Clinical trial results:
Effects of N-Acetyl-L-Leucine on Niemann-Pick disease type C (NPC): A multinational, multi-center, open-label, rater-blinded Phase II study

Summary

EudraCT number	2018-004331-71
Trial protocol	DE GB ES SK
Global end of trial date	07 November 2022

Results information

Result version number	v1 (current)
This version publication date	11 November 2023
First version publication date	11 November 2023

Trial information

Trial identification

Sponsor protocol code	IB1001-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03759639
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IntraBio Ltd.
Sponsor organisation address	Begbroke Science Park, Begbroke Hill; Woodstock Road, Begbroke, United Kingdom, OX5 1PF
Public contact	Taylor Fields, IntraBio Ltd, +44 7426956368, tfields@intrabio.com
Scientific contact	Taylor Fields, IntraBio Ltd, +44 7426956368, tfields@intrabio.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002796-PIP01-20
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 November 2022
Global end of trial reached?	Yes
Global end of trial date	07 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the efficacy of N-Acetyl-L-Leucine based on blinded raters' clinical impression of change in severity (CI-CS) in the treatment of NPC.

For the Extension Phase:
The primary objective in the Extension Phase was to evaluate the efficacy of N-Acetyl-L-Leucine based on the 5-Domain Niemann-Pick Type C Clinical Severity Scale (NPC-CSS) with success defined as no change or a decrease in the 5-domain NPC-CSS score from Visit 7 to Visit 9.

Protection of trial subjects:

The study was performed in accordance with the requirements of the Declaration of Helsinki, ICH-GCP, Directive 2001/20/EC, and by the Food and Drug Administration (FDA) CFR as well as the requirements of national drug and data protection laws and other applicable regulatory requirements. Informed consent was obtained from each patient or their legal representative in writing prior to any study-related procedures.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	04 September 2019
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: 10
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	33
EEA total number of subjects	21

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)	4
Adolescents (12-17 years)	6
Adults (18-64 years)	23
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed from 04-SEP-2019 (first informed consent) to 07-November-2022 (extension phase completion date). Subjects were recruited at sites in Germany, Slovakia, Spain, the United Kingdom, and the United States.

Pre-assignment

Screening details:

At the initial screening visit, patients were classified as either "naïve" or "non-naïve" depending on their use of prohibited medications within the past 42 days.

Period 1

Period 1 title	Treatment with IB1001
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

As the study only had one treatment arm, blinding of treatment was not applicable. However, the primary CI-CS and secondary CI-S assessments were performed by centralized, independent blinded raters based on videos of each patient performing a designated primary anchor test - the 9HPT-D or 8MWT

Arms

Arm title	Total Treatment with IB1001

Arm description:

All subjects in the parent study

Arm type	Experimental
Investigational medicinal product name	N-Acetyl-L-Leucine
Investigational medicinal product code	IB1001
Other name	
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

IB1001 was administered orally. Patients aged ≥13 years in Europe and aged ≥18 years in the United States received 4 g/day, patients aged 6-12 years weighing ≥35 kg received 4 g/day, patients aged 6-12 years weighing 25 to <35 kg received 3 g/day, patients aged 6-12 years weighing 15 to <25 kg received 2 g/day.

Number of subjects in period 1	Total Treatment with IB1001
Started	33
Completed	31
Not completed	2
Intake of study drug did not lead to benefit	1
Adverse event, non-fatal	1

Period 2	
Period 2 title	Post-Treatment Washout
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Total Post-Treatment Washout

Arm description:

After the 6-week treatment period, patients entered a 6-week post-treatment washout period.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Total Post-Treatment Washout
Started	31
Completed	31

Baseline characteristics

Reporting groups

Reporting group title	Treatment with IB1001

Reporting group description: -

Reporting group values	Treatment with IB1001	Total	
Number of subjects	33	33	
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)	4	4	
Adolescents (12-17 years)	6	6	
Adults (18-64 years)	23	23	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	28.8		
standard deviation	± 15.1	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	23	23	
Miglustat at baseline			
Subjects with miglustat use at baseline			
Units: Subjects			
Yes	30	30	
No	3	3	

Subject analysis sets

Subject analysis set title	SAF population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set (SAF) consisted of all patients who received at least one dose of study drug (N-Acetyl-L-Leucine).

Subject analysis set title	mITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The modified ITT (mITT) analysis set consisted of all patients in the SAF with a video recording at either Visit 1 or Visit 2 (or both) and one video recording at either Visit 3 or Visit 4 (or both).

Reporting group values	SAF population	mITT	
Number of subjects	33	32	
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)	4	4	
Adolescents (12-17 years)	6	5	
Adults (18-64 years)	23	23	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	28.8	29.3	
standard deviation	± 15.1	± 15.0	
Gender categorical Units: Subjects			
Female	10	10	
Male	23	22	
Miglustat at baseline			
Subjects with miglustat use at baseline			
Units: Subjects			
Yes	30	29	
No	3	3	

End points

End points reporting groups

Reporting group title	Total Treatment with IB1001
Reporting group description:	
All subjects in the parent study	
Reporting group title	Total Post-Treatment Washout
Reporting group description:	
After the 6-week treatment period, patients entered a 6-week post-treatment washout period.	
Subject analysis set title	SAF population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Analysis Set (SAF) consisted of all patients who received at least one dose of study drug (N-Acetyl-L-Leucine).	
Subject analysis set title	mITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The modified ITT (mITT) analysis set consisted of all patients in the SAF with a video recording at either Visit 1 or Visit 2 (or both) and one video recording at either Visit 3 or Visit 4 (or both).	

Primary: Clinical impression of (Change) in Severity

End point title	Clinical impression of (Change) in Severity[1]
End point description:	
The primary efficacy endpoint was based on the blinded raters' CI-CS score on either the 9-Hole Peg Test of the Dominant Hand (9HPT-D) or the 8-Meter Walk Test (8MWT). The primary endpoint was defined as the CI-CS comparing the end of treatment (Visit 4) with baseline (Visit 2) minus the CI-CS comparing the end of washout (Visit 6) with the end of treatment (Visit 4). A one-sided Wilcoxon signed-rank test was performed to investigate statistical significance of the primary efficacy endpoint as compared to a value of 0 for the mITT population. The (pseudo-) median of the difference in CI-CS using the Hodges-Lehmann estimator was 1.00 (90% CI: 0.25, 1.75). The CI-CS primary endpoint of the study reached statistical significance with p-value: 0.029	
End point type	Primary
End point timeframe:	
Primary endpoint for the partent study; CI-CS comparing the End of treatment (Visit 4) with baseline (Visit 2) minus the CI-CS comparing the end of washout (Visit 6) with the end of treatment (Visit 4)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This was a single-arm study. Thus, inferential statistics comparing two groups were not done.

End point values	mITT			
Subject group type	Subject analysis set			
Number of subjects analysed	32			
Units: CI-CS Score				
arithmetic mean (standard deviation)	0.86 (± 2.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Key Secondary Endpoint: Individual Components of the CI-CS

End point title	Key Secondary Endpoint: Individual Components of the CI-CS

End point description:

The Clinical Impression of Change in Severity assessment will instruct the blinded rater to consider: 'compared to the first video, how has the severity of their performance on the 9 Hole Peg Test of the Dominant Hand (9HPT-D) or 8 Meter Walk Test (8MWT) changed (improved or worsened) in 6-weeks as observed in the second video?'
The Clinical Impression of Change in Severity is evaluated on a 7 point Likert scale (+3=significantly improved to -3= significantly worse).

End point type	Secondary

End point timeframe:

Treatment with IB1001: comparing the End of treatment (Visit 4) with baseline (Visit 2); Post-treatment washout: comparing the end of washout (Visit 6) with the end of treatment (Visit 4)

End point values	Total Treatment with IB1001	Total Post-Treatment Washout		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	28		
Units: Score				
arithmetic mean (standard deviation)	0.48 (± 1.34)	-0.38 (± 1.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Key Secondary Endpoint: Change in Severity Based on Average CI-S

End point title	Key Secondary Endpoint: Change in Severity Based on Average CI-S

End point description:

The Clinical Impression of Change in Severity assessment will instruct the blinded rater to consider: 'compared to the first video, how has the severity of their performance on the 9 Hole Peg Test of the Dominant Hand (9HPT-D) or 8 Meter Walk Test (8MWT) changed (improved or worsened) in 6-weeks as observed in the second video?' The Clinical Impression of Change in Severity is evaluated on a 7 point Likert scale (+3=significantly improved to -3=significantly worse).

End point type	Secondary

End point timeframe:

CI-CS comparing baseline period and end of treatment period minus thechange in CI-S between end of treatment period and end of washout period.

End point values	mITT			
Subject group type	Subject analysis set			
Number of subjects analysed	32			
Units: Score				
arithmetic mean (standard deviation)	0.08 (± 1.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Key Secondary Endpoint: CI-CS Score Reclassified on a 3-Point Scale

End point title	Key Secondary Endpoint: CI-CS Score Reclassified on a 3-Point Scale

End point description:

The Clinical Impression of Change in Severity assessment will instruct the blinded rater to consider: 'compared to the first video, how has the severity of their performance on the 9 Hole Peg Test of the Dominant Hand (9HPT-D)or 8 Meter Walk Test (8MWT) changed (improved or worsened) in 6-weeks as observed in the second video?' The Clinical Impression of Change in Severity is evaluated on a 7 point Likert scale (+3=significantly improved to -3=significantly worse).
CI-CS scores <0 were reclassified as worsened (-1), CI-CS scores 0 remained classified as not changed (0), and CI-CS scores >0 were reclassified as improved (+1).

End point type	Secondary

End point timeframe:

Baseline to end of treatment with IB1001 (Parent Study 6-weekstreatment); End of treatment with IB1001 to the end of post 6-week treatment washout

End point values	Total Treatment with IB1001	Total Post-Treatment Washout		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	28		
Units: participants				
-1 (Worsened)	9	16		
0 (No observable Change)	3	2		
+1 (Improved)	20	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Key Secondary Endpoint: CI-CS Score for the Non-Primary Anchor Test

End point title	Key Secondary Endpoint: CI-CS Score for the Non-Primary Anchor Test

End point description:

The Clinical Impression of Change in Severity is evaluated on a 7 point Likert scale (+3=significantly improved to -3= significantly worse).

End point type	Secondary

End point timeframe:

CI-CS of the non-primary anchor test was evaluated, comparing the CI-CS of Visit 4 versus Visit 2 and

of Visit 6 versus Visit 4 as done for the primary anchor test.

End point values	Total Treatment with IB1001	Total Post-Treatment Washout		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	26		
Units: Score				
arithmetic mean (standard deviation)	-0.20 (± 1.41)	0.15 (± 1.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Spinocerebellar Ataxia Functional Index (SCAFI) [Schmitz-Hübsch et al, 2008]

End point title	Spinocerebellar Ataxia Functional Index (SCAFI) [Schmitz-Hübsch et al, 2008]

End point description:

Spinocerebellar Ataxia Functional Index is composed of the 8 Meter Walk Test(timed assessment), the 9-Hole Peg Test of the Dominant and Non-DominantHand (9HPT-D/9HPT-ND) (timed assessment) and the PATA rate (countednumber of "PATA"), a measure of speech performance.

End point type	Secondary

End point timeframe:

Baseline to end of treatment with IB1001 (Parent Study 6-weeks treatment);End of treatment with IB1001 to the end of post 6-week treatment washout

End point values	Total Treatment with IB1001	Total Post-Treatment Washout		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	26		
Units: Score				
arithmetic mean (standard deviation)	0.0995 (± 0.3058)	0.0076 (± 0.3584)		

Statistical analyses

No statistical analyses for this end point

Secondary: Scale for Assessment and Rating of Ataxia (SARA) Score [Schmitz-Hübsch etal, 2006; Subramony, 2007]

End point title	Scale for Assessment and Rating of Ataxia (SARA) Score [Schmitz-Hübsch etal, 2006; Subramony, 2007]

End point description:

The Scale for Assessment and Rating of Ataxia has 8 items that are related togait, stance, sitting, speech, finger-chase test, nose-finger test, fast alternating movements, and heel-shin test. The range is 0-40 points, with a lower score representing neurological improvement and a higher score representing neurological worsening.

End point type	Secondary

End point timeframe:

Baseline to end of treatment with IB1001 (Parent Study 6-weeks treatment); End of treatment with IB1001 to the end of post 6-week treatment washout

End point values	Total Treatment with IB1001	Total Post-Treatment Washout		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	28		
Units: Score				
arithmetic mean (standard deviation)	-1.19 (± 2.02)	1.45 (± 2.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQuol- 5 Dimension (EQ-5D) Quality of Life Scale

End point title	EuroQuol- 5 Dimension (EQ-5D) Quality of Life Scale

End point description:

The results of EuroQuol- 5 Dimension-5L (for patients 18 years +) as well asthe EuroQuol- 5 Dimension-Y (patients <18 years) were combined into a 5-digit number presenting the health status of the patient. Frequency tables were presented per visit for the 5 domains, as well as for the 5-digit number of the EQ-5D-5L and the EQ-5D-Y separately. EQ-5D VAS was recorded where a score of 0 is worst and 100 is best.

End point type	Secondary

End point timeframe:

Baseline to end of treatment with IB1001 (Parent Study 6-weeks treatment);End of treatment with IB1001 to the end of post 6-week treatment washout

End point values	Total Treatment with IB1001	Total Post-Treatment Washout		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	26		
Units: Score				
arithmetic mean (standard deviation)	72.7 (± 19.3)	68.5 (± 17.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Modified Disability Rating Scale (mDRS) [Iturriaga et al. 2006]

End point title	Modified Disability Rating Scale (mDRS) [Iturriaga et al. 2006]

End point description:

Overall neurological status based on six domains (ambulation, manipulation,language, swallowing, seizures and ocular movements). The Modified Disability Rating Scale ranges from 0-24, where 0 is the best neurological status and 24 is the worst.

End point type	Secondary

End point timeframe:

Baseline to end of treatment with IB1001 (Parent Study 6-weeks treatment); End of treatment with IB1001 to the end of post 6-week treatment washout

End point values	Total Treatment with IB1001	Total Post-Treatment Washout		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	28		
Units: Score				
arithmetic mean (standard deviation)	-0.012 (± 0.050)	0.016 (± 0.051)		

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator's Clinical Global Impressions of Change (CGI-C)

End point title	Investigator's Clinical Global Impressions of Change (CGI-C)

End point description:

The Clinical Global Impression of Change assessed by the investigator is evaluated on a 7 point Likert scale ranging from 1='very much improved' to 7='very much worse'

End point type	Secondary

End point timeframe:

Baseline to end of treatment with IB1001 (Parent Study 6-weeks treatment); End of treatment with IB1001 to the end of post 6-week treatment washout

End point values	Total Treatment with IB1001	Total Post-Treatment Washout		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	28		
Units: Score				
arithmetic mean (standard deviation)	3.4 (± 0.9)	4.5 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Parent/Caregiver's Clinical Global Impression of Change (CGI-C)

End point title	Parent/Caregiver's Clinical Global Impression of Change (CGI-C)

End point description:

The Clinical Global Impression of Change assessed by the parent/caregiver is evaluated on a 7 point Likert scale ranging from 1='very much improved' to 7='very much worse'.

End point type	Secondary

End point timeframe:

Baseline to end of treatment with IB1001 (Parent Study 6-weeks treatment); End of treatment with IB1001 to the end of post 6-week treatment washout

End point values	Total Treatment with IB1001	Total Post-Treatment Washout		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	27		
Units: Score				
arithmetic mean (standard deviation)	3.4 (± 1.0)	4.4 (± 1.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient's Clinical Global Impressions (CGI) if Able

End point title	Patient's Clinical Global Impressions (CGI) if Able

End point description:

The Clinical Global Impression of Change assessed by the patient (if able) is evaluated on a 7 point Likert scale ranging from 1='very much improved' to 7='very much worse'.

End point type	Secondary

End point timeframe:

Baseline to end of treatment with IB1001 (Parent Study 6-weeks treatment); End of treatment with IB1001 to the end of post 6-week treatment washout

End point values	Total Treatment with IB1001	Total Post-Treatment Washout		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: Score				
arithmetic mean (standard deviation)	3.3 (± 1.0)	4.3 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs occurring during the clinical study were to be documented, commencing with the signing of the ICF through the End of Study (EOS) Visit (scheduled at 42 days post last IB1001 dose).

Adverse event reporting additional description:

A treatment emergent adverse event (TEAE) was defined as an AE that appeared during or after study treatment and was absent before, or an AE which was present before treatment and worsened while on treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Parent Study - Treatment with IB1001

Reporting group description:

The Safety Analysis Set (SAF) in the parent study consisted of all patients who received at least one dose of study drug (N-Acetyl-L-Leucine).

Reporting group title	Parent study - Post-treatment washout

Reporting group description: -

Serious adverse events	Parent Study - Treatment with IB1001	Parent study - Post-treatment washout	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 33 (12.12%)	0 / 31 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			

subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Parent Study - Treatment with IB1001	Parent study - Post-treatment washout	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 33 (33.33%)	5 / 31 (16.13%)	
Nervous system disorders			
Seizure			
subjects affected / exposed	3 / 33 (9.09%)	1 / 31 (3.23%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 33 (9.09%)	1 / 31 (3.23%)	
occurrences (all)	4	1	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 33 (6.06%)	0 / 31 (0.00%)	
occurrences (all)	2	2	

Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 33 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Rash pruritic			
subjects affected / exposed	2 / 33 (6.06%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Rhinitis			
subjects affected / exposed	2 / 33 (6.06%)	1 / 31 (3.23%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2019	The reason for this amendment was feedback from United States Food and Drug Administration (FDA) following the Investigational New Drug (IND) review and European National Regulatory Agencies (including Germany, Spain, Slovakia, and United Kingdom) during the review of Clinical Trial Applications and for general protocol updates regarding updates and/or corrections to the study procedures. Key changes were: • Visit 1 for "naïve" patients reclassified as "non-naïve" was not to be confirmed as Visit 0; patients instead returned for a repeat Visit 1 after study run-in; • Addition of a secondary endpoint examining CI-CS for the non-primary anchor test to further directly supplement the analysis of the primary endpoint; • Addition of NPC-CSS at Visit 1 to provide an additional measurement of disease severity at baseline of the Parent Study; • If consensus could not be achieved between 2 blinded raters on the CI-CS assessment, a third rater was used to agree with one of the 2 raters so that a final rating could be determined to improve the process for allowing a final CI CS rating for analysis to be selected; • Detailing of adjudication process for secondary CI-S assessment to improve process for allowing a final CI-S rating for analysis to be selected; • Addition of study protocol for the Extension Phase in Appendix 6 to provide procedures and design of the Extension Phase protocol.
04 February 2020	The reason for this amendment was the inclusion of the new IB1001 sachet formulation manufactured for clinical use in the Extension Phase of the IB1001-201 study Key changes were: • Addition that written informed consent could be obtained by an impartial witness to clarify that it was permissible for an impartial witness to sign the ICF on behalf of an adult patient who was mentally able to consent, physically unable to, and provided verbal consent to participate in the study; • Updating informed consent procedures for identifying adults lacking capacity to consent and legal representatives to ensure correct informed consent was obtained from each eligible participant; • Addition of new IMP dosage form for clinical use in the Extension Phase.
14 September 2020	The reason for this amendment was the inclusion of the impact of COVID-19 pandemic on the IB1001 201 study and inclusion of an additional 1-year treatment period in the Extension Phase. Key changes were: • Modifications to original study schema and study conduct (including, but not limited to, study duration, patient withdrawal, dose scheduling, remote assessments, vital signs, ECGs, safety laboratory measurements, monitoring, reconsent, DSMB involvement [DSMB reviewed the Sponsor guidances related to changes to the protocol due to COVID-19]) to reflect the impact of COVID-19 on the IB1001-201 study; • Addition of 1-year treatment period (Visit 11, Visit 12) in the Extension Phase; • Addition of ITT population and updated definition of mITT population; • Addition of key subgroups; • Addition of sensitivity measurement of secondary endpoint CI-CS on a 3-point scale, caregiver and patient CGI-C measures and EQ-5D VAS to be evaluated descriptively to reflect procedures defined in the SAP; • Updating procedures for analyzing the mITT population, including LOCF approach and sensitivity analysis

10 October 2022	The reason for this amendment was to align the Extension Phase analysis plan with the Pivotal IB1001-301 clinical trial Extension Phase design. Key changes were: • 5-Domain NPC-CSS instated as primary endpoint for the Extension Phase; • All other efficacy endpoints in the Extension Phase were to be considered exploratory and evaluated descriptively. (The amendment was dated 10-Oct-2022 and approved by the regulatory authority on 28-Nov-2022).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

This study was ongoing during the COVID-19 pandemic, and the conduct of this study was impacted by the COVID-19 pandemic.

Notes: