CLINICAL STUDY REPORT

Addendum 17.1 Safety Summary Follow-up

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 LPLV on Day of Premature Screening: 14 Oct 2012 Study Termination: 14 Apr 2014 1st injection: 28 May 2013
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
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GCP Statement:	This study was performed in compliance with the ICH-GCP
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3 Adverse Events

A post-treatment AE is defined as an AE that occurred 30 days after the last study drug injection or an AE that increased in intensity/frequency after 30 days after the last study drug injection. It has to be emphasized that due to the premature study termination the AE's reported during the follow-up phase were not source verified by the CRAs at study sites.

All patients were in the follow-up phase at the time-point of the study termination, **however due to different study start dates for individual subjects, patients were in different study time-points. AEs in the post-treatment phase were therefore not statistically evaluated and the following information has only limited validity.**

According to the Protocol, patients should have performed Visit 8 (end of treatment phase) in the week 12 (±7 days= day81 to 87) and the FU5 visit (last visit in the study) in the week 52 (±7 days = day 358 to 372). No patient finished the study follow up period according to the protocol due to premature study termination. In the table below (Table 3-1) we present number of days patients participated in the study until the premature study termination.

Table 3-1 Number of days patients participated in the study

	placebo (N=89)	**0.3mg (N=91)**	**1.0mg (N=94)**	**2.0mg**
mean (SD)	194 (43)	189 (52)	191(46)	184 (52)
median	169	169	169	168
min-max	43-281	6-283	85-279	21-273

[Source: Listing 16.2.11]

3.1 Brief summary of Adverse Events

None of the adverse events captured in the follow-up phase were considered by the investigator as suspected to be related to the study medication.

It was planned to evaluate the safety aspects of the study in full after the last patient performs the last visit FU5 (12 months study visit). Due to the premature termination of the study, many adverse event still had status "not recovered/not resolved" as the end date is missing.

3.2 Analysis of Adverse Events

At each visit the participants were asked about new events. Due to the premature study termination, the post-treatment AEs are incomplete. AEs were classified according to MedDRA Version 12.1 or higher. See also Listing 16.2.11.1 - for all AE reported in the follow-up phase (prematurely terminated).

Table 3.2-1 Post-treatment AEs: incidence and severity

	Placebo (N = 89)		0.3mg (N = 91)		1.0mg (N = 94)		2.0mg (N = 91)		Total (N = 365)	
	# pts % pts	# evts	# pts % pts	# evts	# pts % pts	# evts	# pts % pts	# evts	# pts % pts	# evts
all post-treatment AEs	22 (22%)	41	21 (23%)	36	27 (29%)	43	22 (24%)	32	92 (25%)	152
mild		15		21		18		21		75
moderate		22		15		25		9		71
severe		4		0		0		2		6
suspected		0		0		0		0		0
not suspected		41		36		43		32		152

[Source: Listing 16.2.11.1]

Severe Post-treatment AE

There were 5 severe post-treatment AEs in 3 patients. Four of those severe AEs also fulfilled the criteria for serious adverse event (SAE). None of the severe AEs were suspected to be related to the study treatment – see more information in sections 4.1.2 and 4.1.4.

Table 3.2-2 Post-treatment AEs: severe AEs

Patient	Treatment	Preferred term	Occurrence after	Outcome
105008	placebo	Urinary tract infection	FU1	recovering/resolving
141002*	placebo	Retro-orbital headache	FU2	recovered/resolved
		Internal carotid artery aneurysm 9.7 x 11 mm	FU2	recovered/resolved
		Tension headache	FU2	recovered/resolved
709003*	2.0mg	Severe asthma exac.	FU1	recovering/resolving

[Source: Listing 16.2.11.1]; FU: Follow-up visit; *fulfilled the seriousness criteria (SAE)

3.3 Listing of Adverse Events by Patient

Please refer to Listing 16.2.11.1

4 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths were reported in the follow-up phase.

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

4.1.1 Deaths in follow-up phase

There were no deaths reported in follow-up phase.

4.1.2 Other Serious Adverse Events in Follow-up Phase

There were 5 patients with 6 serious adverse events (SAEs) reported during the follow-up phase. One serious adverse event was downgraded to a non-serious AE (121003).

All of the reported SAE were considered not to be of suspected to be related to the study drug by the investigator as well as by the sponsor.

Table 4.1.2-1 Post-treatment AEs: SAEs

Patient	Treatment	SAE *(reason for SAE classification)*	Severity	Causality	Occurrence after	Outcome
121003*	placebo	Osteo-arthritis left knee *(hospitalization)*	moderate	not suspected	FU	recovered/resolved
141002	placebo	Internal carotid artery aneurysm 9.7x11mm *(hospitalization)*	severe	not suspected	FU2	recovered/resolved
		Tension Headache *(hospitalization)*	severe	not suspected	FU2	recovered/resolved
408009	1.0mg	Post-laminectomy Syndrome *(hospitalization)*	moderate	not suspected	FU2	recovering/resolving
406010	2.0mg	Benign Liver Tumor *(hospitalization)*	moderate	not suspected	FU1	recovered/resolved
709003	2.0mg	Severe Asthma Exacerbation *(hospitalization)*	severe	not suspected	FU1	recovered/resolved

[Source: Listing 16.2.11.1] *Patient 121003 discontinued the study treatment for other reasons before the adverse start date. SAE Osteo-arthritis left knee was downgraded to non-serious AE.

4.1.3 Other Significant Adverse Events

Infections and Infestations

Table 4.1.3-1 Post treatment AEs: 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)	
	# pts % pts	# evts	# pts % pts	# evts	# pts % pts	# evts	# pts % pts	# evts	# pts % pts	# evts
Any infection	16 (18%)	20	16 (16%)	20	13 (14%)	15	14 (15%)	17	59 (16%)	72

		Placebo (N = 89)		0.3mg (N = 91)		1.0mg (N = 94)		2.0mg (N = 91)		Total (N = 365)	
		# pts % pts	# evts	# pts % pts	# evts	# pts % pts	# evts	# pts % pts	# evts	# pts % pts	# evts
respiratory tract infection		15	18	15	17	11	11	13	15	51	61
	mild		10		11		3		10		34
	moderate		7		5		8		4		24
	severe		0		0		0		0		0
non-respiratory tract infection		2	2	3	3	2	2	2	2	9	9
	mild		0		0		2		2		4
	moderate		1		3		0		0		4
	severe		1		0		0		0		1

[Source: Listing 16.2.11.1]
Included in respiratory tract infections are: nasopharyngitis, respiratory tract infection viral, tracheobronchitis, bronchitis, laryngitis, pneumonia, pharyngitis, sinusitis, upper respiratory tract infection, acute sinusitis, tonsillitis, influenza, rhinitis, viral upper respiratory tract infection, and bronchitis bacterial. Included in non-respiratory tract infections are: herpes zoster, oral candidiasis, urinary tract infection, vulvovaginal mycotic infection, and cystitis. Two patients (105009 and 105018) have a reported AE "viral syndrome" documented under the SOC "infections and infestations". These AEs are not enumerated in the table above.

Asthma exacerbation

It has to be emphasized that asthma exacerbation experienced during the follow-up phase were due to the premature termination not source verified at the study sties. It can also not be verified if the asthma exacerbation in the follow-up phase fulfilled the criteria according to the Protocol (e.g. at least 3 days of systemic corticosteroids). See in the table below a list of the all reported asthma exacerbations in the follow-up phase.

Table 4.1.3-2 Post treatment asthma exacerbations

Patient	Treatment	Severity	SAE	Occurrence	days after 1.injection	Outcome
119003	placebo	moderate	no	in follow-up	109	recovered/resolved
119003	placebo	moderate	no	in follow-up	147	recovered/resolved
134002	placebo	moderate	no	in follow-up	140	recovered/resolved
134002	placebo	moderate	no	in follow-up	154	recovered/resolved
408001	placebo	moderate	no	in follow-up	85	recovered/resolved
408001	placebo	moderate	no	in follow-up	194	recovered/resolved
807005	placebo	moderate	no	in follow-up	170	recovered/resolved
105015	0.3mg	moderate	no	in follow-up	134	recovered/resolved
115004	0.3mg	moderate	no	in follow-up	106	recovered/resolved
137011	0.3mg	moderate	no	in follow-up	132	recovered/resolved
308004	0.3mg	moderate	no	in follow-up	122	recovered/resolved
308004	0.3mg	moderate	no	in follow-up	246	recovered/resolved
506001	0.3mg	moderate	no	in follow-up	161	recovered/resolved
613001	0.3mg	moderate	no	in follow-up	110	recovered/resolved
613001	0.3mg	moderate	no	in follow-up	124	recovered/resolved
613001	0.3mg	moderate	no	in follow-up	167	recovered/resolved
815003	0.3mg	moderate	no	in follow-up	119	recovered/resolved
206004	1.0mg	moderate	no	in follow-up	169	recovered/resolved

Patient	Treatment	Severity	SAE	Occurrence	days after 1.injection	Outcome
408008	1.0mg	moderate	no	7th inj.	92	recovered/resolved
503004	1.0mg	moderate	no	7th inj.	94	recovered/resolved
511001	1.0mg	moderate	no	in follow-up	112	recovered/resolved
813006	1.0mg	moderate	no	in follow-up	141	recovered/resolved
121004	2.0mg	moderate	no	in follow-up	113	recovered/resolved
121004	2.0mg	moderate	no	in follow-up	140	recovered/resolved
203002	2.0mg	moderate	no	in follow-up	110	recovered/resolved
409002	2.0mg	moderate	no	in follow-up	148	recovered/resolved

[Source: Listing 16.2.11.4]; * List may be incomplete due to premature study termination

AE resulting from abnormal laboratory evaluations

In the follow-up phase the investigators reported clinically significant abnormal laboratory parameters for 3 patients, documented in 3 Adverse Events.

Table 4.1.3-3 Post-treatment AEs: abnormal laboratory values

Patient	Treatm.	Assessed parameter	Value	Severity	Measured at	Comment
206004	1.0mg	CRP	78.1 nmol/L	moderate	FU3	ref.range: <47.6 nmol/L
140001	2.0mg	ANA increased	1:40	mild	FU3	Values during the treatment phase <1:40
124008	0.3mg	Total bilirubin	21.9 mcmol/L	mild	FU3	ref. range: 1.7 – 18.8 mcmol/L

[Source: Listing 16.2.11.6]; CRP: C-reactive protein; AST: aspartate aminotransferase; ANA: antinuclear antibody

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

4.1.4.1 Narratives of SAEs in Follow-up Phase

Patient 121003 (placebo) Osteo-arthritis of left knee - <u>downgraded to non-serious AE</u>

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 <u>downgraded from a serious AE to a non-serious AE.</u> 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 141002 (placebo): Internal carotid artery aneurysm + (prophylactic) tension headache

A 55-year-old female was enrolled into the study on 12-Jun-2013 (signed informed consent). The patient was injected for the first time with placebo on 16-Jul-2013 and received the 7th injection on 24-Sep-2013. On 09-Dec-2013 the patient experienced right facial numbness and vomiting. Patient was hospitalized on 10-Dec-2013, when and additional adverse events facial tingling and retro orbital headache started. On the same day an internal carotid artery aneurysm was diagnosed. Surgical procedures endovascular stent coil embolization of right common carotid artery and endovascular stent coil embolization of right internal carotid artery were performed on 12-Dec-2013 to treat the event. This event was considered as not suspected to be related with the study treatment and was recovered/resolved. Patient still has left ophthalmic segment aneurysm (2mm) and left superior hypophyseal artery aneurysm (4mm). Query was sent to the investigator about the future planned treatments for these 2 small aneurysm. Due to premature study termination, the query was not answered.
On 30-Dec-2013 the patient experienced a serious adverse event of tension headache and was hospitalized between 13-Jan-2014 and 15-Jan-2014 due to the history of the aneurysm and previous history of the stent coiling procedure. The event was considered to be not suspected to be related with the study treatment and was recovered/resolved. Later on, the investigator changed the AE verbatim to “prophylactic tension headache”. Due to premature study termination, the query about “prophylactic tension headache” and the reason for the AE verbatim change has not been clarified.

Patient 408009 (1.0mg): Post laminectomy syndrome

A 56-year-old female was enrolled to the clinical study on 26-Aug-2013 (signed informed consent). The patient was injected for the first time with 1.0mg CYT003 on 23-Sep-2013 and received the 7th injection on 01-Dec-2013. On 11-Feb-2014, the patient experienced a ‘post laminectomy syndrome’ due to an intervertebral discus abnormality (documented in medical history). The patient was hospitalized between 11-Feb-2014 and 21-Feb-2014 to receive physiotherapy. The Investigator confirmed that the subject has not undergone any recent surgical procedures and the origin of the event was caused by the operations due to spinal disc herniation in 2000 and 2004. The event was considered as not suspected to be related with the study treatment and the outcome was recovering/resolving (status 28-Apr-2014).

Patient 709003 (2.0mg): Severe asthma exacerbation

A 53-year-old female was enrolled to the clinical study on 24-Sep-2013 (signed informed consent). The patient was injected for the first time with 2.0mg CYT003 on 22-Oct-2013 and received the 7th injection on 30-Dec-2013. On 19-Jan-2014, the patient showed symptoms of cough and increasing dyspnea with the appearance of purulent sputum. The patient was hospitalized for event severe asthma exacerbation between 04-Feb-2014 and 18-Feb-2014. This event was considered as not suspected to be related with the study treatment and was recovered/resolved.

Patient 406010 (2.0mg): Benign liver tumor

A 61-year-old female was enrolled to the clinical study on 04-Sep-2013 (signed informed consent). The patient was injected the first time with 2.0mg CYT003 on 02-Oct-2013 and received the 7th injection on 11-Dec-2013. On 28-Jan-2014 the patient complained about

abdominal pain on the right site. On 13-Feb-2014, the patient was diagnosed with a SAE of 'Benign Liver Tumor'. Computed Tomography scan revealed liver adenoma with 4cm cyst in the liver. The patient was hospitalized between 06-Mar-2014 and 20-Mar-2014, underwent surgery on 10-Mar-2014. Histology tests showed no malignancy, but no other details are available for this histology finding. The event was considered as not suspected to be related with study medication and recovered/resolved.

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

5 Clinical Laboratory Evaluation

For details of blood sampling time-points during the study, please, see Clinical Study Report for the treatment phase. Data from FU phase may have not been source verified and may be incomplete.

No statistical evaluation of the laboratory data in the FU phase was performed.

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

See Listing 16.2.11.6 and 16.2.11.7

5.1.1 Individual Patient Changes / Individual Important Abnormalities in Follow-up Phase

Other important abnormal laboratory values

Please, see Clinical Study Report for the treatment phase. The FU data are presented together with the treatment phase data.

Neutrophils (absolute)

Please, see Clinical Study Report for the treatment phase. The FU data are presented together with the treatment phase data.

Platelets

Platelets: Two cases of very low platelets (<75 x10^9/L) were reported in follow-up phase. Values are displayed in the table below. In both cases the investigators confirmed that the patients did not have any sings of low platelets. For patient 503004 the investigator considered the value as "laboratory error". For patient 402001 the investigator considered the value as "possible laboratory error".

Table 5.1.1-1 Platelets

Patient	Treatment	Value Screening	T5	T8	FU1	FU2	FU3	Unsch.	Comment
402001	1 mg	193	175	185	183	119	73	158	Unscheduled 1 month after FU3
503004	1 mg	203	235	208	47	220	231		

[Source: Listing 16.2.11.6]; Ref. range platelets: 125-375 x 10^9/L. Unsch: unscheduled visit

5.1.2 Urinalysis

See 16.2.11.7.

No patient had documented Adverse Event (clinically significant abnormal urine laboratory value) during the follow-up phase.

5.1.3 Antinuclear Antibodies

Please, see Clinical Study Report for the treatment phase. The FU data are presented together with the treatment phase data.

One mild, not suspected to be related AE (ANA increased) was documented for patient 140001 in 2.0mg treatment group. Titer rose from <1:40 at baseline and during the study to 1:40 (borderline) after FU3. Further test performed 21 days after FU3 visit was again negative (<1:40). The investigator confirmed that patient did not have any clinical signs of autoimmune disease.

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

6.1 Vital Sings

Vital signs were measured at each FU visit. As the study has been prematurely terminated, data were mostly not captured.

6.2 ECG

ECG should have been performed at final visit FU5 (or at early termination visit). As the study has been prematurely terminated, data were mostly not captured.

6.3 Physical Examination

Physical examination should have been performed at final visit FU5 (or at early termination visit). As the study has been prematurely terminated, data were mostly not captured.

6.4 Concomitant Medication

All controller medication needed to be stable at least 4 weeks prior to the signing of informed consent till 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 local current medical practice. All patients had access to short acting bronchodilators (SABA) as needed throughout the study. No evaluation of concomitant medication in the follow-up phase was performed.

7 Safety Conclusions

There were 6 SAEs occurring in 5 patients in the follow-up phase. All were considered as not suspected to the study medication.

Due to incomplete data the safety evaluation in the FU phase has limited validity.