Clinical trial results:
An international, double-blind, randomised, placebo-controlled phase IIb trial to assess the efficacy, safety, and pharmacokinetics of GNbAC1 in patients with relapsing remitting multiple sclerosis

Summary

EudraCT number	2015-004059-29
Trial protocol	HU CZ DE ES EE PL BG HR IT
Global end of trial date	21 December 2017

Results information

Result version number	v1 (current)
This version publication date	05 January 2019
First version publication date	05 January 2019

Trial information

Trial identification

Sponsor protocol code	GNC-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02782858
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GeNeuro SA
Sponsor organisation address	Chemin du Pré-Fleuri 3, Plan-les-Ouates, Switzerland, CH-1228
Public contact	Clinical Trials Information, GeNeuro SA, 0041 22 552 48 00, contact@geneuro.com
Scientific contact	Clinical Trials Information, GeNeuro SA, 0041 22 552 48 00, contact@geneuro.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2017
Global end of trial reached?	Yes
Global end of trial date	21 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of repeated doses of GNbAC1 in patients with relapsing remitting multiple sclerosis (RRMS) based on the cumulative number of gadolinium (Gd)-enhancing T1 lesions on brain magnetic resonance imaging (MRI) scans at Weeks 12, 16, 20, and 24 versus placebo.

Protection of trial subjects:

Patients remained under observation for 2 hours following the end of the infusion for the 3 first study drug administrations and 1 hour for subsequent study drug administrations.
Brain MRI scans were performed at Baseline (Study Day 1) and at Weeks 12, 16, 20, 24, and 48.
Glomerular filtration rate (GFR) was calculated based on the creatinine results from the previous visit and was required to be ≥ 40 mL/min prior to each MRI being performed.
In case of premature discontinuation of the Investigational Medicinal Product (IMP), the patient was withdrawn from the study. Reasons for premature discontinuation of the IMP were: Adverse Events or conditions which, according to the judgement of the investigator, constituted a hazard to the patient if the treatment with the IMP continued, including lack of efficacy; major protocol deviations if they interfered to an unacceptable extent with study procedures or assessments, or if they jeopardised patient's safety, or administration of an unauthorised concomitant treatment; start of any treatment with Multiple Sclerosis disease modifying drugs.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 May 2016
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	Bulgaria: 13
Country: Number of subjects enrolled	Croatia: 5
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Estonia: 10
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Poland: 62
Country: Number of subjects enrolled	Russian Federation: 44
Country: Number of subjects enrolled	Serbia: 26
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Ukraine: 96

Worldwide total number of subjects	270
EEA total number of subjects	104

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)	270
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who met the inclusion criteria at the Screening visit (within 3 weeks prior to dosing) and at the Baseline visit (Study Day 1 [SD1]) were considered eligible to participate in the clinical study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	GNbAC1 6 mg/kg

Arm description:

GNbAC1 6 mg/kg given by IV infusion every 4 weeks for 24 weeks

Arm type	Experimental
Investigational medicinal product name	GNbAC1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

GNbAC1 was administered by IV infusion (200 mL over 2 hours) following dilution into glucose 5% solution.

Arm title	GNbAC1 12 mg/kg

Arm description:

GNbAC1 12 mg/kg given by IV infusion every 4 weeks for 24 weeks

Arm type	Experimental
Investigational medicinal product name	GNbAC1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

GNbAC1 was administered by IV infusion (200 mL over 2 hours) following dilution into glucose 5% solution.

Arm title	GNbAC1 18 mg/kg

Arm description:

GNbAC1 18 mg/kg given by IV infusion every 4 weeks for 24 weeks

Arm type	Experimental
Investigational medicinal product name	GNbAC1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

GNbAC1 was administered by IV infusion (200 mL over 2 hours) following dilution into glucose 5% solution.

Arm title	Placebo

Arm description:

Placebo given by IV infusion every 4 weeks for 24 weeks

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

Dosage and administration details:

Placebo was administered by IV infusion (200 mL over 2 hours) following dilution into glucose 5% solution.

Number of subjects in period 1	GNbAC1 6 mg/kg	GNbAC1 12 mg/kg	GNbAC1 18 mg/kg
Started	67	67	67
Completed	60	60	62
Not completed	7	7	5
Consent withdrawn by subject	4	3	1
Withdrawn from the analysis	-	-	2
Adverse event, non-fatal	2	1	2
Pregnancy	-	-	-
Lack of efficacy	1	1	-
Protocol deviation	-	2	-

Number of subjects in period 1	Placebo
Started	69
Completed	65
Not completed	4
Consent withdrawn by subject	-
Withdrawn from the analysis	2
Adverse event, non-fatal	-
Pregnancy	2
Lack of efficacy	-
Protocol deviation	-

Period 2

Period 2 title	Treatment Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

The study was double-blind during the first 24 weeks (Period 1) and was dose-blind during Period 2. Neither the investigators, nor the raters, nor the patients, nor the local project managers, nor the monitors (apart from the site unblinded Pharmacist, unblinded clinical research associates, or designee) were informed of patient treatment assignment for the 24-week double-blind Treatment Period 1 or during the dose-blind 24-week Treatment Period 2 before the database lock for the whole study

Arms

Are arms mutually exclusive?	Yes
Arm title	GNbAC1 6 mg/kg

Arm description:

GNbAC1 6 mg/kg given by IV infusion every 4 weeks for 24 weeks in Treatment Period 2.
Patients who received GNbAC1 6 mg/kg in Period 1 continued with the same dose in Period 2. Patients randomised to the placebo group in Period 1 were re-randomised to GNbAC1 6, 12, or 18 mg kg (1:1:1) in Period 2.

Arm type	Experimental
Investigational medicinal product name	GNbAC1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

GNbAC1 was administered by IV infusion (200 mL over 2 hours) following dilution into glucose 5% solution.

Arm title	GNbAC1 12 mg/kg

Arm description:

GNbAC1 12 mg/kg given by IV infusion every 4 weeks for 24 weeks in Treatment Period 2.
Patients who received GNbAC1 12 mg/kg in Period 1 continued with the same dose in Period 2. Patients randomised to the placebo group in Period 1 were re-randomised to GNbAC1 6, 12, or 18 mg kg (1:1:1) in Period 2.

Arm type	Experimental
Investigational medicinal product name	GNbAC1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

GNbAC1 was administered by IV infusion (200 mL over 2 hours) following dilution into glucose 5% solution.

Arm title	GNbAC1 18 mg/kg

Arm description:

GNbAC1 18 mg/kg given by IV infusion every 4 weeks for 24 weeks in Treatment Period 2.
Patients who received GNbAC1 18 mg/kg in Period 1 continued with the same dose in Period 2. Patients randomised to the placebo group in Period 1 were re-randomised to GNbAC1 6, 12, or 18 mg kg (1:1:1) in Period 2.

Arm type	Experimental

Investigational medicinal product name	GNbAC1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

GNbAC1 was administered by IV infusion (200 mL over 2 hours) following dilution into glucose 5% solution.

Number of subjects in period 2	GNbAC1 6 mg/kg	GNbAC1 12 mg/kg	GNbAC1 18 mg/kg
Started	81	82	84
Completed	79	73	80
Not completed	2	9	4
Consent withdrawn by subject	1	2	1
Adverse event, non-fatal	-	1	-
Other	-	2	-
Lost to follow-up	1	-	-
Lack of efficacy	-	4	3

Baseline characteristics

Reporting groups	
Reporting group title	GNbAC1 6 mg/kg
Reporting group description:	
GNbAC1 6 mg/kg given by IV infusion every 4 weeks for 24 weeks	
Reporting group title	GNbAC1 12 mg/kg
Reporting group description:	
GNbAC1 12 mg/kg given by IV infusion every 4 weeks for 24 weeks	
Reporting group title	GNbAC1 18 mg/kg
Reporting group description:	
GNbAC1 18 mg/kg given by IV infusion every 4 weeks for 24 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo given by IV infusion every 4 weeks for 24 weeks	

Reporting group values	GNbAC1 6 mg/kg	GNbAC1 12 mg/kg	GNbAC1 18 mg/kg
Number of subjects	67	67	67
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)	67	67	67
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	38.1	38.9	37.9
standard deviation	± 9.69	± 9.18	± 8.53
Gender categorical Units: Subjects			
Female	43	47	34
Male	24	20	33

Reporting group values	Placebo	Total	
Number of subjects	69	270	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	

Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	69	270	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	36.2		
standard deviation	± 9.66	-	
Gender categorical			
Units: Subjects			
Female	50	174	
Male	19	96	

End points

End points reporting groups

Reporting group title	GNbAC1 6 mg/kg
Reporting group description:	
GNbAC1 6 mg/kg given by IV infusion every 4 weeks for 24 weeks	
Reporting group title	GNbAC1 12 mg/kg
Reporting group description:	
GNbAC1 12 mg/kg given by IV infusion every 4 weeks for 24 weeks	
Reporting group title	GNbAC1 18 mg/kg
Reporting group description:	
GNbAC1 18 mg/kg given by IV infusion every 4 weeks for 24 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo given by IV infusion every 4 weeks for 24 weeks	
Reporting group title	GNbAC1 6 mg/kg
Reporting group description:	
GNbAC1 6 mg/kg given by IV infusion every 4 weeks for 24 weeks in Treatment Period 2. Patients who received GNbAC1 6 mg/kg in Period 1 continued with the same dose in Period 2. Patients randomised to the placebo group in Period 1 were re-randomised to GNbAC1 6, 12, or 18 mg kg (1:1:1) in Period 2.	
Reporting group title	GNbAC1 12 mg/kg
Reporting group description:	
GNbAC1 12 mg/kg given by IV infusion every 4 weeks for 24 weeks in Treatment Period 2. Patients who received GNbAC1 12 mg/kg in Period 1 continued with the same dose in Period 2. Patients randomised to the placebo group in Period 1 were re-randomised to GNbAC1 6, 12, or 18 mg kg (1:1:1) in Period 2.	
Reporting group title	GNbAC1 18 mg/kg
Reporting group description:	
GNbAC1 18 mg/kg given by IV infusion every 4 weeks for 24 weeks in Treatment Period 2. Patients who received GNbAC1 18 mg/kg in Period 1 continued with the same dose in Period 2. Patients randomised to the placebo group in Period 1 were re-randomised to GNbAC1 6, 12, or 18 mg kg (1:1:1) in Period 2.	
Subject analysis set title	Per Protocol Set-like
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol Set-like (PPS-like) included all randomised patients who had an assessable MRI at both Baseline (SD1) and Week 24, and did not miss 2 consecutive post-Baseline MRIs between Week 12 and 24. The PPS-like was used for all MRI based endpoints. Patients in the PPS-like were analysed as randomised; only those patients who received the treatment to which they were randomised were included.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) included all patients who took at least 1 dose of IMP following randomisation and had at least 1 of the following post-Baseline efficacy assessments: MRI brain scan, EDSS, MSFC or answer to the question "Did the patient meet the protocol defined MS Relapse criteria since the last visit?" The FAS was used for all clinical endpoints (excluding MRI-based endpoints) and for a sensitivity analysis for the primary and key secondary endpoints. Patients in the FAS were analysed as randomised.	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set included all patients having taken at least 1 dose of IMP. Patients in the Safety Set were analysed as treated.	
Subject analysis set title	Full Analysis Set Entering Period 2
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set Entering Period 2 (FAS Entering Period 2) included all patients in the FAS who received a dose in Period 2.

Subject analysis set title	Alternative grouping: GNbAC1 6 mg/kg / GNbAC1 6 mg/kg
Subject analysis set type	Full analysis

Subject analysis set description:

Alternative treatment grouping used for the Week 48 analyses of efficacy in order to evaluate the comparison of each Active group versus Placebo/GNbAC1 (6, 12 or 18 mg/kg).

Subject analysis set title	Alternative grouping: GNbAC1 12 mg/kg / GNbAC1 12 mg/kg
Subject analysis set type	Full analysis

Subject analysis set description:

Alternative treatment grouping used for the Week 48 analyses of efficacy in order to evaluate the comparison of each Active group versus Placebo/GNbAC1 (6, 12 or 18 mg/kg).

Subject analysis set title	Alternative grouping: GNbAC1 18 mg/kg / GNbAC1 18 mg/kg
Subject analysis set type	Full analysis

Subject analysis set description:

Alternative treatment grouping used for the Week 48 analyses of efficacy in order to evaluate the comparison of each Active group versus Placebo/GNbAC1 (6, 12 or 18 mg/kg).

Subject analysis set title	Alternative grouping: Placebo / GNbAC1 (6, 12 or 18 mg/kg)
Subject analysis set type	Full analysis

Subject analysis set description:

Alternative treatment grouping used for the Week 48 analyses of efficacy in order to evaluate the comparison of each Active group versus Placebo/GNbAC1 (6, 12 or 18 mg/kg).

Primary: Cumulative Number of Gadolinium-enhancing T1 Lesions Measured Using Repeated Magnetic Resonance Imaging Assessments from Weeks 12 to 24, Per Protocol Set-like

End point title	Cumulative Number of Gadolinium-enhancing T1 Lesions Measured Using Repeated Magnetic Resonance Imaging Assessments from Weeks 12 to 24, Per Protocol Set-like

End point description:

The primary endpoint was the cumulative number of Gd-enhancing T1 lesions measured using repeated MRI assessments from Weeks 12 to 24 (ie, the sum of Gd-enhancing T1 lesions assessed by 4 MRI scans from Weeks 12 to 24).

End point type	Primary

End point timeframe:

Week 12 to 24

End point values	GNbAC1 6 mg/kg	GNbAC1 12 mg/kg	GNbAC1 18 mg/kg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	60	63	65
Units: Total number of lesions	506	410	335	568

Statistical analyses

Statistical analysis title	GNbAC1 (18 mg/kg) versus Placebo

Statistical analysis description:

Each dose of GNbAC1 was compared to placebo in the PPS-like population using a Negative Binomial Generalised Linear Model (NBGLM) studying treatment effect and adjusted for the absence or presence

of Baseline (SD1) Gd-enhancing T1 lesions. The estimate of treatment effect, its standard error (SE) and 95% confidence interval (CI), as well as the associated P-value were provided.

Comparison groups	GNbAC1 18 mg/kg v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.721
Method	Negative Binomial GLM
Parameter estimate	Treatment Comparison Ratio
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.64
Variability estimate	Standard error of the mean
Dispersion value	0.28

Statistical analysis title	GNbAC1 (12 mg/kg) versus Placebo

Statistical analysis description:

Each dose of GNbAC1 was compared to placebo in the PPS-like population using a Negative Binomial Generalised Linear Model (NBGLM) studying treatment effect and adjusted for the absence or presence of Baseline (SD1) Gd-enhancing T1 lesions. The estimate of treatment effect, its standard error (SE) and 95% confidence interval (CI), as well as the associated P-value were provided.

Comparison groups	GNbAC1 12 mg/kg v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.998
Method	Negative Binomial GLM
Parameter estimate	Treatment Comparison Ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.84
Variability estimate	Standard error of the mean
Dispersion value	0.31

Statistical analysis title	GNbAC1 (6 mg/kg) versus Placebo

Statistical analysis description:

Each dose of GNbAC1 was compared to placebo in the PPS-like population using a Negative Binomial Generalised Linear Model (NBGLM) studying treatment effect and adjusted for the absence or presence of Baseline (SD1) Gd-enhancing T1 lesions. The estimate of treatment effect, its standard error (SE) and 95% confidence interval (CI), as well as the associated P-value were provided.

Comparison groups	GNbAC1 6 mg/kg v Placebo

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.814
Method	Negative Binomial GLM
Parameter estimate	Treatment Comparison Ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.69
Variability estimate	Standard error of the mean
Dispersion value	0.28

Secondary: Number of Qualifying New T1-hypointense lesions at Week 48 - Treatment Grouping 3, Full Analysis Set Entering Period 2

End point title	Number of Qualifying New T1-hypointense lesions at Week 48 - Treatment Grouping 3, Full Analysis Set Entering Period 2

End point description:

Alternative treatment groupings were predefined by the Sponsor to further explore treatment effects between the placebo-like and Active groups for the Week 48 analyses. Treatment Grouping 3 included all patients originally randomized to placebo in Treatment Period 1, pooling all re-randomized, Period 2, placebo/active GNbAC1 groups (thus preserving the original treatment groups from Treatment Period 1).

End point type	Secondary

End point timeframe:

Week 48

End point values	Alternative grouping: GNbAC1 6 mg/kg / GNbAC1 6 mg/kg	Alternative grouping: GNbAC1 12 mg/kg / GNbAC1 12 mg/kg	Alternative grouping: GNbAC1 18 mg/kg / GNbAC1 18 mg/kg	Alternative grouping: Placebo / GNbAC1 (6, 12 or 18 mg/kg)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	60	62	65
Units: Total number of lesions	42	46	18	60

Statistical analyses

Statistical analysis title	GNbAC1 18 mg/kg versus Comparator group

Statistical analysis description:

GNbAC1 (18 mg/kg)/GNbAC1 (18 mg/kg) versus Placebo/GNbAC1 (6, 12 or 18 mg/kg)

Comparison groups	Alternative grouping: GNbAC1 18 mg/kg / GNbAC1 18 mg/kg v Alternative grouping: Placebo / GNbAC1 (6, 12 or 18 mg/kg)

Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	Negative Binomial GLM
Parameter estimate	Treatment Comparison Ratio
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.82
Variability estimate	Standard error of the mean
Dispersion value	0.15

Secondary: Percentage Change in Brain Volume from Baseline to Week 48 in Whole Brain - Treatment Grouping 3, Full Analysis Set Entering Period 2

End point title	Percentage Change in Brain Volume from Baseline to Week 48 in Whole Brain - Treatment Grouping 3, Full Analysis Set Entering Period 2

End point description:

Alternative treatment groupings were predefined by the Sponsor to further explore treatment effects between the placebo-like and Active groups for the Week 48 analyses. Treatment Grouping 3 included all patients originally randomized to placebo in Treatment Period 1, pooling all re-randomized, Period 2, placebo/active GNbAC1 groups (thus preserving the original treatment groups from Treatment Period 1).

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	Alternative grouping: GNbAC1 6 mg/kg / GNbAC1 6 mg/kg	Alternative grouping: GNbAC1 12 mg/kg / GNbAC1 12 mg/kg	Alternative grouping: GNbAC1 18 mg/kg / GNbAC1 18 mg/kg	Alternative grouping: Placebo / GNbAC1 (6, 12 or 18 mg/kg)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	50	58	63
Units: Percentage change in whole brain volume				
least squares mean (standard error)	-0.65 (± 0.11)	-0.57 (± 0.11)	-0.57 (± 0.10)	-0.72 (± 0.10)

Statistical analyses

Statistical analysis title	GNbAC1 18 mg/kg versus Comparator group

Statistical analysis description:

GNbAC1 (18 mg/kg)/GNbAC1 (18 mg/kg) versus Placebo/GNbAC1 (6, 12 or 18 mg/kg)

Comparison groups	Alternative grouping: GNbAC1 18 mg/kg / GNbAC1 18 mg/kg v

	Alternative grouping: Placebo / GNbAC1 (6, 12 or 18 mg/kg)
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.288
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.43

Secondary: Percentage Change in Brain Volume from Baseline to Week 48 in Cerebral Cortex - Treatment Grouping 3, Full Analysis Set Entering Period 2

End point title	Percentage Change in Brain Volume from Baseline to Week 48 in Cerebral Cortex - Treatment Grouping 3, Full Analysis Set Entering Period 2

End point description:

Alternative treatment groupings were predefined by the Sponsor to further explore treatment effects between the placebo-like and Active groups for the Week 48 analyses. Treatment Grouping 3 included all patients originally randomized to placebo in Treatment Period 1, pooling all re-randomized, Period 2, placebo/active GNbAC1 groups (thus preserving the original treatment groups from Treatment Period 1).

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	Alternative grouping: GNbAC1 6 mg/kg / GNbAC1 6 mg/kg	Alternative grouping: GNbAC1 12 mg/kg / GNbAC1 12 mg/kg	Alternative grouping: GNbAC1 18 mg/kg / GNbAC1 18 mg/kg	Alternative grouping: Placebo / GNbAC1 (6, 12 or 18 mg/kg)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	50	58	63
Units: Percentage change in cerebral cortex vol				
least squares mean (standard error)	-0.55 (± 0.13)	-0.51 (± 0.14)	-0.36 (± 0.13)	-0.63 (± 0.12)

Statistical analyses

Statistical analysis title	GNbAC1 18 mg/kg versus Comparator group

Statistical analysis description:

GNbAC1 (18 mg/kg)/GNbAC1 (18 mg/kg) versus Placebo/GNbAC1 (6, 12 or 18 mg/kg)

Comparison groups	Alternative grouping: GNbAC1 18 mg/kg / GNbAC1 18 mg/kg v Alternative grouping: Placebo / GNbAC1 (6, 12 or 18 mg/kg)

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.134
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.61

Secondary: Percentage Change in Brain Volume from Baseline to Week 48 in Thalamus - Treatment Grouping 3, Full Analysis Set Entering Period 2

End point title	Percentage Change in Brain Volume from Baseline to Week 48 in Thalamus - Treatment Grouping 3, Full Analysis Set Entering Period 2

End point description:

Alternative treatment groupings were predefined by the Sponsor to further explore treatment effects between the placebo-like and Active groups for the Week 48 analyses. Treatment Grouping 3 included all patients originally randomized to placebo in Treatment Period 1, pooling all re-randomized, Period 2, placebo/active GNbAC1 groups (thus preserving the original treatment groups from Treatment Period 1).

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	Alternative grouping: GNbAC1 6 mg/kg / GNbAC1 6 mg/kg	Alternative grouping: GNbAC1 12 mg/kg / GNbAC1 12 mg/kg	Alternative grouping: GNbAC1 18 mg/kg / GNbAC1 18 mg/kg	Alternative grouping: Placebo / GNbAC1 (6, 12 or 18 mg/kg)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	50	58	63
Units: Percentage change in thalamus volume				
least squares mean (standard error)	-1.34 (± 0.25)	-0.85 (± 0.26)	-0.79 (± 0.24)	-1.40 (± 0.23)

Statistical analyses

Statistical analysis title	GNbAC1 18 mg/kg versus Comparator group

Statistical analysis description:

GNbAC1 (18 mg/kg)/GNbAC1 (18 mg/kg) versus Placebo/GNbAC1 (6, 12 or 18 mg/kg)

Comparison groups	Alternative grouping: GNbAC1 18 mg/kg / GNbAC1 18 mg/kg v Alternative grouping: Placebo / GNbAC1 (6, 12 or 18 mg/kg)

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.073
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	1.26

Secondary: Change in Magnetization Transfer Ratio (MTR) in Normal-Appearing Periventricular White Matter Band 1 from Baseline to Week 48 - Treatment Grouping 3, Full Analysis Set Entering Period 2

End point title	Change in Magnetization Transfer Ratio (MTR) in Normal-Appearing Periventricular White Matter Band 1 from Baseline to Week 48 - Treatment Grouping 3, Full Analysis Set Entering Period 2

End point description:

Alternative treatment groupings were predefined by the Sponsor to further explore treatment effects between the placebo-like and Active groups for the Week 48 analyses. Treatment Grouping 3 included all patients originally randomized to placebo in Treatment Period 1, pooling all re-randomized, Period 2, placebo/active GNbAC1 groups (thus preserving the original treatment groups from Treatment Period 1).

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	Alternative grouping: GNbAC1 6 mg/kg / GNbAC1 6 mg/kg	Alternative grouping: GNbAC1 12 mg/kg / GNbAC1 12 mg/kg	Alternative grouping: GNbAC1 18 mg/kg / GNbAC1 18 mg/kg	Alternative grouping: Placebo / GNbAC1 (6, 12 or 18 mg/kg)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	28	35	42
Units: Change in MTR				
least squares mean (standard error)	-0.74 (± 0.54)	0.17 (± 0.57)	0.10 (± 0.51)	-0.73 (± 0.47)

Statistical analyses

Statistical analysis title	GNbAC1 18 mg/kg versus Comparator group
Comparison groups	Alternative grouping: GNbAC1 18 mg/kg / GNbAC1 18 mg/kg v Alternative grouping: Placebo / GNbAC1 (6, 12 or 18 mg/kg)

Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.237
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	2.19

Secondary: Change in Magnetization Transfer Ratio (MTR) in Cerebral Cortex Band 4 from Baseline to Week 48 - Treatment Grouping 3, Full Analysis Set Entering Period 2

End point title	Change in Magnetization Transfer Ratio (MTR) in Cerebral Cortex Band 4 from Baseline to Week 48 - Treatment Grouping 3, Full Analysis Set Entering Period 2

End point description:

Alternative treatment groupings were predefined by the Sponsor to further explore treatment effects between the placebo-like and Active groups for the Week 48 analyses. Treatment Grouping 3 included all patients originally randomized to placebo in Treatment Period 1, pooling all re-randomized, Period 2, placebo/active GNbAC1 groups (thus preserving the original treatment groups from Treatment Period 1).

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	Alternative grouping: GNbAC1 6 mg/kg / GNbAC1 6 mg/kg	Alternative grouping: GNbAC1 12 mg/kg / GNbAC1 12 mg/kg	Alternative grouping: GNbAC1 18 mg/kg / GNbAC1 18 mg/kg	Alternative grouping: Placebo / GNbAC1 (6, 12 or 18 mg/kg)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	28	35	42
Units: Change in MTR				
least squares mean (standard error)	-0.73 (± 0.51)	-0.21 (± 0.54)	0.17 (± 0.48)	-0.65 (± 0.44)

Statistical analyses

Statistical analysis title	GNbAC1 18 mg/kg versus Comparator group
Comparison groups	Alternative grouping: GNbAC1 18 mg/kg / GNbAC1 18 mg/kg v Alternative grouping: Placebo / GNbAC1 (6, 12 or 18 mg/kg)

Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.215
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	2.11

Secondary: Proportion of Patients Free of Qualifying Gd-enhancing T1 Lesions Over 48 Weeks - Treatment Grouping 3, Full Analysis Set Entering Period 2

End point title	Proportion of Patients Free of Qualifying Gd-enhancing T1 Lesions Over 48 Weeks - Treatment Grouping 3, Full Analysis Set Entering Period 2

End point description:

Alternative treatment groupings were predefined by the Sponsor to further explore treatment effects between the placebo-like and Active groups for the Week 48 analyses. Treatment Grouping 3 included all patients originally randomized to placebo in Treatment Period 1, pooling all re-randomized, Period 2, placebo/active GNbAC1 groups (thus preserving the original treatment groups from Treatment Period 1).

End point type	Secondary

End point timeframe:

Weeks 12 to 48

End point values	Alternative grouping: GNbAC1 6 mg/kg / GNbAC1 6 mg/kg	Alternative grouping: GNbAC1 12 mg/kg / GNbAC1 12 mg/kg	Alternative grouping: GNbAC1 18 mg/kg / GNbAC1 18 mg/kg	Alternative grouping: Placebo / GNbAC1 (6, 12 or 18 mg/kg)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	60	62	65
Units: Number of patients free of lesions	15	24	29	17

Statistical analyses

Statistical analysis title	GNbAC1 18 mg/kg versus Comparator group

Statistical analysis description:

GNbAC1 (18 mg/kg)/GNbAC1 (18 mg/kg) versus Placebo/GNbAC1 (6, 12 or 18 mg/kg)

Comparison groups	Alternative grouping: GNbAC1 18 mg/kg / GNbAC1 18 mg/kg v Alternative grouping: Placebo / GNbAC1 (6, 12 or 18 mg/kg)

Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	Fisher exact
Parameter estimate	Difference
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.37

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the signing of informed consent onwards until the patient's last study visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	GNbAC1 6 mg/kg

Reporting group description:

In Period 1, patients received GNbAC1 6 mg/kg or placebo given by IV infusion every 4 weeks for 24 weeks.
In Period 2, patients received GNbAC1 6 mg/kg given by IV infusion every 4 weeks for 24 weeks.
Only events reported during the Period where the patient received GNbAC1 therapy are included.

Reporting group title	GNbAC1 12 mg/kg

Reporting group description:

In Period 1, patients received GNbAC1 12 mg/kg or placebo given by IV infusion every 4 weeks for 24 weeks.
In Period 2, patients received GNbAC1 12 mg/kg given by IV infusion every 4 weeks for 24 weeks.
Only events reported during the Period where the patient received GNbAC1 therapy are included.

Reporting group title	GNbAC1 18 mg/kg

Reporting group description:

In Period 1, patients received GNbAC1 18 mg/kg or placebo given by IV infusion every 4 weeks for 24 weeks.
In Period 2, patients received GNbAC1 18 mg/kg given by IV infusion every 4 weeks for 24 weeks.
Only events reported during the Period where the patient received GNbAC1 therapy are included.

Serious adverse events	GNbAC1 6 mg/kg	GNbAC1 12 mg/kg	GNbAC1 18 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 88 (3.41%)	4 / 90 (4.44%)	1 / 89 (1.12%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 88 (0.00%)	0 / 90 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 88 (1.14%)	0 / 90 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 88 (0.00%)	1 / 90 (1.11%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 88 (0.00%)	1 / 90 (1.11%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 88 (0.00%)	1 / 90 (1.11%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 88 (1.14%)	0 / 90 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast abscess			
subjects affected / exposed	1 / 88 (1.14%)	0 / 90 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 90 (1.11%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2.5 %

Non-serious adverse events	GNbAC1 6 mg/kg	GNbAC1 12 mg/kg	GNbAC1 18 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 88 (57.95%)	51 / 90 (56.67%)	51 / 89 (57.30%)
Investigations			

Activated partial thomboplastin time prolonged			
subjects affected / exposed	3 / 88 (3.41%)	2 / 90 (2.22%)	1 / 89 (1.12%)
occurrences (all)	3	7	1
Alanine aminotransferase increased			
subjects affected / exposed	5 / 88 (5.68%)	2 / 90 (2.22%)	7 / 89 (7.87%)
occurrences (all)	5	2	8
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 88 (3.41%)	1 / 90 (1.11%)	5 / 89 (5.62%)
occurrences (all)	3	1	5
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 88 (4.55%)	1 / 90 (1.11%)	0 / 89 (0.00%)
occurrences (all)	4	3	0
C-reactive protein increased			
subjects affected / exposed	1 / 88 (1.14%)	3 / 90 (3.33%)	2 / 89 (2.25%)
occurrences (all)	1	3	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 88 (5.68%)	4 / 90 (4.44%)	2 / 89 (2.25%)
occurrences (all)	7	4	2
White blood cell count increased			
subjects affected / exposed	0 / 88 (0.00%)	3 / 90 (3.33%)	0 / 89 (0.00%)
occurrences (all)	0	3	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 88 (4.55%)	5 / 90 (5.56%)	6 / 89 (6.74%)
occurrences (all)	10	7	9
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 88 (3.41%)	0 / 90 (0.00%)	1 / 89 (1.12%)
occurrences (all)	3	0	1
Pyrexia			
subjects affected / exposed	1 / 88 (1.14%)	3 / 90 (3.33%)	0 / 89 (0.00%)
occurrences (all)	1	5	0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	4 / 88 (4.55%)	0 / 90 (0.00%)	0 / 89 (0.00%)
occurrences (all)	9	0	0
Nausea			
subjects affected / exposed	3 / 88 (3.41%)	1 / 90 (1.11%)	0 / 89 (0.00%)
occurrences (all)	3	1	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	3 / 88 (3.41%)	1 / 90 (1.11%)	1 / 89 (1.12%)
occurrences (all)	4	1	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 88 (3.41%)	1 / 90 (1.11%)	2 / 89 (2.25%)
occurrences (all)	3	1	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 88 (2.27%)	1 / 90 (1.11%)	3 / 89 (3.37%)
occurrences (all)	2	1	4
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 88 (1.14%)	3 / 90 (3.33%)	2 / 89 (2.25%)
occurrences (all)	1	3	3
Nasopharyngitis			
subjects affected / exposed	12 / 88 (13.64%)	7 / 90 (7.78%)	8 / 89 (8.99%)
occurrences (all)	16	12	8
Respiratory tract infection viral			
subjects affected / exposed	1 / 88 (1.14%)	3 / 90 (3.33%)	3 / 89 (3.37%)
occurrences (all)	1	4	3
Upper respiratory tract infection			
subjects affected / exposed	1 / 88 (1.14%)	4 / 90 (4.44%)	5 / 89 (5.62%)
occurrences (all)	1	5	6
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	2 / 88 (2.27%)	3 / 90 (3.33%)	0 / 89 (0.00%)
occurrences (all)	4	3	0
Hypertriglyceridaemia			

subjects affected / exposed occurrences (all)	1 / 88 (1.14%) 3	3 / 90 (3.33%) 11	1 / 89 (1.12%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 June 2016	The protocol was amended to comply with some requests from Competent Authorities or commitments made by the Sponsor during the review of clinical trial applications. In particular, additional monitoring of patients after study drug administration was added. Additional changes included the removal of the MRI brain scan at Week 36, the clarification of renal function assessment timing details, the addition of MSFC/EDSS assessments at Weeks 12 and 36, the addition of one selection criterion (clinical stability for 30 days prior to selection) and the addition of some non selection criteria. The lack of efficacy in the judgement of the investigator was added as a reason for premature discontinuation of the IMP. Some wording was added to ensure documented discussion with the investigator in case a patient experienced a confirmed relapse or confirmed EDSS progression in the absence of a relapse. The IMP dose recalculation rules during the study and the criteria for a definite relapse on study were clarified.
22 March 2017	The protocol was amended to add change in magnetisation transfer ratio (MTR) within regions of interest, defined by new gadolinium-enhancing T1 and T2 lesions and within pre-specified regions of interest, located in periventricular normal-appearing white matter (NAWM) and cerebral cortex, as secondary endpoints. The opportunity was taken to prioritise annualised relapse rate as the first secondary endpoint, correct certain inconsistencies, revise wording and update study dates.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Quality Control implemented by the Central MRI Reading Center from Week 24 to Week 48 resulted in exclusion of approximately 30% of scans for Week 48 analyses of Magnetisation Transfer Ratio, limiting the power for reliable comparisons across groups

Notes: