Clinical trial results:
A Phase 1/2 Open-Label Dose-Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Intracerebroventricular AX 250 in Patients with Mucopolysaccharidosis Type IIIB (MPS IIIB, Sanfilippo Syndrome Type B)

Summary

EudraCT number	2015-001985-25
Trial protocol	GB DE ES
Global end of trial date	23 June 2020

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	250-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02754076
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allievex Corporation
Sponsor organisation address	P.O. Box 1056, Marblehead, United States, MA, 01945
Public contact	Clinical Trials Information, Allievex Corporation, inquiries@allievex.com
Scientific contact	Clinical Trials Information, Allievex Corporation, inquiries@allievex.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	23 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of AX 250 administered to subjects with MPS IIIB by an implanted intracerebroventricular (ICV) reservoir and catheter.

To evaluate the impact of AX 250 on cognitive function in patients with MPS IIIB as assessed by development quotient (DQ).

Protection of trial subjects:

Non-pharmacological methods (distraction, iPads, movies, etc.) were used whenever possible to facilitate IMP administration. If necessary, subjects were pretreated, at the discretion of the investigator, with age-appropriate sedative medication or general anesthesia administered by a health care professional certified for pediatric sedation/anesthesia by the local institution administered approximately 30 minutes before IMP infusion according to the institution’s standard practices.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	05 April 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	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Colombia: 2
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	22
EEA total number of subjects	9

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)	22
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were screened and enrolled into study according to the inclusion and exclusion criteria listed in the protocol

Pre-assignment

Screening details:

Twenty-three subjects were screened for entry into Study 250-201. One subject withdrew consent after Screening but prior to ICV device implantation; the analysis population excludes this subject.

Period 1

Period 1 title	Overall study period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N.A

Arms

Are arms mutually exclusive?	No
Arm title	Stable Dose Period

Arm description:

The Part 1 - Dose Escalation subjects and 19 subjects previously enrolled in Study 250-901 received weekly AX 250 infusions at the MTTD (300mg) for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	AX 250
Investigational medicinal product code	
Other name	RHNAGLU-IGF2
Pharmaceutical forms	Solution for infusion
Routes of administration	Intraventricular use

Dosage and administration details:

Subjects were treated weekly with the maximum tolerated tested dose (MTTD) of 300 mg for 48 weeks by intracerebroventricular infusion.
The surgical implantation of an ICV device took place prior to the study drug administration.

Arm title	Dose Escalation

Arm description:

In this period, 3 subjects received at least 4 weekly doses of AX 250 at up to 3 escalating dose levels (30, 100, and 300 mg) until the maximum tolerated tested dose (MTTD) was established.

Arm type	Experimental
Investigational medicinal product name	AX 250
Investigational medicinal product code	
Other name	RHNAGLU-IGF2
Pharmaceutical forms	Solution for infusion
Routes of administration	Intraventricular use

Dosage and administration details:

3 subjects received at least 4 weekly doses of AX 250 at up to 3 escalating dose levels (30, 100, and 300 mg) until the maximum tolerated tested dose (MTTD) was established

Number of subjects in period 1	Stable Dose Period	Dose Escalation
Started	22	3
Completed	21	3
Not completed	1	0
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall study period

Reporting group description: -

Reporting group values	Overall study period	Total	
Number of subjects	22	22	
Age categorical			
All 22 subjects met inclusion criteria and were enrolled into study 250-201; 19 of these subjects were 1 to < 6 years of age and 3 subjects were 6 to < 11 years of age			
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)	22	22	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
All 22 subjects met inclusion criteria and were enrolled into study 250-201; 19 of these subjects were 1 to < 6 years of age and 3 subjects were 6 to < 11 years of age			
Units: years			
arithmetic mean	4.96		
standard deviation	± 2.032	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	13	13	
Race			
Units: Subjects			
White	18	18	
Black or African American	0	0	
Asian	3	3	
American Indian or Alaska native	0	0	
Native Hawaiian or Pacific Islander	0	0	
Other	1	1	
Ethnicity			
Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	20	20	
Initial presenting symptoms			
Units: Subjects			
Behavior problem	1	1	
Speech/language problem	11	11	
Sleep problem	0	0	

Failure to achieve developmental milestone	1	1	
Loss of milestone that had previously been achieve	0	0	
Hepatomegaly	2	2	
Hearing loss/deafness	1	1	
Abnormal facies	2	2	
Other	4	4	
Method of first diagnosis			
Units: Subjects			
Enzyme testing	9	9	
Glycoaminoglycans	7	7	
Genetic testing	6	6	
Subject had a history of seizures			
Units: Subjects			
Yes	0	0	
No	22	22	
Age at MPS IIIB onset			
Mean (SD) = 23.0 (12.85)			
Units: month			
median	20.0		
full range (min-max)	4 to 54	-	
Duration from onset of initial symptom of MPS IIIB to First Dose of Study Drug (months)			
Units: month			
arithmetic mean	39.26		
standard deviation	± 17.46	-	
Development Quotient (DQ) score			
Units: DQ Score			
arithmetic mean	55.43		
standard deviation	± 21.096	-	
Age equivalent (AEq) score			
Units: month			
arithmetic mean	30.5		
standard deviation	± 12.1	-	
Height			
Units: centimeter			
arithmetic mean	111.53		
standard deviation	± 13.079	-	
Weight			
Units: kilogram(s)			
arithmetic mean	23.10		
standard deviation	± 5.457	-	
Body Mass index (BMI)			
Units: kilogram(s)/square meter			
arithmetic mean	18.49		
standard deviation	± 2.107	-	

End points

End points reporting groups

Reporting group title	Stable Dose Period

Reporting group description:

The Part 1 - Dose Escalation subjects and 19 subjects previously enrolled in Study 250-901 received weekly AX 250 infusions at the MTTD (300mg) for 48 weeks.

Reporting group title	Dose Escalation

Reporting group description:

In this period, 3 subjects received at least 4 weekly doses of AX 250 at up to 3 escalating dose levels (30, 100, and 300 mg) until the maximum tolerated tested dose (MTTD) was established.

Subject analysis set title	250-901
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Study 250-901 is an observational study of progressive MPS IIIB symptomology in the same set of subjects.

Primary: The rate of change in DQ score after the treatment with data for the same subjects from pre-treatment

End point title	The rate of change in DQ score after the treatment with data for the same subjects from pre-treatment[1]

End point description:

The rate of change in DQ score after the treatment with data for the same subjects from Study pre-treatment; Change in baseline.

Cognitive DQ decline from Baseline to Week 48 was greater than that measured in 250-901 subjects. These data suggest that 48 weeks of treatment with AX 250 is not sufficient to curb cognitive impairment that begins at younger ages; further studies are needed to determine whether treatment with AX 250 for longer durations results in cognitive benefit

End point type	Primary

End point timeframe:

Overall Study period

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period	250-901		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	19	19		
Units: Development Quotient				
arithmetic mean (standard deviation)				
Baseline Values	56.24 (± 17.662)	68.31 (± 19.709)		
Week 48 Values	38.83 (± 22.864)	58.35 (± 18.468)		
Change from Baseline to Week 48	-17.41 (± 13.109)	-11.80 (± 10.804)		

Statistical analyses

Statistical analysis title	DQ; Rate of Change; Within-subject Comparison

Statistical analysis description:

Comparison of Rate of Change of Development Quotient (DQ) vs. Study 250-901 Within-Subject Comparison Set

Comparison groups	Stable Dose Period v 250-901
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence[2]
P-value	= 0.0545
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-6.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.47
upper limit	0.15
Variability estimate	Standard deviation
Dispersion value	13.241

Notes:

[2] - Within subject difference
Mean change from Baseline to Week 48 (SD) = -6.66 (13.241)

Statistical analysis title	Sensitivity Analysis; Rate of Change in DQ

Statistical analysis description:

As a sensitivity analysis, the effect of treatment with AX 250 on DQ score over time will be determined from an analysis of covariance.
The effect of treatment will be summarized by LSMEANs of Treated vs. Not Treated status as of 730 days after the start of Study 250-901 (2 years, approximately the end of Study 250-201). The test for a difference between the 2 LSMEANs at Day 730 will be the test of the effect of treatment.
LS Mean at Day 730 In Treated and untreated Status = 40.586 and 45.514

Comparison groups	Stable Dose Period v 250-901
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0492 [4]
Method	t-test, 2-sided

Notes:

[3] - The following linear model will be fit to the pooled DQ data of Study 250-901 and Study 250-201:
$y_{ijk} = \alpha_i + (\beta_i * t_{ij}) + \gamma_k + \varepsilon_{ij}$
where
y_{ijk} is the DQ score for subject i at who is either being "Treated" (k=l) or "Not Treated" (k=0) at Visit j
α_i is the fixed intercept for Subject i
β_i is a fixed regression slope on t_{ij} for Subject i
t_{ij} is day of Visit j in either study where Day 1 is Day 1 of Study 901
γ_k is a constant effect of treatment and
$\varepsilon_j \sim N(0,\sigma^2)$.

[4] - The model includes a fixed intercept for each subject, a linear slope on Day and an effect of being in Treated Status vs. Not Treated Status.

Estimated Diff. LS Means: 'Treated'-'Not Treated' = -4.928
Standard Error of Estimate = 2.4881
No CI

Primary: Age equivalent score (AEq); Rate of Change of Cognitive Age Equivalent

score from Baseline to Week 48	
End point title	Age equivalent score (AEq); Rate of Change of Cognitive Age Equivalent score from Baseline to Week 48[5]

End point description:

Age Equivalent score based on BSID-III (Bayley Scales of Infant and Toddler Development, Third Edition) cognitive test or KABC-II (Kaufman Assessment Battery for Children, Second Edition) Nonverbal Index (NVI).
The majority of 250-201 subjects showed arrested, below normal cognitive development with AEq scores of 25 to 30 months at Baseline that declined from Baseline to Week 48. This trend is contrary to that seen in Study 250-901, where subjects experienced modest increases in cognitive ability from Baseline to Week 48.
Adaptive behavior AEq scores were below normal for age and declined in most treated subjects, again suggesting that 48 weeks of treatment with AX 250 is not sufficient to curb adaptive behavior impairment that begins at younger ages. Further studies are needed to determine whether treatment with AX 250 for longer durations results in adaptive behavior benefit

End point type	Primary

End point timeframe:

Overall study period

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period	250-901		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	19	17		
Units: month				
arithmetic mean (standard deviation)				
Baseline	32.5 (± 11.42)	29.5 (± 9.89)		
Week 48	27.3 (± 14.99)	32.6 (± 12.44)		
Change from Baseline to Week 48	-5.2 (± 7.56)	1.9 (± 5.02)		

Statistical analyses

Statistical analysis title	AEq: Within Subject Difference; Baseline to Week48

Statistical analysis description:

Comparison of Rate of Change of Cognitive Age Equivalent (AEq) Score vs. Study 250-901 Within-Subject Comparison Set

Comparison groups	Stable Dose Period v 250-901
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[6]
P-value	= 0.0004
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.2
upper limit	-4

Variability estimate	Standard deviation
Dispersion value	6.98

Notes:

[6] - Within subject difference
Mean change from Baseline to Week 48 (SD) = -7.6 (6.98)

Statistical analysis title	Sensitivity Analysis of Rate of Change of AEq

Statistical analysis description:

Sensitivity Analysis of Rate of Change of Cognitive Age Equivalent (AEq) Score vs. Study 250-901 Within-Subject Comparison Set The effect of treatment will be summarized by LSMEANs of Treated vs. Not Treated status as of 730 days after the start of Study 250-901 (2 years, approximately the end of Study 250-201). The test for a difference between the 2 LSMEA at Day 730 will be the test of the effect of treatment.

Comparison groups	Stable Dose Period v 250-901
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.0237 [8]
Method	t-test, 2-sided

Notes:

[7] - The following linear model will be fit to the pooled DQ data of Study 250-901 and Study 250-201:
yijk = αi + (βi * tij) + γk + εij
where
yijk is the DQ score for subject i at who is either being "Treated" (k=l) or "Not Treated" (k=0) at Visit j
αi is the fixed intercept for Subject i
βi is a fixed regression slope on tij for Subject i
tij is day of Visit j in either study where Day 1 is Day 1 of Study 901
γk is a constant effect of treatment and
ε j ~ N(0,σ^2
[8] - LS Mean at Day 730 In Treated and Not treated Status = 29.102 and 32.124
Estimated Diff. in Treated and Not Treated LS Means = -3.021
Standard error of estimate = 1.3239
No confidence interval.

Primary: Maximum concentration of AX 250 detected in Plasma - Part 2 - Stable Period Dose

End point title	Maximum concentration of AX 250 detected in Plasma - Part 2 - Stable Period Dose[9][10]

End point description:

Number of applicable observations varies over time: Week 1, 5, 12 & 36 = 15, 14, 14 & 15 respectively.

End point type	Primary

End point timeframe:

Part 2 - Stable Period Dose

Notes:

[9] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: nanogram(s)/millilitre				
arithmetic mean (standard error)				
Week 1	1120 (± 59)			
Week 5	575 (± 102)			
Week 12	603 (± 110)			
Week 36	273 (± 139)			

Statistical analyses

No statistical analyses for this end point

Primary: Time (hours) for maximum AX 250 concentration in CSF -Part 2 - Stable Period Dose

End point title	Time (hours) for maximum AX 250 concentration in CSF -Part 2 - Stable Period Dose[11][12]

End point description:

Number of applicable observations varies over time: Week 1, 5, 12 & 36 = 16, 14, 15 & 16 respectively.

End point type	Primary

End point timeframe:

Part 2 - Stable Period Dose

Notes:

[11] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hour				
arithmetic mean (full range (min-max))				
Week 1	0.67 (0.33 to 4.33)			
Week 5	0.64 (0.42 to 10.28)			
Week 12	0.67 (0.58 to 0.77)			
Week 36	0.64 (0.25 to 4.17)			

Statistical analyses

No statistical analyses for this end point

Primary: Time (hours) for maximum AX 250 concentration in Plasma -Part 2 - Stable Period Dose

End point title	Time (hours) for maximum AX 250 concentration in Plasma - Part 2 - Stable Period Dose[13][14]

End point description:

Number of applicable observations varies over time: Week 1, 5, 12 & 36 = 16, 13, 13 & 10 respectively.

End point type	Primary

End point timeframe:

Part 2 - Stable Period Dose

Notes:

[13] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hour				
arithmetic mean (full range (min-max))				
Week 1	10.00 (3.97 to 10.62)			
Week 5	10.27 (4.18 to 24.42)			
Week 12	10.23 (4.12 to 24.28)			
Week 36	17.10 (4.00 to 48.08)			

Statistical analyses

No statistical analyses for this end point

Primary: Area under the AX 250 CSF concentration-time curve from time 0 to infinity - Part 2 - Stable Period Dose

End point title	Area under the AX 250 CSF concentration-time curve from time 0 to infinity - Part 2 - Stable Period Dose[15][16]

End point description:

Weeks 5, 12 and 36 values not applicable for this data set; values not entered.

End point type	Primary

End point timeframe:

Part 2 - Stable Period Dose

Notes:

[15] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: hour. nanogram(s) / millilitre(s)				
arithmetic mean (standard error)				
Week 1	19100000 (± 55)			

Statistical analyses

No statistical analyses for this end point

Primary: Area under the AX 250 Plasma concentration-time curve from time 0 to infinity - Part 2 - Stable Period Dose

End point title	Area under the AX 250 Plasma concentration-time curve from time 0 to infinity - Part 2 - Stable Period Dose[17][18]

End point description:

Weeks 5, 12 and 36 values not applicable for this data set; values not entered.

End point type	Primary

End point timeframe:

Part 2 - Stable Period Dose

Notes:

[17] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: hour(s). nanogram(s)/Millilitre(s)				
arithmetic mean (standard error)				
Week 1	18300 (± 41)			

Statistical analyses

No statistical analyses for this end point

Primary: Area under the AX 250 CSF concentration-time curve from 0 to time of last measurable concentration - Part 2 - Stable Period Dose

End point title	Area under the AX 250 CSF concentration-time curve from 0 to time of last measurable concentration - Part 2 - Stable Period Dose[19][20]

End point description:

End point type	Primary

End point timeframe:

Part 2 - Stable Period Dose

Notes:

[19] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: hour(s). nanogram(s) / milligram(s)				
arithmetic mean (standard error)				
Week 1	19100000 (± 55)			
Week 5	16000000 (± 43)			
Week 12	20400000 (± 50)			
Week 36	19000000 (± 39)			

Statistical analyses

No statistical analyses for this end point

Primary: AX 250 CSF: Elimination half-life - Part 2 - Stable Dose Period

End point title	AX 250 CSF: Elimination half-life - Part 2 - Stable Dose

End point description:

Number of applicable observations varies over time: Week 1, 5, 12 & 36 = 17, 12, 15 & 1 respectively

End point type	Primary

End point timeframe:

Part 2 - Stable Dose Period

Notes:

[21] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: hour				
arithmetic mean (standard error)				
Week 1	4.92 (± 33)			
Week 5	4.71 (± 18)			
Week 12	5.22 (± 29)			
Week 36	5.58 (± 32)			

Statistical analyses

No statistical analyses for this end point

Primary: AX 250 Plasma: Elimination half-life - Part 2 - Stable Dose Period

End point title	AX 250 Plasma: Elimination half-life - Part 2 - Stable Dose Period[23][24]

End point description:

Number of applicable observations varies over time: Week 1, 5, 12 & 36 = 6, 3, 3 & <3 respectively. As Week 36 has <3 applicable observations, no value was calculated and reported as '0' zero value.

End point type	Primary

End point timeframe:

Part 2 - Stable Dose Period

Notes:

[23] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint. t.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: hour				
arithmetic mean (standard error)				
Week 1	82.5 (± 45)			
Week 5	58.2 (± 82)			
Week 12	31.7 (± 30)			
Week 36	0 (± 0)			

Statistical analyses

No statistical analyses for this end point

Primary: Clearance of AX 250 from CSF - Part 2 - Stable Dose Period

End point title	Clearance of AX 250 from CSF - Part 2 - Stable Dose

End point description:

Number of applicable observations varied over time: Week 1, 5, 12 & 36 = 17, 15, 16 & 16 respectively
Note, Week 5 mean value was affected by a single outlier value; Median value = 17.4ml/h

End point type	Primary

End point timeframe:

Part 2 - Stable Dose Period

Notes:

[25] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: millilitre(s)/hour				
arithmetic mean (standard error)				
Week 1	20.2 (± 59)			
Week 5	107 (± 317)			
Week 12	18.5 (± 53)			
Week 36	17.3 (± 26)			

Statistical analyses

No statistical analyses for this end point

Primary: Clearance of AX 250 from Plasma - Part 2 - Stable Dose Period

End point title	Clearance of AX 250 from Plasma - Part 2 - Stable Dose

End point description:

Number of applicable observations varies over time: Week 1, 5, 12 & 36 = 6, 13, 13 & 11 respectively

End point type	Primary

End point timeframe:

Part 2 - Stable Dose Period

Notes:

[27] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Litre(s)/hour				
arithmetic mean (standard error)				
Week 1	18.2 (± 30)			
Week 5	76.7 (± 105)			
Week 12	91.2 (± 113)			
Week 36	240 (± 156)			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent volume of distribution in CSF of AX 250 - Part 2- Stable Dose Period

End point title	Apparent volume of distribution in CSF of AX 250 - Part 2- Stable Dose Period[29][30]

End point description:

Number of applicable observations varies over time: Week 1, 5, 12 & 36 = 6, 3, 3 & >3 respectively
As Week 36 has <3 applicable observations, no value was calculated and reported as '0' zero value.

End point type	Primary

End point timeframe:

Part 2- Stable Dose Period

Notes:

[29] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: litre(s)				
arithmetic mean (standard error)				
Week 1	138 (± 63)			
Week 5	131 (± 32)			
Week 12	131 (± 48)			
Week 36	135 (± 36)			

Statistical analyses

No statistical analyses for this end point

Primary: RCmax: Accumulation ratio (in percent) for Cmax of AX 250 in CSF - Part 2 - Stable Dose Period

End point title	RCmax: Accumulation ratio (in percent) for Cmax of AX 250 in CSF - Part 2 - Stable Dose Period[31][32]

End point description:

Week 1 not applicable in this instance, and therefore not tabulated.

End point type	Primary

End point timeframe:

Part 2 - Stable Dose Period

Notes:

[31] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percent				
arithmetic mean (standard error)				
Week 1	0 (± 0)			
Week 5	92.1 (± 71)			
Week 12	93.4 (± 36)			
Week 36	83.3 (± 46)			

Statistical analyses

No statistical analyses for this end point

Primary: RCmax: Accumulation ratio (in percent) for Cmax of AX 250 in Plasma - Part 2 - Stable Dose Period

End point title	RCmax: Accumulation ratio (in percent) for Cmax of AX 250 in Plasma - Part 2 - Stable Dose Period[33][34]

End point description:

Week 1 not applicable in this instance, and therefore not tabulated.

End point type	Primary

End point timeframe:

Part 2 - Stable Dose Period

Notes:

[33] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percent				
arithmetic mean (standard error)				
Week 1	0 (± 0)			
Week 5	55.2 (± 122)			
Week 12	58.1 (± 108)			
Week 36	21.2 (± 143)			

Statistical analyses

No statistical analyses for this end point

Primary: RAUC(0-τ) accumulation ratio (in percent) for AUC(0-τ) for AX 250 in CSF

End point title	RAUC(0-τ) accumulation ratio (in percent) for AUC(0-τ) for AX 250 in CSF[35][36]

End point description:

Week 1 not applicable in this instance, and therefore not tabulated.

End point type	Primary

End point timeframe:

Part 2 - Stable Dose Period

Notes:

[35] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: percent				
arithmetic mean (standard error)				
Week 1	0 (± 0)			
Week 5	104 (± 37)			
Week 12	114 (± 44)			
Week 36	114 (± 50)			

Statistical analyses

No statistical analyses for this end point

Primary: RAUC(0-τ) accumulation ratio (in percent) for AUC(0-τ) for AX 250 in

Plasma

End point title	RAUC(0-τ) accumulation ratio (in percent) for AUC(0-τ) for AX 250 in Plasma[37][38]

End point description:

Week 1 not applicable in this instance, and therefore not tabulated.

End point type	Primary

End point timeframe:

Part 2 - Stable Dose Period

Notes:

[37] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: percent				
arithmetic mean (standard error)				
Week 1	0.0379 (± 74)			
Week 5	0.0260 (± 101)			
Week 12	0.0252 (± 111)			
Week 36	0.0103 (± 143)			

Statistical analyses

No statistical analyses for this end point

Primary: PCRatioCmax plasma to CSF ratio (in percent) for Cmax

End point title	PCRatioCmax plasma to CSF ratio (in percent) for Cmax[39][40]

End point description:

Number of applicable observations varies over time: Week 1, 5, 12 & 36 = 15, 14, 13 & 15 respectively

End point type	Primary

End point timeframe:

Part 2 - Stable Dose Period

Notes:

[39] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: percent				
arithmetic mean (standard error)				
Week 1	0.130 (± 57)			
Week 5	0.0669 (± 97)			
Week 12	0.0608 (± 109)			
Week 36	0.0463 (± 151)			

Statistical analyses

No statistical analyses for this end point

Primary: PC Ratio AUC(0-τ) plasma to CSF ratio (in percent) for AUC(0-τ)

End point title	PC Ratio AUC(0-τ) plasma to CSF ratio (in percent) for AUC(0-τ)[41][42]

End point description:

Week 1 not applicable in this instance, and therefore not tabulated.

End point type	Primary

End point timeframe:

Part 2 - Stable Dose Period

Notes:

[41] - 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: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percent				
arithmetic mean (standard error)				
Week 1	0 (± 0)			
Week 5	49.7 (± 99)			
Week 12	41.3 (± 131)			
Week 36	36.2 (± 188)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum concentration of AX 250 detected in CSF - Part 2 - Stable

Period Dose

End point title	Maximum concentration of AX 250 detected in CSF - Part 2 - Stable Period Dose[43]

End point description:

Number of applicable observations varies across the categories: Week 1,5,12 & 36 = 16,14,15 & 16 respectively.

End point type	Secondary

End point timeframe:

Part 2 - Stable Period Dose

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: nano				
arithmetic mean (standard error)				
Week 1	3440000 (± 43)			
Week 5	2500000 (± 56)			
Week 12	3010000 (± 39)			
Week 36	3010000 (± 42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the AX 250 Plasma concentration-time curve from 0 to time of last measurable concentration - Part 2 - Stable Period Dose

End point title	Area under the AX 250 Plasma concentration-time curve from 0 to time of last measurable concentration - Part 2 - Stable Period Dose[44]

End point description:

Number of applicable observations varies over time: Week 1, 5, 12 & 36 = 15, 14, 14 & 16 respectively

End point type	Secondary

End point timeframe:

Part 2 - Stable Period Dose

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: hour(s). nanogram(s)/Milliliter(s)				
arithmetic mean (standard error)				
Week 1	19200 (± 40)			
Week 5	10900 (± 108)			
Week 12	9700 (± 113)			
Week 36	7260 (± 146)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent volume of distribution in Plasma of AX 250 - Part 2- Stable Dose Period

End point title	Apparent volume of distribution in Plasma of AX 250 - Part 2- Stable Dose Period[45]

End point description:

Number of applicable observations varies over time: Week 1, 5, 12 & 36 = 6, 3, 3 & <3 respectively. As Week 36 has <3 applicable observations, no value was calculated and reported as '0' zero value.

End point type	Secondary

End point timeframe:

Part-2

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pharmacokinetic parameter, no statistical analysis planned for this endpoint.

End point values	Stable Dose Period			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: litre(s)				
arithmetic mean (standard error)				
Week 1	2100 (± 46)			
Week 5	2420 (± 82)			
Week 12	1840 (± 124)			
Week 36	0 (± 0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall Study Period	
Adverse event reporting additional description:	
Participants of Part 1 and Part 2 are combined under 'Group Part 2' in the reporting of AEs	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Stable Dose Period
Reporting group description:	
The Part 1 - Dose Escalation subjects and 19 subjects previously enrolled in Study 250-901 received weekly AX 250 infusions at the MTTD (300mg) for 48 weeks.	

Serious adverse events	Stable Dose Period		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 22 (68.18%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
CSF culture positive			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Pleocytosis			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences causally related to treatment / all	8 / 15		
deaths causally related to treatment / all	0 / 0		
Seizure			

subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Subdural hygroma			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Consciousness fluctuating			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial pressure increased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	6 / 22 (27.27%)		
occurrences causally related to treatment / all	5 / 6		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Retained deciduous tooth				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Angioedema				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Device related infection				
subjects affected / exposed	2 / 22 (9.09%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device malfunction				
subjects affected / exposed	2 / 22 (9.09%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Stable Dose Period		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)		
General disorders and administration site conditions			
Pyrexia	Additional description: Note; there are instances of Pyrexia that have been designated as SAEs have also been recorded in that section. Both serious and non-serious adverse events are reported below.		
subjects affected / exposed	20 / 22 (90.91%)		
occurrences (all)	91		
adverse drug reaction			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	4		
medical device site swelling			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		
Infusion site extravasation			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Localised oedema			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Medical device site erythema			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Social circumstances			
Loss of personal independence in daily activities			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Reproductive system and breast disorders			

Breast swelling			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	11		
Nasal congestion			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		
Aspiration			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Adenoidal hypertrophy			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Atelectasis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Bronchospasm			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Choking			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Pharyngeal erythema			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Pneumonia aspiration			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Sleep apnoea syndrome			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Psychiatric disorders			
Attention deficit hyperactivity disorder			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		
Affect lability			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Aggression			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hallucination			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Mania			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Stereotypy			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Product issues			
Device malfunction	Additional description: Note; there are instances of Device Malfunction that have been designated as SAEs have also been recorded in that section. Both serious and non-serious adverse events are reported below.		
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		
Thrombosis in device			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		
Investigations			

CSF culture positive	Additional description: Note; there are instances of CSF culture positive that have been designated as SAEs have also been recorded in that section. Both serious and non-serious adverse events are reported below.		
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
CSF protein increased			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
CSF granulocyte count abnormal			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
CSF lymphocyte count increased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
CSF neutrophil count increased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Oxygen saturation decreased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
White blood cell count increased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	12		
Head injury			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	6		
Contusion			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		
Injury			

subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Procedural pain			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Scratch			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		
Foreign body			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Joint injury			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Laceration			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Multiple injuries			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Postoperative fever			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Thermal burn			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Tooth injury			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Traumatic haemorrhage			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Laryngomalacia			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	8		
Nervous system disorders			
Pleocytosis	Additional description: Note; there are instances of Pleocytosis that have been designated as SAEs and have also been recorded in that section. Both serious and non-serious adverse events are reported below.		
subjects affected / exposed	10 / 22 (45.45%)		
occurrences (all)	19		
Subdural hygroma	Additional description: Note; there are instances of Subdural hygroma that have been designated as SAEs and have also been recorded accordingly. Both serious and non-serious adverse events are reported below.		
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Cerebrospinal fluid leakage	Additional description: Note; there are instances of CSF leakage that have been designated as SAEs and have been recorded accordingly. Both serious and non-serious adverse events are reported below.		
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	6 / 22 (27.27%)		
occurrences (all)	27		
Psychomotor hyperactivity			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Somnolence			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Epilepsy			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Lethargy			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Speech disorder			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		

Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Abdominal lymphadenopathy			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Anaemia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Eye disorders			
Eye irritation			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Visual impairment			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting	Additional description: Note; there are instances of Vomiting that have been designated as SAEs and have been recorded accordingly. Both serious and non-serious adverse events are reported below.		
subjects affected / exposed	21 / 22 (95.45%)		
occurrences (all)	130		
Constipation	Additional description: Note; there are instances of Constipation that have been designated as SAEs and have also been recorded in that section. Both serious and non-serious adverse events are reported below.		
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	8 / 22 (36.36%)		
occurrences (all)	14		
Abdominal pain			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	7		
Nausea			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	4		
Abdominal pain upper			

subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Abdominal discomfort			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Anal haemorrhage			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Anal incontinence			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Anorectal discomfort			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Chronic gastritis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Haematochezia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Mucous stools			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	7		
Erythema			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		

Dermatitis allergic subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Dermatitis diaper subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Papule subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Rash maculo-papular subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Scab subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Polyuria subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Urinary incontinence subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Endocrine disorders			
Precocious puberty subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Hyperthyroidism subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Musculoskeletal and connective tissue disorders			
Joint range of motion decreased subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		

Infections and infestations			
Gastroenteritis	Additional description: Note; there are instances of Gastroenteritis that have been designated as SAEs and have also been recorded in that section. Both serious and non-serious adverse events are reported below.		
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	7		
Urinary tract infection	Additional description: Note; there are instances of UTI's that have been designated as SAEs have also been recorded in that section. Both serious and non-serious adverse events are reported below.		
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Upper respiratory fungal infection			
subjects affected / exposed	12 / 22 (54.55%)		
occurrences (all)	37		
Rhinitis			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	12		
Otitis media			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	10		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	7		
Nasopharyngitis			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	5		
Ear infection			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	4		
Viral infection			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	4		
Respiratory tract infection			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	2		
Acute sinusitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Bronchiolitis			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Cellulitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hand-foot-and-mouth disease			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hordeolum			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Otitis externa			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Otitis media acute			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Viral diarrhoea			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		

Hypoglycaemia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Polydipsia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2015	Amendment 1 Date: 28 October 2015 RATIONALE AND SUMMARY OF MAJOR CHANGES The major changes and rationale for amending Protocol 250-201 (original protocol) are as follows: 1. In the original protocol, Section 9.3.3.1 (Stopping Criteria) provided guidance on the disposition of subjects who experience unacceptable drug-related toxicity. 2. In the original protocol, Section 9.4.4.1 (Safety Monitoring) provided guidance on monitoring infusions
11 June 2017	Amendment 2 Date: 1 June 2017 A summary of major changes covered by Amendment 2 to the 250-201 protocol is provided below: 1. CSF glucose measurements have been added to the intensive sampling of CSF for GAG and PK analysis. 2. Language has been added to improve the monitoring of neurological symptoms during Part 2 of the study in three ways as detailed in the Protocol 3. Details concerning the use of an independent Data Monitoring Committee (DMC) during Part 2 of the study have been added. 4. It has been clarified that, for Part 2 of the study, pre-ICV placement imaging could be either a CT scan or an MRI, but that such a scan is mandatory. 5. Text has been added requesting that, as much as possible, subjects keep a consistent antipsychotic medication regimen during the study, and that an attempt should be made prior to enrollment to ensure that the subject is receiving a stable antipsychotic medication regimen. 6. Language has been added to clarify that sedatives and general anesthesia should be given to aid in BMN 250 dosing only when absolutely necessary. The use of sedation should be minimized in favor of distraction techniques. 7. Evaluation of the impact of BMN 250 on cognitive function in patients with MPS IIIB as assessed by age equivalent score (AEq) has been added as a secondary efficacy variable. 8. The Part 2 Baseline, Week 24, and Week 48 visits may occur over 2-3 days (rather than 3 days). 9. The Parenting Stress Index (PSI) has been removed as an outcome measure. 10. Anti-BMN250 total antibodies (TAb) and neutralizing antibodies (NAb) in CSF and anti-BMN250 TAb in serum will be measured at Week 2 of Part 2 in all subjects. 11. Hypoglycemia-specific stopping criteria have been added. 12. Language around the age requirements for enrollment has been modified for clarity. 13. To correct an inconsistency in previous versions of the protocol, the Vineland Adaptive Behavior Scales, 14. The identity of the Medical Monitor has been changed.

11 September 2017	Amendment 3 Date: 11 September 2017 A summary of major changes covered by Amendment 3 to the 250-201 protocol is provided below: 1. Cell count and protein were added as analyses to be performed on cerebrospinal fluid (CSF) samples already collected 4, 10, 24, 48, 72, and 96 hours post-dose as part of serial PK analyses at Part 2 Baseline and Weeks 5, 12, and 36. 2. Glycosaminoglycans (GAGs) were removed from analyses to be performed on CSF samples collected 4, 10, 24, 48, and 96 hours post-dose as part of serial PK analyses at Part 2 Baseline and Weeks 5, 12, and 36. 3. Section 12.2.4 (Part 2 Treatment Visits) has been amended with the addition of a bowel habits questionnaire to be administered by the site staff at Part 2 Baseline and every 4 weeks thereafter. 4. Section 12.2.4 (Part 2 Treatment Visits) has been amended to specify that for subjects below 14.3 kg in weight at the 250-201 Part 2 Baseline, blood normally collected for exploratory analyses will not be drawn at Week 4 or Week 8. 5. Section 9.3.3.1 (Stopping Criteria) has been amended. This change strengthens trial subject safety monitoring by more clearly defining BioMarin actions and DMC involvement in the face of potential treatment-related SAEs. 6. Language has been added in Section 9.4.6 (Selection of Doses Used in the Study) to allow for dose reductions in individual subjects should they experience serious treatment-related adverse events. 7. Language has been added to Section 9.3.4 (Subject Identification and Replacement of Subjects) stating, “Subjects previously enrolled in Study 250-901 before enrolling into Part 2 of this study will receive a new subject ID for the 250-201 study.” Additional major changes listed within Summary of Changes documentation.
06 December 2019	Amendment 4 Date: 06 December 2019 A summary of major changes covered by Amendment 4 to the 250-201 protocol is provided below: Sponsor change from BioMarin Pharmaceutical Inc to Allievex Corporation
31 January 2020	Amendment 5 Date: 31 January 2020 A summary of the major changes in Amendment 5 of the 250-201 protocol is provided below: 1. Brain imaging (MRI or CT) should be performed up to Q4W to monitor for asymptomatic subdural hygroma formation. 2. Immediate pre-infusion, immediate post-infusion and 24 hour post-infusion brain imaging (MRI or CT) will be performed up to once for each patient. 3. The amount of CSF withdrawn prior to administering AX 250 has been changed from “10mL” to “up to 10mL”. 4. BMN 250 is now referred to as AX 250. 5. The contact information for Pharmacovigilance has been updated consistent with the change in sponsor from BioMarin to Allievex. 6. For the Children’s Sleep Health Questionnaire (CSHQ), 3 additional subscale scores (sleep initiation, sleep distress, and sleep transition) based on regrouping of item scores on the standard CSHQ are added to the score outputs. 7. Mentions of a version of the CSHQ adapted by researchers at the University of Minnesota were removed from the protocol. 8. Change to language in Appendix 1; These changes clarify how subjects who score below the range at which the KABC can accurately determine age equivalent scores will be evaluated at subsequent study visits. This ensures that cognitive test data will be as accurate as possible. 9. Nonclinical study data have been updated. 10. The Summary of Overall Risks and Benefits (Section 7.4) has been updated. 11. Minor changes have been made for purposes of clarity and consistency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported