2 SYNOPSIS

Name of sponsor/company:

Athera Biotechnologies AB
c/o Business Center, level 4, Sankt Eriksgatan 117
SE-113 43 Stockholm, Sweden

Name of test product:

3G10

Name of active ingredient:

3G10

Study title:

Double-blind, randomised, placebo-controlled, multicentre, Phase IIa study to investigate the effect of phosphorylcholine human monoclonal antibody (PC-mAb) 3G10 on arterial inflammation, together with safety and tolerability, in subjects with elevated lipoprotein a (Lp [a])

Coordinating principal investigator:

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Department of Vascular Medicine, AMC, Amsterdam, the Netherlands

Study centres:

- Site 1: Department of Vascular Medicine, AMC, Amsterdam, the Netherlands
- Site 2: CTC Clinical Trial Consultants AB, Uppsala, Sweden

Publication(s) based on the study (reference):

Not applicable

Studied period:	**Phase of development:**
• First subject screened: 2017-09-22 • Last subject's last visit: 2018-03-19	Phase IIa

Objectives:

Primary objective

To assess the effects of four 250 mg 3G10 once monthly intravenous injections on monocyte function *ex vivo*.

Secondary objective(s)

- To assess functional effects of 3G10 on arterial inflammation *in vivo*
- To assess 3G10 effects on arterial stiffness
- To assess the safety and tolerability of 3G10

Exploratory objectives

- To assess the effects of 3G10 on heart function and limb flow reserve (LFR) in a subgroup of the study population
- To study the pharmacodynamics of 3G10 by scavenger receptor and adhesion molecule expression on circulating monocytes and other circulating biomarkers
- To study the pharmacokinetics of 3G10
- To further assess 3G10 effects on arterial stiffness over time
- To further assess functional effects of 3G10 on arterial inflammation *in vivo*
- To study the change in plasma protein patterns

Study design:

This was a Phase IIa, prospective, double-blind, randomised, placebo-controlled multicentre study investigating the effects of treatment with phosphorylcholine human monoclonal antibody 3G10 (PC-mAb 3G10, referred to as 3G10) in four monthly intravenous injections/infusions.

The study population consisted of male and female subjects, age above 50 years, with elevated Lp(a) (above 50 mg/dL). A total of 40 subjects were planned to be enrolled in the study, 20 subjects were planned to receive 250 mg 3G10 and 20 subjects to receive placebo.

Potential study subjects were identified by advertising in local media and by review of pre-existing databases at the study sites.

Subjects were planned to receive treatment with 3G10/placebo for four times and a total of 12 visits were planned to be performed by each subject.

First subject was screened (Visit 1, Lp [a] screening) on 2017-09-22 and first subject received treatment with 3G10/placebo on 2017-10-25.

On 2017-11-23, a subject reported a suspected anaphylactic reaction after 7 minutes of infusion of dose 2. The event was reported as a suspected unexpected serious adverse reaction (SUSAR) as the subject had been administered with active investigational medicinal product (IMP) 3G10 (code broken by investigator). The subject was withdrawn from the study and a voluntary temporary halt in dosing took place between 2017-11-23 and 2017-11- 27. After recommendation from the internal safety review committee (iSRC, including principal investigators) and subsequent decision from the Sponsor, as well as phone and mail contacts with the assigned clinical assessor at the Swedish competent authority (CA), further exposure in the study was continued on 2017-11-28 for all remaining enrolled subjects. At this time point, 4 subjects had received dose 1 and 1 subject had received dose 1 and dose 2.

All enrolled and screened subjects received information about the suspected anaphylactic reaction before deciding to continue with the study treatment. One subject in screening decided to withdraw consent for further participation. After the restart of the study, 4 additional subjects were randomised to treatment and received dose 1, 1 subject received dose 2, 3 subjects received dose 2 and dose 3 and 1 subject received dose 3. All doses were given without any reported deviations during administration.

On 2018-01-10, another subject reported a suspected anaphylactic reaction after 6 minutes of infusion of dose 3. This event was also reported as SUSAR as the subject had been administered active IMP 3G10 (code broken by investigator). After this, the Sponsor decided, after consulting the iSRC, to put the study on temporary halt (notification submitted in the Netherlands 2018-01-17 and in Sweden 2018-01-23). This was to ensure the safety and wellbeing of the study participants and no study participants were exposed to the study drug after 2018-01-10. Up to this date, a total of 10 subjects had been randomised and received treatment with 3G10/placebo, whereof 5 subjects had received one dose only, 1 subject had received two doses and 4 subjects had received three doses.

An extensive cause investigation was initiated. Since it was considered unlikely to restart the study within the treatment windows, a decision was taken by the iSRC to handle all subjects as early withdrawals e.g. they were invited to attend visits 11 and 12 (End of Trial safety visit). The last study visit (Visit 12) was attended on 2018-03-19.

On 2018-07-03, the study was formally terminated and the declaration of the end of trial form was submitted to the CA in Sweden and on 2018-07-04 to the CA in the Netherlands.

A total of 10 subjects were randomised and received treatment with 3G10/placebo, whereof 5 subjects received one dose, 1 subject received two doses and 4 subjects received three doses.

Due to the early termination of the study, it was decided by the Sponsor that the formal statistical analysis planned in the clinical study protocol (CSP) was not to be performed and an abbreviated clinical study report (CSR) should be created. This report therefore contains only descriptive presentation of study data.

Number of subjects (planned and analysed):

	Total	3G10	Placebo
No. planned:	40	20	20
No. randomised and treated:	10	6	4
Males/females:	5/5	3/3	2/2
Mean age (range) years:	65.3 (50 – 74)	66.7 (58 – 74)	63.3 (50 – 70)
No. analysed for efficacy:	N/A	N/A	N/A
No. analysed for safety:	10	6	4
No. completed:	0	0	0

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Provision of a signed written informed consent
2. Lp(a) above 50 mg/dL at screening
3. Male or female, ≥ 50 years of age at screening
4. Weight of at least 63 kg and maximum 125 kg at screening (dose = 2-4 mg/kg body weight)

Test product, dose and mode of administration, batch number:

PC-mAb 3G10 (referred to as 3G10), 250 mg, intravenous injections/infusions.
Batch numbers: 8047563 (Apotek Produktion & Laboratorier [APL], expiry date: 2018-03-31), 8047627 (APL, expiry date: 2018-03-31)

Reference product, dose and mode of administration, batch number:

Placebo: Sodium chloride, 0.9%, intravenous injections/infusions.
Batch numbers: 13LGF19 (Fresenius Kabi, expiry date:2020-06) and 8047627 (Baxter Viaflo, expiry date:2018-03)

Duration of treatment:

Monthly treatment for 3 months (4 administrations)

Planned assessments:

Primary endpoint(s)

- Change in trans-endothelial migration (TEM) in monocytes isolated from treated subjects from baseline to visit 11

Secondary endpoint(s)

- Change in tissue to background ratio (TBR_{max}) in common carotid arteries by fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) from baseline to Visit 11
- Change in pulse wave velocity (PWV) (m/sec) assessed by Sphygmocor Xcel from baseline to Visit 11
- Safety and tolerability: Adverse events (AEs)/serious adverse events (SAEs), vital signs, physical examination, electrocardiogram (ECG) and laboratory assessments including haematology, clinical chemistry and immunogenicity

Exploratory endpoints

- Change from baseline in cardiac variables and LFR variables, as assessed by magnetic resonance imaging (MRI), in a subgroup of the study population
- Immunoglobulin M (IgM) anti-PC level, Lp(a), other circulating biomarkers, monocyte adhesion markers and scavenger receptors assessed by fluorescence-activated cell sorting (FACS) over time
- Pharmacokinetics: 3G10 serum levels
- Arterial stiffness variables assessed by Sphygmocor Xcel
- TBR_{mean} (carotid and aorta), TBR_{gluc} (carotid and aorta) and TBR_{max} (aorta) assessed by 18F-FDG PET/CT
- Change in protein pattern from baseline to Visit 11 as assessed by proteomics measurements

Statistical methods:
Due to the early termination of the study, no formal statistical analyses were performed.
All data are presented descriptively in subject data listings.

SUMMARY OF RESULTS

Due to two subjects experiencing Suspected Unexpected Serious Adverse Reactions (SUSARs) at the second and third dose, respectively, the study was prematurely terminated. By the time of termination, a total of 10 subjects had been randomized to dosing with either ATH3G10 (6 subjects) or placebo (4 subjects). One (1) subject received three complete active doses and three (3) subjects received one complete dose only. Two (2) subjects did not receive complete active doses following a serious adverse event (SAE) during the second and third dose, respectively, and treatment was discontinued. None of the randomized subjects completed the study due to the temporary hold and early termination. Three (3) complete doses was the maximum number of doses any single patient received in the study.

In total, 22 AEs were reported by eight (8) subjects in the study. Two subjects both in the placebo group did not report any AE. There were no deaths in the study.

Non-fatal SAEs occurred in two (2) subjects and both these events of suspected anaphylactic reaction were reported as SUSARs. The two subjects were withdrawn from the study due to the SAEs. No other subjects withdrew due to AEs.

The most common AEs (preferred terms) were diarrhoea (2 AEs reported by 2 subjects), nasopharyngitis (3 AEs reported by 2 subjects), anaphylactic reaction (2 AEs reported by 2 subjects) and headache (2 AEs reported by 2 subjects). Other AEs occurred only in single subjects.

Of the 22 AEs that occurred in the study, 14 AEs were judged as unlikely related to study treatment, while 8 AEs were judged as possibly or probably related to the IMP/ ATH3G10.

All subjects in the active ATH3G10-group reported AEs (17 AEs in total), while 2 of 4 subjects in the placebo group reported AEs (5 AEs in total). Most AEs were of mild to moderate intensity. There were 2 severe AEs: 2 events of anaphylactic reaction occurring in 2 subjects during the second and third dose, respectively, and treatment was discontinued.

The levels of the functional biomarkers at baseline were as expected. IgM anti-PC levels were lower than expected in a general population. Biomarkers reflecting inflammatory stress and CVD as measured using PEA indicated that high Lp(a) levels is associated with increased systemic inflammatory activity. No subjects completed the study due to early termination and visit 11 was generally performed more than one month after the last dose. No conclusions on the effects of 3G10 on vascular inflammation and function were drawn.

A cause investigation was done following the two SAEs, to investigate the cause of events. In the investigations it could not be confirmed that both subjects with SAEs suffered an anaphylactic reaction.

ADA were detected in three of six subjects receiving ATH3G10 in the study, including the two subjects with SAEs. It is suggested that development of ADA and the subsequent SAEs was due to formation of complexes between ATH3G10 and Lp(a), and that this complex triggered immunogenicity upon repeated administration, rather than free ATH3G10.

OVERALL CONCLUSIONS:

The objectives of this study could not be met.

The study was terminated early due to 2 SAEs, initially classified as anaphylactic reactions, occurring in 2 subjects receiving active treatment with ATH3G10. Both subjects were withdrawn from the study and fully recovered upon discontinuation of treatment with ATH3G10. Further investigation could not confirm that both subjects with SAEs suffered an anaphylactic reaction and suggested that this reaction was due to complex formation between ATH3G10 and Lp(a) that trigger immunogenicity upon repeated administration, rather than free ATH3G10.