Clinical trial results:
A Long-Term International, Extension of Study GNC-003, with GNbAC1 in Patients with Relapsing Remitting Multiple Sclerosis

Summary

EudraCT number	2016-004935-18
Trial protocol	HU DE CZ ES PL BG HR IT
Global end of trial date	14 November 2018

Results information

Result version number	v1 (current)
This version publication date	23 June 2019
First version publication date	23 June 2019

Trial information

Trial identification

Sponsor protocol code	GNC-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03239860
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 4800, contact@geneuro.com
Scientific contact	Clinical Trials Information, GeNeuro SA, 0041 22 552 4800, 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	14 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 November 2018
Global end of trial reached?	Yes
Global end of trial date	14 November 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the long term safety of GNbAC1 in patients with RRMS.

Protection of trial subjects:

In case of premature discontinuation of the Investigational Medicinal Product, the patient was withdrawn from the study. After discontinuation of the IMP, the investigator was allowed to introduce a new treatment. 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; starting of any treatment with MS disease modifying drugs.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 52
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Croatia: 5
Country: Number of subjects enrolled	Bulgaria: 8
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Estonia: 6
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Russian Federation: 27
Country: Number of subjects enrolled	Ukraine: 87
Country: Number of subjects enrolled	Serbia: 22
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	220
EEA total number of subjects	84

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)	220
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first study drug administration during study GNC-004 was to occur at least 25 days (as the interval between two IMP administrations in study GNC-003 was 28 ± 3 days) and not more than 90 days after the last study drug administration from the previous study (GNC-003).

Pre-assignment

Screening details:

Inclusion criteria included patients who had completed Period 2 of study GNC-003 (EudraCT number 2015-004059-29), were using highly effective methods of birth control, and the patients had to have tolerated the study drug according to the investigator's opinion and could have benefitted from receiving long-term treatment with GNbAC1 infusion.

Period 1

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

Blinding implementation details:

Randomisation occurred in the parent study GNC-003 (EudraCT number 2015-004059-29). At entry in the extension study GNC-004, all patients continued, on a dose-blind fashion, on the dose they were administered in Period 2 of study GNC-003 (6, 12 or 18 mg/kg, every 4 weeks, via a 2-h IV infusion). Note: Period 1 of study GNC-003 was placebo-controlled (24 weeks). 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 of GNC-003.

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

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 at doses of 6, 12, or 18 mg/kg, every 4 weeks from Study Day 1 to Week 92.

Arm title	GNbAC1 12 mg/kg

Arm description:

GNbAC1 12 mg/kg given by IV infusion every 4 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 at doses of 6, 12, or 18 mg/kg, every 4 weeks from Study Day 1 to Week 92.

Arm title	GNbAC1 18 mg/kg

Arm description:

GNbAC1 18 mg/kg given by IV infusion every 4 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 at doses of 6, 12, or 18 mg/kg, every 4 weeks from Study Day 1 to Week 92.

Number of subjects in period 1[1]	GNbAC1 6 mg/kg	GNbAC1 12 mg/kg	GNbAC1 18 mg/kg
Started	74	68	77
Completed	0	0	0
Not completed	74	68	77
Consent withdrawn by subject	7	4	9
Study terminated by Sponsor	65	62	66
Adverse event, non-fatal	1	-	2
Sponsor decision due to Adverse Event	-	1	-
Lost to follow-up	1	-	-
Lack of efficacy	-	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One patient withdrew consent before receiving any IMP in the frame of study GNC-004 and was therefore not included in the Safety Set, which was the dataset planned for this study.

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	
Reporting group title	GNbAC1 12 mg/kg
Reporting group description:	
GNbAC1 12 mg/kg given by IV infusion every 4 weeks	
Reporting group title	GNbAC1 18 mg/kg
Reporting group description:	
GNbAC1 18 mg/kg given by IV infusion every 4 weeks	

Reporting group values	GNbAC1 6 mg/kg	GNbAC1 12 mg/kg	GNbAC1 18 mg/kg
Number of subjects	74	68	77
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)	74	68	77
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	38.0	39.8	39.4
full range (min-max)	21 to 56	21 to 57	23 to 56
Gender categorical Units: Subjects			
Female	52	48	44
Male	22	20	33

Reporting group values	Total		
Number of subjects	219		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	219		

From 65-84 years	0		
85 years and over	0		

Age continuous Units: years arithmetic mean full range (min-max)	- 		
Gender categorical Units: Subjects			
Female	144		
Male	75		

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	
Reporting group title	GNbAC1 12 mg/kg
Reporting group description: GNbAC1 12 mg/kg given by IV infusion every 4 weeks	
Reporting group title	GNbAC1 18 mg/kg
Reporting group description: GNbAC1 18 mg/kg given by IV infusion every 4 weeks	
Subject analysis set title	GNbAC1 6 mg/kg / GNbAC1 6 mg/kg
Subject analysis set type	Full analysis
Subject analysis set description: This treatment group corresponds to patients who had received GNbAC1 6 mg/kg for 48 weeks in study GNC-003 study (during both Periods 1 and 2), and who continued on this dose in study GNC-004.	
Subject analysis set title	GNbAC1 12 mg/kg / GNbAC1 12 mg/kg
Subject analysis set type	Full analysis
Subject analysis set description: This treatment group corresponds to patients who had received GNbAC1 12 mg/kg for 48 weeks in study GNC-003 study (during both Periods 1 and 2), and who continued on this dose in study GNC-004.	
Subject analysis set title	GNbAC1 18 mg/kg / GNbAC1 18 mg/kg
Subject analysis set type	Full analysis
Subject analysis set description: This treatment group corresponds to patients who had received GNbAC1 18 mg/kg for 48 weeks in study GNC-003 study (during both Periods 1 and 2), and who continued on this dose in study GNC-004.	
Subject analysis set title	Placebo / GNbAC1 6, 12, 18 mg/kg
Subject analysis set type	Full analysis
Subject analysis set description: This treatment group corresponds to patients who had received Placebo in Period 1 of study GNC-003, had been re-randomised to GNbAC1 6, 12, or 18 mg/kg (1:1:1) in Period 2 of study GNC-003, and who continued with the same dose in study GNC-004.	
Subject analysis set title	Safety Set
Subject analysis set type	Full analysis
Subject analysis set description: The data set planned for this study was the Safety Set, which was to comprise all patients who had taken at least 1 dose of GNbAC1 in the GNC-004 study.	

Primary: Adverse Events

End point title	Adverse Events[1]
End point description:	
End point type	Primary
End point timeframe: Baseline to End of Study	

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: Data are summarised for this endpoint per protocol.

End point values	GNbAC1 6 mg/kg	GNbAC1 12 mg/kg	GNbAC1 18 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	68	77	
Units: number of patients				
Treatment-Emergent Adverse Events	33	32	34	
Serious Adverse Events	6	1	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change in Brain Volume from Baseline in GNC-003 to Extension Week 48 in Whole Brain, Safety Set

End point title	Percentage Change in Brain Volume from Baseline in GNC-003 to Extension Week 48 in Whole Brain, Safety Set

End point description:

In the Whole Brain, there was a 15.4% relative reduction in median brain volume loss for the GNbAC1 18 mg/kg / GNbAC1 18 mg/kg group compared to the Comparator group (Placebo / GNbAC1 6, 12, 18 mg/kg).

End point type	Secondary

End point timeframe:

Baseline in GNC-003 to Extension (GNC-004) Week 48

End point values	GNbAC1 6 mg/kg / GNbAC1 6 mg/kg	GNbAC1 12 mg/kg / GNbAC1 12 mg/kg	GNbAC1 18 mg/kg / GNbAC1 18 mg/kg	Placebo / GNbAC1 6, 12, 18 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	35	36	41
Units: percentage change in brain volume				
median (standard deviation)	-1.070 (± 1.4785)	-1.250 (± 1.1907)	-0.880 (± 1.1228)	-1.040 (± 1.3981)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change in Brain Volume from Baseline in GNC-003 to Extension Week 48 in Cerebral Cortical Volume, Safety Set

End point title	Percentage Change in Brain Volume from Baseline in GNC-003 to Extension Week 48 in Cerebral Cortical Volume, Safety Set

End point description:

In the Cerebral Cortex, there was a 41.9% relative reduction in median brain volume loss for the GNbAC1 18 mg/kg / GNbAC1 18 mg/kg compared to the Comparator group (Placebo / GNbAC1 6, 12, 18 mg/kg).

End point type	Secondary

End point timeframe:

Baseline in GNC-003 to Extension (GNC-004) Week 48

End point values	GNbAC1 6 mg/kg / GNbAC1 6 mg/kg	GNbAC1 12 mg/kg / GNbAC1 12 mg/kg	GNbAC1 18 mg/kg / GNbAC1 18 mg/kg	Placebo / GNbAC1 6, 12, 18 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	34	36	41
Units: percentage change in brain volume				
median (standard deviation)	-1.270 (± 1.6062)	-1.295 (± 1.5342)	-0.750 (± 1.2772)	-1.290 (± 1.5049)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change in Brain Volume from Baseline in GNC-003 to Extension Week 48 in Thalamus, Safety Set

End point title	Percentage Change in Brain Volume from Baseline in GNC-003 to Extension Week 48 in Thalamus, Safety Set

End point description:

In the Thalamus, there was a 47.5% and a 42.7% relative reduction in median brain volume loss for the GNbAC1 12 mg/kg / GNbAC1 12 mg/kg and the GNbAC1 18 mg/kg / GNbAC1 18 mg/kg, respectively, compared to the Comparator group (Placebo / GNbAC1 6, 12, 18 mg/kg).

End point type	Secondary

End point timeframe:

Baseline in GNC-003 to Extension (GNC-004) Week 48

End point values	GNbAC1 6 mg/kg / GNbAC1 6 mg/kg	GNbAC1 12 mg/kg / GNbAC1 12 mg/kg	GNbAC1 18 mg/kg / GNbAC1 18 mg/kg	Placebo / GNbAC1 6, 12, 18 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	34	36	41
Units: percentage change in brain volume				
median (standard deviation)	-2.310 (± 4.2180)	-1.700 (± 3.0428)	-1.855 (± 4.0328)	-3.240 (± 3.7966)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Magnetisation Transfer Ratio (MTR) in Normal-Appearing Periventricular White Matter Band 1 from Baseline in GNC-003 to Extension Week 48, Safety Set

End point title	Change in Magnetisation Transfer Ratio (MTR) in Normal-Appearing Periventricular White Matter Band 1 from Baseline in GNC-003 to Extension Week 48, Safety Set

End point description:

The GNbAC1 18 mg/kg / GNbAC1 18 mg/kg group had a 47.9% relative reduction in median MTR change from Baseline compared to patients in the Comparator Group (Placebo / GNbAC1 6, 12, 18 mg/kg).

End point type	Secondary

End point timeframe:

Baseline in GNC-003 to Extension (GNC-004) Week 48

End point values	GNbAC1 6 mg/kg / GNbAC1 6 mg/kg	GNbAC1 12 mg/kg / GNbAC1 12 mg/kg	GNbAC1 18 mg/kg / GNbAC1 18 mg/kg	Placebo / GNbAC1 6, 12, 18 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	21	23	26
Units: Change in MTR				
median (standard deviation)	-3.390 (± 3.7399)	-3.550 (± 3.0218)	-1.830 (± 4.8409)	-3.515 (± 2.0464)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Magnetisation Transfer Ratio (MTR) in Cerebral Cortex Band 4 from Baseline in GNC-003 to Extension Week 48, Safety Set

End point title	Change in Magnetisation Transfer Ratio (MTR) in Cerebral Cortex Band 4 from Baseline in GNC-003 to Extension Week 48, Safety Set

End point description:

The GNbAC1 18 mg/kg / GNbAC1 18 mg/kg group had an absolute increase in median MTR compared to the expected decline in patients in the Comparator Group (Placebo / GNbAC1 6, 12, 18 mg/kg) over 96 weeks of treatment across both the GNC-003 and GNC-004 studies.

End point type	Secondary

End point timeframe:

Baseline in GNC-003 to Extension (GNC-004) Week 48

End point values	GNbAC1 6 mg/kg / GNbAC1 6 mg/kg	GNbAC1 12 mg/kg / GNbAC1 12 mg/kg	GNbAC1 18 mg/kg / GNbAC1 18 mg/kg	Placebo / GNbAC1 6, 12, 18 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	21	23	26
Units: change in MTR				

median (standard deviation)	-1.120 (± 2.7477)	-1.110 (± 2.4042)	0.130 (± 3.8599)	-1.405 (± 1.6168)

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Patients with Confirmed Worsening in Neurological Disability from Baseline in GNC-003 to Extension Week 48, Safety Set

End point title	Proportion of Patients with Confirmed Worsening in Neurological Disability from Baseline in GNC-003 to Extension Week 48, Safety Set

End point description:

At Week 48, 4 (8.3%) patients in the GNbAC1 6 mg/kg / GNbAC1 6 mg/kg group had worsening disability, compared to 2 (4.8%) patients in the GNbAC1 12 mg/kg / GNbAC1 12 mg/kg group, 2 (3.8%) patients in the GNbAC1 18 mg/kg / GNbAC1 18 mg/kg group, and 5 (9.1%) patients in the Comparator Group (Placebo / GNbAC1 6, 12, 18 mg/kg).

End point type	Secondary

End point timeframe:

Baseline in GNC-003 to Extension (GNC-004) Week 48

End point values	GNbAC1 6 mg/kg / GNbAC1 6 mg/kg	GNbAC1 12 mg/kg / GNbAC1 12 mg/kg	GNbAC1 18 mg/kg / GNbAC1 18 mg/kg	Placebo / GNbAC1 6, 12, 18 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	48	42	53	55
Units: number of patients	4	2	2	5

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the signing if the informed consent onwards until the patient's last study visist.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	GNbAC1 6 mg/kg

Reporting group description:

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

Reporting group title	GNbAC1 12 mg/kg

Reporting group description:

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

Reporting group title	GNbAC1 18 mg/kg

Reporting group description:

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

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	6 / 74 (8.11%)	1 / 68 (1.47%)	5 / 77 (6.49%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 68 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 74 (0.00%)	0 / 68 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibroadenoma of breast			

subjects affected / exposed	2 / 74 (2.70%)	0 / 68 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Metabolic cardiomyopathy			
subjects affected / exposed	1 / 74 (1.35%)	0 / 68 (0.00%)	0 / 77 (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			
Cervix enlargement			
subjects affected / exposed	1 / 74 (1.35%)	0 / 68 (0.00%)	0 / 77 (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
Cervix haemorrhage uterine			
subjects affected / exposed	1 / 74 (1.35%)	0 / 68 (0.00%)	0 / 77 (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
Ovarian cyst			
subjects affected / exposed	1 / 74 (1.35%)	0 / 68 (0.00%)	0 / 77 (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
Hepatobiliary disorders			
Hepatitis toxic			
subjects affected / exposed	0 / 74 (0.00%)	0 / 68 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 74 (0.00%)	0 / 68 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bartholin's abscess			

subjects affected / exposed	0 / 74 (0.00%)	1 / 68 (1.47%)	0 / 77 (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
Complicated appendicitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 68 (0.00%)	0 / 77 (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
Endotoxaemia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 68 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 68 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pyelonephritis acute			
subjects affected / exposed	0 / 74 (0.00%)	0 / 68 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulvovaginitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 68 (1.47%)	0 / 77 (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	33 / 74 (44.59%)	32 / 68 (47.06%)	34 / 77 (44.16%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 74 (0.00%)	1 / 68 (1.47%)	2 / 77 (2.60%)
occurrences (all)	0	1	2
Neoplasms benign, malignant and			

unspecified (incl cysts and polyps) Fibroadenoma of breast subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 2	0 / 68 (0.00%) 0	0 / 77 (0.00%) 0
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 3	0 / 68 (0.00%) 0	0 / 77 (0.00%) 0
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 2	0 / 68 (0.00%) 0	0 / 77 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 3 3 / 74 (4.05%) 3	0 / 68 (0.00%) 0 3 / 68 (4.41%) 4	0 / 77 (0.00%) 0 4 / 77 (5.19%) 4
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 2	0 / 68 (0.00%) 0	0 / 77 (0.00%) 0
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Haemorrhoids subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 2 2 / 74 (2.70%) 2 0 / 74 (0.00%) 0	0 / 68 (0.00%) 0 0 / 68 (0.00%) 0 0 / 68 (0.00%) 0	0 / 77 (0.00%) 0 1 / 77 (1.30%) 1 2 / 77 (2.60%) 2
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	0 / 74 (0.00%) 0	2 / 68 (2.94%) 3	0 / 77 (0.00%) 0
Psychiatric disorders			

Depression			
subjects affected / exposed	2 / 74 (2.70%)	1 / 68 (1.47%)	2 / 77 (2.60%)
occurrences (all)	2	2	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 74 (4.05%)	1 / 68 (1.47%)	1 / 77 (1.30%)
occurrences (all)	5	1	1
Back pain			
subjects affected / exposed	2 / 74 (2.70%)	2 / 68 (2.94%)	1 / 77 (1.30%)
occurrences (all)	2	2	1
Muscle spasms			
subjects affected / exposed	2 / 74 (2.70%)	1 / 68 (1.47%)	0 / 77 (0.00%)
occurrences (all)	2	1	0
Muscular weakness			
subjects affected / exposed	1 / 74 (1.35%)	0 / 68 (0.00%)	2 / 77 (2.60%)
occurrences (all)	1	0	2
Osteoarthritis			
subjects affected / exposed	2 / 74 (2.70%)	0 / 68 (0.00%)	0 / 77 (0.00%)
occurrences (all)	3	0	0
Infections and infestations			
Cystitis			
subjects affected / exposed	2 / 74 (2.70%)	0 / 68 (0.00%)	1 / 77 (1.30%)
occurrences (all)	2	0	1
Nasopharyngitis			
subjects affected / exposed	5 / 74 (6.76%)	6 / 68 (8.82%)	6 / 77 (7.79%)
occurrences (all)	6	7	6
Oral herpes			
subjects affected / exposed	2 / 74 (2.70%)	0 / 68 (0.00%)	1 / 77 (1.30%)
occurrences (all)	3	0	1
Pharyngitis			
subjects affected / exposed	3 / 74 (4.05%)	2 / 68 (2.94%)	2 / 77 (2.60%)
occurrences (all)	3	2	2
Respiratory tract infection			
subjects affected / exposed	1 / 74 (1.35%)	3 / 68 (4.41%)	2 / 77 (2.60%)
occurrences (all)	1	3	2
Respiratory tract infection viral			

subjects affected / exposed	0 / 74 (0.00%)	0 / 68 (0.00%)	2 / 77 (2.60%)
occurrences (all)	0	0	2
Tonsillitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 68 (0.00%)	2 / 77 (2.60%)
occurrences (all)	1	0	2
Upper respiratory tract infection			
subjects affected / exposed	2 / 74 (2.70%)	3 / 68 (4.41%)	6 / 77 (7.79%)
occurrences (all)	3	4	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2017	The protocol was amended to add routine urinary analysis as a safety endpoint to be consistent with the GNC-003 study, to clarify one of the Magnetic Resonance Imaging (MRI) efficacy endpoints to be measured in regions of interest (ROIs) defined by Gadolinium-enhancing and T2 lesions, and to update the number of expected patients in the study to 240. Inconsistencies were corrected and some wording was revised.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 September 2018	A company press release was issued on 18th September 2018 to announce that the funding partner for this study had made the strategic decision not to further fund the development of GNbAC1 in Multiple Sclerosis. As the study could no longer be funded, it was decided to terminate the study from this date forward and patients were asked to return to clinic to complete study termination assessments.	-

Notes:

Limitations and caveats

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

This active-only extension study was dose-blind to patients and investigators but not to the sponsor; a 90-day gap was allowed prior to entering the study which resulted in a dosing interruption for most patients; the study was terminated prematurely

Notes: