Clinical trial results:
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])

Summary

EudraCT number	2017-002106-13
Trial protocol	SE NL
Global end of trial date	03 July 2018

Results information

Result version number	v1 (current)
This version publication date	29 October 2021
First version publication date	29 October 2021
Summary attachment (see zip file)	Synopsis (Synopsis-ATH3G10-005 CSR, Final 1.0, 2019-06-25.pdf)

Trial information

Trial identification

Sponsor protocol code	ATH3G10-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03320265
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Athera Biotechnologies AB
Sponsor organisation address	c/o Business Center, level 4, Sankt Eriksgatan 117, Stockholm, Sweden, SE-113 43
Public contact	James Hall, Athera Biotechnologies AB, 0046 87955555, j.hall@athera.se
Scientific contact	James Hall, Athera Biotechnologies AB, 0046 87955555, j.hall@athera.se

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 March 2018
Global end of trial reached?	Yes
Global end of trial date	03 July 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the effects of four 250 mg 3G10 once monthly intravenous injections on monocyte function ex vivo.

Protection of trial subjects:

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki that are consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Sweden: 9
Worldwide total number of subjects	10
EEA total number of subjects	10

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	4
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 40 Male and female subjects, age above 50 years, with elevated Lp(a) (above 50 mg/dL) were planned for inclusion. Potential study subjects were identified by advertising in local media and by review of pre-existing databases at the study sites. The study was conducted in two countries–the Netherlands and Sweden.

Pre-assignment

Screening details:

Assessments included: informed consent; demographics, medications, and med./surg. history; eligibility; weight; height; physical exam.; vital signs (blood press. & body temp); ECG (incl. heart rate); pregnancy; FSH & oestradiol; HIV, Hepatitis B, C; Lp(a); Haematology, clin. chemistry, coagulation complement; urine analysis; and concomitant meds

Pre-assignment period milestones

Number of subjects started	10
Number of subjects completed	10

Period 1

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

Blinding implementation details:

This was a double-blinded study, the treatment was blinded to the subject, the investigators and the personnel administering IMP.
The code envelopes were to be kept in a secure place with limited access. In case of emergency or other situation that it was crucial for the Investigator to know which treatment the subject had received, the code envelope might be opened. If the code was broken, this was to be documented on the treatment code envelope and in the subject's hospital records.

Arms

Are arms mutually exclusive?	Yes
Arm title	3G10

Arm description:

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)

Arm type	Experimental
Investigational medicinal product name	PC-mAb 3G10
Investigational medicinal product code	
Other name	3G10
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were allocated to receive either 250 mg of the test product 3G10 or the reference product, matching placebo. Each subject was to receive once monthly intravenous injections for four months. At the dosing day, subjects received each dose of IMP as an intravenous infusion for 30 minutes and remained in the clinic for supervision for 1 hour after each dosing.

Arm title	Placebo

Arm description:

The reference product/placebo was commercially available acquired at the local hospital pharmacies and contained sterile sodium chloride 0.9% solution for infusion compliant to the European Pharmacopoeia (Ph.Eur).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were allocated to receive either 250 mg of the test product 3G10 or the reference product, matching placebo. Each subject was to receive once monthly intravenous injections for four months. At the dosing day, subjects received each dose of IMP as an intravenous infusion for 30 minutes and remained in the clinic for supervision for 1 hour after each dosing.

Number of subjects in period 1	3G10	Placebo
Started	6	4
Completed	6	4

Baseline characteristics

Reporting groups	
Reporting group title	3G10
Reporting group description:	
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)	
Reporting group title	Placebo
Reporting group description:	
The reference product/placebo was commercially available acquired at the local hospital pharmacies and contained sterile sodium chloride 0.9% solution for infusion compliant to the European Pharmacopoeia (Ph.Eur).	

Reporting group values	3G10	Placebo	Total
Number of subjects	6	4	10
Age categorical			
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	1	4
From 65-84 years	3	3	6
85 years and over	0	0	0
Age continuous			
Age continous			
Units: years			
arithmetic mean	66.7	63.3	
full range (min-max)	58 to 74	50 to 70	-
Gender categorical			
Units: Subjects			
Female	3	2	5
Male	3	2	5
Race			
Ethnic origin			
Units: Subjects			
Caucasian	6	4	10
Weight			
(at Visit 2)			
Units: kg			
arithmetic mean	73.3	68.8	
full range (min-max)	66 to 87	65 to 72	-

End points

End points reporting groups

Reporting group title	3G10
Reporting group description:	
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)	
Reporting group title	Placebo
Reporting group description:	
The reference product/placebo was commercially available acquired at the local hospital pharmacies and contained sterile sodium chloride 0.9% solution for infusion compliant to the European Pharmacopoeia (Ph.Eur).	

Primary: Trans-endothelial migration

End point title	Trans-endothelial migration[1]
End point description:	
Blood sampling for assessment of the primary endpoint, TEM in monocytes isolated from treated subjects, was performed pre-dose at Visit 4 (1st dose) and at follow-up (Visit 11). The ex vivo measurement of monocyte function was performed using the TEM assay. The total number of monocytes and the number of transmigrated monocytes were counted using images obtained with a confocal laser microscope and results were presented as % of migrated monocytes.	
End point type	Primary
End point timeframe:	
From Visit 4 to Visit 11	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analysis (statistical tests etc.) was performed, efficacy data are presented descriptively in subject data listings.

End point values	3G10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[2]	4[3]		
Units: percent	0	0		

Notes:

[2] - Only listings available, see attachment.

[3] - Only listings available, see attachment.

Attachments (see zip file)	Trans-endothelial migration/Trans-endothelial migration (%).

Statistical analyses

No statistical analyses for this end point

Secondary: Change in tissue to background ratio in common carotid arteries

End point title	Change in tissue to background ratio in common carotid arteries
End point description:	
The PET/CT examinations were to be performed at Visit 3 and at follow-up (Visit 11). No PET/CT	

assessments were performed at Visit 11 as judged to be of little value for the evaluation of the study compared to the radiation dose received, as the study was on hold

End point type	Secondary

End point timeframe:

Visit 3 to Visit 11

End point values	3G10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[4]	4[5]		
Units: ratio	0	0		

Notes:

[4] - No PET/CT assessments were performed at Visit 11.

[5] - No PET/CT assessments were performed at Visit 11.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in pulse wave velocity

End point title	Change in pulse wave velocity

End point description:

Assessment of arterial stiffness were to be performed at the dosing visits (pre-dose at Visit 4 and postdose at Visit 6, Visit 8 and Visit 10), at follow-up (Visit 11) and at the end of study visit (Visit 12)

End point type	Secondary

End point timeframe:

Visit 4 to Visit 11

End point values	3G10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[6]	4[7]		
Units: meter/sec	0	0		

Notes:

[6] - Only listings available, see attachment.

[7] - Only listings available, see attachment.

Attachments (see zip file)	Pulse way velocity (m/sec)/Pulse wave velocity.pdf Aortic augmentation index (AIx [AP/PP]) (%)/Aortic

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Magnetic resonance imaging

End point title	Magnetic resonance imaging

End point description:

Magnetic resonance imaging (MRI) examinations were performed in a subgroup of the population prior to randomisation at Visit 3 and
at follow-up (Visit 11). MRI scans were assessed for cardiac function (cardiac MRI variables) and limb flow reserve (LFR).

End point type	Other pre-specified

End point timeframe:

Visit 3 and Visit 11

End point values	3G10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[8]	4[9]		
Units: NA	0	0		

Notes:

[8] - Only listings available, see attachment.

[9] - Only listings available, see attachment.

Attachments (see zip file)	Left vent. global diast. circ./Left ventricular global diastolic Left ventr. global long. strain/Left ventricular global Limb flow reserve T2* grad. dur. reac. hyperaemia/Limb flow

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Biomarker analysis

End point title	Biomarker analysis

End point description:

Blood sampling for biomarker analysis (including IgM anti-PC, Lp(a) and proteomic biomarkers) were to be performed at the dosing visits (pre-dose at Visit 4 and post-dose at Visit 4, Visit 6, Visit 8 and Visit 10), at follow-up (Visit 11) and at end of study (Visit 12). The biomarkers related to monocyte function were assessed by FACS analysis. The proteomic biomarkers were analysed using Proximity Extension Assay (PEA; OLINK kits CVDII, CVDIII and Inflammation).

End point type	Other pre-specified

End point timeframe:

At dosing visits

End point values	3G10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[10]	4[11]		
Units: NA	0	0		

Notes:

[10] - Only listings available, see attachment.

[11] - Only listings available, see attachment.

Attachments (see zip file)	IgM anti-PC (U/mL)/IgM anti-PC.pdf Lipoprotein (a) levels (mg/dL)/Lipoprotein (a) levels.pdf

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetics

End point title	Pharmacokinetics

End point description:

Blood sampling for pharmacokinetic analysis of 3G10 concentration in serum was to be performed predose, and at 5 minutes and at 1-hour post-dose at the dosing visits (Visit 4, Visit 6, Visit 8 and Visit 10), at follow-up (Visit 11) and at end of study (Visit 12).

End point type	Other pre-specified

End point timeframe:

Pre-dose and at dosing visits

End point values	3G10	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[12]	4[13]		
Units: nanogram/millilitre	0	0		

Notes:

[12] - Only listings available, see attachment.

[13] - Only listings available, see attachment.

Attachments (see zip file)	3G10 concentration (ng/mL)/Concentration 3G10.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and SAEs were to be reported from the first dose of IMP (Visit 4) until the end of study visit (Visit 12).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	3G10

Reporting group description:

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)

Reporting group title	Placebo

Reporting group description:

The reference product/placebo was commercially available acquired at the local hospital pharmacies and contained sterile sodium chloride 0.9% solution for infusion compliant to the European Pharmacopoeia (Ph.Eur).

Serious adverse events	3G10	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	0 / 4 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Immune system disorders			
Anaphylactic reaction	Additional description: Lowest level term (LLT): Anaphylaxis		
subjects affected / exposed	2 / 6 (33.33%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	3G10	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	2 / 4 (50.00%)	
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Feeling cold			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye swelling			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 6 (50.00%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 September 2017	Clarification of exclusion criterion 2 to ensure exclusion of subjects having illnesses between the screening visit and the randomization visit. Clarification of exclusion criterion 8. A majority of patients with Lp(a) >50 mg/dL, which is required to be included in the study, have ongoing treatment with statins or other lipid lowering medications. New data indicates that the added population is equally treatment sensitive as statin/PCSK9 naïve patients with Lp(a) >50 mg/dL. Excluding these patients will also greatly prolong the inclusion time and exceptions are therefore needed. Correction of study schedule.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 November 2017	On 2017-11-23, a subject reported a suspected anaphylactic reaction. The event was reported as a SUSAR as the subject had been administered with active IMP 3G10 (code broken by investigator). The subject was withdrawn and a voluntary temporary halt in dosing took place between 2017-11-23 and 2017-11- 27. After recommendation from the 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 CA, further exposure in the study was continued on 2017-11-28 for all remaining enrolled subjects. All enrolled and screened subjects received information about the reaction before deciding to continue. One subject in screening decided to withdraw consent. After the restart of the study, 4 additional subjects were randomised to treatment. All doses were given without any reported deviations during administration.	28 November 2017

17 January 2018	On 2018-01-10, another subject reported a suspected anaphylactic reaction. 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 participants and no participants were exposed to the study drug after 2018-01-10. An cause investigation was initiated and 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.	-

Notes:

Limitations and caveats

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

Due to the early termination of the study, it was decided by the Sponsor that the formal statistical analysis planned in the CSP was not to be performed. Only subject listings were created.

Notes: