Clinical trial results:
Ensayo clínico en adrenomieloneuropatía (AMN): validación de biomarcadores de estrés oxidativo, eficacia y tolerancia de la combinación de antioxidantes N-acetilcisteína, ácido lipoico y vitamina E

Summary

EudraCT number	2010-024084-40
Trial protocol	ES
Global end of trial date	22 July 2013

Results information

Result version number	v1 (current)
This version publication date	01 November 2022
First version publication date	01 November 2022
Summary attachment (see zip file)	Neurotherapeutics article (2019-Casasnovas_EC antiox_Neurotherapeutics.pdf)

Trial information

Trial identification

Sponsor protocol code	XAMNANTIOXAP2010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01495260
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IDIBELL
Sponsor organisation address	AV. GRAN VIA DE L'HOSPITALET 199, L'HOSPITALET DE LLOBREGAT, Spain, 08908
Public contact	UICEC, Bellvitge University Hospital, Neurometabolic Diseases Laboratory, +34 932607500, phereu@bellvitgehospital.cat
Scientific contact	UICEC, Bellvitge University Hospital, Neurometabolic Diseases Laboratory, +34 932607500, phereu@bellvitgehospital.cat

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	11 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 July 2013
Global end of trial reached?	Yes
Global end of trial date	22 July 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is the validation and identification of markers and evaluation of the biological effects on these markers as well as the tolerance and safety of a combination of antioxidants (NAC, lipoic acid and vitamin E), in patients with adrenomyeloneuropathy (AMN) . This is the study of a combination of drugs in a new therapeutic indication.

Protection of trial subjects:

A physical examination and measurement of vital signs of the subjects has been done at each visit. Also biochemical and hematological tests will be requested at each visit including: blood count, ionogram, kidney function, liver function, proteins, lipid profile and urine analysis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

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)	13
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

13 AMN subjects were recruited through the patient association (ELA-España, Spanish Association against Leukodystrophies). Visits were done in the Bellvitge University Hospital were recruited from September 2011 to December 2011.

Pre-assignment

Screening details:

Symptomatic subjects over 18 years of age, with confirmed diagnosis of AMN by elevation in VLCFA and the presence of a mutation in the ABCD1 gene. Subjects with cerebral inflammatory disease verified with gadolinium enhancement were excluded.

Pre-assignment period milestones

Number of subjects started	13
Number of subjects completed	13

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	AMN M0

Arm description:

AMN subjects

Arm type	Experimental
Investigational medicinal product name	NAC + Lipoic Acid + Vitamin E
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

All AMN subjects initially received a lower dose A: NAC (800 mg), LA (300 mg), and vit E (150 IU) orally daily for 2 months.

Number of subjects in period 1	AMN M0
Started	13
Completed	13

Period 2

Period 2 title	Dose A-2 months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	AMN Dose A 2-months

Arm description:

All AMN subjects initially received a lower dose A: NAC (800 mg), LA (300 mg), and vit E (150 IU) orally daily for 2 months. After this period, a 2-month washout period was introduced, during which oxidative damage biomarkers in plasma were tested. Subjects showing normalization of biomarkers restarted dose A for 12 months at the same dose

Arm type	Experimental
Investigational medicinal product name	NAC + Lipoic Acid + Vitamin E
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

All AMN subjects initially received a lower dose A: NAC (800 mg), LA (300 mg), and vit E (150 IU) orally daily for 2 months.

Number of subjects in period 2	AMN Dose A 2-months
Started	13
Completed	13

Period 3

Period 3 title	Dose B-3 months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	AMN Dose B-3 months

Arm description:

Subjects showing no normalization of oxidative damage biomarkers, the dosage was increased to dose B for 3 months: NAC (2400 mg), LA (600 mg), and vit E (300 IU).

Arm type	Experimental

Investigational medicinal product name	NAC + Lipoic Acid + Vitamin E
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Subjects showing no normalization of oxidative damage biomarkers with Dose A, after 2 months of washout the dosage was increased to dose B for 3 months: NAC (2400 mg), LA (600 mg), and vit E (300 IU) daily.

Number of subjects in period 3[1]	AMN Dose B-3 months
Started	12
Completed	12

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Patients showing normalization of biomarkers with Dose A, the treatment was restarted for 12 months at the same dose (only 1 patient). Patients showing no normalization of oxidative damage biomarkers with Dose A, the dosage was increased to dose B for 3 months: NAC (2400 mg), LA (600 mg), and vit E (300 IU) (the other 12 patients)

Period 4

Period 4 title	Dose B-12 months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	AMN Dose B-12 months

Arm description:

After the period Dose B-3 months, the biomarkers were tested again. If normalization of the levels was attained with dose B, after a 2 months period of washout Dose B was restarted for 12 months. In the eventuality that protein oxidative damage biomarkers were not reduced, the patient was considered a non-responder, and the treatment was discontinued at that point.

Arm type	Experimental
Investigational medicinal product name	NAC + Lipoic Acid + Vitamin E
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

NAC (2400 mg), LA (600 mg), and vit E (300 IU) daily during 12 months

Number of subjects in period 4	AMN Dose B-12 months
Started	12
Completed	12

Period 5	
Period 5 title	Dose A-12 months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	AMN Dose A-12 months

Arm description: -

Arm type	Experimental
Investigational medicinal product name	NAC + Lipoic Acid + Vitamin E
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

All AMN subjects initially received a lower dose A: NAC (800 mg), LA (300 mg), and vit E (150 IU) orally daily for 12 months.

Number of subjects in period 5[2]	AMN Dose A-12 months
Started	1
Completed	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Patients showing normalization of biomarkers with Dose A, the treatment was restarted for 12 months at the same dose (only 1 patient). Patients showing no normalization of oxidative damage biomarkers with Dose A, the dosage was increased to dose B for 3 months: NAC (2400 mg), LA (600 mg), and vit E (300 IU) (the other 12 patients)

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
13 subjects with AMN and 25 healthy subjects were used to determine if biomarkers are altered in AMN subjects	

Reporting group values	Baseline	Total	
Number of subjects	13	13	
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)	13	13	
From 65-84 years	0	0	
85 years and over	0	0	
Adults	0	0	
Gender categorical Units: Subjects			
Female	1	1	
Male	12	12	

End points

End points reporting groups

Reporting group title	AMN M0
Reporting group description:	
AMN subjects	

Reporting group title	AMN Dose A 2-months
Reporting group description:	
All AMN subjects initially received a lower dose A: NAC (800 mg), LA (300 mg), and vit E (150 IU) orally daily for 2 months. After this period, a 2-month washout period was introduced, during which oxidative damage biomarkers in plasma were tested. Subjects showing normalization of biomarkers restarted dose A for 12 months at the same dose	

Reporting group title	AMN Dose B-3 months
Reporting group description:	
Subjects showing no normalization of oxidative damage biomarkers, the dosage was increased to dose B for 3 months: NAC (2400 mg), LA (600 mg), and vit E (300 IU).	

Reporting group title	AMN Dose B-12 months
Reporting group description:	
After the period Dose B-3 months, the biomarkers were tested again. If normalization of the levels was attained with dose B, after a 2 months period of washout Dose B was restarted for 12 months. In the eventuality that protein oxidative damage biomarkers were not reduced, the patient was considered a non-responder, and the treatment was discontinued at that point.	

Reporting group title	AMN Dose A-12 months

Reporting group description: -

Primary: 8-Oxo-dG

End point title	8-Oxo-dG
End point description:	
8-Oxo-dG (7,8-dihydro-8-oxo-2-deoxyguanosine) was tested in the urine by HPLC according to the methodology described by Haghdoost et al. (Int J Radiat Oncol Biol Phys 2001;50:405–410). The reference values were calculated according to the sample distribution of 25 healthy individuals. The point that defines a superior moderate outlier in the sample of controls was taken as the reference limit (Q75 + 1.5 × IQR, Q75 = 75% percentile, IQR = interquartile range). 25 healthy subjects were used to determine the control biomarker values.	
End point type	Primary
End point timeframe:	
8-Oxo-dG was measured in urine at baseline, after 2 months with dose A (13 subjects) and after 3 months with dose B in subjects who do not normalize oxidative biomarkers (12 subjects)	

End point values	AMN M0	AMN Dose A 2-months	AMN Dose B-3 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	13	12	
Units: ng/mg creatine				
arithmetic mean (standard error)	4.03 (± 0.73)	2.91 (± 0.25)	1.69 (± 0.27)	

Statistical analyses

Statistical analysis title	AMN/AMN-Dose A-2 months

Statistical analysis description:

Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student's T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Comparison groups	AMN Dose A 2-months v AMN M0
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01181
Method	paired t-test
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	1-sided
Variability estimate	Standard error of the mean

Statistical analysis title	AMN/AMN-Dose B-3 months

Statistical analysis description:

Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student's T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Comparison groups	AMN Dose B-3 months v AMN M0
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0097
Method	paired t-test
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	1-sided
Variability estimate	Standard error of the mean

Primary: GSA

End point title	GSA

End point description:

GSA (glutamic semialdehyde) is a metal-catalyzed oxidation product. GSA was tested in the plasma by GC/MS according to the methodology described by Fourcade et al. (Hum Mol Genet 2008;17:1762–1773). The reference values were calculated according to the sample distribution of 12 healthy individuals. The point that defines a superior moderate outlier in the sample of controls was taken as the reference limit (Q75 + 1.5 × IQR, Q75 = 75% percentile, IQR = interquartile range). 25 healthy subjects were used to determine the control biomarker values.

End point type	Primary

End point timeframe:

GSA was measured in plasma at baseline, after 2 months with dose A (13 subjects) and after 3 months with dose B in subjects who do not normalize oxidative biomarkers (12 subjects)

End point values	AMN M0	AMN Dose A 2-months	AMN Dose B-3 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	10	12	
Units: umol/mol lysine				
arithmetic mean (standard error)	8793.0 (± 689.4)	8851.2 (± 693.1)	13579.8 (± 654.0)	

Statistical analyses

Statistical analysis title	AMN/AMN-Dose A-2 months

Statistical analysis description:

Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student's T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Comparison groups	AMN Dose B-3 months v AMN M0
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.000057
Method	paired t-test
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	1-sided

Statistical analysis title	AMN/AMN-Dose B-3 months

Statistical analysis description:

Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student's T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Comparison groups	AMN Dose B-3 months v AMN M0
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0
Method	paired t-test
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	1-sided
Variability estimate	Standard error of the mean

Notes:

[1] - Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student's T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Primary: AASA

End point title	AASA

End point description:

AASA (aminoadipic semialdehyde) is a metal-catalyzed oxidation product. AASA was tested in the plasma by GC/MS according to the methodology described by Fourcade et al. (Hum Mol Genet 2008;17:1762–1773). The reference values were calculated according to the sample distribution of 12 healthy individuals. The point that defines a superior moderate outlier in the sample of controls was taken as the reference limit (Q75 + 1.5 × IQR, Q75 = 75% percentile, IQR = interquartile range). 25 healthy subjects were used to determine the control biomarker values.

End point type	Primary

End point timeframe:

AASA was measured in plasma at baseline, after 2 months with dose A (13 subjects) and after 3 months with dose B in subjects who do not normalize oxidative biomarkers (12 subjects)

End point values	AMN M0	AMN Dose A 2-months	AMN Dose B-3 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	13	12	
Units: umol/mol lysine				
arithmetic mean (standard error)	75.7 (± 13.8)	103.4 (± 19.2)	36.0 (± 3.0)	

Statistical analyses

Statistical analysis title	AMN/AMN-Dose A-2 months

Statistical analysis description:

Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student's T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Comparison groups	AMN Dose A 2-months v AMN M0
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	paired t-test
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	1-sided

Statistical analysis title	AMN/AMN-Dose B-3 months

Statistical analysis description:

Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student’s T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Comparison groups	AMN Dose B-3 months v AMN M0
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0244
Method	paired t-test
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	1-sided

Primary: CML

End point title	CML

End point description:

CML (Nepsilon-(carboxymethyl) - lysine)) is a mixed glycoxidation/lipoxidation product. CML was tested in the plasma by GC/MS according to the methodology described by Fourcade et al. (Hum Mol Genet 2008;17:1762–1773). The reference values were calculated according to the sample distribution of 12 healthy individuals. The point that defines a superior moderate outlier in the sample of controls was taken as the reference limit (Q75 + 1.5 × IQR, Q75 = 75% percentile, IQR = interquartile range). 25 healthy subjects were used to determine the control biomarker values.

End point type	Primary

End point timeframe:

CML was measured in plasma at baseline, after 2 months with dose A (13 subjects) and after 3 months with dose B in subjects who do not normalize oxidative biomarkers (12 subjects)

End point values	AMN M0	AMN Dose A 2-months	AMN Dose B-3 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	13	12	
Units: umol/mol lysine				
arithmetic mean (standard error)	1947.1 (± 577.2)	1347.8 (± 759.9)	315.9 (± 48.0)	

Statistical analyses

Statistical analysis title	AMN/AMN-Dose A-2 months

Statistical analysis description:

Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student’s T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Comparison groups	AMN Dose A 2-months v AMN M0

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.00097
Method	paired t-test
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	1-sided
Variability estimate	Standard error of the mean

Notes:

[2] - Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student's T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Statistical analysis title	AMN/AMN-Dose B-3 months

Statistical analysis description:

Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student's T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Comparison groups	AMN Dose B-3 months v AMN M0
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.00097
Method	paired t-test
Parameter estimate	Mean difference (final values)
Confidence interval	
sides	1-sided
Variability estimate	Standard error of the mean

Notes:

[3] -
Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student's T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Primary: CEL

End point title	CEL

End point description:

CEL (Nepsilon-(carboxyethyl)-lysine) is a mixed glycoxidation/lipoxidation product. CEL was tested in the plasma by GC/MS according to the methodology described by Fourcade et al. (Hum Mol Genet 2008;17:1762–1773). The reference values were calculated according to the sample distribution of 12 healthy individuals. The point that defines a superior moderate outlier in the sample of controls was taken as the reference limit (Q75 + 1.5 × IQR, Q75 = 75% percentile, IQR = interquartile range). 25 healthy subjects were used to determine the control biomarker values.

End point type	Primary

End point timeframe:

CEL was measured in plasma at baseline, after 2 months with dose A (13 subjects) and after 3 months with dose B in subjects who do not normalize oxidative biomarkers (12 subjects)

End point values	AMN M0	AMN Dose A 2-months	AMN Dose B-3 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	13	12	
Units: umol/mol lysine				
arithmetic mean (standard error)	65.1 (± 13.7)	22.3 (± 5.9)	2.4 (± 0.7)	

Statistical analyses

Statistical analysis title	AMN/AMN-Dose A-2 months

Statistical analysis description:

Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student's T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Comparison groups	AMN Dose A 2-months v AMN M0
Number of subjects included in analysis	26
Analysis specification	Post-hoc
Analysis type	superiority[4]
P-value	= 0.0019
Method	paired t-test
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	1-sided
Variability estimate	Standard error of the mean

Notes:

[4] - Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student's T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Statistical analysis title	AMN/AMN-Dose B-3 months

Statistical analysis description:

Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student's T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Comparison groups	AMN Dose B-3 months v AMN M0
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0009
Method	paired t-test
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	1-sided
Variability estimate	Standard error of the mean

Notes:

[5] - Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student's T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Primary: MDAL

End point title	MDAL

End point description:

MDAL (Nepsilonmalondialdehyde-lysine) is a lipid peroxidation-derived product. MDAL was tested in the plasma by GC/MS according to the methodology described by Fourcade et al. (Hum Mol Genet 2008;17:1762–1773). The reference values were calculated according to the sample distribution of 12 healthy individuals. The point that defines a superior moderate outlier in the sample of controls was taken as the reference limit (Q75 + 1.5 × IQR, Q75 = 75% percentile, IQR = interquartile range). 25 healthy subjects were used to determine the control biomarker values.

End point type	Primary

End point timeframe:

MDAL was measured in plasma at baseline, after 2 months with dose A (13 subjects) and after 3 months with dose B in subjects who do not normalize oxidative biomarkers (12 subjects)

End point values	AMN M0	AMN Dose A 2-months	AMN Dose B-3 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	13	12	
Units: umol/mol lysine				
arithmetic mean (standard error)	230.4 (± 35.6)	207.9 (± 45.5)	34.9 (± 3.1)	

Statistical analyses

Statistical analysis title	AMN/AMN-Dose A-2 months

Statistical analysis description:

Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student’s T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Comparison groups	AMN Dose A 2-months v AMN M0
Number of subjects included in analysis	26
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0068
Method	paired t-test
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	1-sided
Variability estimate	Standard error of the mean

Statistical analysis title	AMN/AMN-Dose B-3 months

Statistical analysis description:

Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student’s T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Comparison groups	AMN Dose B-3 months v AMN M0
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00097
Method	paired t-test
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	1-sided
Variability estimate	Standard error of the mean

Secondary: 6MWT

End point title	6MWT

End point description:

6 Minute Walk Test (6MWT): this test is used as a physical performancebased measure of global responses of all systems to submaximal exercise. It measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes. The individual is allowed to selfpace and rest as needed as he traverses back and forth along a marked walkway.

End point type	Secondary

End point timeframe:

6MWT was measured at baseline, and after 12 months with dose B (11 subjects)

End point values	AMN M0	AMN Dose B-12 months		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: metre				
arithmetic mean (standard error)	323.2 (± 41.0)	378.8 (± 41.3)		

Statistical analyses

Statistical analysis title	6MWT

Statistical analysis description:

Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student’s T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Comparison groups	AMN M0 v AMN Dose B-12 months
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0361
Method	paired t-test
Parameter estimate	Mean difference (final values)

Confidence interval	
level	95 %
sides	1-sided

Secondary: Neopterin

End point title	Neopterin

End point description:

Neopterin is a sensitive marker of immune system activation for neurodegenerative disorders such as Parkinson’s disease, which was not previously reported in AMN.

End point type	Secondary

End point timeframe:

Neopterin was measured in cerebrospinal fluid at baseline, and after 12 months with dose B (6 subjects)

End point values	AMN M0	AMN Dose B-12 months		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	6		
Units: nmol/L				
arithmetic mean (standard error)	26.9 (± 1.1)	23.3 (± 2.0)		

Statistical analyses

Statistical analysis title	AMN/AMN-Dose B-12 months

Statistical analysis description:

Data were examined for normality by the Shapiro–Wilk test. Significant differences were determined using a 1-tailed Student’s T test if the data were normally distributed or a 1-tailed Wilcoxon rank sum test otherwise.

Comparison groups	AMN M0 v AMN Dose B-12 months
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0038
Method	paired t-test
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	1-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The evaluation, registration and analysis of the security parameters were carried out at each visit, from the initial visit to the end of the study.

Assessment type	Systematic

Dictionary used

Dictionary name	None
Dictionary version	0

Reporting groups

Reporting group title	AMN-Dose A

Reporting group description:

AMN patients treated 12 months with dose A

Reporting group title	AMN-Dose B

Reporting group description:

AMN patients treated 12 months with dose B

Serious adverse events	AMN-Dose A	AMN-Dose B	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	AMN-Dose A	AMN-Dose B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	3 / 12 (25.00%)	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	8	
Dyspepsia			
subjects affected / exposed	0 / 1 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	17	
Gastroenteritis			

subjects affected / exposed	0 / 1 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	8	
Musculoskeletal and connective tissue disorders			
left ankle sprain			
subjects affected / exposed	1 / 1 (100.00%)	0 / 12 (0.00%)	
occurrences (all)	100	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2011	- Selection and inclusion visits are unified - The 300 mg capsules are replaced by 2 of 150 mg due to patient swallowing problems - The 6 minutes walking test (6MWT) and the Expanded Dissability Status Scale (EDSS) are incorporated
23 January 2012	A sub-study is introduced in which all patients who want to freely participate are offered the possibility of performing a 2-[F-18] fluoro-2-deoxy-D-glucose or PET-FDG. The objectives of the sub-study are: 1-Determine if the use of PET-FDG has diagnostic or prognostic interest in AMN patients with MRI without conclusive findings in Flair and T1IR sequences. 2-Determine if the use of PET-FDG provides new information useful in monitoring the evolution of brain lesions compared to that obtained with MRI, and is modulable with the treatment proposed in this or in future clinical trials.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31077039