finding studies had not been performed. Dose-finding and clinical safety and efficacy investigations with CYT003 in patients with allergic asthma not sufficiently controlled on current standard therapy were considered justified based on the current risk versus benefit considerations.

8 Study Objectives

The objective of this Phase IIb study was to assess the therapeutic potential and safety/tolerability of CYT003 at three dose levels versus placebo in patients with persistent moderate to severe allergic asthma not sufficiently controlled (ACQ≥1.5) on current standard ICS (±LABA) therapy (GINA Steps 3 and 4)(GINA, 2011).

9 Investigational Plan

9.1 Overall Study Design

This randomized, placebo-controlled, double-blind, parallel-group, multicenter, dose finding study with 7 sc injections of CYT003 or placebo included 365 patients (0.3mg = 91 patients, 1.0mg = 94 patients, 2.0mg = 91 patients, placebo = 89 patients) with persistent allergic asthma. The patients enrolled had to be insufficiently controlled on current standard therapy: medium/high dose ICS with or without LABA (GINA Step 3 and 4). See also table below.

Table 9.1-1 Use of SABA/LABA at Baseline

	ICS medium	ICS high	Total
with LABA n (%)	117 (32%)	205 (56%)	322
without LABA n (%)	4 (1%)	39 (11%)	43
Total	**121**	**244**	**365 (100%)**

[Source: Listing 16.2.4.3]

The study consisted of 3 distinct phases, i.e., Screening/Run-in, treatment, and follow-up phase, involving a total of 15 ambulatory visits per patient (Figure 9.1-1) from the screening visit to the end of the study.

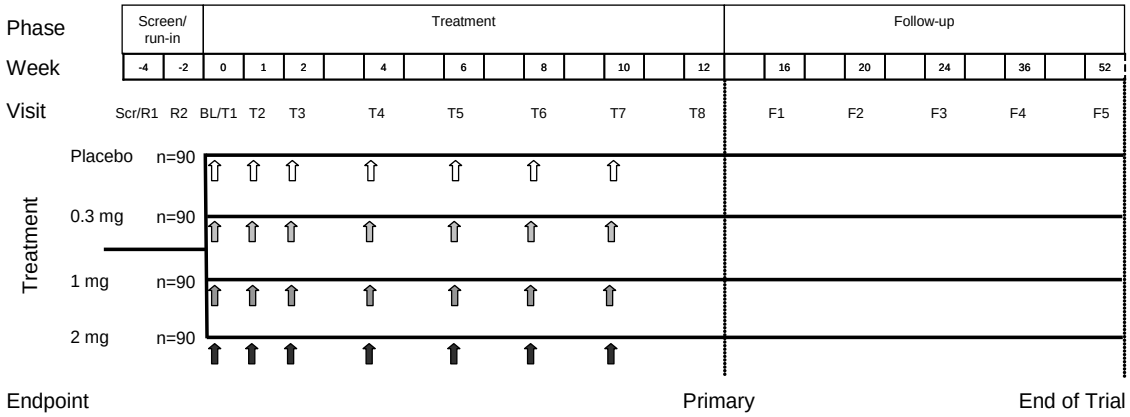


Figure 9.1-1 Study Overview

Injections of CYT003 (0.3, 1.0 or 2.0 mg) versus placebo, weekly for the first 3 weeks, were given at baseline visit (BL/T1) and at weeks 1, 2, 4, 6, 8, and 10. Visit Windows were ±3 for Visit R2 and Visit T4 to T8, ±1 for Visits T2 and T3, and ±7 for Visits F1 to F5.

Scr = screening visit, R1-R2 = run-in visits, BL = baseline visit, T1-T8 = treatment visits, F1-F5 = follow-up visits

Screening/Run-in Phase was a 4-week phase with 2 visits to evaluate eligibility, to teach patients how to use eDiaries and devices used for recording clinical endpoints, and to ensure that these screening efficacy readouts were stable within certain acceptance limits of reproducibility. Controller therapy was recorded at the screening visit and maintained throughout the run-in phase and the treatment phase of the study.

The patients were assigned to 1 of 4 treatment arms based on a stratified randomization schedule via an interactive voice response system (IVRS). Two stratification criteria were applied: current use of LABA (yes/no) and current dose of ICS (fluticasone or equivalent: medium dose >250 to 500 µg per day/high dose >500 to 1000 µg per day).

A final confirmation of eligibility was performed at the **Baseline Visit**.

Treatment Phase (Core Study) was a 12-week phase with 8 visits during which the study drug was administered as 7 sc injections. The study drug was given as an add-on therapy to current controller medication (ICS with or without LABA) and patients continued to administer their usual brand and dose of ICS (and LABA if used) throughout the study. The patients experiencing an asthma exacerbation were discontinued from study drug and managed with systemic steroid therapy as deemed necessary by the investigator.

Study assessments were performed according to the study schedule (Table 9.5.1-1). During a study visit, the patients stayed at the study site for the time required to conduct all necessary investigations. On days of study drug administration, the patients stayed for at least 1 hour after injection or longer if deemed appropriate by the investigator. Patients had access to their usual SABA reliever medication and recorded its use in the patient e-diary.

Follow-up Phase was a 9-month phase with on-site visits at months 4, 5, 6, 9 and 12. Each patient was followed with standard "step-up" or "step-down" therapy as indicated by the clinical status and according to local current medical practice (GINA, 2011; NHLBI, 2007).

Premature Study Termination: At the end of the treatment phase after 12 weeks primary and secondary efficacy endpoints were analyzed. As the primary endpoint was not achieved and no secondary analyses revealed any significant treatment effect of any of the 3 doses compared to that of placebo, the study was prematurely terminated and no further patient visits recorded. All patients in the study discontinued follow-up visits on the 14-Apr-2014. Therefore, complete data sets were only available up to and including week 12.

9.1.1 Efficacy Analysis performed

As defined in the Statistical Analysis Plan for the 12-week-treatment phase (version 2.2 dated 20-Feb-2014).

Primary Efficacy Endpoint:

- Change from baseline in Asthma Control Questionnaire (ACQ) score at Week 12 (7-item ACQ: average of 5 self-rated symptom scores + 1 score for number of puffs of SABA + 1 score for FEV1 % predicted)

Secondary Efficacy Endpoints:

- Change from baseline in pre-bronchodilator FEV1 at Week 12
- Change from baseline in ACQ score at all time points up to Week 12 including ACQ responder analyses
- Change from baseline in pre-bronchodilator FEV1 at all time points including FEV1 responder analyses up to Week 12
- Percent change from baseline in pre-bronchodilator FEV1 and change of % predicted FEV1 at all time points up to Week 12
- Change from baseline in Mini Asthma Quality of Life Questionnaire (MiniAQLQ) score at all time points up to Week 12
- Change from baseline in eosinophils and FeNO at all time points up to Week 12
- Subgroup analyses were performed for the following: ICS dose at baseline, eosinophil counts, FeNO values at baseline, age at asthma onset, baseline BMI, and study regions. If not otherwise stated in the SAP, for each subgroup the change from baseline was analyzed for the following parameters: ACQ, FEV1, MiniAQLQ, eosinophils, FeNO.

Safety Endpoints:

- Descriptive statistics of adverse events and concomitant medications

- Descriptive statistics of physical examination and ECG
- Summary and shift from baseline in hematology, clinical chemistry, urinalyses
- Summary of vital signs (blood pressure, heart rate, body temperature) before and 1 hour after injection

9.1.2 Efficacy Analysis planned but not performed

The following efficacy analyses had been planned according to the study protocol but were not performed due to the premature termination of the clinical trial.

Secondary Efficacy Endpoints:

- Daytime/nighttime symptoms, use of reliever medication (SABA) and morning and evening PEF rate as self-reported by patients in e-diaries
- Number of and time to asthma exacerbations:
    - Moderate asthma exacerbation: need for systemic steroids for at least 3 days.
    - Severe asthma exacerbation: need for systemic steroids for at least 3 days and either emergency room treatment or hospitalization (overnight or for a longer period).
- Additional exploratory analyses:
    - An increase in the use of SABA defined as at least a doubling of the number of puffs from baseline (baseline is defined as the average puffs per day over the last 10 days prior to the baseline visit [BL/T1]), or as an increase to 8 or more puffs of SABA over a 24-hour period.
    - A 30% decrease from baseline (baseline is defined as the average of best morning PEF values over the last 10 days prior to the baseline visit [BL/T1]) in PEF provided that the decrease persists for 2 or more consecutive days.

Pharmacodynamic Markers:

- Descriptive statistics by time point and treatment of total IgE and IgG antibodies (data available)
- Descriptive statistics of the kinetic of specific anti-Qb IgG (measurements not performed)
- Biochemical markers in serum for postulated mode of action (measurements not performed)

Safety Endpoints:

- Descriptive statistics of entries in patient e-diaries for local reactions (data available)
- Asthma exacerbations (number of and time to first asthma exacerbation)

9.2 Discussion of Study Design, Including the Choice of Control Groups

9.2.1 Design and Control Groups

This was a randomized, placebo-controlled, double-blind, parallel-group, multicenter, dose finding study of 7 sc injections of CYT003 versus placebo.

Randomization and blinding were used to minimize bias in assessing subjective parameters of asthma control. A parallel group design was selected considering the potential long-lasting effect of CYT003 and because of the need for adequate follow-up periods to assess duration of efficacy and long-term safety.

A placebo control was considered appropriate because patients were maintained on their current controller medication, and had access to reliever medication (SABA) as required to treat asthma symptoms. Injections with CYT003 were add-on therapy.

The multicenter and multi-national design was selected in order to facilitate rapid recruitment and to improve the quality of evidence as a result of regional variations in the patient mix.

The four equal sized treatment groups have been chosen to identify the optimal dosage for CYT003 late stage development. The treatment schedule of 7 sc injections on weeks 0, 1, 2, 4, 6, 8 and 10 has been tested before in the proof-of-concept study (study CYT003-QbG10 11) and showed clinical efficacy, while found to be safe and well tolerated.

9.2.2 Trial Duration

Total study duration for an individual patient was planned to be 56 weeks, involving a total of 15 visits per patient from screening visit to end of study. The Screening/Run-in phase had a duration of 4 weeks. The treatment phase (core study) lasted up to week12 and the follow-up phase for another 9 months.

At the end of the treatment phase (Week 12) the study was analyzed. An independent Data Monitoring Committee reviewed the safety data and concluded that there were no safety concerns. As the primary efficacy end point was not met the study was prematurely terminated on 14-Apr-2014. At that time no patient had completed the follow-up phase according to the protocol.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Each patient must have met the following criteria to be enrolled in this study:

1. Able and willing to provide written informed consent
2. Able and willing to complete all protocol requirements
3. Between 18 to 65 years of age
4. Persistent asthma with all of the following:
    - Present for at least 6 months according to GINA 2011 guidelines at Steps 3 or 4 of treatment

- Stable doses of controller therapy for at least 4 weeks prior to signing the ICF
- Symptoms were not sufficiently controlled with medium to high doses of ICS (>250 to ≤1000 µg/day fluticasone or equivalent) in combination with or without LABA
- ACQ score ≥1.5

Note: Use of stable doses of other controller therapies according to GINA Steps 3 and 4 (leukotriene modifiers, sustained-release theophylline) were also acceptable provided doses were stable for 4 weeks prior to signing the ICF. Treatment with anti-IgE antibodies (Xolair®) within the past 6 months were not allowed (see exclusion criterion 18).

5. Stable but insufficiently controlled baseline conditions as documented by ACQ ≥1.5 at the screening and the baseline visits
6. Positive skin prick test (SPT) or radioallergosorbent test (RAST) to at least 1 aero-allergen during the screening visit
7. An FEV_1 ≥40% to ≤90% of predicted value
8. Reversibility of airway obstruction as demonstrated by:
   - FEV_1 improvement of ≥12%, and
   - FEV_1 improvement of ≥200 mL after inhaled β2-agonist (400 µg salbutamol or equivalent)

If a patient did not meet reversibility criteria at the screening visit, reversibility could be retested once prior to or at the run-in visit (R2). Reversibility testing should have occurred after at least 6 hours of SABA withhold and at least 12 hours of LABA withhold. Reversibility testing could be performed after a longer LABA withhold at the discretion of the principal investigator.

9. Patients meeting the contraception requirements as specified in the protocol.

9.3.2 Exclusion Criteria

Patients meeting any of the following criteria were excluded from the study. Note: Any patient who failed during the screening visit was allowed to rescreen once with the approval of the medical monitor.

1. Failure to meet at least 80% compliance of use of the patient e-diary/ peak expiratory flow (PEF) meter (AM3) at baseline visit, after initial instructions at the screening visit and, where necessary, additional training at the R2 run-in visit. The 80% AM3 compliance was calculated over the 10 days prior to and including the morning session of the baseline visit (BL/T1). A scheduled AM3 session was considered to be compliant if a complete set of answers and at least 1 PEF measurement is available.
2. Treatment or hospitalization for asthma exacerbation within 2 months prior to signing the ICF. Patients who had an exacerbation during the screening visit/run-in period were considered screen failures.
3. Current use or use of systemic corticosteroids within 2 months prior to signing the ICF
4. Current smokers

5. Ex-smokers with a smoking history of >10 pack years (1 pack per day for 10 years)
6. Major surgery within 4 weeks prior to enrollment or anticipated within the 12-week treatment period that might impact study procedures (e.g., spirometry)
7. Presence or history of clinically relevant cardiovascular, renal, pulmonary, endocrine, autoimmune, dermatological, neurological, psychiatric, or ocular disease as judged by the investigator
8. Any malignancy within the previous 5 years except completely excised and cured squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma or squamous cell carcinoma
9. Presence of suspicious lymphadenopathy or splenomegaly on physical examination
10. Confirmed or suspected current infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV)
11. Presence of active infectious disease as judged by the investigator (e.g., respiratory infections)
12. Active autoimmune diseases or prior diagnosis of autoimmune disease including but not limited to rheumatoid arthritis, lupus, and colitis ulcerosa
13. Pregnancy (based on positive urine test at screening visit) or lactation
14. Female planning to become pregnant during the study period
15. Patients with any history of abuse of alcohol or other recreational drugs
16. Ongoing or planned SIT during the whole study period or SIT completed within the last 3 years
17. Use of investigational unapproved drugs within 30 days or within 5 half-lives of the investigational drug, whichever is longer, or planned use during the whole study period
18. Use of investigational and approved biologics including IgE antibodies (Xolair®) within the last 6 months
19. Previous participation in a clinical study with a VLP Qb-based vaccine
20. Possible dependency of the patient on sponsor and/or investigator

9.3.3 Removal of Patients from Therapy or Assessment

Patients were to be discontinued from the study drug during the randomized 12-week treatment period but continued with study visits in case of:

- Asthma exacerbation defined as need for systemic steroids for at least 3 days (moderate asthma exacerbation) or either emergency room treatment or hospitalization overnight or for a longer period (severe asthma exacerbation)
- Asthma controller medication change (step-up or step-down)
- Patients using systemic steroids (including intramuscular injections) for non-asthma conditions during the study for ≥3 days

- In case of unacceptable toxicity /clinical significance as judged by the investigator or unacceptable in the opinion of the patient), the study drug should be discontinued particularly in case of:
    - Local reactions Grade 4; Local reactions Grade 3 or lower, according to protocol, if the patient was significantly limited in his daily activities, or wished to discontinue, or if the investigator decided this was in the best interest of the patient
    - Systemic urticaria of suspected relationship with the study drug
    - Anaphylactic clinical symptoms related to injection of study drug
    - Clinical manifestations of autoimmune disease, with or without clinically significant increase of serological markers (ANA,anti-ds-DNA titers)

Patients who discontinued study drug treatment were encouraged to complete the study through the follow-up period including completing all assessments required at each visit.

A patient may have been withdrawn from the study prior to completion of the study requirements if 1 or more of the following events occur:

- Patient requested to be withdrawn
- Significant protocol deviation or noncompliance on the part of the patient or investigator
- Refusal of the patient to continue treatment or observations
- Patient unable or unwilling to comply with the requirements for study evaluations or visits
- The clinical condition of the patient was such that the investigator recommended that it was in the patient's best medical interest to withdraw the patient from the current treatment and to use alternative therapies
- Unrelated medical illness or complication
- Sponsor decision

9.4 Treatments

9.4.1 Treatments Administered

The treatment consisted of 7 injections of CYT003 or placebo at baseline and weeks 1, 2, 4, 6, 8 and week 10. Patients allocated to the active treatment received either 7 injections with 0.3mg, 1.0mg or 2.0mg CYT003. The injections were administered subcutaneously into the lateral side of the upper arm alternating between right and left from visit to visit. If the proposed injection site was contraindicated for any reason, the study drug could be injected into the thigh. The maximal cumulative dose of CYT003 within 10 weeks was 14.0mg (7 x 2.0mg).

9.4.2 Identity of Investigational Product(s)

Table 9.4.2-1 Study Drug Details

	CYT003-QbG10 (CYT003)	**Placebo**
Drug Product	CYT003-QbG10 (Qb-derived biologic carrier filled with the deoxyoligonucleotide G10)	Placebo: Succinate buffered saline solution; pH=6.3, injection grade
Concentrations	0.30 ± 0.06 mg/mL for 0.3mg dose, 1.00 ± 0.20 mg/mL for 1.0mg dose, 2.00 ± 0.20 mg/mL for 2.0mg dose.	20 mM Succinate 150 mM Sodium Chloride, 0.005 % Tween
Vial content	1.2 mL	1.2 mL
Injection volume	1.0 mL	1.0 mL
Quality	Good Manufacturing Practice	Good Manufacturing Practice
Manufacturer of study drug substance	Cytos Biotechnology AG, Schlieren, Switzerland	BAG Health Care GmbH, Lich, Germany
Manufacturer of bulk study drug	BAG Health Care GmbH, Lich, Germany	BAG Health Care GmbH, Lich, Germany
Batch No.	0.3mg dose: BAG 130802 1.0mg dose: BAG 130803 2.0mg dose: BAG 130804	Placebo: BAG 130801
Manufacturer of finished study drug	PPD Ireland Development Ltd., Athlone, Ireland	PPD Ireland Development Ltd., Athlone, Ireland
Batch No.	PPD 13B001	PPD 13B001
Route of administration	subcutaneous	subcutaneous
Usage	For clinical study use only	For clinical study use only

The vials with the study drug were filled by BAG Health Care GmbH, Germany, and sent to PPD, Ireland, for blinding, labeling, packaging, and release.

The study drug was available as ready for use solutions in glass vials stored at +2°C to +8°C. The blinded patient kit with 2 and 5 vials were sent to the site after ordering it via a telephone-based interactive voice response system (IVRS) call at the screening visit R2 and at the baseline visit BL/T1, respectively. The patient kits could be identified with a unique kit number. Further details are given in Table 9.4.2-1.

9.4.3 Method of Assigning Patients to Treatment Groups

The randomization and stratification was facilitated by IVRS. The randomization schedule for IVRS linked sequential patient randomization numbers to treatment codes allocated at random with a 1:1:1:1 randomization ratio. The randomization numbers were blocked and within each block of 8 patients the same number of patients were allocated to each treatment group.

Two stratification criteria were applied: current use of LABA (yes/no) and current dose of ICS (fluticasone or equivalent: medium dose >250 to 500 µg per day/high dose >500 to 1000 µg per day). For every eligible patient, the study site personnel called the IVRS at the R2 visit to execute the randomization and order the study drug shipment to the site. At the BL/T1 visit, the final eligibility of the patient was confirmed prior to the study drug administration.

9.4.4 Selection of Doses in the Study

In initial studies with CYT003, 6 or 7 sc injections at intervals of 1 to 2 weeks were administered. In the proof-of-concept Phase IIa study, 7 injections of 0.9 mg CYT003 per injection were investigated in patients with allergic asthma under a condition of ICS reduction and withdrawal. The purpose of the current study was to reproduce that previous outcome in patients with uncontrolled allergic asthma as add-on therapy. Therefore, the injection regimen of the previous study was maintained.

For dose-finding purposes, a lower dose of 0.3mg CYT003 was considered likely suboptimal, the dose of 1.0mg optimal and the dose of 2.0mg was the highest dose in order to explore the upper end of the dose response.

9.4.5 Selection and Timing of Dose for Each Patient

No dose adjustments (e.g. reductions) or deviations from the treatment schedule were foreseen and no specific day time for injection was required by the protocol.

9.4.6 Blinding

The study was performed with a double-blind design. The blinded patient kits containing the study drug were prepared by the PPD Ireland. Neither investigators nor patients could distinguish between placebo and active treatment. An interactive voice response system (IVRS) was used for drug management and permitted as well a rapid unblinding in the event of a medical emergency.

One patient was unblinded during the Screening/Run-in phase in error. It happened by error that the documents delivered together with the study medication for this patient (patient kit) to the study site 807 in the Ukraine contained the full unblinded study medication description. The patient was excluded from further participation in the study and was not permitted to be re-screened.

The treatment phase analysis with unblinded data took place after all randomized patients had completed the week 12 visit. For this a separate sponsor representative team (independent of the clinical study team) and an unblinded PPD biostatistics team were selected. Cytos and PPD project management and operations teams, the clinical research associates (CRAs), patients, investigators and site staff remained fully blinded. All communications with study centers continued blinded (no reference to treatment) until the termination of the study. A separate unblinded team was in place for the data monitoring committee (DMC) deliverables for the duration of the study.

9.4.7 Prior and Concomitant Therapy

Due to the postulated mode of action as immune modulator of CYT003 the usual presumptions of drug-drug interactions cannot be applied.

In general, patients were advised to try to avoid concomitant medications, other than those accepted by the investigator at study entry or upon consultation with the investigator during the course of the study. Stable medications used prior to the screening visit for treatment or prevention of chronic conditions, e.g., antihypertensives, lipid-lowering drugs, or hormone replacement could be maintained throughout the study.

Flu-like symptoms, painful local reactions, and lymphadenopathy could be treated with standard doses of paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, excluding acetylsalicylic acid.

Asthma reliever and controller medications were permitted. For asthma symptom relief the use of SABA (salbutamol or equivalent) was allowed as needed and the number of puffs was documented in the patient e-diary. Current controller treatment (ICS, LABA and regular use of leukotrienes antagonist or sustained-release theophylline according to GINA Step 4) was to be maintained during the treatment phase until treatment phase analysis.

The patients requiring a step-up or step down of their asthma controller therapy as well as patients with an asthma exacerbation requiring systemic steroids therapy for at least 3 days during the treatment phase were discontinued from the study drug but continued with the study visits.

9.4.8 Treatment Compliance

The study medication was administered only at the study centers by the investigators. Treatment compliance was acceptable if 5 or more injections were administered.

9.5 Efficacy, Pharmacodynamic/Immunogenicity and Safety Variables

9.5.1 Efficacy, Pharmacodynamic/Immunogenicity and Safety Measurements Assessed and Flow Chart

Study assessments for all patients during the treatment phase (up to week 12) were performed according to the study schedule (Table 9.5.1-1). After the treatment phase analysis according to protocol the trial was prematurely terminated, i.e. before all patients completed the follow-up phase.

The patient started their study visits with the completion of ACQ and MiniAQLQ using the VIAPen device followed by non-invasive assessments, and then any invasive assessments (e.g., blood sampling). VIAPen is a portable data capture tool that enables the simultaneous collection of data electronically and on paper.

Patients received a patient e-diary with integrated peak flow meter (AM3 device) at the screening visit for daily recording of their nighttime asthma symptoms (in the morning), their daytime asthma symptoms (in the evening) as well as the number of puffs of SABA (relief medication), and to measure their PEF during the Screening/Run-in and Treatment phase. Patients performed their daily sessions on the AM3 from the screening (Scr/R1) to follow-up visits (FU1). However, patient e-diary data was not analyzed due to premature termination of the study.

Table 9.5.1-1 Study Schedule

Study Schedule	**Screening/Run-in Phase**		**Treatment Phase**								**Follow-up Phase**				
Visits	**Scr/R1 w-4**	**R2 w-2**	**BL/T1 w 0**	**T2 w 1**	**T3 w 2**	**T4 w 4**	**T5 w 6**	**T6 w 8**	**T7 w 10**	**T8 w 12**	**FU1 w 16**	**FU2 w 20**	**FU3 w 24**	**FU4 w 36**	**FU5/ET w 52**
Visit Windows (days)		±3		±1	±1	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7
Informed consent	X														
Inclusion/Exclusion criteria	X														
Demographics	X														
Height	X														
Medical & surgical history	X														
Physical examination[1], ECG	X									X					X[7]
SPT/RAST	X														
Call to IVRS	X	X	X		X					X					
Injection of study drug			X	X	X	X	X	X	X						
Local reaction patient e-diary			X	X	X	X	X	X	X						
Examination of injection site			X[8]	X	X	X	X	X	X	X					
AEs & concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[7]
Asthma exacerbations since last visit	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[7]
Vital signs[3]	X		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	X	X	X	X	X[7]
Patient e-diary & PEF (since last visit)[7]		X	X	X	X	X	X	X	X	X	X				
MiniAQLQ	X		X	X	X	X	X	X	X	X	X	X	X	X	X[7]
ACQ/Pre-bronchodilator FEV_1	X		X	X	X	X	X	X	X	X	X	X	X	X	X[7]

…Continued

Study Schedule	**Screening/Run-in Phase**		**Treatment Phase**								**Follow-up Phase**				
Visits	**Scr/R1 w-4**	**R2 w-2**	**BL/T1 w 0**	**T2 w 1**	**T3 w 2**	**T4 w 4**	**T5 w 6**	**T6 w 8**	**T7 w 10**	**T8 w 12**	**FU1 w 16**	**FU2 w 20**	**FU3 w 24**	**FU4 w 36**	**FU5/ET w 52**
Visit Windows (days)		±3		±1	±1	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7
Post-bronchodilator FEV_1	X[5]		X			X		X		X					
Exhaled NO	X		X			X		X		X	X	X	X	X	X[7]
HBV, HCV, HIV *(serum)*	X														
Blood chemistry *(serum)*	X						X			X			X		X[7]
Antibodies[6]			X				X			X			X		X[7]
Hematology and eosinophils	X						X			X	X	X	X	X	X[7]
Biomarker (Periostin) *serum*			X				X			X	X	X	X	X	X[7]
β-hCG urine pregnancy test	X		X	X	X	X	X	X	X						X[7]
Urinalysis	X						X			X					X[7]

Abbreviations: ACQ-asthma control questionnaire 7 items, AE-Adverse event, ANA-anti nuclear antibodies, anti-ds-DNA-anti double stranded deoxyribonucleic acid, AQLQ-asthma quality of life questionnaire, BL-baseline, β-hCG- β-human chorionic gonadotropin, ECG-electrocardiogram, ET-Early termination, FEV_1-forced expiratory volume in 1 second, FU-follow-up, HBV-hepatitis B virus, HCV-hepatitis C virus, HIV-human immunodeficiency virus, IgG-immunoglobulin G, IgE-immunoglobulin E, IVRS-interactive voice response system, NO-nitric oxide, PEF-peak expiratory flow, Qb-recombinantly expressed viral capsid shell, RAST- radioallergosorbent test, R-run-in, Scr-screening visit, SPT-skin prick test, T-treatment, w - week

1. Includes body weight assessment
2. Last 6 months
3. Blood pressure, pulse rate, body temperature
4. Pre- and 1 hour after injection on dosing days
5. Includes reversibility criteria; post-bronchodilator FEV_1 should be performed between 15 to 30 minutes after bronchodilator dosing.
6. Total IgG, Total IgE, Anti-Qb IgG, ANA, Anti-ds-DNA (serum)
7. Early Termination Visit (withdrawal or discontinuation) – where the patient was willing and able to, all procedures were expected to be performed as per Week 52 (priority to ACQ)
8. One hour after injection only

9.5.1.1 Efficacy Parameters

ACQ is a validated composite score based on the average of 7 items each scored 0 (full asthma control) to 6 (no asthma control), including patient's scores of 5 disease-related items (woken at night by asthma, awake in the morning with symptoms, limitation of daily activities, shortness of breath, wheezing) plus a score for on-site measured FEV1 and a score for use of short-acting reliever medication. An ACQ score of ≥1.5 indicates "not sufficiently controlled asthma", and a score ≤0.75 indicates "well controlled asthma".

The **MiniAQLQ** is a validated 15-item short version of the original 32-item Asthma Quality of Life Questionnaire developed by Juniper and Coworkers to measure the functional impairment of adult patients with asthma (Juniper *et al*, 1999a). The MiniAQLQ was recorded at the time points indicated in the study schedule using the VIAPen device immediately after the ACQ assessment, prior to any other assessments. The total questionnaire score can range from 15 to 105, where 15 indicates the lowest impact and 105 the highest impact of asthma to the patient's life.

Lung function measurement (Spirometry) was measured according to the ATS/ERS 2005 guidelines (Miller *et al*, 2005) by means of centralized spirometry using the same equipment for every measurement. Forced expiratory volume in 1 second (FEV1) is the volume of air that can forcibly be blown out in 1 second, after full inspiration. Predicted normal values for FEV1 depend on age, gender, height, and ethnicity. The predicted values were calculated according to the formula of the European Community for Coal and Steel (Quanjer *et al*, 1993). Spirometry assessments for each patient were performed between 7 AM and 12 PM in the morning as per the time points specified in the study schedule. SABA should not have been used within 6 hours before recording of FEV1 and LABA should not have been used within 12 hours before recording of FEV1.

9.5.1.2 Pharmacodynamic Parameters

The **fraction of nitric oxide (FeNO)** in the exhaled air of asthma patients is a marker for the degree of inflammation in the bronchial tissue. The FeNO in exhaled air was measured according to American Thoracic Society (ATS) guidelines (Dweik *et al*, 2011) with a NIOX Minoanalyzer (Aerocrine, Sweden).

FeNO measurements were performed before other spirometry assessments. For each patient, a minimum of 2 correctly executed exhalations with the device were required. Additional measurements could be performed up to a maximum of 8 exhalations. Exhaled FeNO was measured at the time points specified in the study schedule. This value was part of the data transferred to the eResearchTechnology GmbH (ERT) database.

Increased **eosinophils in peripheral blood** is a marker of lower airway inflammation. Blood samples were collected at the time points specified in the study schedule (Table 9.5.1-1) and analyzed for eosinophils (absolute and percentage) at the central laboratory together with other hematology measurements.

Total IgE and **IgG, anti-Qb antibodies** and the planned biomarker **Periostin** were not analyzed due to premature termination of the study.

9.5.1.3 Demographic and Safety Parameters

Demographic information, complete medical/surgical history, allergy anamnesis (Skin Prick Test or RAST), asthma duration and other general parameters were captured at screening.

Vital signs (blood pressure, heart rate, body temperature) were assessed at the time points specified in the study schedule. On days of study drug administration, vital signs were measured before, as well as 1 hour after injection. Blood pressure and heart rate measurements were obtained after the patient had been seated/lying down for at least 5 minutes and measured using the same arm. Oral/axillary/tympanic temperature were obtained (keeping to the same method for each patient) and heart rate were counted for a full minute and documented in beats per minute.

A standard **12-lead ECG** was performed at the time points specified in the study schedule. The QT interval was recorded in the eCRF with and without correction for heart rate.

Physical examination results for skin, head, eyes/ears/nose/throat, neck and thyroid, heart, lungs, abdomen (spleen), lymph nodes, nervous system, musculoskeletal system were recorded at the time points specified in the study schedule.

Weight and Height were measured at time points specified in the study schedule.

For **safety laboratory analyses** (clinical chemistry, hematology, urinalysis, antibody assessment, and serology) blood and urine samples were collected at the time points specified in the study schedule (Table 9.5.1-1).

The following laboratory analyses were performed:

Clinical Chemistry	Sodium, potassium, phosphate, urea, creatinine, bilirubin (total and direct), albumin, globulin, albumin/globulin ratio, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase, cholesterol (total), creatine phosphokinase (CPK), C-reactive protein (CRP)
Hematology	Complete blood count (includes hemoglobin, hematocrit, red blood cell count, erythrocyte count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood count with neutrophils, monocytes, eosinophils, basophils, lymphocytes, and thrombocytes (as absolute cell numbers)
Urinalysis	pH, leukocyte esterase, protein, glucose, ketone, urobilinogen, bilirubin, and blood. If positive for corpuscular elements (nitrites, etc) or protein, urine sediment was obtained and examined microscopically for presence of erythrocytes, leukocytes, cylinders (casts), microorganisms, and epithelial cells (if the results of the urine dipstick analysis were clinically significantly abnormal, urine was sent to central laboratories for microscopic analysis)
Antibodies	ANA, anti-ds-DNA, total IgG, total IgE
Serology	HIV, HCV and HBV
Pregnancy	A urine pregnancy test was performed for women of childbearing potential who have not been surgically sterilized at the time points specified in the study schedule. In case the β human chorionic gonadotropin (β-hCG) test in urine is positive, serum hCG is sent to central laboratories for confirmation.

The patient was asked to record the presence and severity of **local reactions at the injection site** (pain, itching, swelling/induration, and erythema/reddening,) in a patient e-diary for a period of 4 days following each injection visit. Recording of local reactions has been adapted

from recommendations for grading local reactions in preventive vaccine trials in healthy volunteers as per US Food and Drug Administration (FDA) 2007 guidance (FDA, 2007). The severity grading of pain and induration/swelling included a functional element; in addition, swelling and erythema/reddening are recorded as the greatest single diameter self-measured by the patient. Patients also recorded intake of medications for local reactions in the patient diaries. Due to premature study termination e-diary data were not analyzed.

All **AEs** were captured and documented throughout the whole study duration. Severity of an AE was assessed by the investigator as mild, moderate, severe or life threatening. Investigators also assessed the relatedness to the study medication as not suspected or suspected. Serious Adverse Events (SAEs) were captured according to GCP definitions.

9.5.2 Appropriateness of Measurements

The primary endpoint was the 7-item ACQ. This questionnaire has been shown to be a valid, and reliable instrument that allows accurate and reproducible assessment of asthma control that compares favorably with other commonly used instruments (Barnes *et al*, 2014).

Besides answering questions of six disease-related items experienced during the prior week (subjective clinical outcome) the patient's lung function was assessed. The forced expiratory volume in 1 second (FEV1) as an objective clinical outcome was the secondary efficacy endpoint which was used In addition to FEV1 % predicted was analyzed.

As a second subjective asthma-specific instrument patients filled out a MiniAQLQ (Wilson *et al*, 2012), a valid questionnaire that measures health-related quality of life in adults.

As worsening of asthma is known to be accompanied by increasing markers of inflammation. Such markers are exhaled nitric oxide (FeNO) (Pedrosa *et al*, 2010) and eosinophils in sputum or peripheral blood (Velthove *et al*, 2009). FeNO and blood eosinophils were both measured in this trial as they can serve as surrogate endpoints of airway inflammation.

The assessments of adverse events including local injection site reactions, laboratory and other safety examinations, as well as immunogenicity parameters were considered appropriate for safety and tolerability measurements for this type of clinical trial.

9.5.3 Primary Efficacy Assessment

The Asthma Control Questionnaire provides a validated composite score developed for measuring the adequacy of asthma control in clinical research studies and clinical practice with strong and discriminative properties (Juniper *et al*, 1999b). It is based on the average of 7 items each scored 0-6, including patient's scores of 5 disease-related items (woken at night by asthma, awake in the morning with symptoms, limitation of daily activities, shortness of breath, wheezing) plus a score for on-site measured forced expiratory volume in the first second and a score for use of short-acting reliever medication. An ACQ score of $\geq$1.5 indicates "not sufficiently controlled asthma", and a score $\leq$0.75 indicates "well controlled asthma" (Juniper *et al*, 2006).

The primary efficacy endpoint is the change from baseline of ACQ score at week 12. The 7-item ACQ was administered using the VIAPen device at the time points specified in the study schedule. Questionnaires must have been completely filled out by patients on-site in a quiet

space and before any other interventions and assessments are made. Incomplete questionnaires and multiple answers in the questionnaires were not considered for the ACQ calculation.

9.6 Data Quality Assurance

The clinical monitoring, data management, and statistical analysis were performed under contract with PPD, in collaboration with Cytos Biotechnology AG (Cytos).

The Data Quality Assurance was accomplished in part by having thorough edit checks written, programmed, and updated as needed to guarantee high quality data. The PPD and Cytos study team reviewed the cleanliness and completeness of the data periodically, to evaluate whether any edit check should be added.

Site initiation visits took place before the study start to prepare the investigators and their staff and to standardize the procedures required by the protocol.

For a standardized quality and comparability of laboratory data, the services of two central laboratories (PPD Central Laboratory USA for North America and PPD Central Laboratory Belgium for Europe and Middle East) were chosen.

100% source data verification was performed by qualified clinical research associates (CRA) for data of the treatment phase up to week 12. All queries were resolved before database lock.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

Treatment Phase (Core Study) Analysis

The treatment phase comprises the first 12 weeks of the study. A full data base lock-up to week 12 was performed when all patients completed Visit T8 (end of treatment phase, two weeks after last injection). All queries were resolved and the database was clean. Events/treatments that were ongoing beyond the day of data cut were marked as “ongoing”. For the treatment phase analysis key tables, listings, and figures as defined in the SAP (Part I) from 20-Feb-2014 were generated.

End of Study Analysis

An end of study analysis was planned at the end of the follow-up phase at week 52 and included the 9-months follow-up phase and data (e.g. baseline values) from the treatment phase. The planned end of study analyses are described in a SAP (Part II) from 21-Feb-2014, however, described tables, listings and figures were not generated due to premature study termination.

See Appendix 16.1.9 for SAP Part I and II.

9.7.1.1 Analysis Populations

There were five total analysis sets utilized in this study.

Screening Set: The screening set included all patients who signed the ICF and were evaluated for study eligibility.

Randomized Set: The randomized set included all patients randomly assigned to treatment. In the Randomized Set, patients were grouped according to randomized treatment, not necessarily according to treatment received.

Safety Set: The Safety Set consisted of all patients who had received at least 1 injection of study drug. All patients in the Safety Set were analyzed according to the treatment actually received, with the highest dose level given where placebo counted as a dose of zero, and not according to the treatment they were randomized to receive, in the event there was a discrepancy.

Full Analysis Set (FAS): The Full Analysis Set consisted of those randomized patients who had received at least 1 injection of study drug and had at least one data value post baseline. All patients in the FAS were analyzed according to the Intent-to-Treat (ITT) principle, i.e., analyzed according to the treatment they were randomized to receive and not according to what they had actually received, if different.

Per-Protocol (PP) Set: The PP set consisted of those patients in the FAS without any significant protocol deviations with respect to key efficacy endpoints. Significant protocol deviations were defined in the latest signed version of the Significant Protocol Deviation (PD) Rules document (PPD SOP-PM-09) before database lock (see Appendix 16.1.13).

The per-protocol set was used for supportive efficacy analyses assessing the robustness of the primary and key secondary analysis results. All patients in the PP set were analyzed according to the treatments they had actually received.

9.7.1.2 Other Important Considerations

Patients who had a change (step-up or step-down) in their stable controller treatment from baseline (BL/T1) up to Visit T8 were treated in the analyses as premature discontinuations, as the protocol required them to stop study drug treatment.

Last Observation Carried Forward (LOCF): For ACQ and FEV1 at week 12, an LOCF procedure was adopted to impute missing data. The last valid value at the most recent time point before or on the date of the visit was carried onwards provided that at the time of that last valid value the patient had at least two injections a week or more earlier. If no such value was available then the endpoint remained missing.

Intent-to-Treat (ITT) Principle: According to the intent-to-treat principle each patient was allocated in analyses to the treatment group he or she was randomized to, regardless of the actual treatment the patient received. The ITT principle was applied to analyses using the FAS but not to those using the PP or Safety Sets.

9.7.1.3 Pooling of Countries

One sub-group efficacy analysis was performed by regions. Geographically neighboring countries and countries with similar cultural and demographic backgrounds were pooled:

- Region A (United States)
- Region B (Germany, Israel, Czech Republic, Hungary)
- Region C (Ukraine, Russia, Poland)

'REGION' taking the possible values A, B or C were used as a factor in the statistical analysis models.

9.7.2 Statistical Analysis

If not stated otherwise, statistical analyses of efficacy and safety endpoints were performed as defined in the SAP (Part I) from 20-Feb-2014.

9.7.2.1 Primary Efficacy Analysis

The primary efficacy endpoint, change from baseline in ACQ score at week 12, was analyzed using analysis of covariance (ANCOVA) on the FAS with baseline values as covariate as well as other factors. The treatment effect was evaluated as a contrast of each active treatment versus placebo. To control the type 1 error rate due to multiple comparisons, the Hochberg procedure for the comparison between treatment group and control was implemented for the two higher doses. The primary efficacy endpoint was be summarized descriptively and graphically by treatment group and compared with placebo.

For the primary analysis missing values in patients who prematurely withdraw or were discontinued from the study were imputed using the last observation carried forward (LOCF) method. Patients who changed (step-up or step-down) their stable controller treatment (Scr/R1 up to T8) were formally treated as premature discontinuations and for the analysis of the primary endpoint, such an LOCF procedure, the last time point before treatment change onwards was used.

Sensitivity Analysis of Primary Endpoint

The primary analysis was repeated but with the FAS replaced by the PP set and analyzed without imputation and with no adjustment for multiplicity.

9.7.2.2 Secondary Efficacy Analysis

No corrections for multiple testing were made. Unless specified otherwise, the secondary efficacy endpoints were analyzed on the FAS without imputation and summarized as Standard Summary Tables.

Each endpoint was analyzed with an ANCOVA model where the baseline value is used as a continuous covariate and with ICS, LABA and REGION included as factors (as in the primary analysis). For weeks 1 to 12 the fitted (least square) means, SEM, and 95% confidence intervals of the contrasts for each active treatment versus placebo are presented together with the p-values for two sided testing of the 'no difference' hypothesis at the 5% significance level.

ACQ Change from Baseline at all Time Points

For the FAS the change from baseline of ACQ for each time point from week 1 to week 12 are analyzed using the same ANCOVA model as used for the primary analysis providing the fitted (least square) means, SEM, and 95% confidence intervals of the contrasts for each active treatment versus placebo together with the p-values for two sided testing of the 'no difference' hypothesis at the 5% significance level. Only observed values are used.

The ACQ score is summarized by visit and treatment group, for each scheduled visit from Week 0 (i.e. baseline) to Week 12 and change from baseline summarized from Week 1 to Week 12.

ACQ Response Rate Analysis

An ACQ score of ≥1.5 indicates "not sufficiently controlled asthma", a score ≤0.75 indicates "well controlled asthma" and a score between 0.75 and 1.5 indicates "borderline control". Number and percent of patients having ACQ scores ≤0.75, between 0.75 and 1.5, and ≥1.5 as well as <1.5 are presented on summary tables by treatment group and overall by visit. The proportion of patients who are "well controlled" at week 12 based on ACQ ≤ 0.75 and who have an ACQ <1.5 were analyzed as a secondary outcome. A standard chi-square test was used to compare the response rate for (ACQ ≤ 0.75 and < 1.5) across treatment groups. If expected cell count less than 5 then the Fisher's exact analysis was employed.

FEV1 and % predicted FEV1 Change from Baseline

FEV1 change from baseline at week 12 was a secondary endpoint. Pre-bronchodilator forced expiratory volume in the first second (FEV1) at week 12 was summarized as for the primary endpoint imputed with LOCF and analyzed on the FAS using a model similar to that used for the primary analysis but with baseline FEV1 as a covariate.

In addition pre-bronchodilator forced expiratory volume in the first second (FEV1) as (i) observed value and change of observed value; (ii) change in percent of observed value (iii) % predicted and change of percent predicted for all time points from week 1 onwards was analyzed with an ANCOVA model where the baseline value was used as a continuous covariate and with ICS, LABA and REGION included as factors (as in the primary analysis).

MiniAQLQ Score

The MiniAQLQ is a validated questionnaire with scores between 15 and 105. The change from baseline in MiniAQLQ total score was analyzed using an ANCOVA model where the baseline value was used as a continuous covariate and ICS, LABA and REGION are included as factors. For Weeks 1 to 12 the fitted (least square) means, SEM, and 95% confidence intervals of the contrasts for each active treatment versus placebo are presented together with the p-values for two sided testing of the 'no difference' hypothesis at the 5% significance level.

The MiniAQLQ score is summarized as a Standard Summary Table by visit and treatment group, for each scheduled visit from Week 0 (i.e. baseline) to week 12 and change from baseline summarized from week 1 to week 12.

Blood Eosinophils

Change from 'baseline' (in fact the value at the screening visit at week -4) in blood eosinophil count (in cells $x10^9$ per liter) was analyzed using an ANCOVA model where the baseline value (screening visit) was used as a continuous covariate and with ICS, LABA and REGION included as factors. For weeks 6 and 12 the fitted (least square) means, SEM, and 95% confidence intervals of the contrasts for each active treatment versus placebo are presented together with the p-values for two sided testing of the 'no difference' hypothesis at the 5% significance level for each of these contrasts. The blood eosinophil count is summarized as a Standard Summary Table by visit and treatment group, for weeks -4, 6 and 12 and change from 'baseline' summarized for weeks 6 and 12.

FeNO

Change in FeNO (ppb) from baseline was analyzed using an ANCOVA model where the baseline value (Week 0) was used as a continuous covariate with ICS, LABA and REGION included as factors. For weeks 4, 8 and 12 the fitted (least square) means, SEM, and 95% confidence intervals of the contrasts for each active treatment versus placebo are presented together with the p-values for two sided testing of the 'no difference' hypothesis at the 5% significance level for each of these contrasts.

The FeNO values are summarized by visit and treatment group, for weeks 0, 4, 8 and 12 and change from 'baseline' summarized for weeks 4, 8 and 12.

9.7.2.3 Subgroup Analyses

Efficacy analyses with the FAS were performed with patient subgroups for pre-defined classifications on 6 baseline characteristics. The four treatment groups were analyzed in these subgroups as given below for change from baseline in ACQ, Pre-bronchodilator FEV1 and in % predicted, MiniAQLQ, eosinophils, FeNO, and its contrasts with placebo.

Subgroup ICS

Two subgroups were defined as follows:

- ICS medium = daily dose of fluticasone or equivalent >250 to 500µg
- ICS high = daily dose of fluticasone or equivalent >500 to 1000µg

Subgroup Eosinophils

Eosinophil counts measured at screening visit were used to define the following subgroups:

- two subgroups where the median on the FAS of the measurements is the cut-off for the subgroups.
    - Eosinophils low = counts ≤ median
    - Eosinophils high = counts > median
- two subgroups where 0.1 cells/nL is the cut-off for the subgroups.
    - Eosinophils low = counts ≤ 0.1
    - Eosinophils high = counts > 0.1

Subgroup FeNO

FeNO measurements in ppb at baseline visit will be used to define two subgroups where the median of the measurements on the FAS is the cut-off for the subgroups.

- FeNO low = ppb ≤ median
- FeNO high = ppb > median

Subgroup Age of Asthma Onset

Asthma age of onset will be calculated as the follows: Current age – Duration of Asthma +1.

Two subgroups were defined according to the age of onset of asthma:

- Asthma onset early: ≤ 18 years
- Asthma onset late: > 18 years

Subgroup Body Mass Index (BMI)

Two subgroups were defined according to the BMI:

- BMI medium: < 30 kg/m²
- BMI high: ≥ 30 kg/m²

Subgroup Geographic Regions

To analyze potential effects of different cultural and/or geographical backgrounds, the sites were grouped into 3 regions according to standards of care, demographics and/or geographical proximity.

- Region A: United States
- Region B: Germany, Israel, Czech Republic, Hungary
- Region C: Ukraine, Russia, Poland

The 3 regions were analyzed for ACQ, FEV1 (observed and % predicted), and MiniAQLQ only.

9.7.3 Determination of Sample Size

The sample size of 90 patients per treatment arm assumed a mean difference in the change of ACQ from baseline between an active dose arm and placebo of 0.5 and a SD of 1.0, and allowed for 90% power to detect a statistically significant difference at an α level of 0.05. A difference of 0.5 in ACQ score is considered a "medically important difference" (Juniper *et al*, 2006). The SD of 1.0 at a mean change of ACQ score of 0.5 from baseline is based on the Study CYT003-QbG10 11 data as well as on published data from a study with a similar patient population and design (Corren *et al*, 2011).

9.8 Changes in the Conduct of the Study or Planned Analyses

There were two country-specific amendments. These were incorporated at a later time point into the global Amendment I, which was followed by Amendment II. Find below the created, notified and applied versions of the protocol:

- Protocol V1.0 26Jul2012
- Germany V1.1 06Dec2012
- Czech Republic V1.2 14Dec2012
- Amendment I V2.0 20Mar2013
- Amendment II V3.0 20Dec2013

The local amendments for Germany and Czech Republic were created following the comments of the local regulatory authorities PEI, Germany and SUKL, Czech Republic.

The Czech Republic amendment V1.2 from 14Dec2012 included update of following information:

- Statement that the injections will always be administered at a clinic with guaranteed angioresuscitation care
- Update of the information on blinding to comply with GCP guidelines
- Specification of all devices which are supplied by the Sponsor for assessments
- Other minor editorial changes and typos

The Germany amendment V1.1 from 06Dec2012 included an update on the following information:

- Statement that the “step up” or “step down” routines during the follow up will be performed according to GINA, 2011 and NHLBI Guidelines, 2007.
- Specification of Skin Prick Test/RAST
- Specification of contraception requirements
- Specification of exclusion criterion #11
- Statement that during the study no specific measures to control for environmental/seasonal allergen exposure are to be observed
- Specification of protocol section 3.4.1 “Handling of Withdrawals”
- Update of the information on unblinding
- Other minor editorial changes and typos.

The global Amendment I V.2.0 from 20March2013 included the updates stated above for the two country-specific amendments and included an update on the following information:

- Allowance for a reversibility retest
- Correction on Formula for ASMS
- Removal of Statement on grading severity of AEs by the Common Terminology Criteria for AEs
- Correction on wording on randomizations procedure with IVRS
- Added details on analysis populations
- Corrected Study Schedule accordingly
- Added a table with Clinical Criteria for Diagnosis Anaphylaxis and its Reference
- Other minor editorial changes

The global Amendment II V3.0 from 20December2013 included updates on the following information:

- Update on contact name for sponsor
- Added Periostin and removed IP-10 as biomarkers with regard to pharmacodynamics assessments
- Specification on analysis population and planned sensitivity analyses
- Specification into treatment phase (core study) and follow up analysis
- Specification on blinding/unblinding procedure for treatment phase (core study) analysis
- Corrected Study Schedule accordingly
- Other minor editorial changes

Since the primary end point was not achieved the trial was prematurely discontinued after analysis of the treatment phase, although not all patients had completed the Follow-up phase. An independent Data Monitoring Committee reviewed the safety data and concluded that there were no safety concerns. The clinical study had been planned to continue with a blinded observation period of 9 months. Considering this outcome, Cytos decided to unblind and terminate the study. The treatment phase analyses was perform according to SAP (Part I) V2.2 from 20-Feb-2014. The End of study analyses according to SAP (Part II) from 21-Feb-2014 was not followed.

10 Study Patients

10.1 Disposition of Patients

A total of 606 patients provided written informed consent and entered the screening phase of the study. Of these, 423 patients were randomly assigned to one of the 4 treatment arms and formed the Randomized Set. Inclusion/Exclusion criteria were fulfilled at baseline for 365 patients, who received the first injection. These 365 patients were included in the Safety Set as well as the Full Analysis Set (FAS) for the treatment phase and the efficacy evaluation. All patients in the FAS were analyzed according to the Intention-to-Treat (ITT) principle. There were 83 patients with at least one significant protocol deviation (PD) leaving 282 in the Per-Protocol Set. The patient disposition is shown in the figure below.

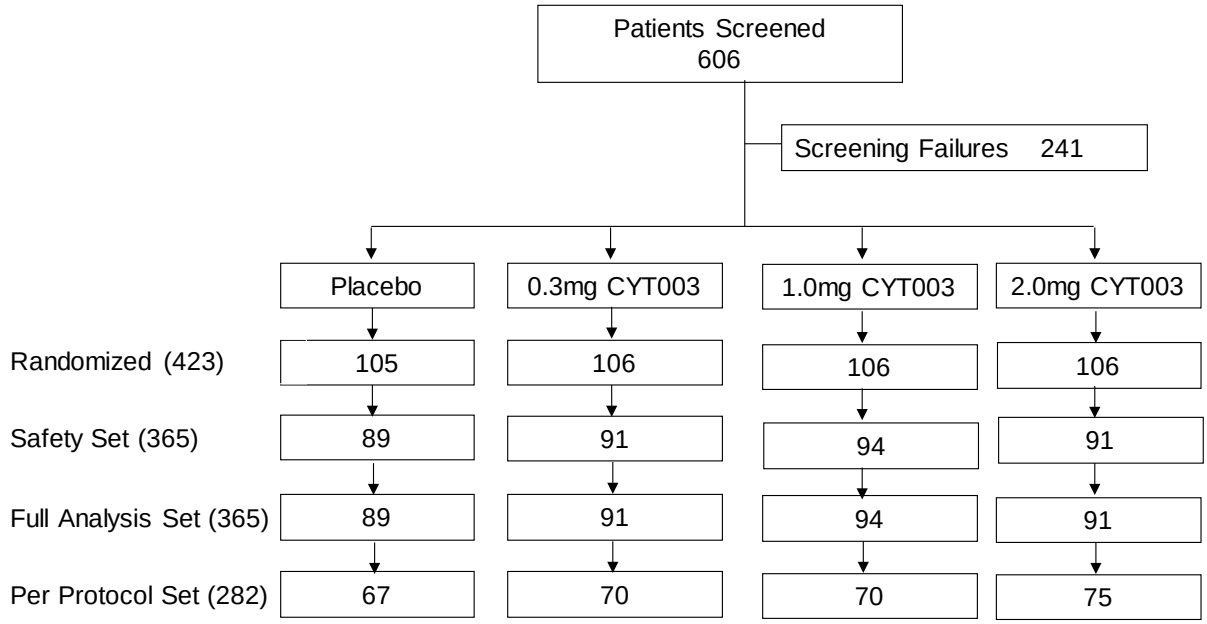


Figure 10.1-1 Patient Disposition

The Safety Set consisted of all patients who received at least 1 injection of study drug and the FAS of those randomized patients who received at least 1 injection of study drug and had at least one data value post baseline. Safety Set and the FAS were identical for treatment phase efficacy analysis in this trial. [Source: Table 14.1.1.1]

241 patients failed the screening process and were not injected with the study drug at baseline, visit BL/T1. There were 181 patients who failed the screening process because of the following five main reasons: Not meeting FEV1 ≥40 to ≤90% of predicted value (inclusion criterion # 7, 54 patients), the specified reversibility criteria (inclusion criterion # 8, 48 patients), not able and willing to complete all protocol requirements (inclusion criterion # 2, 44 patients), not meeting at least 80% compliance in the use of the patient e-diary/PEF meter at visit BL/T1 (exclusion criterion # 1, 20 patients), and a ACQ score < 1.5 at screening and at baseline (inclusion criterion # 5, 15 patients).

60 patients who did not enter the trial with treatment were not included mainly because they were not diagnosed with persistent asthma as defined by the protocol (inclusion criterion # 4), or did not show a positive SPT or RAST for at least 1 aero-allergen (inclusion criterion # 6), or had a confirmed or suspected current infection with HIV, HBV, or HCV (exclusion criterion # 10). There were further patients with more than one reason for failing the screening process (details are given in Listings 16.2.1.3 and 16.2.1.4).

10.1.1 Premature Discontinuations

There were 2 types of discontinuations: treatment discontinuation and study discontinuation.

Treatment discontinuations

If the patient discontinued the treatment for any reason, he/she was asked to remain in the study and to complete all study procedures according to the protocol. 29 patients discontinued treatment prematurely See tables below and Section 12.2.3 Analysis of Adverse Events (Table 12.2.3-4) in this report for TEAEs leading to study drug discontinuation. Most of these patients continued the study procedures without receiving further study medication.

Table 10.1.1-1 Number of Patients and Primary Reason for Treatment Discontinuation

	Voluntary Withdrawal	Adverse Event	Asthma Exacerbation	Others[2)]	Total
Placebo	2	2	1	1	6
0.3mg CYT003	2	1	1		4
1.0mg CYT003		5	3[1)]		8
2.0mg CYT003	1	7	2	1	11
Total	5	15	7	2	29

[1)] Patient 802008 included, for details see below.

[2)] Two times Sponsor Decision: Patient 805003 was discontinued after injected IP was reported to have had a significant temperature excursion and 601008 because a diagnosis of Graves Basedow (Exclusion Criterion #12) [Source: Table 14.1.1.2, Listing 16.2.1.1]For details of patients experiencing an AE that led to discontinuation – please refer to Table 12.2.3-4 in the section Safety Evaluation.

Table 10.1.1-2 Patients who discontinued Treatment prematurely due to Asthma Exacerbation

Patient	Treatment	Occurrence
119003	Placebo	after 6th injection
709001	0.3mg	after 6th injection
407003	1.0mg	after 6th injection
108005	1.0mg	after 4th injection
802008*	1.0mg	after 4th injection
403005	2.0mg	after 6th injection
502005	2.0mg	After 5th injection

[Source: Listing 16.2.1.1] * Listing gives term “AE” as reason for study drug discontinuation, in fact an asthma exacerbation was the reason for discontinuation.

Study participation discontinuation

There were 11 of the 365 enrolled and injected patients (Safety Set) who discontinued the study treatment phase prematurely with an incomplete set of injections. All of those patients discontinued the study participation voluntarily by withdrawing the informed consent, though the reasons for the treatment discontinuation were different: 5 patients withdrew ICF and discontinued the treatment as well as the study participation voluntarily. 3 patients had a AEs (injection site swelling and erythema, influenza-like illness) leading to the study drug discontinuation and then they withdrew consent. Two patients had an asthma exacerbation during the treatment phase which resulted in study drug discontinuation and then they withdrew consent. Patient 805003 was discontinued from the study by sponsor decision after the patient was injected with study medication that was reported to have had a significant temperature excursion – was possibly frozen. Patient did not want to continue the study and withdrew consent. Table 10.1.1-3 below describes the details on these patients.

Table 10.1.1-3 Patients who discontinued the Study during the Treatment Phase

Patient	Treatment	Occurrence after	Reason for treatment discontinuation	Reason for study discontinuation
805003	Placebo	1st injection	IP damage	voluntary withdrawal
506003	Placebo	3rd injection	voluntary withdrawal	voluntary withdrawal
306010	0.3mg	2nd injection	voluntary withdrawal	voluntary withdrawal
501003	0.3 mg	3rd injection	voluntary withdrawal	voluntary withdrawal
608008	0.3mg	1st injection	voluntary withdrawal	voluntary withdrawal
132003	1.0mg	2nd injection	AE (injection site reaction)	voluntary withdrawal
108005	1.0mg	4th injection	Asthma exacerbation	voluntary withdrawal
503002	1.0mg	4th injection	AE (injections site reaction)	voluntary withdrawal
810003	1.0mg	4th injection	AE (influenza-like illness)	voluntary withdrawal
141004	2.0mg	2nd injection	voluntary withdrawal	voluntary withdrawal
502005	2.0mg	5th injection	asthma exacerbation	voluntary withdrawal

[Source: Listing 16.2.1.1]

10.2 Protocol Deviations

Protocol deviations are listed in Appendix 16.2, summarized from Listing 16.2.2.1 All Protocol Deviations and Listing 16.2.2.2 Significant Protocol Deviations. Further details are described under Section 11.1 Data Sets Analyzed.

11 Efficacy Evaluation

11.1 Data Sets Analyzed

The Safety Set included all 365 injected patients and was identical to the FAS which was analyzed according to the ITT principle. In total, 83 patients were excluded from the PP Set due to significant protocol deviations keeping 282 patients in the PP Set (Tables below). Significant PDs were defined in a Significant Protocol Deviation (PD) Rules document which listed all PDs qualifying to be significant with a corresponding Rule No. (see Appendix 16.1.13 for the latest signed Version 1.8 from 03 October 2013). Two efficacy analyses were performed as

sensitivity analyses with the patients from PP* and PP** as described below. PP* distinguishes from PP by including patients who performed ACQ after any other study procedure at visits BL/T1 or T8 although they should have filled in the ACQ as the very first assessment (Rule No. 7.3). There were 37 patients who fell under this criterion. Furthermore, PP** distinguishes from PP by 41 patients including the ones who fall under the mentioned Rule No. 7.3 plus patients who did not complete ACQ at all at visits BL/T1 or T8 (Rule No. 6.1) or did not complete ACQ themselves at visits BL/T1 or T8 (Rule No. 7.4). In Appendix 16.1.14 all 83 patients with specified significant PDs are listed.

Table 11.1-1 Number of Patients per Statistical Analysis Populations and Treatment Arm

		Efficacy			
Treatment	Safety Set	FAS	PP	PP*	PP**
Placebo	89	89	67	79	79
0.3mg CYT003	91	91	70	80	83
1.0mg CYT003	94	94	70	80	82
2.0mg CYT003	91	91	75	80	80
Total	**365**	**365**	**282**	**319**	**324**

* Not excluding patients who fall under Rule No. 7.3 of the significant PD Rules document

** Not excluding patients who fall under Rule No. 6.1, 7.3 and 7.4 of the significant PD Rules document [Source Tables 14.1.1.2, 14.2.2.3, and 14.2.3.2]

For the efficacy endpoints ACQ and FEV1 at week 12 with the FAS population a Last Observation Carried Forward (LOCF) procedure was adopted to impute missing (e.g. patient discontinued prematurely) or invalid data. Data points became invalid because the patient changed his/her controller treatment (step-up) between BL/T1 and T8, the patient did not adhere to the visit timing in the protocol, or the patient experienced an asthma exacerbation and used systemic glucocorticoids. Details on the 44 patients for whom LOCF was adopted for at least one data point can be found in Appendix 16.2. Patient data Listings (16.2.11.12).

11.2 Demographics and Other Baseline Characteristics

11.2.1 Demographics

The mean age of the 365 patients included in this trial (Safety Set and FAS Population) was 47.5 years (median 50 years) and mean BMI 28.82 (range 17.8 – 49.8, median 28.09). This patient population consisted of 142 (38.9%) males and 223 (61.1%) females. The duration of asthma and further details on baseline characteristics are presented in the table below. The characteristics were balanced between the three dose groups and placebo. Further detail is provided in Table 14.2.1.1 and Listings 16.2.4.1 to 16.2.4.2.

Table 11.2.1-1 Demographics and other Baseline Characteristics (Full Analysis Set)

Characteristics	Placebo	0.3mg CYT003	1.0mg CYT003	2.0mg CYT003	Total
Sex n (%)					
Male	37 (41.6)	35 (38.5)	36 (38.3)	34 (37.4)	142 (38.9)
Female	52 (58.4)	56 (61.5)	58 (61.7)	57 (62.6)	223 (61.1)
Age (years)					
mean (SD)	47.5 (12.37)	47.2 (11.94)	47.3 (12.39)	48.0 (12.05)	47.5 (12.15)
Race					
White	82	88	83	81	334
Black or African American	6	3	9	7	25
Asian	1		2	2	5
Other				1	1
Ethnicity n					
Hispanic or Latino	6	3	4	2	15
Not Hispanic or Latino	83	88	90	89	350
Body mass index (kg/m2)					
mean (SD)	28.21 (5.58)	28.19 (5.15)	29.10 (5.75)	29.78 (6.82)	28.82 (5.87)
Duration of Asthma (years)					
mean (SD)	21.8 (16.4)	22.1 (16.4)	22.2 (14.3)	19.2 (13.8)	21.3 (15.2)
Smoking Classification n (%)					
Never smoked	74 (83.1)	72 (79.1)	81 (86.2)	73 (80.2)	300 (82.2)
Current smoker	0	0	0	0	0
Ex-smoker	15 (16.9)	19 (20.9)	13 (13.8)	18 (19.8)	65 (17.8)
Number of Years patient has smoked					
n	15	19	13	18	65
mean (SD)	5.9 (4.59)	7.4 (4.82)	6.2 (4.78)	3.9 (2.99)	5.8 (4.43)
ACQ Score					
mean (SD)	2.63 (0.61)	2.57 (0.61)	2.62 (0.65)	2.56 (0.69)	n/a

Characteristics	Placebo	0.3mg CYT003	1.0mg CYT003	2.0mg CYT003	Total
FEV1 (L)					
mean (SD)	2.135 (0.651)	2.140 (0.664)	2.186 (0.606)	2.130 (0.709)	n/a
mean % of predicted value (SD)	68.3 (13.8)	69.8 (14.8)	72.4 (14.6)	69.5 (14.14)	n/a
range % of predicted value	33-100	39-108	34-101	34-96	n/a
MiniAQLQ Score					
mean (SD)	61.5 (14.3)	63.0 (13.9)	60.5 (14.6)	61.9 (15.4)	n/a
FeNO (ppb)					
mean (SD)	23.6 (18.3)	31.8 (30.4)	31.8 (29.2)	32.6 (28.9)	n/a
Eosinophil count in blood (10^9/L)					n/a
mean (SD)	0.28 (0.23)	0.28 (0.26)	0.3 (0.28)	0.32 (0.38)	n/a
IgE (IU/mL)					
n	87	84	94	86	n/a
geometric mean (SD)	150.9 (1301.6)	160.3 (1973.4)	166.1 (724.5)	172.2 (552.0)	n/a

n/a: these numbers are not available due to premature discontinuation of the study
[Sources: Tables 14.1.2, 14.2.1.1, 14.2.3.1, 14.2.5.3,14.2.6.1,14.2.7.2, and 14.2.7.1, Listing 16.2.11.6]

11.2.2 Medical History at Screening

All findings in the medical history of enrolled patients were considered by the investigator compatible with inclusion of the respective patients. However, during the course of the study two patients (309007 and 601008) had a medical history of autoimmune disease. Patient 601008 (treated with 2.0mg CYT003) had a medical history of morbus Basedow-Graves and was discontinued from the study drug treatment immediately after the sponsor was notified (patient received 3 injections). For patient 309007 the history of autoimmune disease (Hashimoto disease) was revealed only after the patient had received all 7 injections with study drug (treated with 1.0mg CYT003). For detailed information about the medical history at screening see Listing 16.2.4.2.

11.2.3 Physical Examination

Findings at screening were considered compatible with inclusion of the respective patients as judged by the investigators. No clinically significant new findings were reported at visit T8, week 12. For detailed information see Section 12.5.3, Listing 16.2.9.2 and Table 14.3.2.3.1.

11.2.4 Vital Signs and ECG

Descriptive statistics for the vital signs and ECG at screening are shown in Table 11.2.4-1 and 11.2.4-2, respectively. Vital signs and ECG parameters were comparable between the treatment groups. There were no clinically significant findings as judged by the investigators. For detailed information about vital signs and ECG during the study see Section 12.5.1 and 12.5.2 and Tables 14.3.2.2.1 and 14.3.2.4.1.

Table 11.2.4-1 Vital Signs at Screening (Full Analysis Set)

Vital signs		Placebo	0.3mg	1.0mg	2.0mg
Systolic blood pressure (mmHg)	mean	123.4	122.8	124.0	122.2
	median	124	120	125	120
	range	90 - 162	90 – 144	92 – 155	88 - 151
Diastolic blood pressure (mmHg)	mean	78.5	77.5	77.4	77.6
	median	80	78	79.5	78
	range	54 – 98	47 - 100	54 - 100	59 – 100
Body temperature (°C)	mean	36.5	36.5	36.5	36.5
	median	36.5	36.6	36.6	36.6
	range	35.2 – 37.1	35.5 – 37.3	35.3 – 37.4	32.2 – 37.2
Pulse rate (beats/min)	mean	74.3	72.3	75.0	74.2
	median	72	72	74.5	74
	range	57 - 94	56 - 72	54 - 104	58 - 99

[Source Table 14.3.2.2.1]

Table 11.2.4-2 ECG Parameters at Screening (Full Analysis Set)

ECG parameters		Placebo	0.3mg	1.0mg	2.0mg
Heart rate (beats/min)	mean	69.9	68.7	72.3	69.0
	median	68	68	71	68.0
	(range)	53 - 92	47 - 103	47 - 100	49 - 100
P-R Interval (msec)	mean	159.2	159.4	154.6	158.8
	median	160.0	155	156.5	160
	(range)	84 - 234	80 - 368	97 - 215	100 - 240
QRS Duration (msec)	mean	89.9	90.0	91.9	91.5
	median	90.0	86.0	90	90
	(range)	71 - 120	60 - 132	60 - 160	69 - 200
Q-T Interval (msec)	mean	381.8	380.4	376.0	382.4
	median	380.0	385.0	381.5	383.0
	(range)	313 - 464	200 - 466	205 - 464	200 - 488
Q-Tc Interval (msec)	mean	400.4	395.4	398.0	397.9
(Fridericia`s corrected)	median	402.2	400.5	403.4	402.7
	(range)	322 - 459	200 - 472	227 - 485	237 - 456

[Source: Table 14.3.2.4.1]

11.3 Measurements of Treatment Compliance

The study medication was administered only at the study centers by the investigators. The investigator entered the performed injection into the appropriate page of the eCRF. For each injection, one vial of study drug had to be used. Injections logs and drug vial logs were monitored regularly throughout the treatment phase.

A minimum of 5 injections was considered sufficient for treatment compliance.

11.4 Efficacy Results

11.4.1 Analysis of Efficacy

11.4.1.1 Primary Efficacy Endpoint

According to the study protocol the primary efficacy endpoint was the change from baseline in ACQ score at week 12. The analysis was performed on the FAS population. Where appropriate, missing values have been imputed using the LOCF procedure or otherwise remained missing (for details on LOCF see also Section 11.1 Data Sets Analyzed). Patients who had a step-up in their controller treatment between baseline and week 12 were formally treated as premature discontinuations. As shown in the figure below, all treatment groups revealed a drop in ACQ score bigger than 0.5 that is considered as clinically relevant.

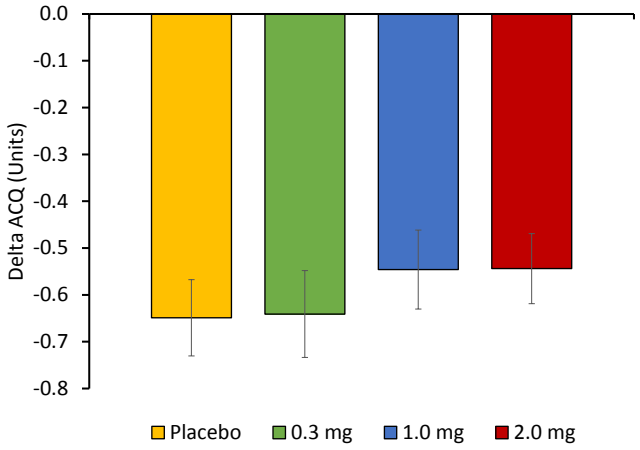


Figure 11.4.1.1-1 ACQ Score – Change from Baseline at Week 12 (FAS)

The columns represent the mean ± standard error of the mean (SEM) of the change in ACQ at week 12 per treatment group of the FAS population with LOCF. ACQ scores could vary from 0 to 6. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10. [Source: Table 14.2.1.1]

With respect to the contrast of the active treated groups to placebo obtained with the ANCOVA model, no treatment group compared with that of placebo reached a clinically relevant difference as shown in the figure below. The model contained treatment as a fixed effect with the baseline ACQ measurement as a covariate. To reflect the randomization scheme the model included baseline use of LABA and baseline dose of ICS as factors. To adjust for potential regional differences "REGION" has also been included in the analysis model as a factor.

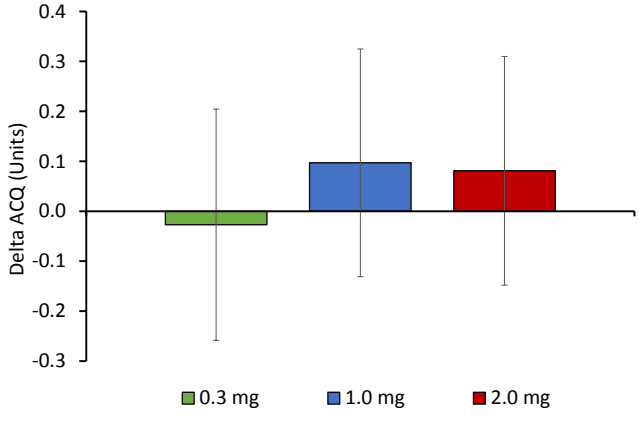


Figure 11.4.1.1-2 ACQ Score – Change from Baseline at Week 12 (FAS) - Contrasts

The columns represent the LS mean and 95% CI of the change in ACQ at week 12 per active treatment group compared to placebo of the FAS population with LOCF. ACQ scores could vary from 0 to 6. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10. [Source: Table 14.2.1.1]

11.4.1.2 Sensitivity Analysis of Primary Endpoint

The primary analysis was performed again with the FAS but this time without LOCF. No significant differences between the treatment groups compared with that of placebo could be detected.

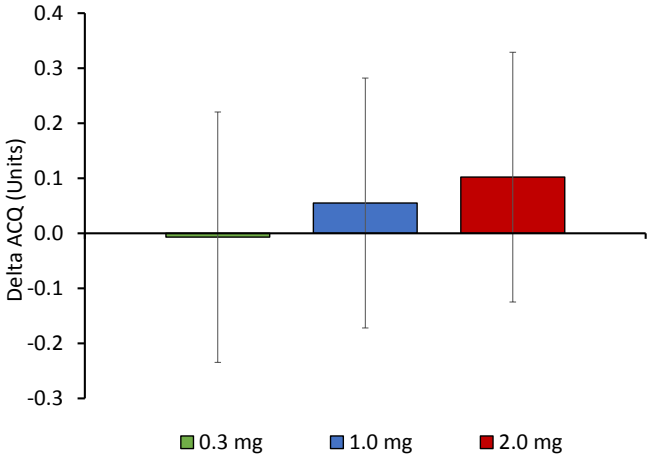


Figure 11.4.1.2-1 ACQ Score – Change from Baseline at Week 12 (FAS, no LOCF) - Contrasts

The columns represent the LS mean and 95% CI of the change in ACQ at week 12 per active treatment group compared to placebo of the FAS population without LOCF. ACQ scores could vary from 0 to 6. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10. [Source: Table 14.2.2.2]

To assess the robustness of the results of the primary analysis the tests were repeated with the per protocol (PP) set. Only patients with no significant deviation from the protocol that could affect the primary outcome parameter were included.

The contrasts of the active treatment groups compared to placebo revealed no significant difference for either dose group compared with that of placebo.

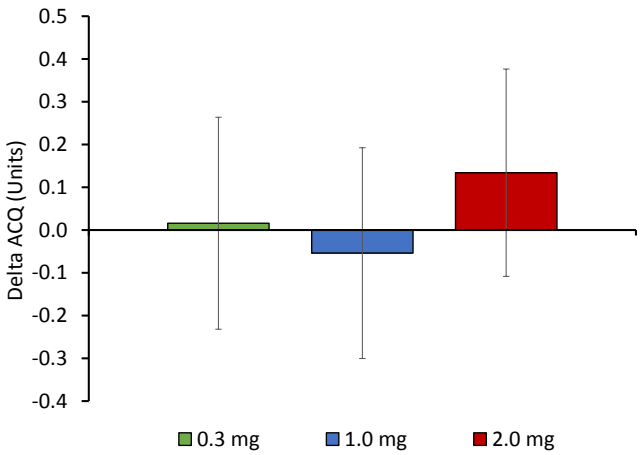


Figure 11.4.1.2-2 ACQ Score – Change from Baseline at Week 12 (PP) - Contrasts

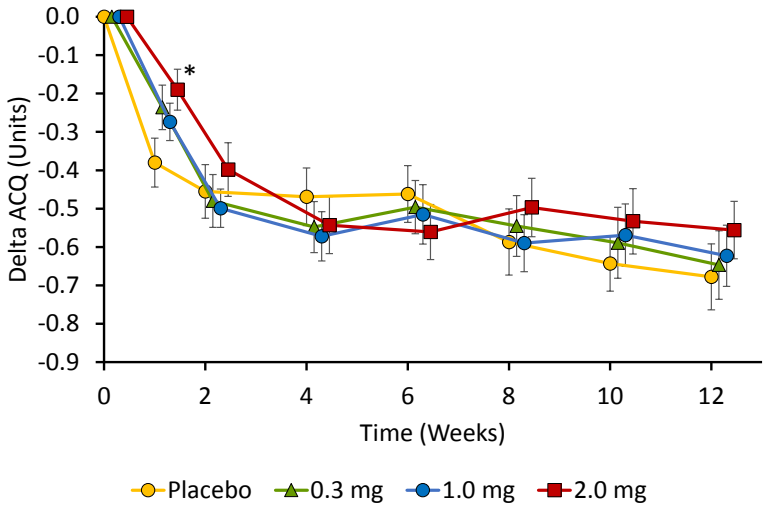
The columns represent the LS mean and 95% CI of the change in ACQ at week 12 per active treatment group compared to placebo of the PP population without LOCF. ACQ scores could vary from 0 to 6. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10. [Source: Table 14.2.2.1]

11.4.1.3 Secondary Efficacy Endpoints

11.4.1.3.1 ACQ

The development of the ACQ over the 12-weeks treatment phase revealed a medically relevant decrease of the score across all treatment groups. The steepest drop occurred during the first 2 weeks. Then, the curve flattened towards week 12 showing ACQ delta scores around -0.55. No meaningful difference between the treatment groups is observed. The contrast analysis using an ANCOVA model showed statistical significance only for the 2.0mg group compared to placebo at week 1 but in a negative way, since the placebo group showed the largest decrease in ACQ score.

A



B

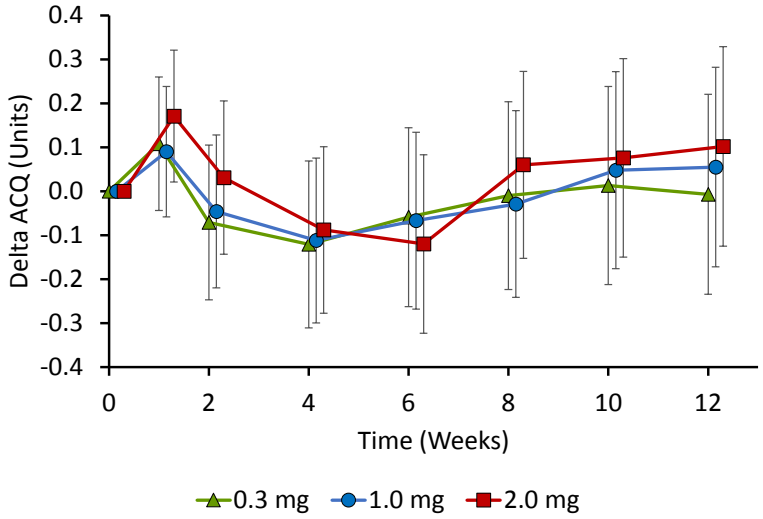


Figure 11.4.1.3.1-1 ACQ Score – Change from Baseline at all Time Points

Panel A: The curves represent the mean (±SEM) of the change in ACQ at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. ACQ scores could vary from 0 to 6. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

Panel B: The curves represent the LS mean and 95% CI of the change in ACQ at each time point over the 12-weeks treatment phase, where the active treatment groups are compared to placebo of the FAS population without LOCF.

*p=0.0256 for contrast to placebo from ANCOVA [Source: Table 14.2.4.1]

ACQ scores of 0.75 and below indicate that the asthma is “well controlled”. The figure below presents the percentage of patients whose asthma is well controlled during the 12-weeks treatment phase. At baseline, all patients are uncontrolled, as it is an inclusion criterion. Strong

variability is noticed over the weeks and between the treatment groups while the maximum at week 12 is not exceeding 14 % of the patients.

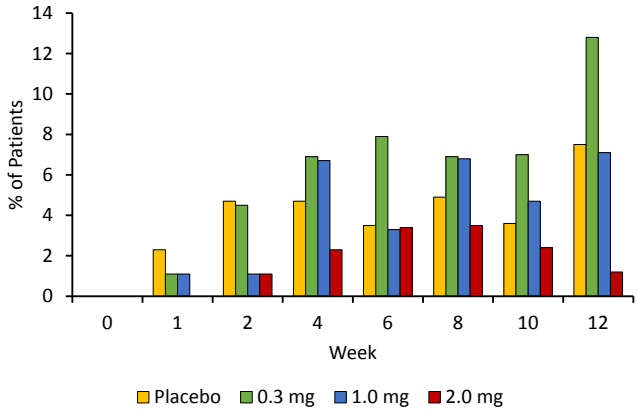


Figure 11.4.1.3.1-2 ACQ Score – % of Patients with ACQ ≤ 0.75

The columns represent the percentage of patients with "well controlled" asthma at each time point up to week 12. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10. [Source: Table 14.2.4.2]

In order to assess the general improvement of the patient population, all patients with an ACQ score of below 1.5 were determined. An ACQ score of 1.5 and higher indicates "uncontrolled asthma" and was an inclusion criterion. Therefore, no patient is present at baseline (week 0) in the figure below. For all treatment groups the number of patients increase to about 30 to 35% until week 12 with inverse dose titration where the placebo group has the most patients with improvement and the 2.0mg group the least.

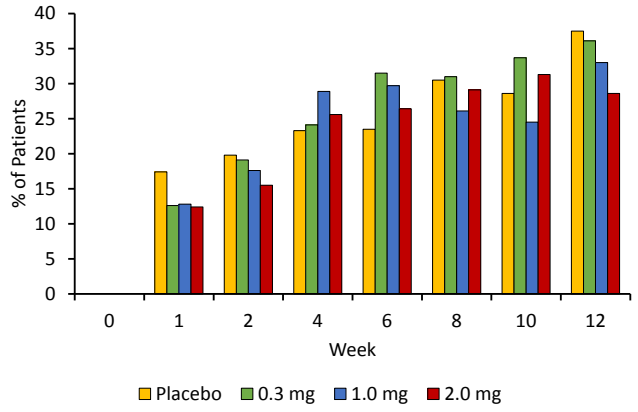


Figure 11.4.1.3.1-3 ACQ Score – % of Patients with ACQ < 1.5

The columns represent the percentage of patients with at least "partially controlled" asthma at each time point up to week 12. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10. [Source: Table 14.2.4.2]

11.4.1.3.2 FEV1

As part of the ACQ, the forced expiratory volume in one second (FEV1) has been analyzed separately. After an initial increase over the first 4 weeks in all treatment groups the volumes dropped back to more or less pre-treatment values at the end of the treatment phase. There were no significant differences between the active treatment groups and placebo. This is true for absolute values in liter as well as for relative values in %.

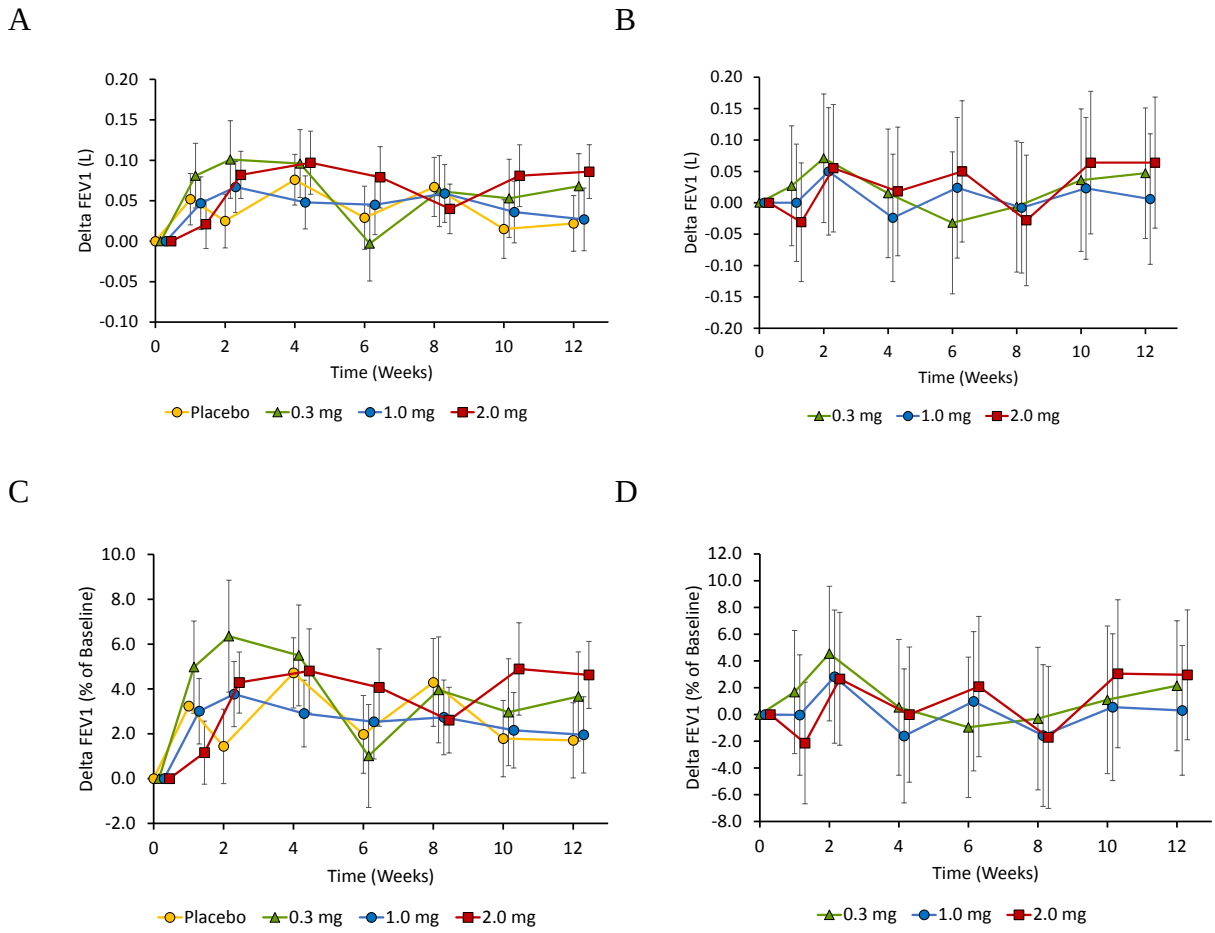


Figure 11.4.1.3.2-1 FEV1 – Change from Baseline

Panel A: The curves represent the mean (±SEM) of the change in FEV1 (in liter) at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

Panel B: The curves represent the LS mean and 95% CI of the change in FEV1 at each time point over the 12-weeks treatment phase, where the active treatment groups are compared to placebo of the FAS population without LOCF.

Panel C: The curves represent the mean (±SEM) of the change in FEV1 (in % of baseline) at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

Panel D: The curves represent the LS mean and 95% CI of the change in FEV1 at each time point over the 12-weeks treatment phase, where the active treatment groups are compared to placebo of the FAS population without LOCF. [Source: Tables 14.2.5.1, 14.2.5.2]

A clinically relevant difference in FEV1 has been identified as 100mL (Donohue, 2005). From the first week onwards on average 30 – 40% of patients experienced an improvement of at least 100mL at each time point regardless of the treatment they received.

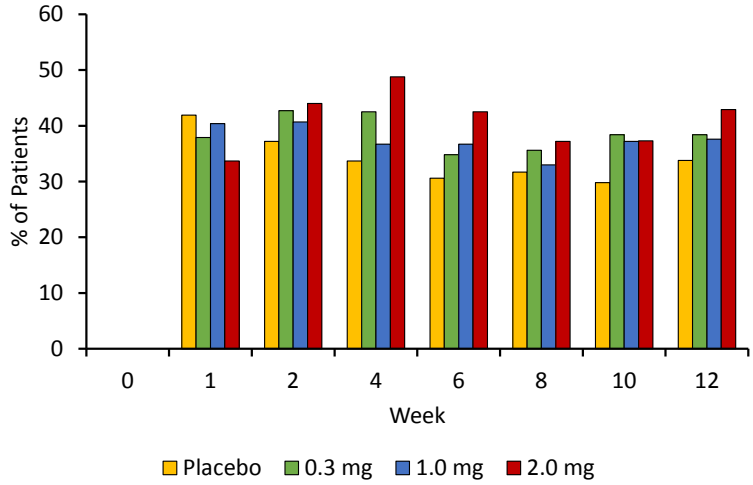


Figure 11.4.1.3.2-2 FEV1 – % of Patients with Improvement ≥ 100mL from Baseline

The columns represent the percentage of patients with at least an improvement of 100mL in FEV1 at each time point up to week 12. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10. [Source: Table 14.2.5.4]

The FEV1 in % predicted respects age, height and sex of the patient. Similar to what is seen for FEV1 in liter, the changes in % predicted do not differ significantly between the active treatment groups and placebo.

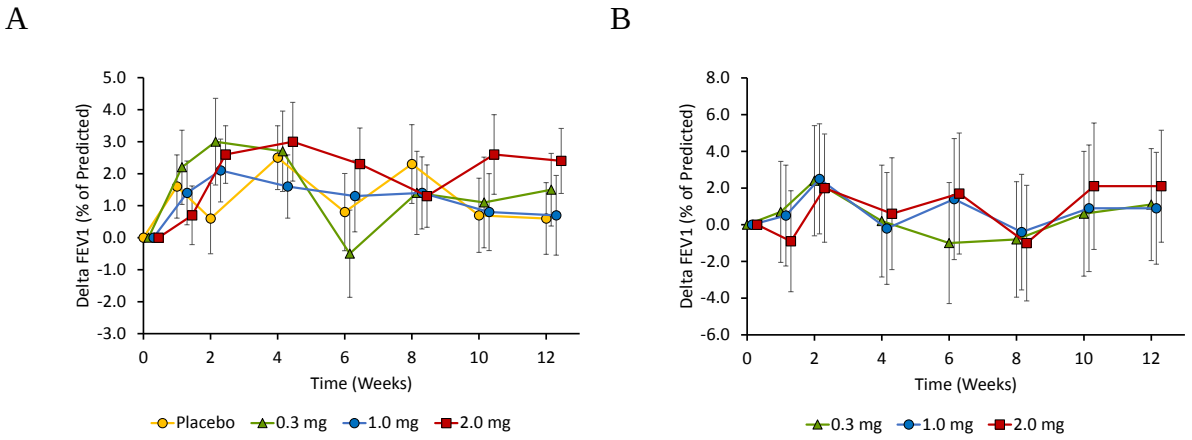


Figure 11.4.1.3.2-3 FEV1 (% of Predicted) – Change from Baseline

Panel A: The curves represent the mean (±SEM) of the change in FEV1 (in % predicted) at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

Panel B: The curves represent the LS mean and 95% CI of the change in FEV1 (in % predicted) at each time point over the 12-weeks treatment phase, where the active treatment groups are compared to placebo of the FAS population without LOCF. [Source: Table 14.2.5.3]

11.4.1.3.3 MiniAQLQ

The mini asthma quality of life questionnaire (MiniAQLQ) revealed increasing scores over the 12-weeks study period for all treatment groups and showed no significance between the treatment groups.

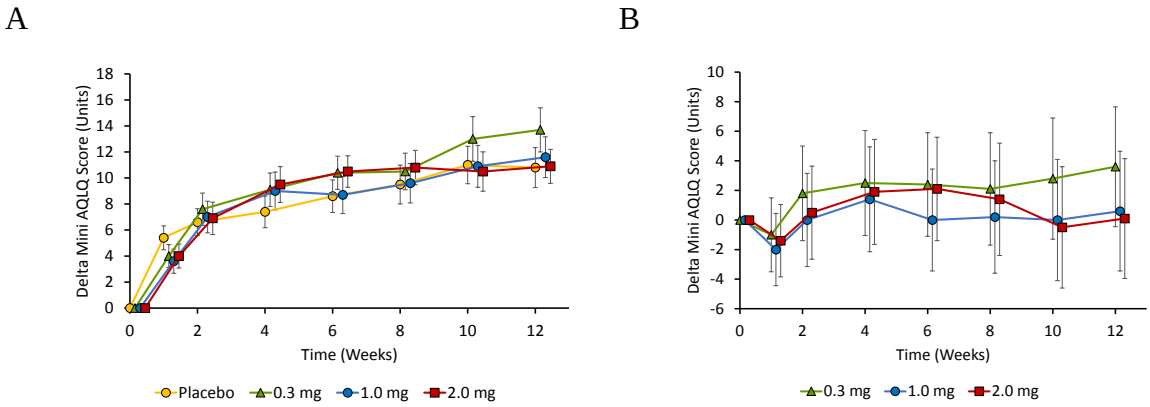


Figure 11.4.1.3.3-1 MiniAQLQ – Change from Baseline

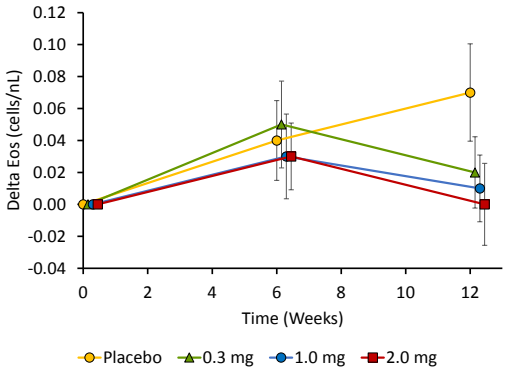
Panel A: The curves represent the mean (±SEM) of the change in MiniAQLQ score at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. MiniAQLQ scores could vary from 15 to 105. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

Panel B: The curves represent the LS mean and 95% CI of the change in MiniAQLQ score at each time point over the 12-weeks treatment phase, where the active treatment groups are compared to placebo of the FAS population without LOCF. [Source: Table 14.2.6.1]

11.4.1.3.4 Eosinophils

Eosinophils in the peripheral blood as a marker for possible lower airway inflammation showed a marginal increase at week 6 in numbers during the treatment phase. At week 12 eosinophils returned to baseline values for all three active treatment groups. However, the mean value for placebo further increased to 0.06 cells per nL at study end. None of the changes including the contrast to placebo for ANCOVA model revealed any statistical significance. When interpreting the curves it has to be taken into consideration that differences smaller than 0.1 are not considered clinically relevant.

A



B

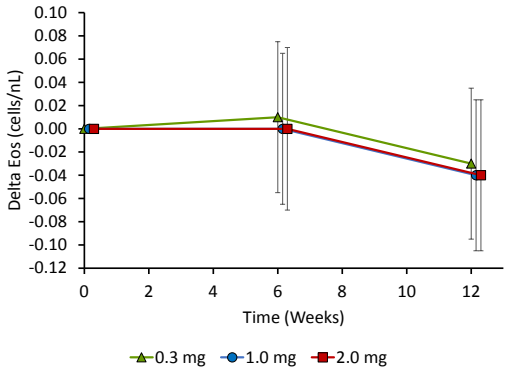


Figure 11.4.1.3.4-1 Eosinophil Cell Counts – Change from Baseline

Panel A: The curves represent the mean (±SEM) of the change in eosinophil cell count at week 6 and 12 of the treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

Panel B: The curves represent the LS mean and 95% CI of the change in eosinophil cell count at week 6 and 12 of the treatment phase, where the active treatment groups are compared to placebo of the FAS population without LOCF. [Source: Table 14.2.7.1]

11.4.1.3.5 FeNO

At four visits during the treatment phase the fraction of exhaled nitric oxide (FeNO) was measured as another marker for the inflammation in the bronchial tissue. At no time point the values differed significantly between the treatment groups and the overall change from baseline did not exceed 4ppm on average at any time point.

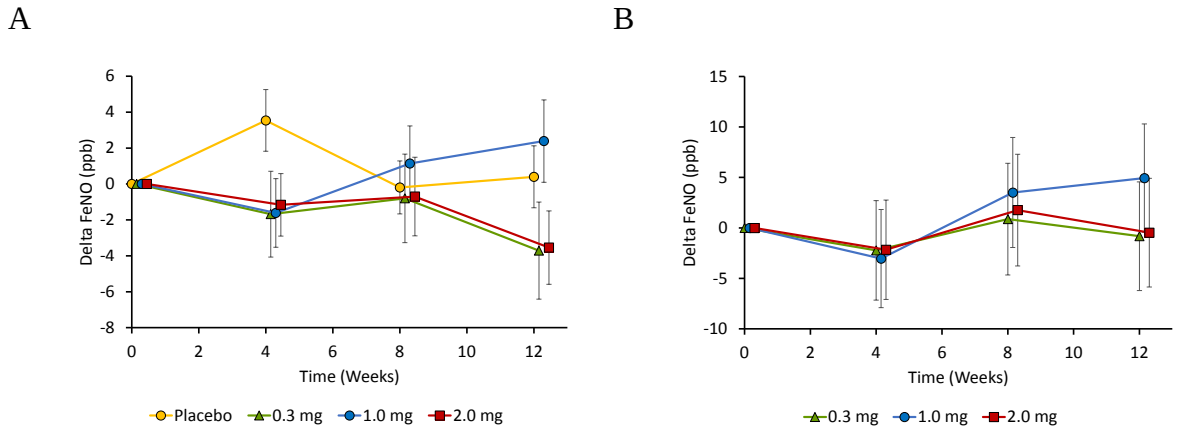


Figure 11.4.1.3.5-1 Fraction of exhaled Nitric Oxide (FeNO) – Change from Baseline

Panel A: The curves represent the mean (±SEM) of the change in FeNO at week 4, 8 and 12 of the treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

Panel B: The curves represent the LS mean and 95% CI of the change in FeNO at week 4, 8 and 12 of the treatment phase, where the active treatment groups are compared to placebo of the FAS population without LOCF. [Source: Table 14.2.7.2]

11.4.1.3.6 Subgroups ICS

A subgroup analysis per ICS dose did not reveal any relevant differences between the treatment groups as shown below.

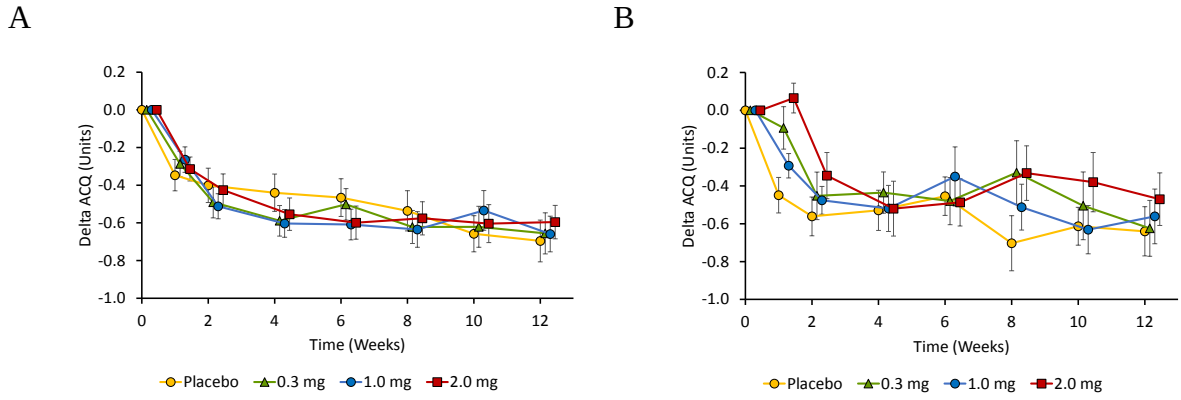


Figure 11.4.1.3.6-1 ACQ – Change from Baseline – ICS medium/high

Panel A: Patient subgroup on medium ICS (daily dose of fluticasone or equivalent >250 to 500µg). The curves represent the mean (±SEM) of the change in ACQ score at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

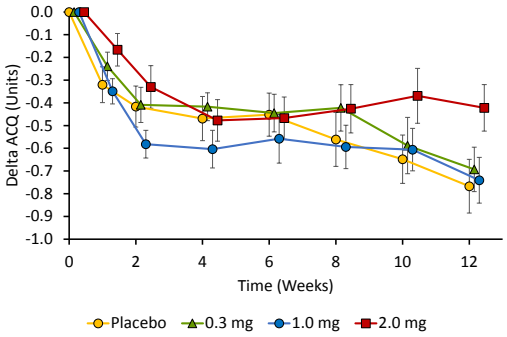
Panel B: Patient subgroup on high ICS (daily dose of fluticasone or equivalent >500 to 1000µg). The curves represent the mean (±SEM) of the change in ACQ score at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10. [Source: Table 14.2.8.1]

Subgroup analyses were performed as well for other efficacy parameters such as FEV1 absolute and % predicted, MiniAQLQ, eosinophil cell count, and FeNO values. None of the analyses revealed any relevant differences between active treatments and placebo.

11.4.1.3.7 Subgroups Eosinophils

A subgroup analysis per eosinophil counts did not reveal any relevant differences between the treatment groups as shown below.

A



B

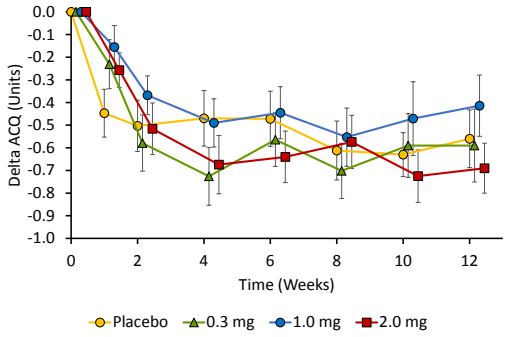


Figure 11.4.1.3.7-1 ACQ – Change from Baseline – Eos cut-off 0.2cells/nL

Panel A: Patient subgroup on low Eos (eosinophil counts ≤ median; median = 0.2cells/nL). The curves represent the mean (±SEM) of the change in ACQ score at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

Panel B: Patient subgroup on high Eos (eosinophil counts > median; median = 0.2cells/nL). The curves represent the mean (±SEM) of the change in ACQ score at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10. [Source: Table 14.2.9.1]

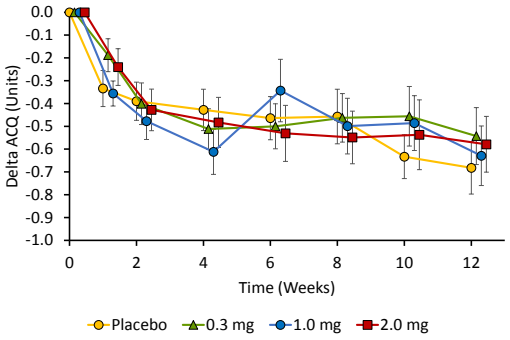
Subgroup analyses were performed for other efficacy parameters such as FEV1 absolute and % predicted, MiniAQLQ, eosinophil cell count, and FeNO values. None of the analyses revealed any relevant differences between active treatments and placebo.

A subgroup analysis with an eosinophil cell count cut-off of 0.1 (eosinophil low = counts ≤ 0.1cells/nL; eosinophil high = counts > 0.1cells/nL) showed no relevant differences between the groups for ACQ and FEV1 % predicted.

11.4.1.3.8 Subgroups FeNO

A subgroup analysis per FeNO measurements did not reveal any relevant differences between the treatment groups as shown below.

A



B

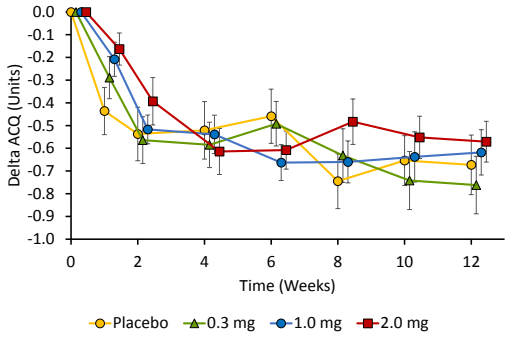


Figure 11.4.1.3.8-1 ACQ – Change from Baseline – FeNO cut-off 20.6ppb

Panel A: Patient subgroup on low FeNO (fraction of exhaled nitric oxide ≤ median; median = 20.6ppb). The curves represent the mean (±SEM) of the change in ACQ score at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

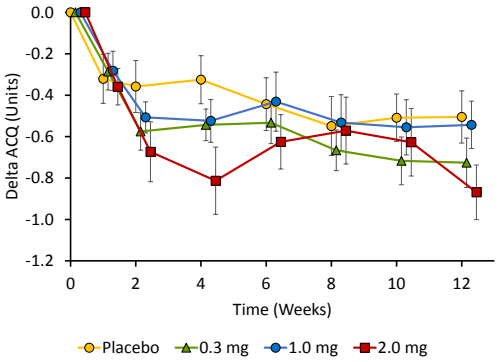
Panel B: Patient subgroup on high FeNO (fraction of exhaled nitric oxide > median; median = 20.6ppb). The curves represent the mean (±SEM) of the change in ACQ score at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10. [Source: Table 14.2.10.1]

Subgroup analyses were performed as well for other efficacy parameters such as FEV1 absolute and % predicted, MiniAQLQ, eosinophil cell count, and FeNO values. None of the analyses revealed any relevant differences between active treatments and placebo.

11.4.1.3.9 Subgroups Age at Asthma Onset

A subgroup analysis per age at asthma onset did not reveal any relevant differences between the treatment groups as shown below.

A



B

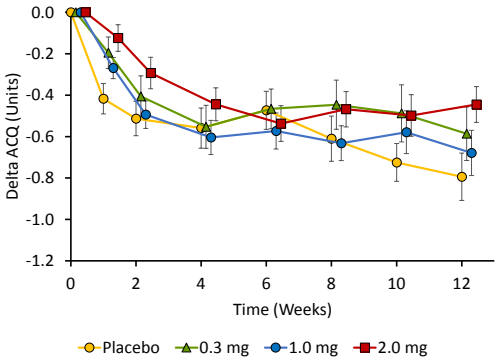


Figure 11.4.1.3.9-1 ACQ – Change from Baseline – Asthma onset cut-off 18years

Panel A: Patient subgroup with asthma onset at age of 18 or younger (age at asthma onset ≤ 18 years). The curves represent the mean (±SEM) of the change in ACQ score at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

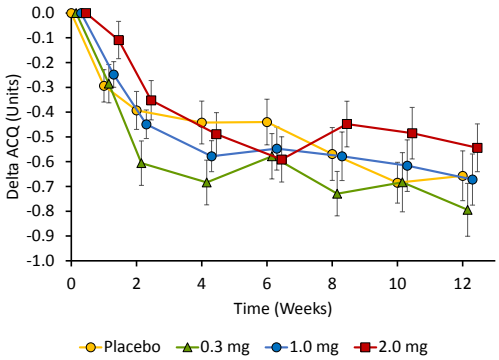
Panel B: Patient subgroup with asthma onset at age older than 18 (age at asthma onset > 18 years). The curves represent the mean (±SEM) of the change in ACQ score at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10. [Source: Table 14.2.11.1]

Subgroup analyses were performed for other efficacy parameters such as FEV1 absolute and % predicted, MiniAQLQ, eosinophil cell count, and FeNO values. None of the analyses revealed any relevant differences between active treatments and placebo.

11.4.1.3.10 Subgroups BMI

A subgroup analysis per BMI did not reveal any relevant differences between the treatment groups as shown below.

A



B

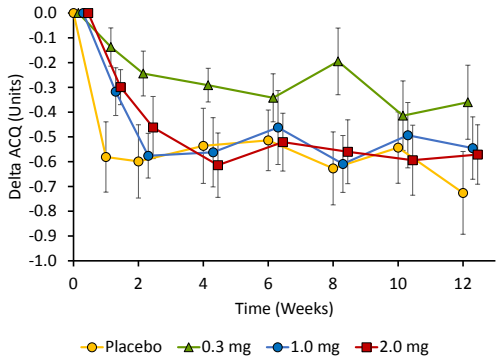


Figure 11.4.1.3.10-1 ACQ – Change from Baseline – BMI cut-off 30Kg/m^2

Panel A: Patient subgroup with BMI below 30 (BMI < 30Kg/m^2). The curves represent the mean (±SEM) of the change in ACQ score at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

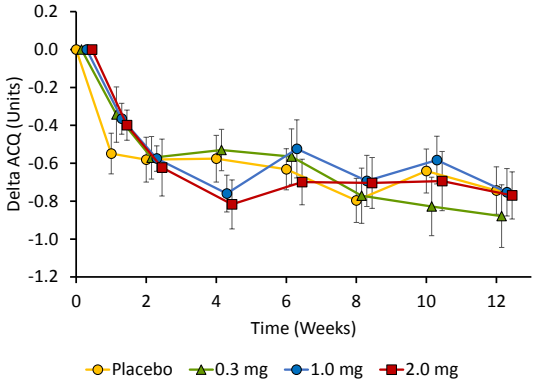
Panel B: Patient subgroup with BMI above or equal 30 (BMI ≥ 30Kg/m^2). The curves represent the mean (±SEM) of the change in ACQ score at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10. [Source: Table 14.2.12.1]

Subgroup analyses were performed for other efficacy parameters such as FEV1 absolute and % predicted, MiniAQLQ, eosinophil cell count, and FeNO values. None of the analyses revealed any relevant differences between active treatments and placebo.

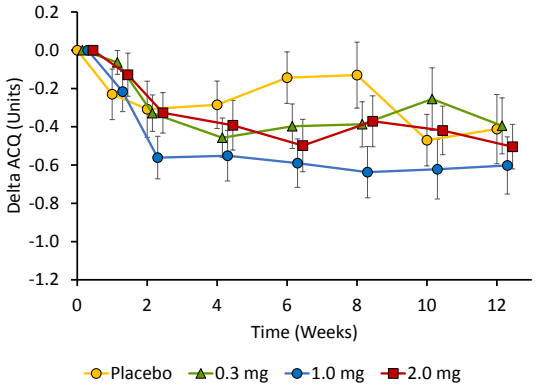
11.4.1.3.11 Subgroups Geographic Regions

A subgroup analysis per region revealed a transient reduced placebo effect in region B (see Panel B, Figure below) compared to other regions and compared to the active treatment groups within the same region. The effect started at week 4, was clearly visible at weeks 6 and 8, and disappeared at week 10, while the ACQ improvement for the 1mg treatment group remained relatively constant from week 2 onwards.

A



B



C

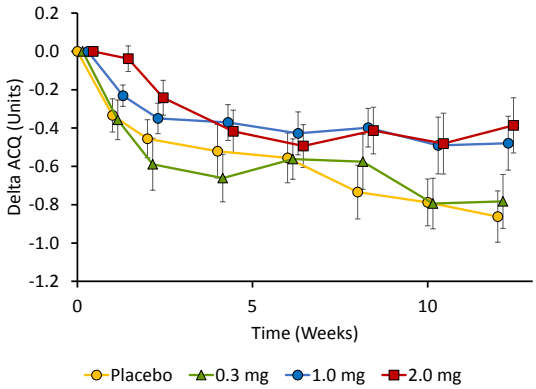


Figure 11.4.1.3.11-1 ACQ – Change from Baseline – per Study Region

Panel A: Patient subgroup from study region A (USA). The curves represent the mean (±SEM) of the change in ACQ score at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

Panel B: Patient subgroup from study region B (Germany, Israel, Czech Republic, Hungary). The curves represent the mean (±SEM) of the change in ACQ score at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

Panel C: Patient subgroup from study region C (Ukraine, Russia, Poland). The curves represent the mean (±SEM) of the change in ACQ score at each time point over the 12-weeks treatment phase. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10. [Source: Table 14.2.13.1]

Subgroup analyses were performed for other efficacy parameters such as FEV1 absolute and % predicted, MiniAQLQ. None of the analyses revealed any relevant differences between active treatments and placebo.

11.4.2 Statistical/Analytical Issues

11.4.2.1 Adjustment for Covariates

The first part of the primary analysis was the evaluation of the contrasts with placebo of the primary endpoint which was analyzed using an analysis of covariance (ANCOVA) model. The model contained treatment as a fixed effect with the baseline ACQ measurement as a covariate. To reflect the randomization scheme the model included baseline use of LABA (yes/no) and baseline dose of ICS (medium/high) as factors. To adjust for potential regional differences 'REGION' was also included in the analysis model as a factor.

The fitted (least square) means, SEM (standard error of the mean), and 95% confidence intervals of the contrasts for each active treatment versus placebo (unadjusted for multiplicity) are presented together with the unadjusted p-values for two sided testing of the 'no difference' hypothesis at the 5% significance level; however, these p-values are only to be regarded as 'descriptive'.

The normality and homoscedasticity assumptions for the ANCOVA model has also been assessed.

The second part of the primary analysis was the formal testing for superiority of the two higher doses over placebo. The superiority of CYT003 1.0mg or 2.0mg over placebo was evaluated by testing, for each of these doses separately, the following null hypothesis (Ho) versus the alternative hypothesis (Ha):

Ho: There is no difference in the mean response of the primary endpoint compared to placebo

Ha: There is a difference in the mean response of the primary endpoint compared to placebo

Two sided hypothesis testing was based on the two contrasts of change from baseline in ACQ score at Week 12, namely: 1.0mg dose versus placebo, and 2.0mg dose versus placebo.

11.4.2.2 Handling of Dropouts and Missing Data

The primary efficacy analysis was performed on the Full Analysis Set (FAS). In general, only observed and valid data were used. Where appropriate missing values of the primary endpoint had been imputed using the last observation carried forward (LOCF) procedure and otherwise remain missing. Patients who had a change (step-up or step-down) in their stable controller treatment from BL/T1 up to T8 were formally treated as premature discontinuations. For ACQ and FEV1 at week 12 only, an LOCF procedure was adopted to impute missing data (see also Section 11.1 Data Sets Analyzed). The last valid value at the most recent time point before or on the date of the visit was carried onwards provided that at the time of that last valid value the patient has had at least two injections a week or more earlier. If no such value was available then the endpoint remained missing.

11.4.2.3 Interim Analyses and Data Monitoring

The treatment period was double blinded and during this time the overall randomization code was broken only for reporting purposes.

The treatment phase analysis with unblinded data took place after all randomized patients had completed the week 12 visit. For this a separate Cytos and PPD biostatistics team was unblinded while Cytos and PPD project management and operations teams, the clinical research associates (CRAs), patient, investigator and site staff remained blinded. All communications with study centers continued blinded (no reference to treatment) until the termination of the study. A separate unblinded team was in place for data monitoring committee (DMC) deliverables and potential individual trigger report for the duration of the study. Final analysis including follow-up was planned to occur once all final clinical data up to Week 52 had been entered and finalized for analysis in the database. Final determination of the analysis sets occurred prior to finalizing the database at the end of the treatment phase.

Independent Data Monitoring

This study was conducted under the auspices of a DMC. The membership and activities are outlined in the DMC charter (see Appendix 16.1.15). This committee had to review the accumulating data as the study progressed. Three regular DMC meetings took place in intervals of approximate 2 months. DMC recommendations from all 3 planned meetings was to “continue the study without modification”. As it was planned to keep the study blinded also after interim analysis, Cytos requested DMC to give an opinion on the safety data from completed treatment phase evaluations. At this additional meeting the DMC approved sponsor’s request to unblind the study – as the primary efficacy endpoint had not been met. For all DMC meetings the unblinded information was made available to the DMC through separate unblinded statistical team at PPD. Cytos study team had at no time point access to the unblinded information. Unblinded information was only available to Cytos study team after the formal unblinding of the study after the study has been prematurely terminated.

11.4.2.4 Multicenter Studies

The study included 365 patients in 81 sites distributed over 8 countries. Most of the sites enrolled 4 patients which was the anticipated target. No evaluation of single sites took place.

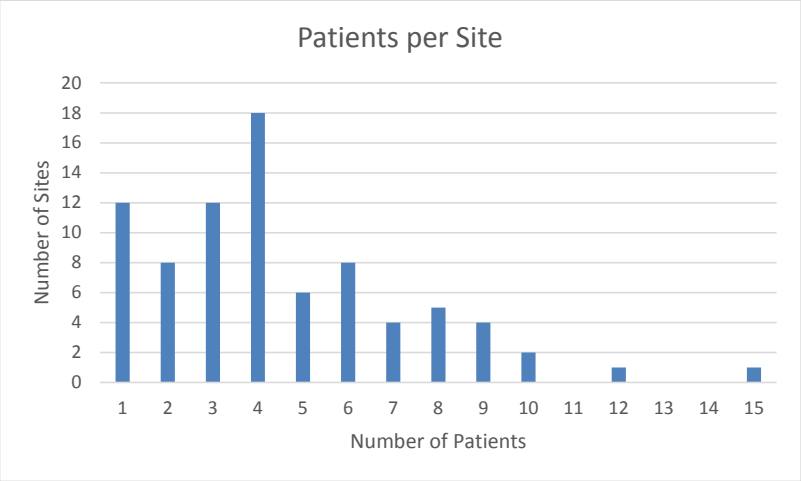


Figure 11.4.2.4-1 Patients per Site

The columns indicate how many sites have included a certain number of patients.

11.4.2.5 Multiple Comparison/Multiplicity

Hochberg's procedure is adopted to take account of multiplicity in the primary analysis for the 1mg and the 2mg dose, by controlling the type 1 error rate and is described below. It refers to two unadjusted p-values from the above tests and proceeds as follows:

If both p-values are ≤ 0.05 then both doses are declared different from placebo and, provided these primary endpoint contrasts (drug - placebo) are negative, then superiority over placebo can be declared for both doses of study drug.

If not, and if the smaller P-value is $\leq 0.05/2$ then the dose corresponding to this is declared as different from placebo and provided its contrast (drug - placebo) is negative then superiority over placebo can be declared for this dose of study drug.

If neither of the above are true then superiority over placebo would not have been established for either dose. This procedure ensures that the overall type 1 error rate is alpha ≤ 0.05. The adjustment for multiplicity is applied to the primary analysis only for the 1mg and 2mg dose groups.

11.4.2.6 Use of an "Efficacy Subset" of Patients

Efficacy analyses were performed with subsets of patients as sensitivity analyses, namely the PP set. See details on Section 11.1 and Table 11.1-1. Results are given in Section 11.4.1.3.6 to 11.4.1.3.11.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

No active comparator was included in this study.

11.4.2.8 Examination of Subgroups

For several parameters subgroups were made. The tables below gives the respective cut-off values and the group size.

Table 11.4.2.8-1 Number of Patients per Subgroup

Parameter		Cut-off	Placebo	0.3mg	1.0mg	2.0mg	Total
ICS	Medium	>250 to 500µg	59	66	59	60	244
	High	>500 to 1000µg	30	25	35	31	121
Eos	Low	Counts ≤ 0.2 cells/nL	48	53	58	50	209
	High	Counts > 0.2 cells/nL	40	38	33	37	148
Eos	Low	Counts ≤ 0.1 cells/nL	33	34	23	28	118
	High	Counts > 0.1 cells/nL	55	57	68	59	239
FeNO	Low	≤ 20.6ppb	50	48	42	42	182
	High	> 20.6ppb	39	43	52	48	182
Asthma Age of Onset	Early	≤ 18 years	33	40	38	25	136
	Late	> 18 years	56	51	56	66	229
BMI	Medium	< 30Kg/m^2	63	60	58	52	233
	High	≥ 30Kg/m^2	26	31	36	39	132

[Source: Tables 14.2.8.1 to 14.2.12.1]

Sub-group analyses were performed by regions (see Section 11.4.1.3.11). Geographically neighboring countries and countries with similar cultural and demographic backgrounds were pooled.

Table 11.4.2.8-2 Number of Patients per Region and Treatment Arm

	Placebo	0.3mg	1.0mg	2.0mg	Total
Region A (United States)	31	20	34	30	115
Region B (Germany, Israel, Czech Republic, Hungary)	27	37	31	32	127
Region C (Ukraine, Russia, Poland)	31	34	29	29	123
Total	89	91	94	91	365

[Source: Tables 14.2.13.1 to 4]

The criteria “region” with the possible values A, B or C were used as a factor in the statistical analysis model.

11.4.3 Tabulation of Individual Response Data

All individual efficacy data are provided in Appendix 16.2 - Patient Data Listings.

11.4.4 Drug Dose, Immunogenicity, and Relationships to Response

Three active treatment doses were compared with placebo (0.3mg, 1.0mg, and 2.0mg of CYT003). Each patient received 7 injections summing up to a total drug exposure per patient of 2.1mg, 7.0mg, and 14.0mg, respectively. Direct immunogenicity as discussed in Section 11.5 was not measured because of the premature termination of the study. A dose-response

relationship with respect to efficacy parameters was not detected. All dose groups including placebo revealed comparable efficacy responses.

11.4.5 Drug-Drug and Drug-Disease Interactions

These were not an objective of this study.

11.4.6 By-Patient Displays

Individual patients of interest are described in narratives in Section 12.3.2.

11.4.7 Efficacy Summary and Conclusions

Efficacy was assessed at the end of the 12-weeks treatment phase. The primary endpoint was ACQ score change from baseline at Week 12. ACQ scores could vary from 0 to 6, where the higher scores indicate increasing loss of asthma control. FAS set was used for the evaluation and LOCF was applied when data were missing or invalid. The contrasts to placebo obtained from the ANCOVA model revealed no statistical significance for the three dose groups.

Table 11.4.7-1 ACQ Score Change as Contrast to Placebo from ANCOVA

	0.3mg	1.0mg	2.0mg
LS mean	-0.027	0.097	0.081
95% CI low	-0.259	-0.131	-0.148
95% CI high	0.204	0.325	0.315
p-value	0.8180	0.4025	0.4883

[Source: Table 14.2.1.1]

Sensitivity analyses of the primary endpoint were performed. The first sensitivity analysis repeated the primary analysis without LOCF. Only observed values were taken. Missing or invalid measurements were left blank. No statistically significant change from baseline of the dose groups compared to placebo were detected at Week 12.

Table 11.4.7-2 ACQ Score Change as Contrast to Placebo from ANCOVA without LOCF

	0.3mg	1.0mg	2.0mg
LS mean	-0.007	0.055	0.102
95% CI low	-0.234	-0.172	-0.125
95% CI high	0.221	0.282	0.329
p-value	0.9528	0.6326	0.3777

[Source: Table 14.2.2.2]

The second sensitivity analysis evaluated the ACQ score change from baseline at Week 12 per protocol (PP) set. Those patients fulfilled all requirements of the study protocol without any significant deviation (see more details in section 11.1 Data Sets Analyzed). This most stringent population with respect to adherence to the protocol is supposed to show a potential treatment effect in a clean way with least variation. No statistical significance for the three dose groups was seen.

Table 11.4.7-3 ACQ Score Change as Contrast to Placebo from ANCOVA for PP

	0.3mg	1.0mg	2.0mg
LS mean	0.016	-0.054	0.134
95% CI low	-0.232	-0.301	-0.109
95% CI high	0.264	0.192	0.376
p-value	0.8979	0.6649	0.2783

[Source: Table 14.2.2.1]

The third sensitivity analyses evaluated a less stringent PP set herewith called PP*. PP* distinguishes from PP by including patients who performed ACQ after any other study procedure at visits BL/T1 or T8 although they should have filled in the ACQ as the very first assessment. For details see Section 11.1 Data Sets Analyzed. Again, no statistically significant difference was observed.

Table 11.4.7-4 ACQ Score Change as Contrast to Placebo from ANCOVA for PP*

	0.3mg	1.0mg	2.0mg
LS mean	0.038	0.030	0.136
95% CI low	-0.193	-0.201	-0.094
95% CI high	0.269	0.260	0.366
p-value	0.7451	0.8000	0.2465

* = Not excluding patients who fall under rule 7.3 of the latest signed version of significant PD Rules document [Source: Table 14.2.2.3]

An important secondary efficacy parameter is FEV1. Although part of the ACQ the lung function measurement was analyzed separately as well. No statistical significance could be detected when comparing the change from baseline at week 12 between the treatment groups and placebo with LOCF.

Table 11.4.7-5 FEV1 (L) Change as Contrast to Placebo from ANCOVA

	0.3mg	1.0mg	2.0mg
LS mean	0.071	0.011	0.066
95% CI low	-0.029	-0.088	-0.033
95% CI high	0.171	0.110	0.165
p-value	0.1646	0.8267	0.1917

[Source: Table 14.2.3.1]

The above test was repeated with a PP set called PP**. P** distinguishes from PP by including patients who performed ACQ not according to the protocol timing of recording the ACQ. Again, no statistically significant difference was observed.

Table 11.4.7-6 FEV1 (L) Change as Contrast to Placebo from ANCOVA for PP**

	0.3mg	1.0mg	2.0mg
LS mean	0.051	0.026	0.069
95% CI low	-0.056	-0.081	-0.039
95% CI high	0.159	0.133	0.176
p-value	0.3462	0.6309	0.2115

** = Not excluding patients who fall under rule 6.1, 7.3, and 7.4 of the latest signed version of significant PD Rules document [Source: Table 14.2.3.2]

The lung function parameter FEV1 can also be expressed as % of the predicted value that is individually calculated for each patient. The change from baseline at Week 12 revealed no statistically significant difference to placebo.

Table 11.4.7-7 FEV1 (% predicted) Change as Contrast to Placebo from ANCOVA

	0.3mg	1.0mg	2.0mg
LS mean	1.1	0.9	2.1
95% CI low	-2.0	-2.2	-1.0
95% CI high	4.1	3.9	5.1
p-value	0.4915	0.5745	0.1809

[Source: Table 14.2.5.3]

As another secondary endpoint the MiniAQLQ was completed by the patients regularly during the study. The score could vary between 15 and 105, while higher scores indicate increasing quality of life. The change from baseline at week 12 revealed no statistically significant difference to placebo.

Table 11.4.7-8 MiniAQLQ Score Change as Contrast to Placebo from ANCOVA

	0.3mg	1.0mg	2.0mg
LS mean	3.6	0.6	0.1
95% CI low	-0.5	-3.5	-4.0
95% CI high	7.6	4.6	4.1
p-value	0.0835	0.7809	0.9711

[Source: Table 14.2.6.1]

Eosinophils in the peripheral blood were counted as markers of inflammation. The change from baseline at week 12 revealed no statistically significant difference to placebo.

Table 11.4.7-9 Eosinophil (cells/nL) Change as Contrast to Placebo from ANCOVA

	0.3mg	1.0mg	2.0mg
LS mean	-0.03	-0.04	-0.04
95% CI low	-0.10	-0.11	-0.10
95% CI high	0.03	0.02	0.03
p-value	0.3170	0.1640	0.2325

[Source: Table 14.2.7.1]

The fraction of exhaled nitric oxide (FeNO) was measured as markers of inflammation. The change from baseline at week 12 revealed no statistically significant difference to placebo.

Table 11.4.7-10 FeNO (ppb) Change as Contrast to Placebo from ANCOVA

	0.3mg	1.0mg	2.0mg
LS mean	-0.82	4.94	-0.47
95% CI low	-6.21	-0.42	-5.85
95% CI high	4.56	10.31	4.91
p-value	0.7639	0.0710	0.8645

[Source: Table 14.2.7.2]

Furthermore, none of the additionally performed subgroup analyses revealed any statistically significant results.

Conclusions:

- The primary endpoint of the study defined as ACQ score change from baseline at week 12 did not show a statistically significant difference between the active treatment groups compared to that of placebo.
- Secondary endpoints:
    - All other ACQ score analyses including changes from baseline at all time points and responder analyses revealed no significant differences between active and placebo treatment groups.
    - All FEV1 changes from baseline including absolute values, % changes and % predicted values did not show any significant differences between active and placebo treatment.
    - The MiniAQLQ score change from baseline at all time points as well as the eosinophil counts and FeNO measurements did not reveal any statistically significant difference between the active dose groups and placebo.
- All subgroup analyses (i.e. per ICS dose, eosinophil counts or FeNO measurement at baseline, age at asthma onset, baseline BMI, or study region) performed for the outcome parameters ACQ, FEV1, MiniAQLQ, eosinophils, and FeNO showed no significant difference between the active treatment groups and placebo.
- There was no consistent dose response observed between the 0.3mg, 1.0mg, and 2.0mg treatment groups.
- A strong and persistent placebo effect was observed for change from baseline in ACQ scores.

11.5 Immunogenicity Results

The present clinical trial was terminated prematurely after the 12 week treatment phase. Immunogenicity in terms of anti-drug antibodies was not assessed. Immunogenicity in terms of a shift of other pharmacodynamic markers as part of the proposed mode of action (e.g. eosinophils and FeNO) where relevant can be found in the efficacy section of this report.

12 Safety Evaluation

12.1 Extent of Drug Exposure

See also Appendix 16 - Patient Data Listings. Table 12.1-1 shows the extent of drug exposure of all 365 patients included in the study.

Table 12.1-1 Extent of Drug Exposure

	Placebo	0.3mg	1.0mg	2.0mg	Total
7 Injections (all as planned)	80	87	85	79	**331**
6 Injections	3 (119003, 139011, 306001)	1 (709001)	2 (309007, 407003)	2 (109005, 403005)	**8**
5 Injections	2 (105012, 408001)	0	0	2 (139014, 502005)	**4**
4 Injections	1 (121003)	0	4 (108005, 503002 802008, 810003)	0	**5**
3 Injections	2 (501003,506003)	0	0	1 (601008)	**3**
2 Injections	0	2 (301001, 306010)	3 (107009, 132003,702001)	7 (107006, 141004,203004, 304003,309003, 607005,702002)	**12**
1 Injection	1 (805003)	1 (608008)	0	0	**2**
Total	**89**	**91**	**94**	**91**	**365**

[Source: Table 14.1.5 and Listing 16.2.5.2]

12.2 Adverse Events

Adverse Events (AEs) are divided into three categories according to their start date (time) in the study: Pretreatment-Emergent Adverse Events (PTEAE), Treatment-Emergent Adverse Events (TEAE) and post-treatment Adverse Events. A *PTEAE* is defined as an AE that occurred prior to the administration of the first dose of study drug. A *TEAE* is defined as an AE that is not present prior to the administration of the first dose of study drug but occurred before 30 days after the administration of the last dose of study drug. An AE that is already present prior to the administration of the first dose of study drug, but increases in the intensity/frequency during the study treatment period or before 30 days after the administration of the last dose of study drug is also considered as a TEAE. *A post-treatment AE* is defined as an AE that occurred 30 days (or later) after the last injection of study drug or an AE that increased in intensity/frequency after 30 days (or later) after the last study drug injection. It has to be emphasized that due to the premature study termination only PTEAE and TEAE were source-verified by the CRAs at the study sites.

The study was prematurely terminated on 14-Apr-2014. All patients were in the follow-up phase (follow-up visits are abbreviated as “FU” in tables) at the day of the study termination.

However, due to different study start dates, individual patients were at different study time-points (visit FU1 to FU4). Therefore, AEs in the post-treatment phase were not statistically evaluated and are discussed in the Addendum to the Clinical Study Report. None of the captured post-treatment AEs were considered by the investigator as suspected to be related to the study medication.

Asthma exacerbations as defined in the protocol were documented separately from AEs, whereas “worsening of asthma” or “asthma aggravation” that did not fulfil the definition of asthma exacerbation per protocol were documented as AEs. Asthma exacerbations during the treatment phase are presented in a separate section 12.3.1.3. Asthma exacerbations during the follow-up phase are discussed in the Addendum to the Clinical Study Report.

It was planned to evaluate the safety aspects of the study in full after the last patient had performed the last visit FU5 (12 months study visit). Due to the premature discontinuation of the study, many AEs still have the status “not recovered/not resolved” since the end date is missing. Where possible, tables and listings produced by PPD were used as source for the presentation of the TEAEs. For manually prepared listings see appendix 16.2.11.

12.2.1 Brief Summary of Adverse Events

In summary, 58% of all included patients experienced at least one TEAE. The incidence of TEAEs in the treatment groups was 3-4 times higher than in the placebo group. This was mainly because the majority of the TEAEs were injection site reactions (63% of all TEAEs, source Listing 16.2.11.1).

Most TEAEs (64% of all TEAEs) were mild in intensity, followed by moderate (29%) and severe (7%).

12.2.2 Display of Adverse Events

At each visit patients were asked about new events. Due to the premature study termination only TEAEs were fully recorded and rated throughout the study. AEs were classified according to MedDRA Version 12.1 or higher. For all PTAEs and TEAEs see also listing 16.2.7.1.

12.2.3 Analysis of Adverse Events

Overall, 212 patients (58% of the included 365 patients) experienced at least one TEAE. 40% of the patients in the placebo group, 58% of the patients in the 0.3mg group, 66% of the patients in the 1.0mg group and 67% of the patients in the 2.0mg group experienced at least on TEAE. An overview of all PTEAEs and TEAEs are given in the table and figures below.

Table 12.2.3-2 shows TEAEs that were experienced by at least 3% of patients in any treatment group.

Table 12.2.3-1 PTEAEs and TEAEs: Incidence and Severity

		Placebo (N = 89)		0.3mg (N = 91)		1.0mg (N = 94)		2.0mg (N = 91)		Total (N = 365)	
		n % pts	n evts	n % pts	n evts	n % pts	n evts	n % pts	n evts	n % pts	n evts
PTEAEs	all	9 (6%)	10	5 (7%)	5	6 (7%)	7	7 (10%)	10	27 (7%)	32
	mild		8		3		6		7		24
	moderate		2		2		1		3		8
	severe		0		0		0		0		0
TEAEs	all	36 (40%)	66	53 (58%)	208	62 (66%)	265	61 (67%)	213	212 (58%)	752
	mild	20	47	28	124	24	157	26	155	98	483
	moderate	14	17	19	53	31	95	31	54	95	219
	severe	2	2	6	31	7	13	4	4	19	50

[Source: Tables 14.3.1.2, 14.3.1.3, 14.3.1.4, 14.3.1.5, and 14.3.1.6].

Table 12.2.3-2 TEAEs in >3% of Patients in any Treatment Group

SOC Preferred Term	Placebo (N = 89) n (% pts)	0.3mg (N = 91) n (% pts)	1.0mg (N = 94) n (% pts)	2.0mg (N = 91) n (% pts)	Total (N=365) n (% pts))
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
injection site erythema	0	20 (22.0%)	24 (25.5%)	27 (29.7%)	71 (19.5%)
injection site swelling	0	20 (22.0%)	27 (28.7%)	23 (25.3%)	70 (19.2%)
injection site pruritus	2 (2.2%)	11 (12.1%)	19 (20.2%)	11 (12.1%)	43 (11.8%)
injection site pain	1 (1.1%)	10 (11.0%)	12 (12.8%)	16 (17.6%)	39 (10.7%)
injection site induration	0	3 (3.3%)	2 (2.1%)	4 (4.4%)	9 (2.5%)
injection site reaction	0	0	3 (3.2%)	1 (1.1%)	4 (1.1%)
influenza-like illness	2 (2.2%)	0	7 (7.4%)	3 (3.3%)	12 (3.3%)
pyrexia	2 (2.2%)	0	2 (2.1%)	5 (5.5%)	9 (2.5%)
fatigue	0	3 (3.3%)	0	0	3 (0.8%)
INFECTIONS AND INFESTATIONS					
nasopharyngitis	4 (4.5%)	5 (5.5%)	5 (5.3%)	6 (6.6%)	20 (5.5%)
bronchitis	1 (1.1%)	5 (5.5%)	1 (1.1%)	2 (2.2%)	9 (2.5%)
upper respiratory tract infection	1 (1.1%)	0	4 (4.3%)	4 (4.4%)	9 (2.5%)
acute sinusitis	0	2 (2.2%)	3 (3.2%)	0	5 (1.4%)
resp. tract infection viral	3 (3.4%)	0	0	0	3 (0.8%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS					
asthma	2 (2.2%)	2 (2.2%)	4 (4.3%)	2 (2.2%)	10 (2.7%)
wheezing	1 (1.1%)	1 (1.1%)	1 (1.1%)	3 (3.3%)	6 (1.6%)
oropharyngeal pain	0	2 (2.2%)	3 (3.2%)	0	5 (1.4%)
rhinitis allergic	0	3 (3.3%)	0	1 (1.1%)	4 (1.1%)
NERVOUS SYSTEM DISORDERS					
headache	6 (6.7%)	6 (6.6%)	3 (3.2%)	7 (7.7%)	22 (6.0%)
INVESTIGATIONS					
blood creatinkinase increased	0	3 (3.3%)	1 (1.1%)	0	4 (1.1%)
body temperature increased	0	0	0	4 (4.4%)	4 (1.1%)

[Source: Table 14.3.1.3]

Figures 12.2.3-1 and 12.2.3-2 show the severity of TEAEs that were experienced by at least 3% of patients in any treatment group.

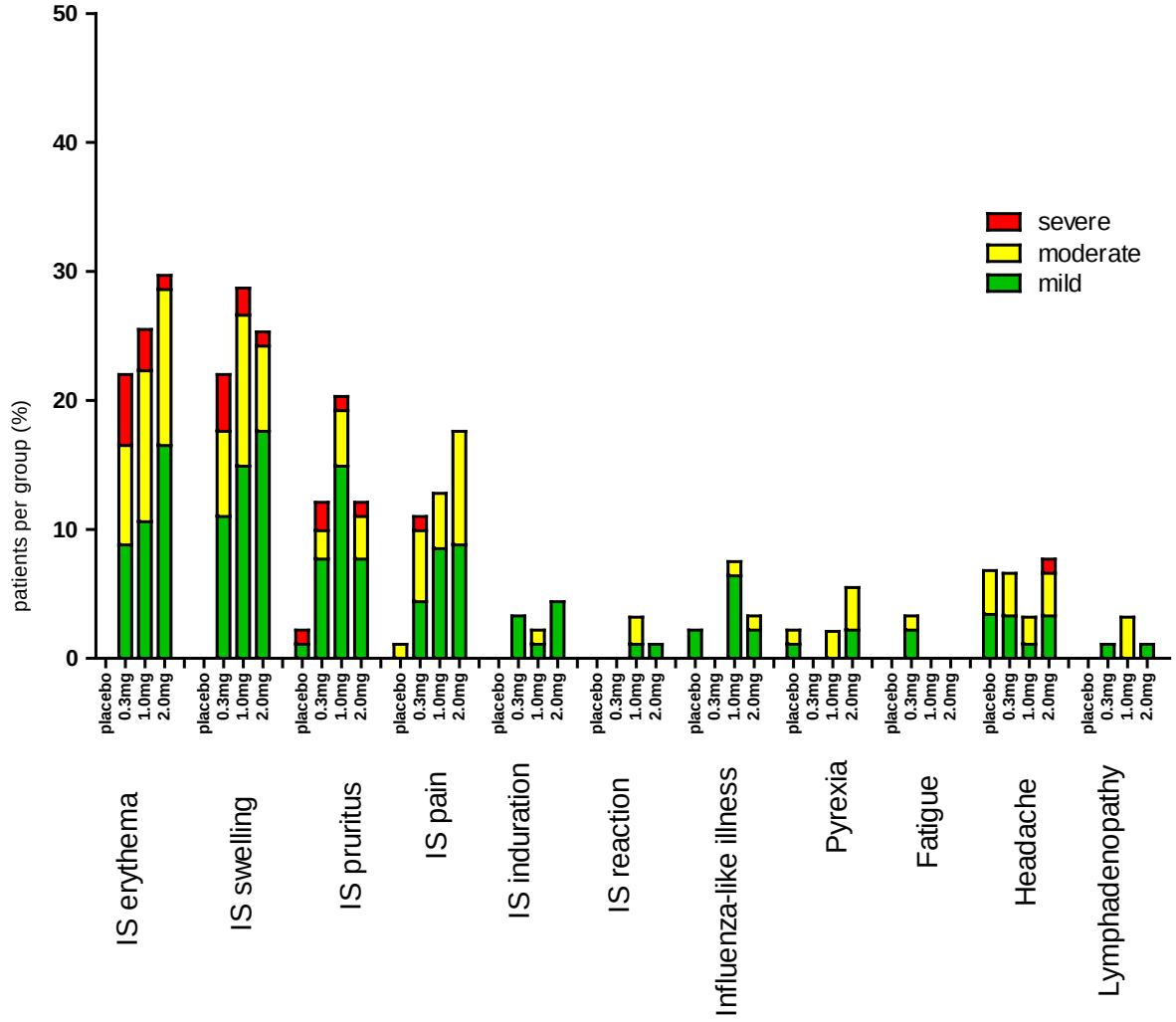


Figure 12.2.3-1 TEAEs: Preferred Terms (>3% in any group): severity part 1

[Source: Table 14.3.1.6]

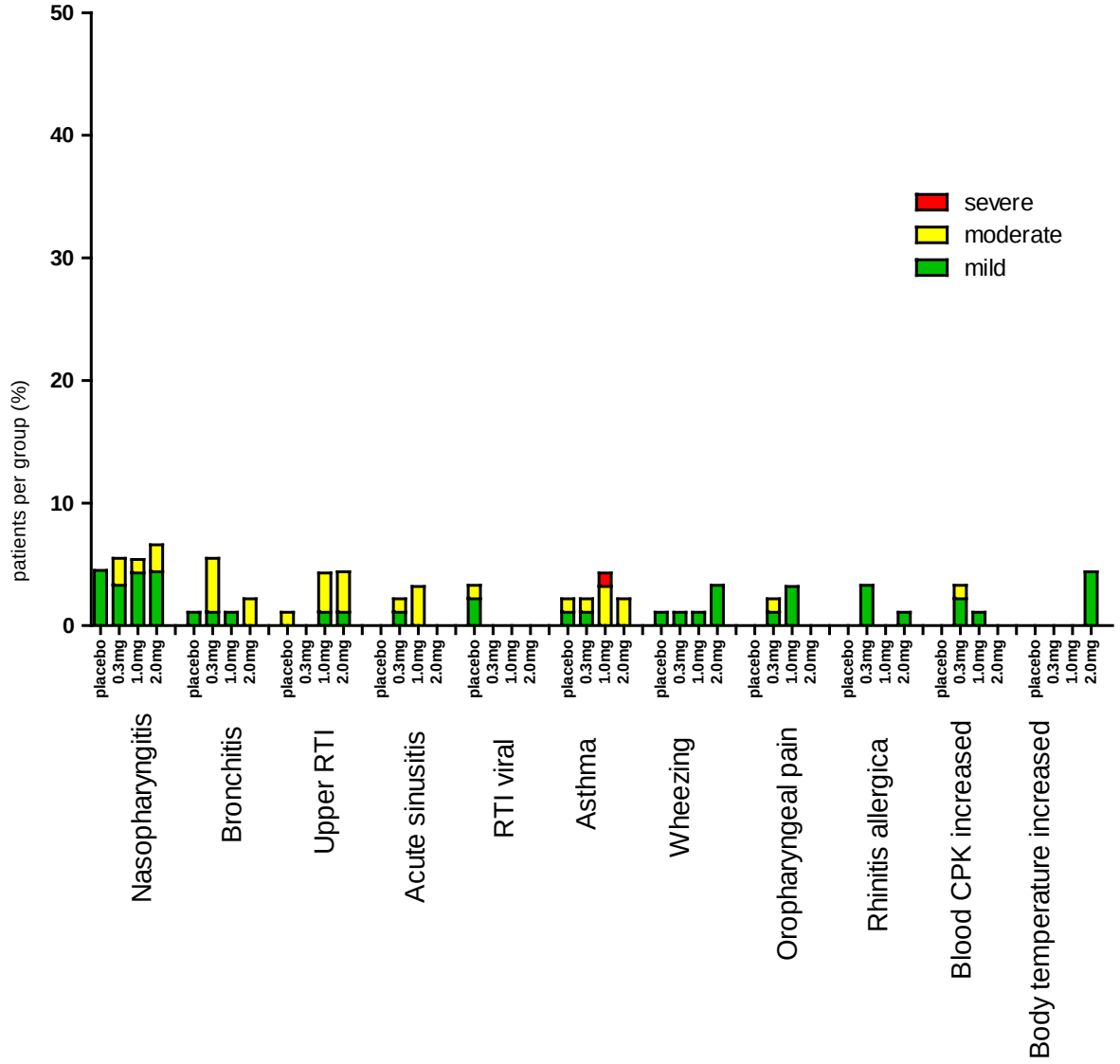


Figure 12.2.3-2 TEAEs: Preferred Terms (>3% in any group): severity part 2

[Source: Table 14.3.1.6]

Severe TEAEs

Severe injection site reactions documented as AEs were experienced as one event in the placebo group, 30 events in 6 patients in the 0.3mg group, 12 events in 6 patients in the 1.0mg group and 3 events in 3 patients in the 2.0mg group. For details see the tables below. Injection site reactions documented as AEs are discussed further in Section 12.5.5. All of the injection site reactions were considered by the investigators as non-serious. In the active treatment groups, the less amount of severe injection site reactions were in 2.0mg group (3 patients), followed by 0.3mg group (6 patients) and 1.0mg group (6 patients).

Table 12.2.3-2 TEAEs: severe (Injection Site Reactions)

Patient	Treatment	Preferred term	Occurrence after	Outcome
105012	Placebo	Injection site pruritus	4th injection	recovered/resolved
206005	0.3mg	Injections site swelling	3rd injection	recovered/resolved
		Injection site erythema	3rd injection	recovered/resolved
305002	0.3mg	Injection site erythema	4th injection	recovered/resolved
		Injections site swelling	4th injection	recovered/resolved
307004	0.3mg	Injection site erythema	3rd injection	recovered/resolved
506001	0.3mg	Injection site erythema	3rd injection	recovered/resolved
		Injection site erythema	4th injection	recovered/resolved
		Injection site erythema	5th injection	recovered/resolved
		Injection site erythema	6th injection	recovered/resolved
506012	0.3mg	Injection site pruritus	2nd injection	recovered/resolved
		Injection site swelling	2nd injection	recovered/resolved
		Injection site erythema	2nd injection	recovered/resolved
		Injection site pruritus	3rd injection	recovered/resolved
		Injection site swelling	3rd injection	recovered/resolved
		Injection site erythema	3rd injection	recovered/resolved
		Injection site swelling	4th injection	recovered/resolved
		Injection site erythema	4th injection	recovered/resolved
		Injection site swelling	5th injection	recovered/resolved
		Injection site erythema	5th injection	recovered/resolved
		Injection site swelling	6th injection	recovered/resolved
		Injection site erythema	6th injection	recovered/resolved
506013	0.3mg	Injection site pain	4th injection	recovered/resolved
		Injection site pruritus	4th injection	recovered/resolved
		Injection site swelling	4th injection	recovered/resolved
		Injection site pruritus	5th injection	recovered/resolved
		Injection site swelling	5th injection	recovered/resolved
		Injection site pain	6th injection	recovered/resolved
		Injection site pruritus	6th injection	recovered/resolved
		Injection site swelling	6th injection	recovered/resolved
		Injection site pruritus	7th injection	recovered/resolved
132003	1.0mg	Injection site swelling	2nd injection	recovered/resolved
135006	1.0mg	Injection site erythema	3rd injection	recovered/resolved
206006	1.0mg	Injection site swelling	3rd injection	recovered/resolved
		Injection site erythema	3rd injection	recovered/resolved
		Injection site erythema	4th injection	recovered/resolved
		Injection site swelling	4th injection	recovered/resolved
		Injection site erythema	5th injection	recovered/resolved
308006	1.0mg	Injection site erythema	2nd injection	recovered/resolved
503002	1.0mg	Injection site erythema	2nd injection	recovered/resolved
		Injection site erythema	4th injection	recovered/resolved
605003	1.0mg	Injection site pruritus	3rd injection	recovered/resolved
		Injection site pruritus	6th injection	recovered/resolved
206009	2.0mg	Injection site swelling	3rd injection	recovered/resolved
501001	2.0mg	Injection site erythema	2nd injection	recovered/resolved
808001	2.0mg	Injection site pruritus	2nd injection	recovered/resolved

[Source: Safety Listing 16.2.7.2]. Only patients 132003 and 503002 discontinued the study drug treatment due to *severe* injection site reactions.

Additionally, there was one severe AE in each treatment group. For patient 305002, the shortness of breath was classified by the investigator as suspected to be related to the study medication. For narrative, please see in Appendix 16.2.11.11.

One event (802008, asthma exacerbation) was reported as serious, not suspected to be related to the study medication. See narrative in Section 12.3.2-1.

Table 12.2.3-3 TEAEs: severe (without Injection Site Reactions)

Patient	Treatment	Preferred term (eCRF verbatim)	Occurrence after	Outcome
123005	Placebo	Gastroenteritis (Gastroenteritis)	4th injection	recovered/resolved
305002	0.3mg	Dyspnea (Shortness of breath)	3rd injection	recovered/resolved
802008*	1.0mg	Asthma (Severe asthma exacerbation)	4th injection	recovered/resolved
116003	2.0mg	Headache (Headache)	1st injection	recovered/resolved

[Source: Safety Listing 16.2.7.2] *This event is a SAE. Other events are non-serious AEs.

TEAEs leading to study drug discontinuation

In the study, 29 patients discontinued from the study drug treatment for different reasons. See also section 10.1.1. Premature Discontinuation (Table 10.1.1-1). Out of these 29 patients, following 15 patients discontinued the study drug treatment due to an TEAE (Table 12.2.3-4), see section 12.3.2 for narratives.

Table 12.2.3-4 TEAEs: leading to Study Drug Discontinuation

Patient	Treat.	Preferred term (eCRF verbatim)	Severity	Occurrence after	Outcome
121003*	placebo	Double strained DNA antibody positive (Elevated ds-DNA values)	mild	pre-treatment AE*	no end date
408001	placebo	Herpes Zoster	moderate	5th inj.	recovering/resolving
301001	0.3 mg	Injection site reactions (erythema, swelling, flare-up of previous ISR)	moderate	2nd inj.	recovered/resolved
107009	1.0mg	Injection site induration	moderate	2nd inj.	recovered/resolved
132003	1.0mg	Injection site swelling	severe	2nd inj.	recovered/resolved
503002	1.0mg	Injection site erythema	severe	4th inj.	recovered/resolved
702001	1.0mg	Lymphadenopathy (lymphadenop.dx axilla) and injection site erythema	moderate	2nd inj.	recovered/resolved
810003	1.0mg	Influenza like illness	mild	4th inj.	recovered/resolved
107006	2.0mg	Injection site pain	moderate	2nd inj.	recovered/resolved
139014	2.0mg	Injection site pain (upper body muscle pain injection site reaction)	moderate	5th inj.	recovered/resolved
203004	2.0mg	Injection site pain	moderate	2nd inj.	recovered/resolved
304003	2.0mg	Injection site pain	moderate	2nd inj.	recovered/resolved
309003	2.0mg	Injection site erythema	moderate	2nd inj.	recovered/resolved
607005	2.0mg	Asthma (worsening of asthma) and injection site reactions	moderate	2nd inj.	recovered/resolved
702002	2.0mg	Injection site swelling	moderate	2nd inj.	recovered/resolved

[Source: Listing 16.2.11.1] ISR: injection site reaction
Patient 121003 received four injections. The reason for discontinuation was out of reference range value of dsDNA at baseline

Table 12.2.3-5 displays the number of patients that discontinued the study drug treatment due to injection site reaction or enlarged /painful lymph nodes. 8% of the patients in the 2.0mg treatment group discontinued from the study drug due to injection site reactions, followed by 6% of the patients in the 1.0mg group and 1% of the patients in the 0.3mg group. Is has to be emphasized, that most of the injection site reactions leading to a discontinuation of the study drug treatment were rated as "moderate". Most of the patients on the active treatment, experiencing a severe injection site reaction (see Table 12.2.3-2), continued with further injections of the study medication.

Table 12.2.3-5 TEAEs: Injection Site Reactions leading to Discontinuation

	Placebo (N = 89) n (%pts)	**0.3mg (N = 91) n (%pts)**	**1.0mg (N = 94) n (%pts)**	**2.0mg (N = 91) n (%pts)**	**Total (N = 365) n (%pts)**
Discontinued due to ISR /lymphadenopathy	0 (0%)	1 (1%)	4 (4%)	7 (8%)	**11 (3%)**

[Source: Listing 16.2.1.1.] ISR: injection site reaction; n: number of patients discontinued due to ISR.

12.2.4 Listing of Adverse Events by Patient

See Listing 16.2.7.1

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events - treatment phase

There was one SAE reported during the treatment phase (patient 802008, Table 12.3-1). Further SAEs were reported in the follow-up phase – see Addendum to this Clinical Study Report.

Table 12.3-1 TEAEs: SAEs

Patient	**Treatment**	**SAE *(reason for SAE classification)***	**Severity**	**Causality**	**Occurrence after**	**Outcome**
802008	1.0mg	Asthma exacerbation *(hospitalization)*	severe	not suspected	4th inj.	recovered/resolved

[Source: Listing 16.2.4.3 and 16.2.7.1]

12.3.1 Listing of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1.1 Deaths

There were no deaths reported.

12.3.1.2 Other Serious Adverse Events

For narratives see section 12.3.2.

12.3.1.3 Other Significant Adverse Events

Infections and Infestations

15% of the patients in the placebo group, 19% of the patients in the 0.3mg group, 23% of the patients in the 1.0mg group, and 19% of the patients in the 2.0mg group experience at least one TEAE in the SOC ”Infections and Infestations”. Since patients with severe asthma are known to be more susceptible and to have more incidence and higher severity of respiratory tract infections, AEs were evaluated as respiratory tract infections and non-respiratory tract infections (see tables below).

Table 12.3.1.3-1 TEAE: Respiratory tract and non-respiratory Tract Infections

		Placebo (N = 89)		0.3mg (N = 91)		1.0mg (N = 94)		2.0mg (N = 91)		Total (N = 365)	
		n % pts	n evts	n % pts	n evts	n % pts	n evts	n % pts	n evts	n % pts	n evts
Any Infection		13 (15%)	17	17 (19%)	21	22 (23%)	24	17 (19%)	20	69 (19%)	82
Respiratory Tract Infection		12 (12%)	14	16 (18%)	19	17 (18%)	18	13 (14%)	16	58 (16%)	67
	mild		11		8		9		8		36
	moderate		3		11		9		8		31
	severe		0		0		0		0		0
non-respiratory Tract Infection		3 (3%)	3	2 (2%)	2	6 (6%)	6	4 (4%)	4	13 (4%)	13
	mild		1		0		5		3		8
	moderate		1		2		1		1		4
	severe		1		0		0		0		1

Data in brackets indicate the number of AEs. Included in respiratory tract infections are: nasopharyngitis, respiratory tract infection viral, tracheobronchitis, bronchitis, pharyngitis, sinusitis, upper respiratory tract infection, acute sinusitis, acute tonsillitis, influenza, rhinitis, and viral pharyngitis. Included in non-respiratory tract infections are: gastroenteritis, herpes zoster, oral herpes, breast abscess, cellulitis, eye Infection, herpes dermatitis, oral candidiasis, otitis externa, otitis media, and staphylococcal skin infection. [Source: Listing 16.2.11.1]

Asthma Exacerbations

It was planned to evaluate asthma exacerbations only after the completed follow-up phase. Due to the nature of asthma exacerbations (events are rather rare), the occurrence or absence of asthma exacerbations in patients need to be observed and captured during a long time-period (e.g. one year). At the time-point of the premature study termination most of the patients had been in the study for max. 6-9 months.

Due to the premature termination of the study asthma exacerbations are presented as “Treatment Emerged Asthma Exacerbations” (TE asthma exacerbations) when they occurred before 30 days after the last injection with study medication. Asthma exacerbations with a start date 30 days or later after the last injection with study medication are listed in the Addendum to this Clinical Study Report.

An evaluation of “TE asthma exacerbation” is of limited value and a judgment of wherever there are differences between the treatment arms is not possible.

Asthma exacerbations were defined in the protocol as follows:

- Moderate asthma exacerbation: need for systemic steroids for at least 3 days
- Severe asthma exacerbation: need for systemic steroids for at least 3 days and either emergency room treatment or hospitalization (overnight or for a longer period)

Therefore, all asthma exacerbations according to the protocol fulfilled the criteria of *severe* asthma exacerbation according to “An Official American Thoracic Society/European

Respiratory Society Statement: Asthma Control and Exacerbations Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice, 2009"

If a patient did not take systemic corticosteroids to treat the worsening of asthma, the investigators documented the event under AE as "worsening of asthma" or "asthma aggravation".

As per study protocol, patients should have stopped further study drug treatment after experiencing an asthma exacerbation. An overview of patients that discontinued the study drug treatment due to an asthma exacerbation (per protocol), see Table 12.2.3-2 for all asthma exacerbations during the treatment phase.

During the treatment phase, two patients in the placebo group, two patients in the 0.3mg group, nine patients in the 1.0mg group, and five patients in the 2.0mg group experienced an asthma exacerbation as defined in the protocol (Table 12.3.1.3-2). Seventeen of these events were moderate and one was severe in severity. One event qualified for a SAE (802008) as the patient was hospitalized. For administrative reasons severe asthma exacerbations were also documented in the AE section. For detailed information see also Section 12.3.2: Narratives of SAEs. Asthma exacerbations in follow-up phase are discussed in the Addendum to the Clinical Study Report.

Table 12.3.1.3-2 TE Asthma Exacerbations

Patient	Trt	Severity	SAE	Occurrence after	days after 1st inj.	Outcome
119003	placebo	moderate	no	6th inj.	65	recovered/resolved
807005	placebo	moderate	no	7th inj.	81	recovered/resolved
613001	0.3mg	moderate	no	7th inj.	78	recovered/resolved
709001	0.3mg	moderate	no	6th inj.	57	recovered/resolved
103008	1.0mg	moderate	no	7th inj.	77	recovered/resolved
108005	1.0mg	moderate	no	4th inj.	35	recovered/resolved
407003	1.0mg	moderate	no	6th inj.	68	recovered/resolved
408008	1.0mg	moderate	no	7th inj.	92	recovered/resolved
503004#	1.0mg	moderate	no	6th inj.	65	recovered/resolved
	1.0mg	moderate	no	7th inj.	94	recovered/resolved
605003	1.0mg	moderate	no	7th inj.	89	recovered/resolved
607006	1.0mg	moderate	no	6th inj.	65	recovered/resolved
802008	1.0mg	severe**	yes	4th inj.	42	recovered/resolved
136004	2.0mg	moderate	no	on the day of 7th inj.	71	recovered/resolved
137012	2.0mg	moderate	no	7th inj.	96	recovered/resolved
403005	2.0mg	moderate	no	6th inj.	59	recovered/resolved
502005	2.0mg	moderate	no	5th inj.	45	recovered/resolved
709003	2.0mg	moderate/ severe*	no / yes in FU*	7th inj.	89	recovered/resolved

* Patient 709003: asthma exacerbation started as moderate non serious event in the treatment phase but increased in severity and became a SAE in the follow-up phase. #patients 503004 and 607006 and 136004 continued to receive the study drug treatment after asthma exacerbation. A protocol deviation was recorded;** Qualified for SAE (802008). [Source: Listing 16.2.11.1]

Headache, Pyrexia, Body Temperature increased, influenza-like Illness and Fatigue

The incidence of possible symptoms of systemic reactogenicity such as pyrexia, body temperature increased, influenza-like illness or fatigue was generally low, details are given in the table below.

Table 12.3.1.3-3 Headache, Influenza-like illness, Pyrexia, elev. Body Temp. and Fatigue

		Placebo (N = 89)		0.3mg (N = 91)		1.0mg (N = 94)		2.0mg (N = 91)		Total (N = 365)	
		n % pts	n evts	n % pts	n evts	n % pts	n evts	n % pts	n evts	n % pts	n evts
headache		6 (7%)	8	6 (6%)	7	3 (3%)	3	7 (8%)	7	22 (6%)	25
	mild		5		4		1		3	11	13
	moderate		3		3		2		3	11	11
	severe		0		0		0		1	1	1
influenza-like illness		2 (2%)	7	0 (0%)	0	7 (8%)	8	3 (3%)	3	12 (3%)	18
	mild		7		0		7		2	10	16
	moderate		0		0		1		1	2	2
	severe		0		0		0		0	0	0
pyrexia		2 (2%)	2	0 (0%)	0	3 (3%)	5	5 (5%)	8	10 (3%)	15
	mild		1		0		2		5		8
	moderate		1		0		3		3		7
	severe		0		0		0		0		0
body temperature increased		0 (0%)	0	0 (0%)	0	0 (0%)	0	5 (5%)	5	5 (1%)	5
	mild		0		0		0		5		5
	moderate		0		0		0		0		0
	severe		0		0		0		0		0
fatigue		0 (0%)	0	3 (3%)	3	0 (0%)	0	0 (0%)	0	3 (1%)	3
	mild		0		2		0		0	2	2
	moderate		0		1		0		0	1	1
	severe		0		0		0		0	0	0

[Source: Listing 16.2.11.1]

Number and severity of headaches are comparable between the active treatment groups and the placebo group. Patient 116003 (2.0mg) experienced a severe headache six days after the first injection, that lasted for two days. The event was considered as not suspected to be related to the study medication and was recovered/resolved. The patient did not report another AE during the study.

Influenza-like illness occurred approximately as often as they were reported in previous studies (up to 6 % in active treatment groups), they were mostly mild in severity. Two times the influenza-like illness was judged as suspected to be related to the study drug and resolved within 1 to 6 days. In one case (402004, 1.0mg) the influenza-like illness (not suspected) was resolved within 17 days.

Investigators were asked to documented elevated body-temperature / pyrexia as following : <37.5 °C normal body temperature, 37.5 – 38.0 elevated body temperature (mild), 38.1 – 38.9 pyrexia (mild), 39.0 – 40.0 pyrexia (moderate) and >40.0 pyrexia (severe). They were asked not only to document the AE term and severity, they were also asked to document the measured value. However, in many cases, the measured value was not documented.

Pyrexia and elevated body temperature were mostly reported in the 2.0mg group. They were all of mild or moderate severity. All pyrexia events resolved within 1-2 days, except pyrexia in

patient 601009 (1.0mg) that was resolved within 4 days and the elevated body temperature, eCRF verbatim "elevated body temperature till 37.6° C", in patient 813004 (2.0mg) was resolved within 14 days.

In general there were only a few other AEs that could be classified as possible systemic reaction to the study medication. Fatigue was reported only in 3 patients (all in the 0.3mg group). These events were mild to moderate and resolved mostly within 1 to 3 days. Patient 709001(0.3mg) reported (eCRF verbatim) "unmotivated general fatigue" that resolved within 50 days. For narrative, please see in Appendix 16.2.11.11.

For patient 305002, the dyspnea, eCRF verbatim "shortness of breath" was classified as suspected to be related to the study medication. A narrative can be found in appendix 16.2.11.8 One case of oral pruritus, suspected to be related to the study mediation was reported in patient 134002 (placebo).

One hour after each injection, the vital signs (blood pressure, pulse rate and body temperature) were measured in each patient. None of these values resulted in an AE.

There is no change in the safety profile of AEs possibly representing systemic reactions after study drug injection compared to the previous studies.

Urticaria, Allergic Dermatitis, Rash, Pruritus

There were nine AEs reported for seven patients during the treatment phase for urticaria, allergic dermatitis, rash or pruritus. All of these events were graded by the investigators as mild or moderate, four of them were reported by the investigators as suspected to be related to the study drug, see also narratives in Appendix 16.2.11.11. For narrative for the patient 607005, see section 12.3.2.

Table 12.3.1.3-4 TEAE + post treatment AE: Urticaria ,Allergic Dermatitis, Rash

Patient	Treat.	preferred term (eCRF verbatim)	Severity	Occurrence after	Outcome
104004	pla.	Rash (bilateral underarm rash)	mild	5th injection	recovered/resolved
709001	0.3mg	Dermatitis allergic (allergic dermatitis of low extremities)	mild	6th injection	recovered/resolved
506013	0.3mg	Rash (rash hands)	mild	Visit T8	no end date
		Rash (rash stomach)	mild	Visit T8	no end date
605003	1.0mg	Dermatitis allergic (face and hands allergic dermatitis)	moderate	3rd injection	recovered/resolved
403006	1.0mg	Pruritus (pruritus of lower extremities)	moderate	7th injection	no end date
814001	2.0mg	Urticaria (Generalized urticaria)	mild	2nd injection	recovered/resolved
607005*	2.0mg	Urticaria (Face and both arms urticaria)	moderate	3rd injection	recovered/resolved
		Urticaria (urticaria – is not an injection site reaction)	mild	Patient disc. treatment before. Event occurred 19 days after 2nd injection	recovered/resolved

[Source: Listing 16.2.7.1] * Patient 607005 experienced moderate urticaria also in the follow-up phase, 76 days after the second (last) injection.

AE resulting from abnormal Laboratory Evaluations

For other abnormal laboratory parameters see also Section 12.4.

If an investigator considered an abnormal laboratory value being clinically significant, an AE was documented.

In the treatment phase the investigators reported clinically significant abnormal laboratory parameters for 10 patients, documented in 14 TEAEs (see table below).

Table 12.3.1.3-5 TEAE: abnormal Laboratory Values

Patient	Treat.	Assessed parameter	Value	Severity	Measured at	Comment
613005	0.3mg	CPK	5595 U/L	moderate	T8	*"intensive exercise several days before"* ref range: 24-207 U/L
613007	0.3mg	CPK	3236 U/L	mild	T5	ref.range: 24-207 U/L
806006	0.3mg	CPK	336 U/L	mild	T5	ref.range: 24-207 U/L
110004	1.0mg	CPK	356 U/L 486 U/L	mild	T5 /T8	ref.range: 24-207 U/L
810004	pla	CRP	179.1 nmol/L	mild	T8	ref.range: <47.6 nmol/L
813002	pla	CRP	235.2 nmol/L /135.2 nmol/L	mild	T5 /T8	ref.range: <47.6 nmol/L
806006	0.3mg	CRP	151.4 nmol/L	mild	T5	ref.range: <47.6 nmol/L
815008	0.3mg	Neu. decreased	0.9 x 10^9/L /0.3 x 10^9/L	mild	T8 /Unsch	*see also further section "absolute neutrophils".* ref range: 1.7 – 7.9 x 10^9/L
110006	pla	ANA increased	1:640 / >1:640	mild	T8 /Unsch.	*increase from 1:320 at BL,* ref. range <1:40, *see also section "Antinuclear antibodies"*
138001	pla	ALT	160 U/L	mild	T5	ref. range: 10-40 U/L
138001	pla	AST	85 U/L	mild	T5	ref. range:10-43 U/L
138001	pla	Cholesterol	7.87 mmol/L	mild	T5	ref. range: 3.24-5.18 mmol/L
138001	pla	RBC in urine	present 3-5	mild	T5	ref. range: absent
807007	pla	ALT	111 U/L	mild	T5	ref. range: 10-40 U/L

[Source: Table 14.3.1.3 and Listing 16.2.7.1 and Listing 16.2.11.6]
CPK: creatinphosphokinase, CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, RBC: red blood cells, ANA: antinuclear antibody. Unsch: measured at unscheduled visit

Overall, the individual abnormal blood laboratory values do not suggest a specific pattern related to study treatment. They are rather concomitant findings and are expected within the usual population fluctuations.

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

For narratives in the follow-up phase, please refer to Addendum to the Clinical Study Report.

12.3.2.1 Narratives of SAEs during the treatment phase

Patient 802008 (1.0mg)
A 53-year-old male was enrolled into the clinical study on 25-Sep-2013 (signed informed consent). The patient was injected for the first time with 1.0mg CYT003 on 23-Oct-2013 and received the 4th injection on 19-Nov-2013. One day after the 4th dose patient reported moderate nausea, the investigator considered as suspected to be related. Nausea lasted for 9 days and resolved on 29-Nov-2013. On 21-Nov-2013 the patient showed symptoms of AE worsening of asthma, with dyspnea and nocturnal asthma, which included tightness of breath. The patient was developed a SAE severe asthma exacerbation and was hospitalized between 04-Dec-2013 and 13-Dec-2013. According to the study protocol, the patient did not receive further injections with the study medication. The investigator did not consider the events worsening of asthma and severe asthma exacerbation as suspected to be related to the study medication. Patient continued further study visits without receiving further study drug treatment.

12.3.2.2 Narratives of adverse events that led to discontinuation of study drug treatment

Patient 107006 (2.0mg)
A 28-year-old female was enrolled into the study on 15-Aug-2013 (signed informed consent). The patient received two injections with 2.0mg CYT003, the first dose on 11-Sep-2013 and the second dose on 19-Sep-2013. She experienced a flare-up of erythema at previous injection site (mild) on 19-Sep-2013 for one day, an "injection site pain grade 3 that prevented daily activity" (moderate) from 20-Sept-2013 to 21-Sept-2013 and influenza –like illness (mild) from 20-Sept-2013 to 21-Sept-2013. The investigator considered all of the events to be related to the study drug. Subject discontinued further study drug medication injections. Patient continued further study visits without receiving further study drug treatment.

Patient 107009 (1.0mg)
A- 44-year-old female was enrolled into the study on 18-Jul-2013 (signed informed consent). The patient received two injections with 1.0mg CYT003, the first dose on 14-Aug-2013 and the second dose on 22-Aug-2013. She experienced an injection site swelling/induration (moderate) from 23-Aug-2013 to 25-Aug-2013. The investigator considered the event to be related to the study drug. Patient continued further study visits without receiving further study drug treatment.

Patient 121003 (placebo)
A 51-year-old female was enrolled into the study on 15-May-2013 (signed informed consent). The patient was injected for the first time with placebo on 12-Jun-2013 and received the 4th and last injection on 11-Jul-2013.
On 25-Jul-2013, the study drug was discontinued and the patient was withdrawn from the study treatment due to abnormal double stranded DNA (dsDNA) laboratory results at baseline (12-Jun-2013; dsDNA=36 IU/mL, ref range <20 IU/mL) before study medication was applied. Higher values were confirmed at an unscheduled visit 2 weeks later on 26-Jun-2013 with dsDNA value of 38 IU/mL (ref. range <20IU/mL).
In the follow-up phase the patient was hospitalized for two days from 25–Sep-2013 to 26-Sep-2013 to undergo an elective left knee "MAKOplasty due to the osteo-arthritis of left knee". Since this procedure was planned before the patient signed the informed consent form, this event was downgraded from a serious AE to a non-serious AE. The investigator confirmed there

was no worsening of osteoarthritis during the study. The AE was considered as not suspected to be related to the study medication and was recovered/resolved.

Patient 132003 (1.0mg)
A 23-year old male was enrolled into the study on 30-Jul-2013 (signed informed consent). The patient received two injections with 1.0mg CYT003, the first dose on 26-Aug-2013 and the second dose on 03-Sep-2013. Patient experienced AE "shakey" on the day of the first dose, lasting one day. Event was mild, not suspected to be related to the study medication. On 26-Aug-2013 patient also experienced "lower respiratory tract congestion", recovering on 30-Aug-2013. Event was mild, treated with antibiotic treatment (azithromycin), not suspected to be related to the study medication. After the second injection the patient experienced a severe injections site swelling form 04-Sep-2013 to 08-Sep-2013, an injection site erythema (moderate) from 04-Sep-2013 to 19-Sep-2013, influenza -like illness (moderate) from 04-Sep-2013 to 08-Sept-2013 and "swollen lymph nodes" (moderate) from 04-Sep-2013 to 19-Sep-2013. The investigator considered all of the events to be related to the study drug. Patient continued further study visits without receiving further study drug treatment.

Patient 139014 (2.0mg)
A 23-year-old female was enrolled into the study on 30-Sept-2013 (signed informed consent). The patient received five injections with 2.0mg CYT003, the first dose on 29-Oct-2013 and the 5th dose on 10-Dec-2013. After the first dose she experienced moderate injection site erythema. From 16-Oct-2013 patient experienced moderate, not suspected to be related scabies treated with permethrin cream, resolved on 17-Nov-2013. One day after the third injection a moderate injection site swelling occurred, resolved in 8 days. On the day after the 4th injection on 22-Nov-2013 patient experienced mild somnolence, suspected to be related to the study medication, resolved within 1 day. After the fifth dose the patient experienced an "upper body muscle pain" (moderate) from 10-Dec-2013 to 30-Dec-2013 and discontinued from the study drug. The investigator considered the event to be related to the study drug. Patient continued further study visits without receiving further study drug treatment.

Patient 203004 (2.0mg)
A 48-year-old female was enrolled into the study on 14-Jun-2013 (signed informed consent). The patient received two injections with 2.0mg CYT003, the first dose on 12-Jul-2013 and the second dose on 18-Jul-2013. She experienced an injection site pain (moderate) from 19-Jul-2013 to 22-Jul-2013 and discontinued from the study drug. The investigator considered the event to be related to the study drug. Patient continued further study visits without receiving further study drug treatment.

Patient 301001 (0.3mg)
A 43-year-old female was enrolled into the study on 5-Jun-2013 (signed informed consent). The patient received two injections with 0.3mg CYT003, the first dose on 5-Jul-2013 and the second dose on 12-Jul-2013. After the second injection she experienced an injection site swelling >10cm (moderate) and injection site erythema >10cm (moderate) and a flare up erythema (moderate) from 14-Jul-2013 to 18-July-2013 and discontinued from the study drug. The investigator considered all of the events to be related to the study drug. Patient continued further study visits without receiving further study drug treatment.

Patient 304003 (2.0mg)
A 59-year-old male was enrolled into the study on 14-Aug-2013 (signed informed consent). The patient received two injections with 2.0mg CYT003, the first dose on 18-Sep-2013 and the

second dose on 2-Oct-2013. He experienced an injection site erythema (moderate), injection site pain (moderate) and injection site pruritus (moderate) from 2-Oct-2013 to 8-Oct-2013 and discontinued from the study drug. The investigator considered all of the injection site reactions to be related to the study drug.

Patient 309003 (2.0mg)
A 31-year-old female was enrolled into the study on 22-May-2013 (signed informed consent). The patient received two injections with 2.0mg CYT003, the first dose on 21-Jun-2013 and the second dose on 28-Jun-2013. She experienced injection site swelling (moderate), injection site pain (moderate) and injection site erythema (moderate) from 29-Jun-2013 to 3-Jul-2013 and pyrexia (mild) on 29-Jun-2013. The investigator considered all of the events to be related to the study drug. Patient continued further study visits without receiving further study drug treatment.

Patient 408001 (placebo)
A 62-year-old female was enrolled into the study on 17-May-2013 (signed informed consent). The patient received five injections with placebo, the first dose on 17-Jun-2013 and the 5th dose on 31-Jul-2013. After the first injection the patient experienced AEs “metal taste in the mouth” (mild, suspected) at 17-Jun-2013, lasting one day. After the third dose (02-Jul-2013) patient reported vertigo (mild, not suspected) from 11-Jul-2013 to 14-Jul-2013, headache (mild, not suspected) on 13-Jul-2013, acute bronchitis (mild, not suspected) from 22-Jul-2013 to 2-Aug-2013 and herpes zoster (moderate, not suspected) from 5-Aug-2013 to stop date not known. The patient suspected that the study drug has caused all of her AEs and asked the investigator to stop the study treatment. According to the investigator the study drug could not have caused these AEs (except metal taste in mouth). The patient discontinued the study drug treatment after the 5th injection on 31-Jul-2013. Patient continued further study visits without receiving further study drug treatment.

Patient 503002 (1.0mg)
A 63-year-old female was enrolled into the study on 15-Jul-2013 (signed informed consent). The patient received four injections with 1.0mg CYT003, the first dose on 12-Aug-2013 and the 4th dose on 30-Sept-2013. Four days after the 2nd dose the patient experienced a severe injection site erythema. She continued the study drug treatment. After the 4th injection she experienced another severe injection site erythema from 30-Sept-2013 to 01-Oct-2013 and discontinued the study. The investigator considered the events to be related to the study drug**.** Patient did not want to continue the study and withdrew consent approximately 1 month after the last dose received.

Patient 607005 (2.0mg)
A 31-year-old male was enrolled into the study on 25-Sep-2013 (signed informed consent). The patient received two doses of 2.0mg CYT003, the first one on 23-Oct-2013 and the second dose on 30-Oct-2013. The patient was prematurely discontinued from the study treatment due to worsening of asthma that he experienced from 31-Oct-2013 to 02-Nov-2013. The patient also experienced pyrexia (moderate) from 31-Oct-2013 to 31-Oct-2013 as well as injection site reactions (erythema, pruritus as well as flare-up of previous site erythema and pruritus), all AEs were was judged by the investigator as suspected to be related to the study medication. Patient continued further study visits without receiving further study drug treatment.
After the patient was discontinued from study medication he experienced two events of urticaria, one lasting one day from 18-Nov-2013 to 18-Nov-2013 (mild) and one during the follow-up phase starting on 14-Jan-2014 (moderate). Both urticaria were considered by the

investigator as not suspected to be related to the study medication. The end date of the second urticaria is not available due to premature termination of the study.

Patient 702001 (1.0mg)
A 64-year-old female was enrolled into the study on 20-Jun-203 (signed informed consent). The patient received two doses of 1.0mg CYT003, the first dose on 26-Sept-2013 and the second dose on 03-Oct-2013. She experienced an injection site swelling (moderate) and erythema (moderate) and a lymphadenopathy (moderate) from 05-Oct-2013 to 09-Oct-2013 and discontinued the study drug treatment. The investigator considered all of the event to be related to the study drug. Patient continued further study visits without receiving further study drug treatment.

Patient 702002 (2.0mg)
A 48-year-old female was enrolled into the study on 16-Aug-2013 (signed informed consent). The patient received two doses of 2.0mg CYT003, the first dose on 16-Sept-2013 and the second dose on 23-Sept-2013. She experienced an injection site swelling (moderate) and an erythema (moderate) from 23-Sept-2013 to 02-Oct-2013 and discontinued from the study drug. The investigator considered the events to be related to the study drug. Patient continued some study visits without receiving further study drug treatment.

Patient 810003 (1.0mg)
A 25-year-old male was enrolled into the study on 04-Jun-2013 (signed informed consent). The patient received four doses of 2.0mg CYT003, the first dose on 02-Jul-2013 and the 4th dose on 29-Jul-2013. After the 3rd and 4th injection patient experienced twice a mild influenza-like illness from 17-Jul-2013 until 21-Jul-2013, and from 29-Jul-2013 until 3-Aug-2013 and discontinued from the study drug. The investigator considered the events to be related to the study drug. Patient withdrew consent approximately 1 month after the last dose of study medication.

For narratives of other significant Adverse Events see Appendix 16.2.11.11.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

In summary, 58% of all included patients experienced at least one TEAE. The incidence of TEAEs in the treatment groups was 3-4 times higher than in the placebo group. This was mainly because the majority of the TEAEs were injection site reactions (63% of all TEAEs). The vast majority of the AEs in the active treatment groups were injection site reactions.

Except for the injection site reactions (incl. lymphadenopathy), and pyrexia (body temperature increased) no pattern was seen that would indicate higher rates of a specific AEs in the active treatment groups compared to the placebo group.

Seven patients discontinued the study due to asthma exacerbations (required per protocol to stop the treatment after an asthma exacerbation), 15 patients discontinued the study due to AE (10 for injection site reactions, 1 due to injection site reaction together with suspected to be related worsening of asthma, 1 due to pre-treatment emergent AE and 1 due to non-related herpes zoster). In general, as expected, the most discontinuations were due to injection site reactions (8% in the 2.0mg, 6% in the 1.0mg and 1% in the 0.3mg group.) In the previous

studies, 1.9% of patients on active treatment (any dose) discontinued the study treatment due to injection site reactions. In this study, this number is higher: 3.9% (11 out of 276 patients on active treatment). Is has to be emphasized, that most of the injection site reactions leading to a discontinuation of the study drug treatment were rated as “moderate”.

There was one TEAE classified as SAE, severe asthma exacerbation, not suspected to be related to the study drug (802008, 1.0mg). Other SAEs occurred in the follow-up phase and are discussed in the Addendum to this Clinical Study Report.

An evaluation of asthma exacerbations is of limited value and a judgment of wherever there are differences between the treatment arms is not possible due to premature termination of the study.

Except of the injection site reactions, there were only 4 severe TEAE, one in each treatment group. One of them was considered as suspected to be related to the study medication (dyspnea “shortness of breath”, 305002, 0.3mg)

Number and severity of headaches are comparable between the active treatment groups and the placebo group. Influenza-like illness occurred approximately as often as reported in previous studies (up to 6 % in active treatment groups) and they were mostly mild in severity. Pyrexia occurred mostly in 5% of patients in 2.0mg group, followed by 3% in 1.0mg and 2% in placebo group. No pyrexia was reported for patients in 0.3mg group. Pyrexia resolved within 1-2 days, in one patient (601009, 1.0mg) in 4 days. Fatigue was generally reported less frequently than in previous studies (3% of patients in 0.3mg group only).

Suspected urticaria/allergic dermatitis was reported as 4 AEs in 3 patients (1 patient in 0.3mg group, 1 in 1mg group and 1 in 2.0mg group). No patient discontinued the study treatment due to urticaria. In patient 814001 urticaria appeared after 2nd and 3rd injection, but not after further injections with the study medication.

12.4 Clinical Laboratory Evaluation

See Tables 14.3.2.1.1, 14.3.2.3.2, 14.3.2.1.3 and 14.3.2.1.4 as well as Listing 16.2.8.1, 16.2.8.2, 16.2.11.6 and 16.2.11.8 for source data.

For details of blood sampling time-points during the study, see figure 12.4.2.1 below. The blood examinations were performed in the central laboratory. Descriptive statistics was performed for hematology and blood chemistry parameters. It was not planned to statistically evaluate the antibodies results after the treatment phase. It was planned to evaluate it only after the follow-up phase.

As the study has been prematurely terminated, data from the treatment phase of the study (up to T8) are presented and discussed. Data from the follow-up phase may have not been source verified and are incomplete. If not otherwise indicated in the text, the follow-up laboratory data are presented in the addendum.

12.4.1 Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

Detailed listings of individual laboratory measurements are given in Appendix 16.2 – Patient Data Listing.

12.4.2 Evaluation of Each Blood Laboratory Parameter

12.4.2.1 Laboratory Values over Time

Hematology and clinical chemistry were assessed at screening (week -4), T5 (week 6) and T8 (week 12, end of treatment phase).

Antibodies for ANA, dsDNA, IgE and IGG were assessed at baseline (BL/T1, day 0), T5 (week 6) and T8 (week 12). HIV, HBC and HVC were assessed at screening only and were part of inclusion criteria.

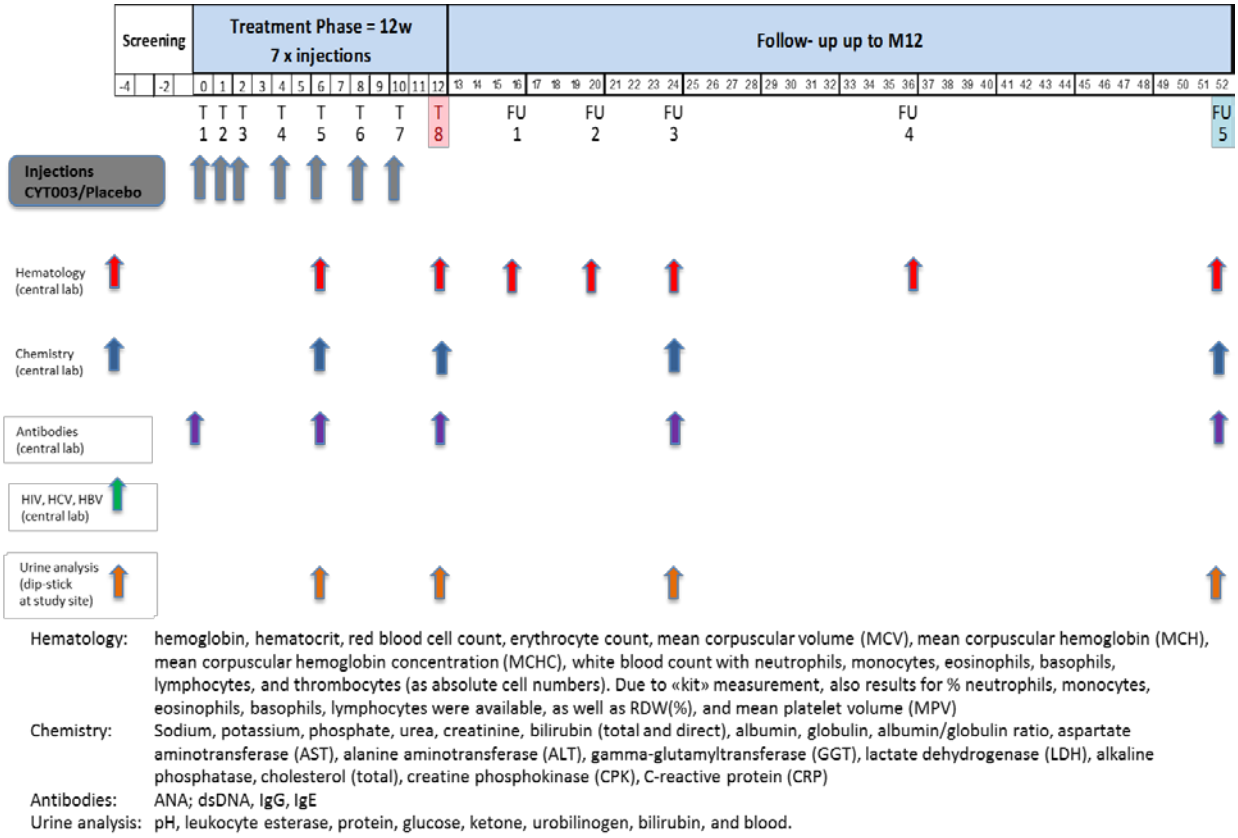


Figure 12.4.2.1 Blood sampling time-points

During the treatment phase, the median as well as mean values of the assessed blood biochemistry, hematology and antibodies (ANA, dsDNA, IgG and IgE) parameters were within normal ranges at all three time points (Screening/baseline, T5 and T8). Changes of the mean and/or median values of assessed blood laboratory parameters over time within patients of the different treatment arms were small and changes appeared similarly in the placebo group.

12.4.2.2 Individual Patient Changes / Individual Important Abnormalities

See also previous Section 12.3.1.3 for AE resulting from laboratory evaluations.

Other abnormal laboratory values – incl. follow-up phase

Not all abnormal laboratory values were documented by the investigators as Adverse Events. For sake of completeness, we list following outliers: ALT >5x ULN (160 U/L), Total Bilirubin >2x ULN (37 mcmol/L), GGT >5x ULN (160 U/L), CPK > 600 U/L. To see the continuity of laboratory values, we also list the values measured in the follow-up phase (see table below).

Table 12.4.2.2-1 Other Laboratory Values – treatment phase + follow-up

Patient	Treatment	Assessed parameter	Scr.	T5	T8	FU3	Comment
138001*	pla	ALT	42	160	49		ref. range: 10-40 U/L
813003	0.3mg	total billi	37.8	15.9	37.8	15.4	ref. range: 1.7 – 18.8 mcmol/L. Chronic cholecystitis in anamnesis
705002	1.0mg	total billi	46.5	45.7	27.9		ref. range: 1.7 – 18.8 mcmol/L
308010	2.0mg	total billi	23.3	25.8	43.4	33.2	ref. range: 1.7 – 18.8 mcmol/L
308008	pla	GGT	280	257	219	256	ref. range 10-49 U/L
120006	0.3mg	GGT	277	777 / 885** / 714**	515	1084	confirmed as NCS by the investigator ref. range 10-49 U/L
403002	1.0mg	GGT	131/247#	288	116	84	ref. range 10-49 U/L
306006	2.0mg	GGT	164	109	81	95	ref. range 5-32 U/L
138001	pla	CPK	603	330	329	492	ref. range: 24-207 U/L
701002	pla	CPK	486	621	242	136	ref. range: 24-169 U/L
613005*	0.3mg	CPK	59	83	5595	240	ref. range: 24-207 U/L
613007*	0.3mg	CPK	265	3236	177	241	ref. range: 24-207 U/L
203001	0.3mg	CPK	473	368	501	684	ref. range: 24-207 U/L
206001	0.3mg	CPK	332	438	339	600	ref. range: 24-207 U/L
105007	1.0mg	CPK	116	106	800	88	ref. range: 24-207 U/L
402005	1.0mg	CPK	653	295	354		ref. range: 24-207 U/L
406011	1.0mg	CPK	637	198	5660	190	ref. range: 24-207 U/L
511001	1.0mg	CPK	662	454	330		ref. range: 24-207 U/L
104005	2.0mg	CPK	142	217	160	251/ 683**	ref. range: 24-207 U/L
105011	2.0mg	CPK	169	135	1782	134	ref. range: 24-207 U/L
105016	2.0mg	CPK	765	330	263	362	ref. range: 24-207 U/L
134001	2.0mg	CPK	772	109	173	136	ref. range: 24-169 U/L
601004	2.0mg	CPK	544	452	215	658	ref. range: 24-207 U/L
813004*	2.0mg	CPK	586	503	849	615	ref. range: 24-207 U/L

[Source: Listing 16.2.11.6]* recorded as AE as well ; **measured at Unscheduled visits; # measured at re-screen, before the first application of study medication.

No patient fulfilling the “Hy’s Law” (ALT/AST > 5xULN and 2x ULN bilirubin) was reported/identified during the study or follow-up-phase.

Neutrophils (absolute) – incl. follow-up phase data

At some sites in Ukraine seven cases of very low absolute neutrophil values (<1.0 x 10^9/L) were reported in 6 patients between December 2013 and January 2014. The summary of all measured values during the study for these patients are in the table below. In all cases the investigators confirmed that the patients did not have any signs of neutropenia. In one case a mild, suspected AE was documented (815008).

The central laboratory reported that “pseudoneutropenia” cases are documented every year during the winter months (Nov-Mar) in countries with very cold winters. Samples came from Ukraine only, very low temperatures were reported between December 2013 and January 2014 and one affected patient was in the placebo group. No more critically low neutrophils were reported after “extreme winter packages” were implemented for the transport of samples from the study sites to the central laboratory. There is no pattern for lower bone marrow function

parameters in any treatment group (source: Table 14.3.2.1.3). Therefore it is suspected that the reported values of critically low neutrophils are rather a pre-analytical error (transport in extreme cold environment) rather than true values of neutropenia.

One additional case of critically low neutrophils was identified during the study. Patient 501001 from Israel, 2.0mg treatment group. The investigator confirmed that this patient is of Yemenite origin and such values are *"normal for her"*. In the medical history it is documented that the patient had "low grade neutropenia" before she entered the study.

For the sake of completeness, the available values from the follow-up phase are listed for these patients in the table below.

Table 12.4.2.2-2 Very low Neutrophils (<1.0x10^9/L) - treatment phase + follow-up phase

Patient	Trt.	Scr.	T5	T8	FU1	FU2	FU3	FU4	Comment
806008	pla	3.4	2.9	3.5	0.3/ 3.2 Unsch	3.6	3.0		
812004	0.3 mg	3.1	2.1	0.2/ 4.8 Unsch	not done*	not done*			*Samples were out of stability
815005	0.3mg	5.8	2.3	0.9 /0.3 Unsch	5.0	4.4			
806001	2.0 mg	3.2	3.4	4.8.	3.4	4.5	0.1/ 3.8 Unsch		
813001	2.0 mg	3.8	n/a	3.9	4.7	4.0	0.6	4.5	
501001	2.0 mg	3.1	2.0	0.8	1.6	1.9	1.6		Patient has known mild neutropenia

Reference range absolute neutrophils: 1.7 – 7.9x 10^9/L. All values presented are values measured in central laboratory.
Unsch: unscheduled visit performed up to 10 days after the low value was measured. [Source: Listing 16.2.8.2]

Overall, the individual abnormal blood laboratory values do not suggest a specific pattern related to the study treatment but are rather concomitant findings or are within the usual population fluctuations.

12.4.2.3 Individual Clinically Significant Abnormalities

If any laboratory value has been considered clinically significant, the investigator was instructed per protocol to document an AE. Therefore, all individual clinically significant abnormalities are discussed in the Section 12.3.

12.4.3 Urinanalysis

Urinalysis (dip-stick test) were performed at screening, at T5 (week 6) and T8 (week 12). Further investigations were planned in the follow-up phase. The urine samples were measured at the study sites using dip-stick for pH, leukocyte esterase, protein, glucose, ketone, urobilinogen, bilirubin and blood. If the results were considered by the investigators as clinically significantly abnormal, an AE should have been documented and the urine sample should have been sent to the central laboratory for further investigations. However, some investigators sent the urine sample to the central laboratory also if the urine sample tests were abnormal – but not clinically significant.

Only one AE was documented during the treatment phase for urinary parameters. Patient 138001 (placebo) experienced an AE "red blood cells in urine". This event was graded as mild, considered by the investigator as suspected to be related to study medication.

12.4.4 Antinuclear Antibodies

See also Listing 16.2.11.6 for source data.

Antinuclear antibodies (ANA), as well as dsDNA were measured at T1 (pre-treatment), and at T5 (week 6) and T8 (week 12). Further investigations were planned at FU3 and FU5. The used method was a "screening LIAISON *ANA* Screen" and "LIAISON dsDNA" chemiluminiscence test from DiaSorin. The LIAISON® ANA Screen assay uses chemiluminescent immunoassay (CLIA) technology for the collective qualitative determination of autoantibodies directed against the following antigens: double-stranded DNA (dsDNA), RNP/Sm (70 kDa), SSA (Ro) (rich in 60 kDa), SS-B (La), Scl-70, Jo-1, centromere (CENP-B) and mitochondria in human serum or plasma, along with detection of sera positive for HEp-2 immunofluorescence antibody test.

The LIAISON® *dsDNA* assay uses chemiluminescent immunoassay (CLIA) technology for the quantitative determination of autoantibodies of IgG class directed against double-stranded DNA (dsDNA) in human serum or plasma samples.

ANA

If a sample was tested ANA positive in the PPD central laboratory, it was sent to Cleveland Laboratory in the USA for confirmatory testing. If the titer at such confirmatory tests was "<1:40" or "negative at 1:40" the sample was considered as ANA negative. If the titer was 1:40 or above, following further tests were performed: ANA pattern and ENA panel (CCF method) for Centromere, Chromatin antibody, Jo-1 antibody, RNP antibody, Ribosomal RNP antibody, SS-A antibody, SS-B antibody, Scleroderma antibody and Smith antibody.

If an ANA titer increased during the study, investigator were asked (actively by the medical monitor) about any clinical signs indicative for autoimmune disease.

ANA titers were negative (Screening LIAISON ANA test) for the majority of patients in the four treatment groups throughout the study. All findings above a threshold titer of 1:40 are listed in the table below. Abnormal ANA values measured in the FU phase are also listed.

Table 12.4.4-1 ANA ≥1:40 – treatment phase + follow-up phase

Patient	Trt. group	T1	T5	T8	FU3	Increase in titer
134002	pla	1:40	1:80	negative	negative	1x
409001	pla	1:40	negative	1:40	negative	no change
110006*	pla	1:320	1:320	1:640	1:320	1x
101012	pla	*not done*	1:320	1:320		no baseline
707003	pla	*not done*	negative	negative	1:40	no baseline
120006	0.3mg	1:40	1:80	negative	*not done**	1x
131002	0.3mg	negative	negative	*not done**	1:40	1x
101008	1.0mg	1:40	*not done**	1:320	1:320	3x
705002	1.0mg	1:80	1:80	1:80		no change
105003	1.0mg	1:80	negative	1:80	1:80	no change
137017	1.0mg	negative	negative	1:160		3x
134001	2.0mg	1:40	1:80	1:80	1:40	1x
121007	2.0mg	1:160	1:160	1:640	*local lab** 1:320	2x

Patient	Trt. group	T1	T5	T8	FU3	Increase in titer
140001*	2.0mg	negative	negative	negative	1:80	2x

[Source: Listing 16.2.11.6]
*sample not measured in the central laboratory due to insufficient quantity. Local laboratory, result 1:320 – measured afterwards. *AE recorded for these patients. See section 12.3.1.

One mild, suspected to be related AE (ANA increased) was documented for patient 110006 in the placebo group at T8. The titer increased from 1:320 at baseline to >1:640 at T8 and further to >1:640 at FU1. The Titer decreased back to baseline values at FU3. The investigator confirmed that the patient did not have any clinical signs of autoimmune disease. For narrative, please see in Appendix 16.2.11.11.

dsDNA

If the values of dsDNA increased above the reference range during the study (<20 IU/mL), investigators were (actively by medical monitor) asked about any clinical signs indicative for autoimmune disease for this patient.

The values for dsDNA were within the reference ranges for the majority of patients in the four treatment groups throughout the study. All findings above the reference range (>20 IU/mL) are listed in the table below. Abnormal dsDNA values measured in the follow-up phase are also listed.

Table 12.4.4-2 dsDNA (>20 mIU/mL) – treatment phase + follow-up phase

Patient	Treat.	T1	T5	T8	FU3	Comment
121003	pla	36 /38*	26	22	30	
501003	pla	26				patient prematurely discontinued, last value measured 30 IU/mL
141002	pla	not done /52*	46	76	74	no baseline value
120006	0.3	50	35	34		
306011	0.3	22	15	15	13	
403002	1 mg	30	21	19	17	
309002	1 mg	26	4	20	18	
403006	1 mg	17	19	30 /23**	14	
408002	2 mg	30 /32*	25	30	31	
203002	2 mg	31	4	13	14	
105011	2 mg	12	17	28	14	

[Source: Listing 16.2.11.6] * Value measured at T3; **value measured 2 weeks after T8;

No case of newly acquired clinically significant autoimmune disease was documented during the treatment phase.

Overall, the individual changes in ANA titer/dsDNA values do not suggest a specific pattern related to the study drug treatment but are rather concomitant findings or are within the usual population fluctuations.

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1 Vital Signs

Systolic and diastolic blood pressure, heart rate and body temperature were measured before and 1 hour after the study medication has been applied at each visit throughout the study. Descriptive statistics was performed to evaluate the vital signs.

Our defined “normal” ranges for vital signs were the following: systolic blood pressure between 80 and 160 mmHg, diastolic blood pressure between 50 and 100 mmHg, pulse rate between 50 – 90 beats/min, and body temperature between 35°C and 38°C. A change from pre- to post-injection of not more than +/- 20% was considered as a “normal” fluctuation for pulse rate and the systolic and diastolic blood pressure, and a change from pre- to post-injection of not more than +/- 1°C was considered as a “normal fluctuation” for the body temperature. See more details in listing 16.2.11.5.

Overall, the individual changes of measured values before and one hour after the study medication was applied do not suggest a specific pattern related to the study drug treatment but are rather concomitant findings or are within the usual population fluctuations.

12.5.2 ECG

See also Listing 16.2.9.3 and Safety Summary Tables 14.3.2.4.1 and 14.3.2.4.2.

ECGs were performed at Baseline/T1 and at visit T8 (week 12). The corrected QT (QTc) intervals measured before the administration of the study drug at baseline and at visit T8 are shown in the table below.

Table 12.5.2-1 ECG Fridericia`s corrected Q-T Interval

	Treatment	N	Mean (SD)	95% CI	Median	Min - Max
Baseline/T1	Placebo	89	400.4 (25.26)	395.0, 405.7	402.2	322 - 459
	0.3mg	91	395.4 (44.36)	386.2, 404.6	400.5	200 - 472
	1.0mg	94	398.0 (40.75)	389.7, 406.4	403.4	227 - 485
	2.0mg	91	397.9 (37.21)	390.2, 405.7	402.7	237 - 456
T8	Placebo	84	400.8 (21.27)	396.2, 405.4	402.4	347 - 445
	0.3mg	85	395.9 (45.14)	386.2, 405.6	398.1	211 - 494
	1.0mg	91	400.2 (35.12)	392.9, 407.5	404.7	210 - 472
	2.0mg	83	398.7 (35.48)	390.9, 406.4	399.3	258 - 530
T8 change from baseline	Placebo	84	0.9 (18.17)	-3.0, 4.8	-2.2	-51 - 95
	0.3mg	85	1.3 (23.71)	-3.9, 6.4	-1.8	-41 - 123
	1.0mg	91	2.5 (26.44)	-3.0, 8.0	1.4	-54 - 157
	2.0mg	83	0.8 (28.81)	-5.5, 7.1	-2.3	-71 - 144

[Source: Table 14.3.2.4.1]

Overall, the individual changes in QT interval do not suggest a specific pattern related to study treatment but are rather concomitant findings or are within the usual population fluctuations.

12.5.3 Physical Examination

See also Listing 16.2.9.2 and Table 14.3.2.3.1.The physical examinations have been performed on SCR/R1-BL/T1 and T8. Due to the premature study termination there was no physical examination at FU5. If there was a new finding or a worsening from screening/baseline visit to visit T8, the investigators were asked to comment on the clinically significance and to document as an AE or to amend the medical history if applicable.

No clinically significant new findings were reported at T8.

12.5.4 Injection Site Reactions (documented in patient e-diaries)

The patients were asked to record the presence and severity of injection site reactions at the injection site (pain, itching, swelling/induration, and erythema/reddening,) in a patient e-diary for a period of 4 days following each injection visit (7 diaries in total). The recording of local reactions has been adapted from recommendations for grading local reactions in preventive vaccine trials in healthy volunteers as per US Food and Drug Administration (FDA) 2007 guidance (FDA, 2007). The severity grading of pain and induration/swelling include a functional element:

Grade	0	1	2	3
Pain	none	does not interfere with daily activity	interferes with daily activity	prevents daily activity
Itching	none	mild	moderate	severe
Induration/Swelling	none	does not interfere with daily activity	interferes with daily activity	prevents daily activity

In addition, swelling and erythema/reddening was recorded as the greatest single diameter self-measured by the patient.

Patients also recorded intake of medications for local reactions in the patient diaries. Grading of reaction diameter (size) was done according to the Protocol.

Grade	**0**	**1**	**2**	**3**
Erythema/Reddening Diameter	0 – 2.5 cm	>2.5 – 5 cm	>5 – 10 cm	>10 cm
Induration/Swelling Diameter	0 – 2.5 cm	>2.5 – 5 cm	>5 – 10 cm	>10 cm

It was planned to evaluate the patients' e-diaries only after completed follow-up phase and not after the treatment phase directly. The data are therefore not statistically evaluated and not presented.

12.5.5 Injection Site Reactions (documented as Adverse Events)

The investigator checked the patient's e-diary entries and discussed the observations with the patient at the next visit. He / she examined the injection site and recorded findings for the local lymph nodes (enlargement and/or pain). They were asked to record injection site reactions (ISRs) as AEs when one of the following criteria was true:

- ISR reached grade 3 (prevented daily activity – severe) or grade 4 (resulted in emergency room visit or hospitalization)
- ISR did not disappeared by the time of the next visit
- ISR lead to medical intervention

Out of the 365 enrolled patients, 106 (29%) experienced at least 1 ISR documented as AE. (Table 12.5.5-1). The investigators were asked to avoid the term "Injection site reactions" and rather list all symptoms (reddening, swelling, pain, pruritus…) as separate AEs. As expected, the percentage of patients with an ISR was very low in the placebo group. Figure 12.5.5-1 shows the maximal severity of the ISRs documented as AEs.

Table 12.5.5-1 TEAEs: Injection Site Reactions

		Placebo (N = 89)		0.3mg (N = 91)		1.0mg (N = 94)		2.0mg (N = 91)		Total (N = 365)	
		n % pts	n evts	n % pts	n evts	n % pts	n evts	n % pts	# evts	n % pts	n evts
any ISR		3 (3%)	3	27 (28%)	142	36 (40%)	177	40 (44%)	147	106 (29%)	473
IS erythema		0 (0%)	0	21 (23%)	48	25 (27%)	57	28 (31%)	45	74 (20%)	150
	mild		0		21		26		30		78
	moderate		0		15		24		14		54
	severe		0		12		7		1		18
IS swelling		0 (0%)	0	20 (22%)	42	27 (29%)	57	23 (25%)	47	70 (19%)	146
	mild		0		22		30		39		91
	moderate		0		10		24		7		41
	severe		0		10		3		1		14

		Placebo (N = 89)		0.3mg (N = 91)		1.0mg (N = 94)		2.0mg (N = 91)		Total (N = 365)	
		n % pts	n evts	n % pts	n evts	n % pts	n evts	n % pts	# evts	n % pts	n evts
IS pruritus		2 (2%)	2	10 (12%)	23	19 (20%)	33	11 (12%)	17	42 (12%)	75
	mild		1		15		27		12		55
	moderate		0		2		4		4		10
	severe		1		6		2		1		10
IS pain		1 (1%)	1	10 (11%)	26	13 (14%)	25	16 (18%)	28	40 (11%)	80
	mild		0		17		20		20		57
	moderate		1		7		5		8		21
	severe		0		2		0		0		2
IS induration		0 (0%)	0	3 (3%)	3	2 (2%)	2	4 (4%)	6	9 (2.5%)	11
	mild		0		3		1		6		10
	moderate		0		0		1		0		1
	severe		0		0		0		0		0
IS “reaction”		0 (0%)	0	0 (0%)	0	3 (3%)	3	1 (1%)	4	4 (1.1%)	11
	mild		0		0		1		4		5
	moderate		0		0		2		0		2
	severe		0		0		0		0		0

[Source: Listing 16.2.11.1] ISR= Injection site reaction reported as AE (not from patient e-diary data). Patient (408009) experienced an injection site extravasation, not suspected to be related to the study medication. This event is not counted in this table.

The Figure 12.5.5-1 below shows percentages of patients experiencing at least one ISR. If a patient reported multiple occurrences of the same ISR, the patient is presented only once with the intensity representing the most extreme severity for the same ISR.

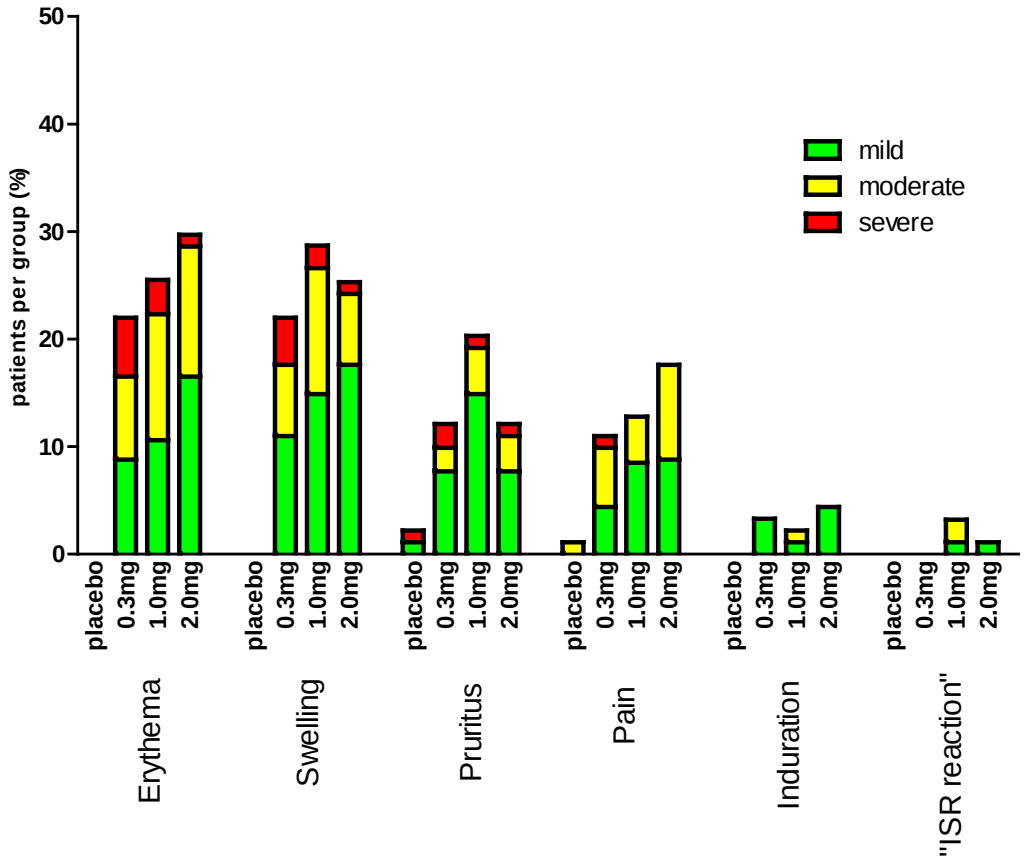


Figure 12.5.5-1 Percent of Patients with Injection Site Reaction: Severity

[Source: Summary Safety Table 14.3.1.6]

No dose related pattern can be found for pruritus, induration and lymphadenopathy reported as adverse events. More patients have erythema and pain reported as adverse events in the 2.0mg group, followed by 1.0mg and 0.3mg.

One to 7% of the patients in the active treatment groups reported a flare-up ISR at the preceding injection site. The investigators were informed about this phenomenon and were asked to document such an AE as “previous injection site” or “flare-up”. See Figure 12.5.5-2 for details.

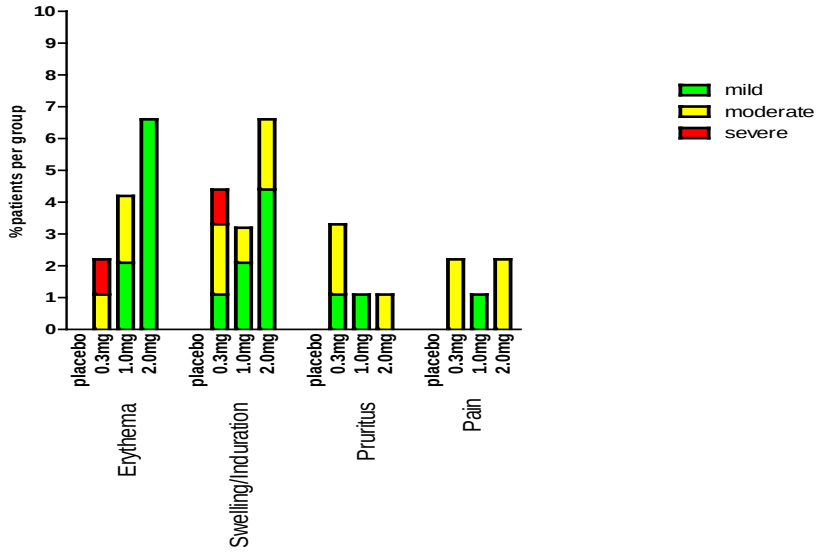


Figure 12.5.5-2 Flare-up of Injection Site Reaction: Severity

[Source: Listing 16.2.11.1]

Few patients reported lymphadenopathy ("enlarged/swollen lymph nodes") as AE. See Table 12.5.5-2

Table 12.5.5-2 TEAEs: Lymphadenopathy

	Placebo (N = 89)		0.3mg (N = 91)		1.0mg (N = 94)		2.0mg (N = 91)		Total (N = 365)	
	n % pts	n evts	n % pts	n evts	n % pts	# evts	n % pts	nevts	n % pts	n evts
Lymphadenopathy	0	0	1 (1%)	1	3 (3%)	3	1 (1%)	1	5 (1%)	5
mild		0		1		0		1		2
moderate		0		0		3		0		3
severe		0		0		0		0		0

[Source: Listing 16.2.11.1]

12.5.6 Concomitant Medication

All patients were treated by medium or high doses of inhaled glucocorticosteroids (ICS) >250 to ≤1000 µg/day fluticasone or equivalent; in combination with or without LABA, for more details about the population composition see table below. The use of stable doses of other controller therapies according to GINA Steps 3 and 4 (e.g. leukotriene modifiers, sustained-release theophylline) was allowed. All controller medication needed to be stable at least 4 weeks prior to the signing of informed consent until the end of the treatment phase. Following the 12-week treatment phase of the study, each patient was allowed to "step-up" or "step-down" the asthma therapy as indicated by their clinical status and according to the local current medical practice. All patients had access to short acting bronchodilators (SABA) as needed throughout the study.

Table 12.5.6-1 Use of SABA/LABA at Baseline

	ICS medium	ICS high	Total
with LABA n (%)	117 (32%)	205 (56%)	322
without LABA n (%)	4 (1%)	39 (11%)	43
Total	**121**	**244**	**365 (100%)**

[Source: Listing 16.2.4.3]

Some patients had a change in controller medication during the treatment phase. Controller changes such as the intake of systemic glucocorticoids for three days or more lead per protocol to an invalidation of all following efficacy parameters. The intake of a different dose of ICS for only a short period of time where the patient returned back to the original dose was not considered as a "step-up or down" of controller medication.

All other recorded concomitant medications were not considered of having an impact on the overall outcome of the study.

12.6 Safety Conclusions

- This clinical study report presents the safety data during the treatment phase (up to 30 days after the last injection). As the study was prematurely terminated, the data collected during the follow-up phase of the study are discussed in a separate document (Addendum to the Clinical Study Report).
- In summary, 58% of all enrolled patients experienced at least one TEAE. The majority of these TEAEs were injection site reactions (63%). Most of the AEs were mild (64%) in intensity, followed by moderate (29%) and severe (7%).
- Except for the injection site reactions (incl. lymphadenopathy), and body temperature increased /pyrexia, which is an expected TEAE for CYT003 there was no pattern that would indicate any higher rate of specific adverse events in the active treatment groups compared to that of placebo.
- There were no suspected unexpected serious adverse drug reactions during the trial (SUSAR).
- There was 1 SAE reported during the treatment phase of the study. (Six SAEs in 5 patients were reported during the follow-up phase.)
- Of the 15 patients that discontinued the study due to an AE, the majority discontinued the study due to injection site reactions (0% in placebo group, 1% in 0.3mg group, 6% in 1.0mg and 8% in 2.0mg group).
- Local injection site reactions as recorded in the patient e-diaries have not been analyzed.
- Due to the premature termination of the study it was not meaningful to perform any analysis of the asthma exacerbations during this period.
- Systemic AEs (headache, pyrexia, body temperature increased, fatigue, influenza-like illness) were no different to that reported in previous studies.
- Changes blood laboratory examinations (hematology, chemistry, ANA titer/dsDNA) values as well as evaluation of vital signs, ECGs, and physical examinations did not show any safety concern and were no different to that reported in previous studies.

13. Discussion and Overall Conclusions

Efficacy

- CYT003 applied with the described regimens as add-on therapy to patients with insufficiently controlled moderate to severe allergic asthma did not show clinical efficacy in any assessed endpoint compared to that of placebo.
- Due to lack of efficacy the clinical trial was prematurely terminated after the analysis of the 12-week-results.
- A strong and persistent placebo effect was observed for the change from baseline in ACQ scores at all time points.

Safety

- CYT003 was generally well tolerated. No suspected serious adverse events were reported. The most prominent adverse events were injection site reactions.

Overall Conclusion

Overall, the TLR9 agonist CYT003 revealed a good safety profile but did not show efficacy compared with placebo in moderate to severe allergic asthma patients.

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