Clinical trial results:
A Phase III Study to Evaluate the Efficacy, Safety, and Tolerability of Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HYQVIA/HyQvia) and Immune Globulin Infusion (Human), 10% (GAMMAGARD LIQUID/KIOVIG) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

Summary

EudraCT number	2014-005496-87
Trial protocol	CZ DK DE SE GB ES NO SK GR AT PL HR IT
Global end of trial date	22 February 2022

Results information

Result version number	v1
This version publication date	10 March 2023
First version publication date	10 March 2023

Trial information

Trial identification

Sponsor protocol code	161403

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02549170
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.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	22 February 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 February 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate the efficacy of HYQVIA/HyQvia as a maintenance therapy for CIDP to prevent relapse of neuromuscular disability and impairment.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Serbia: 26
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Mexico: 6

Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	132
EEA total number of subjects	65

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	99
From 65 to 84 years	32
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 54 investigative sites from December 15, 2015 to February 23, 2022. Participants with a diagnosis of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) were enrolled in this study.

Pre-assignment

Screening details:

Participants received HYQVIA/HyQvia or 0.25% albumin placebo solution with rHuPH20 (Recombinant Human Hyaluronidase) for 6 months or until relapse in Epoch 1, who relapsed during Epoch 1 received GGL/KIOVIG (non-US sites) or GAMUNEX-C (US sites) in Epoch 2. 138 participants were enrolled; 132 participants received atleast one dose of study drug.

Period 1

Period 1 title	Epoch 1: Day 1 to Approximately 32 Weeks
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Epoch 1: Placebo with rHuPH20

Arm description:

Participants received rHuPH20 80 U/10 mL solution, followed by SC placebo infusion at matching infusion volume as per the participant’s pre-randomization monthly equivalent IG dose when administered every 2, 3, or 4 weeks for 31.54 weeks or until relapse.

Arm type	Placebo
Investigational medicinal product name	0.25% albumin placebo solution with rHuPH20
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Participants received placebo solution (0.25% human albumin in Lactated Ringer's solution) and rHuPH20.

Arm title	Epoch 1: HYQVIA/HyQvia

Arm description:

Participants received HYQVIA/HyQvia (rHuPH20) 80 U/g IG, followed by SC injection of immunoglobulin (IGI) 10% at the same monthly equivalent IG dose as per the individual participant’s pre-randomized IG dose when administered every 2, 3, or 4 weeks for 30.28 weeks or until relapse.

Arm type	Experimental
Investigational medicinal product name	HYQVIA
Investigational medicinal product code	
Other name	10%) with recombinant human hyaluronidase (rHuPH20), IGI, Immune Globulin Infusion 10% (Human) (IGI)
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Participants received HYQVIA/HyQvia SC which contains both Immune Globulin Infusion 10% (Human) (IGI, 10%) and recombinant human hyaluronidase (rHuPH20).

Number of subjects in period 1	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia
Started	70	62
Completed	46	48
Not completed	24	14
Relapsed and did not Enter E2	5	2
Did not Relapse;Ended Treatment (ET) From Epoch1	2	8
Relapsed and Entered Epoch 2 (E2)	17	4

Period 2

Period 2 title	Epoch 2: Up to Approximately Week 61
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG

Arm description:

Participants who were enrolled to receive placebo with rHuPH20 and achieved chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) relapse during Epoch 1 received the induction dose of GGL/KIOVIG 2 g/kg bi-weekly (BW), followed by IV infusion at the same monthly equivalent dose as per the participant's pre-randomization IGIV dosing regimen when administered every 3 weeks for 25.63 weeks or until relapse.

Arm type	Experimental
Investigational medicinal product name	IGIV GAMMAGARD LIQUID/KIOVIG
Investigational medicinal product code	
Other name	Immune Globulin Infusion (Human), Intravenous immunoglobulin G, 10% (GAMMAGARD LIQUID/KIOVIG), GAMMAGARD LIQUID
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Participants received GAMMAGARD LIQUID/KIOVIG.

Arm title	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG

Arm description:

Participants who were enrolled to receive HYQVIA/HyQvia (rHuPH20) and achieved CIDP relapse during Epoch 1 received the induction dose of GGL/KIOVIG 2 g/kg BW, followed by IV infusion at the same monthly equivalent dose as per the participant's pre-randomization IGIV dosing regimen when administered every 3 weeks for 28.67 weeks or until relapse.

Arm type	Experimental

Investigational medicinal product name	IGIV GAMMAGARD LIQUID/KIOVIG
Investigational medicinal product code	
Other name	Immune Globulin Infusion (Human), Intravenous immunoglobulin G, 10% (GAMMAGARD LIQUID/KIOVIG), GAMMAGARD LIQUID
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Participants received GAMMAGARD LIQUID/KIOVIG.

Arm title	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C

Arm description:

Participants who were enrolled to receive placebo with rHuPH20 and achieved CIDP relapse during Epoch 1 received the induction dose of GAMMUNEX-C 2 g/kg BW, followed by IV infusion at the same monthly equivalent dose as per the participant's pre-randomization IGIV dosing regimen when administered every 3 weeks for 24.33 weeks or until relapse.

Arm type	Experimental
Investigational medicinal product name	IGIV GAMUNEX®-C
Investigational medicinal product code	
Other name	Immune Globulin Infusion (Human), Intravenous immunoglobulin G, Approved IGIV product for US sites
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Participants received GAMUNEX®-C.

Number of subjects in period 2[1]	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C
Started	16	4	1
Completed	16	4	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Epoch 2 included those participants from Epoch 1 who achieved CIDP relapse.

Baseline characteristics

Reporting groups	
Reporting group title	Epoch 1: Placebo with rHuPH20
Reporting group description:	
Participants received rHuPH20 80 U/10 mL solution, followed by SC placebo infusion at matching infusion volume as per the participant's pre-randomization monthly equivalent IG dose when administered every 2, 3, or 4 weeks for 31.54 weeks or until relapse.	
Reporting group title	Epoch 1: HYQVIA/HyQvia
Reporting group description:	
Participants received HYQVIA/HyQvia (rHuPH20) 80 U/g IG, followed by SC injection of immunoglobulin (IGI) 10% at the same monthly equivalent IG dose as per the individual participant's pre-randomized IG dose when administered every 2, 3, or 4 weeks for 30.28 weeks or until relapse.	

Reporting group values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia	Total
Number of subjects	70	62	132
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	53.9	55.0	
standard deviation	± 13.42	± 14.26	-
Gender categorical Units: Subjects			
Female	32	26	58
Male	38	36	74
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2	1	3
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	64	58	122
More than one race	0	0	0
Unknown or Not Reported	4	3	7
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	14	9	23
Not Hispanic or Latino	46	47	93
Unknown or Not Reported	10	6	16

End points

End points reporting groups

Reporting group title	Epoch 1: Placebo with rHuPH20

Reporting group description:

Participants received rHuPH20 80 U/10 mL solution, followed by SC placebo infusion at matching infusion volume as per the participant's pre-randomization monthly equivalent IG dose when administered every 2, 3, or 4 weeks for 31.54 weeks or until relapse.

Reporting group title	Epoch 1: HYQVIA/HyQvia

Reporting group description:

Participants received HYQVIA/HyQvia (rHuPH20) 80 U/g IG, followed by SC injection of immunoglobulin (IGI) 10% at the same monthly equivalent IG dose as per the individual participant's pre-randomized IG dose when administered every 2, 3, or 4 weeks for 30.28 weeks or until relapse.

Reporting group title	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG

Reporting group description:

Participants who were enrolled to receive placebo with rHuPH20 and achieved chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) relapse during Epoch 1 received the induction dose of GGL/KIOVIG 2 g/kg bi-weekly (BW), followed by IV infusion at the same monthly equivalent dose as per the participant's pre-randomization IGIV dosing regimen when administered every 3 weeks for 25.63 weeks or until relapse.

Reporting group title	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG

Reporting group description:

Participants who were enrolled to receive HYQVIA/HyQvia (rHuPH20) and achieved CIDP relapse during Epoch 1 received the induction dose of GGL/KIOVIG 2 g/kg BW, followed by IV infusion at the same monthly equivalent dose as per the participant's pre-randomization IGIV dosing regimen when administered every 3 weeks for 28.67 weeks or until relapse.

Reporting group title	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C

Reporting group description:

Participants who were enrolled to receive placebo with rHuPH20 and achieved CIDP relapse during Epoch 1 received the induction dose of GAMMUNEX-C 2 g/kg BW, followed by IV infusion at the same monthly equivalent dose as per the participant's pre-randomization IGIV dosing regimen when administered every 3 weeks for 24.33 weeks or until relapse.

Subject analysis set title	Epoch 2: E1: Placebo Relapse - E2: IGIV
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who were enrolled to receive placebo with rHuPH20 and achieved CIDP relapse during Epoch 1 received the induction dose of GGL/KIOVIG or GAMMUNEX-C 2 g/kg BW, followed by IV infusion at the same monthly equivalent dose as per the participant's pre-randomization IGIV dosing regimen when administered every 3 weeks for 25.63 weeks or until relapse.

Subject analysis set title	Epoch 2: E1: HYQVIA Relapse - E2: IGIV
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who were enrolled to receive HYQVIA/HyQvia (rHuPH20) and achieved CIDP relapse during Epoch 1 received the induction dose of GGL/KIOVIG 2 g/kg BW, followed by IV infusion at the same monthly equivalent dose as per the participant's pre-randomization IGIV dosing regimen when administered every 3 weeks for 28.67 weeks or until relapse.

Primary: Epoch 1: Relapse Rate

End point title	Epoch 1: Relapse Rate

End point description:

Relapse rate is defined as the percentage of participants who experience a worsening of functional disability. Worsening of functional disability defined as an increase of >=1 point relative to the pre-subcutaneous (SC) treatment baseline score in 2 consecutive adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability score. The INCAT disability score is an effective and responsive tool to assess clinical response to treatment in CIDP. The disability score ranges from 0 to 10 points, where 0 is normal (eg, no upper limb problems and walking not affected) and 10 is severely incapacitated (eg, inability to move either arm for any purposeful movement and restricted to wheelchair, unable to stand and walk a few steps with help).

End point type	Primary

End point timeframe:

Week 32 End of Epoch 1 Treatment (EOET1)/Unscheduled relapse visit assessment (UV)/Early Termination (ET)

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: percentage of participants				
number (confidence interval 95%)	31.4 (21.76 to 43.03)	9.7 (4.51 to 19.55)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Epoch 1: HYQVIA/HyQvia v Epoch 1: Placebo with rHuPH20
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0045
Method	Chi-squared
Parameter estimate	Newcombe confidence interval
Point estimate	-21.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.45
upper limit	-7.94

Primary: Epoch 2: Responder Rate

End point title	Epoch 2: Responder Rate[1]

End point description:

Responder rate is defined as clinically meaningful improvement in functional ability defined as a decrease of >=1 point in the adjusted INCAT disability score at the completion of the intravenous (IV) treatment period [6 months] or at the last study visit of the IV treatment period, relative to the pre-IV treatment baseline score.

End point type	Primary

End point timeframe:

Up to 6 Months post-Epoch 1 (End of Epoch 2 Treatment [EOE2T])/Unscheduled visit assessment (UV)/Early Termination

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: Only descriptive analysis was performed for this endpoint.

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: percentage of participants				
number (confidence interval 95%)	100 (80.64 to 100.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Percentage of Participants Who Experience a Worsening of Functional Disability

End point title	Epoch 1: Percentage of Participants Who Experience a Worsening of Functional Disability

End point description:

Defined as one or more of the following: an increase of >=1 point relative to the pre-subcutaneous (SC) treatment baseline score in 2 consecutive adjusted Inflammatory Neuropathy Cause and Treatment disability scale (INCAT) scores; who experience CIDP worsening (defined as a >=8 kilo Pascal (kPa) decrease in the hand grip strength in the more affected hand); >=4 points decrease in raw Rasch-built Overall Disability Scale (R-ODS) relative to the pre-SC treatment baseline score (at the time of withdrawal from the SC treatment period). Participants are rounded off to nearest single decimal point.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	56		
Units: percentage of participants				
number (confidence interval 95%)	54.4 (42.66 to 65.70)	37.5 (26.01 to 50.59)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Epoch 1: HYQVIA/HyQvia v Epoch 1: Placebo with rHuPH20

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0896 [2]
Method	Chi-squared corrected
Parameter estimate	Newcombe confidence interval
Point estimate	-16.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.02
upper limit	0.69

Notes:

[2] - The treatment groups were compared using a continuity-corrected chi-square test.

Secondary: Time to Relapse

End point title	Time to Relapse

End point description:

Time to relapse is defined as time from the date of the first SC administration of HYQVIA/HyQvia or placebo with rHuPH20 to the date of relapse. Participants who did not relapse were censored at their end of study.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: days				
median (full range (min-max))	99 (20 to 221)	99 (7 to 217)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Epoch 1: HYQVIA/HyQvia v Epoch 1: Placebo with rHuPH20
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Wilcoxon Survival Test

Secondary: Epoch 1: Change From Pre-Subcutaneous (SC) Treatment Baseline in

Rasch-built Overall Disability Scale (R-ODS)

End point title	Epoch 1: Change From Pre-Subcutaneous (SC) Treatment Baseline in Rasch-built Overall Disability Scale (R-ODS)

End point description:

The Rasch-Built Overall Disability Scale (R-ODS) is a participant self-reported, linearly-weighted overall disability scale that was specifically designed to capture activity and social participation limitations in participant with immune-mediated peripheral neuropathies including CIDP. The R-ODS is comprised of 24 items for which participants are asked to rate their functioning (ie, no difficulty, some difficulty, or could not do) related to a variety of everyday tasks at the moment of completion. The raw summed R-ODS score range is 0 to 48. The centile metric R-ODS score range is 0 to 100. The centile metric R-ODS score was used in the ANCOVA analysis. ANCOVA was used for the analysis.

End point type	Secondary

End point timeframe:

Pre-subcutaneous (SC) treatment baseline, then weekly through Epoch 1 (approximately 7.3 months)

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	59		
Units: score on a scale				
least squares mean (standard error)	-6.1 (± 1.64)	-0.9 (± 1.69)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Epoch 1: HYQVIA/HyQvia v Epoch 1: Placebo with rHuPH20
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	9.9

Secondary: Epoch 1: Number of Participants Experiencing Any Treatment-Emergent Serious and/or Non-serious Adverse Events (SAEs and/or AEs), Regardless of Causality

End point title	Epoch 1: Number of Participants Experiencing Any Treatment-Emergent Serious and/or Non-serious Adverse Events (SAEs and/or AEs), Regardless of Causality

End point description:

An AE is defined as any untoward medical occurrence in participant administered an Investigational Product (IP) that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP. A SAE is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria: outcome is fatal/results in death, is life-threatening, requires inpatient hospitalization or results in prolongation of an existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a medically important event, thromboembolic events, hemolytic anemia. A nonserious AE is an AE that does not meet the criteria.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: participants				
Any TEAE	40	49		
Any Serious TEAE	5	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Number of Participants Experiencing Causally Related Serious and/or Non-Serious Adverse Events (SAEs and/or AEs)

End point title	Epoch 1: Number of Participants Experiencing Causally Related Serious and/or Non-Serious Adverse Events (SAEs and/or AEs)

End point description:

AE=any untoward medical occurrence in participant administered IP. AE can therefore be any unfavorable and unintended sign (e.g.,abnormal laboratory finding), symptom (e.g.,rash, pain, discomfort, fever, dizziness, etc.), disease (e.g.,peritonitis,bacteremia,etc.), outcome of death temporally associated with use of IP,considered causally related to the IP. SAE=untoward medical occurrence that at any dose meets following criteria: outcome is fatal/results in death, is life-threatening, requires inpatient hospitalization/results in prolongation of an existing hospitalization, results in persistent or significant disability/incapacity, is congenital anomaly/birth defect, is medically important event, thromboembolic events, hemolytic anemia. Non-SAE=AE not meeting this criteria. AE recorded by investigator as possibly/probably related to IP is considered related AE, any AE recorded as unlikely/not related is considered unrelated AE.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: participants				
Any IP-related TEAE	19	38		
Any Serious IP-related TEAE	5	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Number of Participants With Serious and/or Non-serious Adverse Reactions (ARs) Plus Suspected ARs

End point title	Epoch 1: Number of Participants With Serious and/or Non-serious Adverse Reactions (ARs) Plus Suspected ARs

End point description:

An AR plus suspected AR is any AE that meets any of the following criteria: an AE considered by either the investigator and/or the sponsor to be possibly or probably related to IP administration, or that begins during infusion of IP or within 72 h following the end of IP infusion, or AE for which causality assessment is missing or indeterminate. A SAE is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria: outcome is fatal/results in death, is life-threatening, requires inpatient hospitalization or results in prolongation of an existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a medically important event, thromboembolic events, hemolytic anemia. A nonserious AE is an AE that does not meet the criteria.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: participants				
All AR/SAR	27	41		
Serious AR/SAR	5	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Number of Causally Related Serious and/or Non-serious Adverse Events (SAEs and/or AEs) Associated With Infusions

End point title	Epoch 1: Number of Causally Related Serious and/or Non-serious Adverse Events (SAEs and/or AEs) Associated With

	Infusions

End point description:

AE=any untoward medical occurrence in participant administered IP.AE can therefore be any unfavorable and unintended sign(e.g.,abnormal laboratory finding),symptom(e.g.,rash,pain,discomfort,fever,dizziness,etc.), disease (e.g.,peritonitis,bacteremia,etc.),outcome of death temporally associated with use of IP, whether or not considered causally related to the IP.SAE=untoward medical occurrence that at any dose meets following criteria:outcome is fatal/results in death,is life-threatening,requires inpatient hospitalization/results in prolongation of an existing hospitalization,results in persistent or significant disability/incapacity,is congenital anomaly/birth defect,is medically important event, (e.g., thromboembolic events,hemolytic anemia).Non-SAE=AE not meeting this criteria.AE recorded by investigator as possibly/probably related to IP is considered related AE,any AE recorded as unlikely/not

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: causally related events in participants				
number (not applicable)				
Casually Related Non-serious Adverse Events	53	223		
Casually Related Serious Adverse Events	5	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Number Treatment-emergent Serious and/or Non-serious Adverse Events (SAEs and/or AEs) Associated With Infusions Regardless of Causality

End point title	Epoch 1: Number Treatment-emergent Serious and/or Non-serious Adverse Events (SAEs and/or AEs) Associated With Infusions Regardless of Causality

End point description:

AE: any untoward medical occurrence in participant administered an IP that does not necessarily have a causal relationship with the treatment. AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP. SAE: an untoward medical occurrence that at any dose meets one or more of the following criteria: outcome is fatal/results in death, is life-threatening, requires inpatient hospitalization or results in prolongation of an existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a medically important event, thromboembolic events, hemolytic anemia. A nonserious AE is an AE that does not meet the criteria. Participants can have more than one adverse event.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: events in participants				
number (not applicable)				
Non-serious AEs	144	340		
Serious AEs	5	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Number Adverse Events (AEs) Temporally Associated With Infusions

End point title	Epoch 1: Number Adverse Events (AEs) Temporally Associated With Infusions

End point description:

AEs occurring during an infusion or within 72 hours after completion of an infusion. An AE is defined as any untoward medical occurrence in participant administered an Investigational Product (IP) that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP. Participants can have more than one temporally associated with infusion adverse event.

End point type	Secondary

End point timeframe:

During an infusion or within 72 hours after completion of an infusion post-Epoch 1

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: events in participants				
number (not applicable)	61	251		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Number of Serious and/or Non-serious Adverse Reactions

(ARs) plus Suspected ARs Associated With Infusions

End point title	Epoch 1: Number of Serious and/or Non-serious Adverse Reactions (ARs) plus Suspected ARs Associated With Infusions

End point description:

AR plus suspected AR: any AE that meets any of the criteria: AE considered by either investigator and/or the sponsor to be possibly or probably related to IP administration, or that begins during infusion of IP or within 72 h following end of IP infusion, or AE for which causality assessment is missing or indeterminate. SAE: untoward medical occurrence that at any dose meets one or more of following criteria: outcome is fatal/results in death, is life-threatening, requires inpatient hospitalization or results in prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a medically important event, thromboembolic events, hemolytic anemia. Nonserious AE is AE that does not meet the criteria. Infusion per event = number of events / total number of infusions administered (started) to participants in analysis set. Participants can have more than one AR/suspected AR associated with infusion.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: events in participants				
number (not applicable)				
Non-Serious AR/Suspected AR	76	261		
Serious AR/Suspected AR	5	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Number of Treatment-emergent Systemic Adverse Events (AEs) Associated With Infusions

End point title	Epoch 1: Number of Treatment-emergent Systemic Adverse Events (AEs) Associated With Infusions

End point description:

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments. Participants can have more than one TEAE associated with infusion.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: events in participants				
number (not applicable)	149	342		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Number Treatment-emergent Local Infusion Site Reactions Associated With Infusions

End point title	Epoch 1: Number Treatment-emergent Local Infusion Site Reactions Associated With Infusions

End point description:

AE=any untoward medical occurrence in participant administered an IP that does not have causal relationship with treatment. AE can be any unfavorable and unintended sign (e.g., abnormal laboratory finding), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP. Adverse reaction/suspected adverse reaction=AE that is considered by the investigator to be possibly or probably related to IP administration, or for which the causality is indeterminate or missing, or that begins during infusion of IP or within 72 hours following the end of IP infusion. Treatment-emergent adverse events (TEAEs) are defined as adverse events that occurred during or after administration of the first dose of IP. Infusion site adverse events and injection site adverse events refer to the same type of adverse events.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: events in participants				
number (not applicable)	20	141		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Number of Infusions in Participants for Which the Infusion Rate Was Reduced And/Or the Infusion Was Interrupted or Stopped Due to Intolerability And/Or Adverse Events (AEs)

End point title	Epoch 1: Number of Infusions in Participants for Which the Infusion Rate Was Reduced And/Or the Infusion Was Interrupted or Stopped Due to Intolerability And/Or Adverse

	Events (AEs)

End point description:

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70[3]	62[4]		
Units: number of infusions				
number (not applicable)	1	3		

Notes:

[3] - Units analysed is 647.

[4] - Units analysed is 600.

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Rates of Systemic and Local Adverse Events (AEs), Regardless of Causality, Expressed as Number of Events Per Infusion

End point title	Epoch 1: Rates of Systemic and Local Adverse Events (AEs), Regardless of Causality, Expressed as Number of Events Per Infusion

End point description:

An AE is defined as any untoward medical occurrence in participant administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP. Data for number of events per infusion is assessed as follows: Per infusion = number of events / total number of infusions administered (started) to participants in the analysis set.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: number of AEs/infusion				
number (not applicable)				
Systemic Adverse Events	0.20	0.34		
Local Adverse Events	0.03	0.24		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Rates of Systemic and Local Adverse Events (AEs), Regardless of Causality, Expressed as Number of Events Per Participant

End point title	Epoch 1: Rates of Systemic and Local Adverse Events (AEs), Regardless of Causality, Expressed as Number of Events Per Participant

End point description:

An AE is defined as any untoward medical occurrence in participant administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP. Data for number of events per participant is assessed as follows: Per participant = number of events / total number of participants in the safety analysis set.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: number of AEs/participant				
number (not applicable)				
Systemic AEs	1.84	3.24		
Local AEs	0.29	2.27		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Rates of Systemic and Local Adverse Events (AEs), Regardless of Causality, Expressed as Number of Events Per 1000 Participant-year

End point title	Epoch 1: Rates of Systemic and Local Adverse Events (AEs), Regardless of Causality, Expressed as Number of Events Per 1000 Participant-year

End point description:

An AE is defined as any untoward medical occurrence in participant administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever,

dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP. Data for number of events per 1000 participant-years is assessed as follows: Per 1000 participant-years = 1000 x (number of events / total number of days of exposure, i.e., the sum of duration of treatment for all participants in the safety analysis set, divided by 365.25)

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: number of AEs/1000 participant-year				
number (not applicable)				
Systemic AEs	4689.22	7341.52		
Local AEs	727.01	5150.02		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Rates of Causally Related Systemic and Local Adverse Events (AEs), Expressed As Number of Events Per Infusion

End point title	Epoch 1: Rates of Causally Related Systemic and Local Adverse Events (AEs), Expressed As Number of Events Per Infusion

End point description:

An AE is defined as any untoward medical occurrence in participant administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP. An AE that is recorded by the investigator as possibly related or probably related to IP was considered a related AE, and any AE recorded as unlikely related or not related was considered unrelated AE.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: number of AEs/infusion				
number (not applicable)				
IP-Related Systemic TEAE	0.06	0.17		

IP-Related Local TEAE	0.02	0.21		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Rates of Causally Related Systemic and Local Adverse Events (AEs), Expressed As Number of Events Per Participant

End point title	Epoch 1: Rates of Causally Related Systemic and Local Adverse Events (AEs), Expressed As Number of Events Per Participant

End point description:

An AE is defined as any untoward medical occurrence in participant administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP. An AE that is recorded by the investigator as possibly related or probably related to IP was considered a related AE, and any AE recorded as unlikely related or not related was considered unrelated AE.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: number of AEs/participant				
number (not applicable)				
IP-related Systemic TEAE	0.54	1.6		
IP-related Local TEAE	0.21	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Rates of Causally Related Systemic and Local Adverse Events (AEs), Expressed as Number of Events per Participant-year

End point title	Epoch 1: Rates of Causally Related Systemic and Local Adverse Events (AEs), Expressed as Number of Events per Participant-year

End point description:

An AE is defined as any untoward medical occurrence in participant administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated

with the use of an IP, whether or not considered causally related to the IP. An AE that is recorded by the investigator as possibly related or probably related to IP was considered a related AE, and any AE recorded as unlikely related or not related was considered unrelated AE.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: number of AEs/1000 participant-year				
number (not applicable)				
IP-related Systemic TEAE	1381.32	3615.98		
IP-related Local TEAE	545.26	4529.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Rates of Systemic and Local Adverse Reactions (ARs) plus Suspected ARs, Expressed as Number of Events per Infusion

End point title	Epoch 1: Rates of Systemic and Local Adverse Reactions (ARs) plus Suspected ARs, Expressed as Number of Events per Infusion

End point description:

An AR plus suspected AR is any AE that meets any of the following criteria: an AE considered by either the investigator and/or the sponsor to be possibly or probably related to IP administration, or that begins during infusion of IP or within 72 h following the end of IP infusion, or AE for which causality assessment is missing or indeterminate. Data for number of events per infusion is assessed as follows: Per infusion = number of events / total number of infusions administered (started) to participants in the analysis set.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: number of ARs/infusion				
number (not applicable)				
Systemic Plus Suspected ARs	0.09	0.20		
Local Plus Suspected ARs	0.03	0.24		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Rates of Systemic and Local Adverse Reactions (ARs) plus Suspected ARs, Expressed as Number of Events per Participant

End point title	Epoch 1: Rates of Systemic and Local Adverse Reactions (ARs) plus Suspected ARs, Expressed as Number of Events per Participant

End point description:

An AR plus suspected AR is any AE that meets any of the following criteria: an AE considered by either the investigator and/or the sponsor to be possibly or probably related to IP administration, or that begins during infusion of IP or within 72 h following the end of IP infusion, or AE for which causality assessment is missing or indeterminate. Data for number of events per participant is assessed as follows: Per participant = number of events / total number of participants in the safety analysis set.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: number of ARs/participant				
number (not applicable)				
Systemic Plus Suspected ARs	0.80	1.94		
Local Plus Suspected ARs	0.29	2.27		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Rates of Systemic and Local Adverse Reactions (ARs) plus Suspected ARs, Expressed as Number of Events per 1000 Participant-Year

End point title	Epoch 1: Rates of Systemic and Local Adverse Reactions (ARs) plus Suspected ARs, Expressed as Number of Events per 1000 Participant-Year

End point description:

An AR plus suspected AR is any AE that meets any of the following criteria: an AE considered by either the investigator and/or the sponsor to be possibly or probably related to IP administration, or that begins during infusion of IP or within 72 h following the end of IP infusion, or AE for which causality assessment is missing or indeterminate. Data for number of events per 1000 participant-years is assessed as follows: Per 1000 participant-years = 1000 x (number of events / total number of days of

exposure, i.e., the sum of duration of treatment for all participants in the safety analysis set, divided by 365.25)

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: number of ARs/1000 Participant year				
number (not applicable)				
Systemic Plus Suspected ARs	2035.63	4383.00		
Local Plus Suspected ARs	727.01	5150.02		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Number of Participants Who Develop Binding and/or Neutralizing Antibodies to Recombinant Human Hyaluronidase (rHuPH20)

End point title	Epoch 1: Number of Participants Who Develop Binding and/or Neutralizing Antibodies to Recombinant Human Hyaluronidase (rHuPH20)

End point description:

Number of participants who developed binding and/or neutralizing antibodies to rHuPH20 in Epoch 1 were reported. High-binding antibodies is defined as number of participants who had at least one anti-rHuPH20 antibody titer ≥1:160 during treatment.

End point type	Secondary

End point timeframe:

Week 32 (EOET1)/UV/ET

End point values	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	62		
Units: participants	1	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Number of Participants Experiencing Any Treatment-emergent Serious and/or Non-serious Adverse Events (SAEs and/or AEs), Regardless of Causality

End point title	Epoch 2: Number of Participants Experiencing Any Treatment-emergent Serious and/or Non-serious Adverse Events (SAEs and/or AEs), Regardless of Causality

End point description:

Number of participants experiencing any treatment-emergent serious and/or non-serious adverse events regardless of causality in Epoch 2 was reported.

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: participants				
Any IP related TEAE	11	3	1	
Any IP related serious TEAE	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Number of Participants Experiencing Causally Related Serious and/or Non-serious Adverse Events (SAEs and/or AEs)

End point title	Epoch 2: Number of Participants Experiencing Causally Related Serious and/or Non-serious Adverse Events (SAEs and/or AEs)

End point description:

AE=any untoward medical occurrence in participant administered IP.AE can therefore be any unfavorable and unintended sign(e.g.,abnormal laboratory finding),symptom(e.g.,rash,pain,discomfort,fever,dizziness,etc.), disease (e.g.,peritonitis,bacteremia,etc.),outcome of death temporally associated with use of IP, whether or not considered causally related to the IP.SAE=untoward medical occurrence that at any dose meets following criteria:outcome is fatal/results in death,is life-threatening,requires inpatient hospitalization/results in prolongation of an existing hospitalization,results in persistent or significant disability/incapacity,is congenital anomaly/birth defect,is medically important event, (e.g., thromboembolic events,hemolytic anemia).Non-SAE=AE not meeting this criteria.AE recorded by investigator as possibly/probably related to IP is considered related AE,any AE recorded as unlikely/not

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: participants				
Causally related AEs	8	3	0	
Causally related SAEs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Number of Participants with Serious and/or Non-serious Adverse Reactions (ARs) plus Suspected ARs

End point title	Epoch 2: Number of Participants with Serious and/or Non-serious Adverse Reactions (ARs) plus Suspected ARs

End point description:

An adverse reaction/suspected adverse reaction is defined as an Adverse Event that is considered by the investigator to be possibly or probably related to IP administration, or for which the causality is indeterminate or missing, or that begins during infusion of IP or within 72 hours following the end of IP infusion.

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: participants				
Any AR/SAR	10	3	0	
Any Serious AR/SAR	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Number of Treatment-emergent Serious and/or Non-serious Adverse Events (SAEs and/or AEs) Associated With Infusions Regardless of Causality

End point title	Epoch 2: Number of Treatment-emergent Serious and/or Non-serious Adverse Events (SAEs and/or AEs) Associated With Infusions Regardless of Causality

End point description:

A SAE is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria: outcome is fatal/results in death, is life-threatening, requires inpatient hospitalization or results in prolongation of an existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a medically important event, thromboembolic events, hemolytic anemia. A nonserious AE is an AE that does not meet the criteria. An AR plus suspected AR is any AE that meets any of the following criteria: an AE considered by either the investigator and/or the sponsor to be possibly or probably related to IP administration, or that begins during infusion of IP or within 72 h following the end of IP infusion, or AE for which causality assessment is missing or indeterminate. Participants can have more than one adverse event.

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: events in participants				
number (not applicable)				
Serious AEs	0	0	0	
Non-serious AEs	35	25	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Number of Causally Related Serious and/or Non-serious Adverse Events (SAEs and/or AEs) Associated With Infusions

End point title	Epoch 2: Number of Causally Related Serious and/or Non-serious Adverse Events (SAEs and/or AEs) Associated With Infusions

End point description:

AE=any untoward medical occurrence in participant administered IP.AE can therefore be any unfavorable and unintended sign(e.g.,abnormal laboratory finding),symptom(e.g.,rash,pain,discomfort,fever,dizziness,etc.), disease (e.g.,peritonitis,bacteremia,etc.),outcome of death temporally associated with use of IP, whether or not considered causally related to the IP.SAE=untoward medical occurrence that at any dose meets following criteria:outcome is fatal/results in death,is life-threatening,requires inpatient hospitalization/results in prolongation of an existing hospitalization,results in persistent or significant disability/incapacity,is congenital anomaly/birth defect,is medically important event, (e.g.; thromboembolic events,hemolytic anemia).Non-SAE=AE not meeting this criteria.AE recorded by investigator as possibly/probably related to IP is considered related AE,any AE recorded as unlikely/not

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: events in participants				
number (not applicable)				
Any TEAE	23	0	0	
Any serious TEAE	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Number of Serious and/or Non-serious Adverse Reactions (ARs) plus Suspected ARs Associated With Infusions

End point title	Epoch 2: Number of Serious and/or Non-serious Adverse Reactions (ARs) plus Suspected ARs Associated With Infusions

End point description:

A SAE is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria: outcome is fatal/results in death, is life-threatening, requires inpatient hospitalization or results in prolongation of an existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a medically important event, thromboembolic events, hemolytic anemia. A nonserious AE is an AE that does not meet the criteria. An AR plus suspected AR is any AE that meets any of the following criteria: an AE considered by either the investigator and/or the sponsor to be possibly or probably related to IP administration, or that begins during infusion of IP or within 72 h following the end of IP infusion, or AE for which causality assessment is missing or indeterminate. Participants can have more than one AR/SAR.

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: events in participants				
number (not applicable)	28	11	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Number of Adverse Events (AEs) Temporally Associated With Infusions

End point title	Epoch 2: Number of Adverse Events (AEs) Temporally Associated With Infusions

End point description:

AEs occurring during an infusion or within 72 hours after completion of an infusion. An AE is defined as any untoward medical occurrence in participant administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP. Participants can have more than one adverse event.

End point type	Secondary

End point timeframe:

During an infusion or within 72 hours after completion of an infusion post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: events in participants				
number (not applicable)	25	11	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Number of Treatment-emergent Systemic Adverse Events (AEs) Associated With Infusions

End point title	Epoch 2: Number of Treatment-emergent Systemic Adverse Events (AEs) Associated With Infusions

End point description:

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments. Participants can have more than one treatment-emergent systemic AEs.

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: events in participants				
number (not applicable)	35	25	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Number of Treatment-emergent Local Infusion Site Reactions Associated With Infusions

End point title	Epoch 2: Number of Treatment-emergent Local Infusion Site Reactions Associated With Infusions

End point description:

AE=any untoward medical occurrence in participant administered an IP that does not have causal relationship with treatment. AE can be any unfavorable and unintended sign (e.g., abnormal laboratory finding), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP. Adverse reaction/suspected adverse reaction=AE that is considered by the investigator to be possibly or probably related to IP administration, or for which the causality is indeterminate or missing, or that begins during infusion of IP or within 72 hours following the end of IP infusion. TEAEs are defined as adverse events that occurred during or after administration of the first dose of IP. Infusion site adverse events and injection site adverse events refer to the same type of adverse events.

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: events in participants				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Number of Infusions for Which the Infusion Rate Was Reduced and/or the Infusion Was Interrupted or Stopped Due to Intolerability and/or Adverse Events (AEs)

End point title	Epoch 2: Number of Infusions for Which the Infusion Rate Was Reduced and/or the Infusion Was Interrupted or Stopped Due to Intolerability and/or Adverse Events (AEs)

End point description:

An AE is defined as any untoward medical occurrence in participant administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and

unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[5]	4[6]		
Units: number of infusions				
number (not applicable)	1	1		

Notes:

[5] - Number of infusion is 328.

[6] - Number of infusion is 61.

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Rates of Systemic and Local Adverse Events (AEs), Regardless of Causality, Expressed as Number of Events Per Infusion

End point title	Epoch 2: Rates of Systemic and Local Adverse Events (AEs), Regardless of Causality, Expressed as Number of Events Per Infusion

End point description:

An AE is defined as any untoward medical occurrence in participant administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: number of AEs/infusion				
number (not applicable)				
Systemic AEs	0.11	0.41	0.06	
Local AEs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Rates of Systemic and Local Adverse Events (AEs), Regardless of Causality, Expressed as Number of Events Per Participant

End point title	Epoch 2: Rates of Systemic and Local Adverse Events (AEs), Regardless of Causality, Expressed as Number of Events Per Participant

End point description:

An AE is defined as any untoward medical occurrence in participant administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: number of AEs/participant				
number (not applicable)				
Systemic AEs	2.19	6.25	1.00	
Local AEs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Rates of Systemic and Local Adverse Events (AEs), Regardless of Causality, Expressed as Number of Events Per 1000 Participant-year

End point title	Epoch 2: Rates of Systemic and Local Adverse Events (AEs), Regardless of Causality, Expressed as Number of Events Per 1000 Participant-year

End point description:

An AE is defined as any untoward medical occurrence in participant administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated

with the use of an IP, whether or not considered causally related to the IP.

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: number of AEs/1000 participant-year				
number (not applicable)				
Systemic AEs	4645.26	12806.80	2135.96	
Local AEs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Rates of Causally Related Systemic and Local Adverse Events (AEs), Expressed As Number of Events Per Infusion

End point title	Epoch 2: Rates of Causally Related Systemic and Local Adverse Events (AEs), Expressed As Number of Events Per Infusion

End point description:

An AE is defined as any untoward medical occurrence in participant administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP. An AE that is recorded by the investigator as possibly related or probably related to IP was considered a related AE, and any AE recorded as unlikely related or not related was considered unrelated AE.

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: number of AEs/infusion				
number (not applicable)				
IP-related Systemic Adverse Events	0.07	0.13	0	
IP-related Local Adverse Events	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Rates of Causally Related Systemic and Local Adverse Events (AEs), Expressed as Number of Events Per Participant

End point title	Epoch 2: Rates of Causally Related Systemic and Local Adverse Events (AEs), Expressed as Number of Events Per Participant

End point description:

An AE is defined as any untoward medical occurrence in participant administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP. An AE that is recorded by the investigator as possibly related or probably related to IP was considered a related AE, and any AE recorded as unlikely related or not related was considered unrelated AE.

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: number of AEs/participant				
number (not applicable)				
IP-related Systemic Adverse Events	1.44	2	0	
IP-related Local Adverse Events	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Rates of Causally Related Systemic and Local Adverse Events (AEs), Expressed as Number of Events Per Participant-Year

End point title	Epoch 2: Rates of Causally Related Systemic and Local Adverse Events (AEs), Expressed as Number of Events Per Participant-Year

End point description:

An AE is defined as any untoward medical occurrence in participant administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever,

dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP. An AE that is recorded by the investigator as possibly related or probably related to IP was considered a related AE, and any AE recorded as unlikely related or not related was considered unrelated AE.

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: number of AEs/1000 participant-year				
number (not applicable)				
IP-related Systemic Adverse Events	3052.6	4098.18	0	
IP-related Local Adverse Events	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Rates of Systemic and Local Adverse Reactions (ARs) plus Suspected Ars, Expressed as Number of Events Per Infusion

End point title	Epoch 2: Rates of Systemic and Local Adverse Reactions (ARs) plus Suspected Ars, Expressed as Number of Events Per Infusion

End point description:

An AR plus suspected AR is any AE that meets any of the following criteria: an AE considered by either the investigator and/or the sponsor to be possibly or probably related to IP administration, or that begins during infusion of IP or within 72 h following the end of IP infusion, or AE for which causality assessment is missing or indeterminate. Data for number of events per infusion is assessed as follows: Per infusion = number of events / total number of infusions administered (started) to participants in the analysis set.

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: number of ARs/infusion				
number (not applicable)				
Systemic plus Suspected ARs	0.09	0.18	0	

Local plus Suspected ARs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Rates of Systemic and Local Adverse Reactions (ARs) plus Suspected ARs, Expressed as Number of Events Per Participant

End point title	Epoch 2: Rates of Systemic and Local Adverse Reactions (ARs) plus Suspected ARs, Expressed as Number of Events Per Participant

End point description:

An AR plus suspected AR is any AE that meets any of the following criteria: an AE considered by either the investigator and/or the sponsor to be possibly or probably related to IP administration, or that begins during infusion of IP or within 72 h following the end of IP infusion, or AE for which causality assessment is missing or indeterminate. Data for number of events per participant is assessed as follows: Per participant = number of events / total number of participants in the safety analysis set.

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: number of ARs/participant				
number (not applicable)				
Systemic plus Suspected ARs	1.75	2.75	0	
Local plus Suspected ARs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Rates of Systemic and Local Adverse Reactions (ARs) plus Suspected ARs, Expressed as Number of Events Per 1000 Participant-Year

End point title	Epoch 2: Rates of Systemic and Local Adverse Reactions (ARs) plus Suspected ARs, Expressed as Number of Events Per 1000 Participant-Year

End point description:

An AR plus suspected AR is any AE that meets any of the following criteria: an AE considered by either the investigator and/or the sponsor to be possibly or probably related to IP administration, or that begins during infusion of IP or within 72 h following the end of IP infusion, or AE for which causality assessment is missing or indeterminate. Data for number of events per 1000 participant-years is

assessed as follows: Per 1000 participant-years = 1000 x (number of events / total number of days of exposure, i.e., the sum of duration of treatment for all participants in the safety analysis set, divided by 365.25)

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	4	1	
Units: number of ARs/1000 participant-year				
number (not applicable)				
Systemic plus Suspected ARs	3716.21	5634.99	0	
Local plus Suspected ARs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Percentage of Participants With Clinically Meaningful Improvement in Functional Ability

End point title	Epoch 2: Percentage of Participants With Clinically Meaningful Improvement in Functional Ability

End point description:

Defined as one or more of the following: a decrease of >=1 point in the adjusted Inflammatory Neuropathy Cause and Treatment disability scale (INCAT) score at 2 consecutive time points; who experience CIDP improvement (defined as ≥8 kilo Pascal (kPa) increase in hand grip strength in the more affected hand; >=4 points increase in Rasch-built Overall Disability Scale (R-ODS)) at the completion of the intravenous (IV) treatment period [6 months] or at the last study visit of the IV treatment period, relative to the pre-IV treatment baseline score.

End point type	Secondary

End point timeframe:

Throughout Epoch 2, up to 6 months post-Epoch 1

End point values	Epoch 2: E1: Placebo Relapse - E2: IGIV	Epoch 2: E1: HYQVIA Relapse - E2: IGIV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	4		
Units: percentage of participants				
number (not applicable)	100	100		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of signing of the informed consent form up to the end of the study, approximately 74 months.

Adverse event reporting additional description:

Epoch 1 safety analysis set included all participants who received any study treatment. Epoch 2 safety analysis set included all participants who had a relapse in Epoch 1, entered Epoch 2, and received IGIV treatment with either GGL/KIOVIG or GAMUNEX-C.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Epoch 1: Placebo with rHuPH20

Reporting group description:

Participants received rHuPH20 80 U/10 mL solution, followed by SC placebo infusion at matching infusion volume as per the participant's pre-randomization monthly equivalent IG dose when administered every 2, 3, or 4 weeks for 30.28 weeks or until relapse.

Reporting group title	Epoch 1: HYQVIA/HyQvia

Reporting group description:

Participants received HYQVIA/HyQvia (rHuPH20) 80 U/g IG, followed by SC injection of immunoglobulin (IGI) 10% at the same monthly equivalent IG dose as per the individual participant's pre-randomized IG dose when administered every 2, 3, or 4 weeks for 31.54 weeks or until relapse.

Reporting group title	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C

Reporting group description:

Participants who were enrolled to receive placebo with rHuPH20 and achieved CIDP relapse during Epoch 1 received the induction dose of GAMMUNEX-C 2 g/kg BW, followed by IV infusion at the same monthly equivalent dose as per the participant's pre-randomization IGIV dosing regimen when administered every 3 weeks for 24.33 weeks or until relapse.

Reporting group title	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG

Reporting group description:

Participants who were enrolled to receive HYQVIA/HyQvia (rHuPH20) and achieved CIDP relapse during Epoch 1 received the induction dose of GGL/KIOVIG 2 g/kg BW, followed by IV infusion at the same monthly equivalent dose as per the participant's pre-randomization IGIV dosing regimen when administered every 3 weeks for 28.67 weeks or until relapse.

Reporting group title	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG

Reporting group description:

Participants who were enrolled to receive placebo with rHuPH20 and achieved CIDP relapse during Epoch 1 received the induction dose of GGL/KIOVIG 2 g/kg BW, followed by IV infusion at the same monthly equivalent dose as per the participant's pre-randomization IGIV dosing regimen when administered every 3 weeks for 25.63 weeks or until relapse.

Serious adverse events	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 70 (7.14%)	2 / 62 (3.23%)	0 / 1 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 62 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 70 (0.00%)	1 / 62 (1.61%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic inflammatory demyelinating polyradiculoneuropathy			
subjects affected / exposed	4 / 70 (5.71%)	0 / 62 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Otitis media chronic			
subjects affected / exposed	0 / 70 (0.00%)	1 / 62 (1.61%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic inflammatory demyelinating polyradiculoneuropathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Otitis media chronic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	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	Epoch 1: Placebo with rHuPH20	Epoch 1: HYQVIA/HyQvia	Epoch 2: E1: Placebo Relapse - E2: GAMMUNEX-C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 70 (27.14%)	42 / 62 (67.74%)	1 / 1 (100.00%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 70 (0.00%)	0 / 62 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 70 (1.43%)	4 / 62 (6.45%)	0 / 1 (0.00%)
occurrences (all)	1	10	0
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 70 (11.43%)	8 / 62 (12.90%)	0 / 1 (0.00%)
occurrences (all)	17	25	0
Dizziness			
subjects affected / exposed	1 / 70 (1.43%)	4 / 62 (6.45%)	0 / 1 (0.00%)
occurrences (all)	1	5	0
Somnolence			
subjects affected / exposed	0 / 70 (0.00%)	1 / 62 (1.61%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Migraine			

subjects affected / exposed	0 / 70 (0.00%)	0 / 62 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 70 (0.00%)	2 / 62 (3.23%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 62 (1.61%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Anaemia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 62 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 62 (1.61%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 70 (0.00%)	0 / 62 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	0 / 70 (0.00%)	1 / 62 (1.61%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	2 / 70 (2.86%)	6 / 62 (9.68%)	0 / 1 (0.00%)
occurrences (all)	2	9	0
Illness			
subjects affected / exposed	0 / 70 (0.00%)	0 / 62 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Infusion site erythema			
subjects affected / exposed	0 / 70 (0.00%)	6 / 62 (9.68%)	0 / 1 (0.00%)
occurrences (all)	0	20	0
Infusion site oedema			
subjects affected / exposed	1 / 70 (1.43%)	4 / 62 (6.45%)	0 / 1 (0.00%)
occurrences (all)	1	24	0
Infusion site pain			

subjects affected / exposed	2 / 70 (2.86%)	5 / 62 (8.06%)	0 / 1 (0.00%)
occurrences (all)	8	11	0
Infusion site pruritus			
subjects affected / exposed	0 / 70 (0.00%)	4 / 62 (6.45%)	0 / 1 (0.00%)
occurrences (all)	0	6	0
Injection site erythema			
subjects affected / exposed	0 / 70 (0.00%)	7 / 62 (11.29%)	0 / 1 (0.00%)
occurrences (all)	0	16	0
Injection site pain			
subjects affected / exposed	2 / 70 (2.86%)	5 / 62 (8.06%)	0 / 1 (0.00%)
occurrences (all)	4	19	0
Injection site pruritus			
subjects affected / exposed	0 / 70 (0.00%)	4 / 62 (6.45%)	0 / 1 (0.00%)
occurrences (all)	0	9	0
Pain			
subjects affected / exposed	0 / 70 (0.00%)	0 / 62 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 70 (1.43%)	7 / 62 (11.29%)	0 / 1 (0.00%)
occurrences (all)	1	9	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 70 (0.00%)	0 / 62 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 70 (2.86%)	7 / 62 (11.29%)	0 / 1 (0.00%)
occurrences (all)	2	8	0
Diarrhoea			
subjects affected / exposed	5 / 70 (7.14%)	0 / 62 (0.00%)	0 / 1 (0.00%)
occurrences (all)	7	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 70 (0.00%)	0 / 62 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Vomiting			

subjects affected / exposed	4 / 70 (5.71%)	1 / 62 (1.61%)	0 / 1 (0.00%)
occurrences (all)	4	1	0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 62 (0.00%)	1 / 1 (100.00%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Nasal dryness			
subjects affected / exposed	0 / 70 (0.00%)	0 / 62 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 70 (1.43%)	5 / 62 (8.06%)	0 / 1 (0.00%)
occurrences (all)	1	14	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 70 (1.43%)	3 / 62 (4.84%)	0 / 1 (0.00%)
occurrences (all)	1	10	0
Back pain			
subjects affected / exposed	2 / 70 (2.86%)	4 / 62 (6.45%)	0 / 1 (0.00%)
occurrences (all)	3	4	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 70 (1.43%)	1 / 62 (1.61%)	0 / 1 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	Epoch 2: E1: HYQVIA Relapse - E2: GGL/KIOVIG	Epoch 2: E1: Placebo Relapse - E2: GGL/KIOVIG	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	11 / 16 (68.75%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 4 (50.00%)	6 / 16 (37.50%)	
occurrences (all)	8	22	
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Chills			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Fatigue			

subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Illness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Infusion site erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Infusion site oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Infusion site pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Infusion site pruritus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Injection site erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Injection site pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Injection site pruritus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	6	0	
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Nasal dryness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 16 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 August 2015	Amendment 1 • The Schedule of Study Procedures and Assessments, Clinical Laboratory Assessments were updated to include assessments that were missed in the original protocol. • Added the text "the Declaration of Helsinki (October 2013)" to the compliance statement. • The text related to unblinding was updated to clarify that the responsibility to break the treatment code in emergency situations resided solely with the investigator. • The safety reporting section was updated to clarify that it was the sponsor's responsibility to inform the relevant regulatory authorities, ethics committees, and investigators worldwide of any suspected unexpected serious adverse reactions (SUSARs) and all other SAEs in a timely manner in accordance with applicable regulations, such as the European Clinical Trial Directive (2001/20/EC).
22 April 2016	Amendment 2 • A secondary outcome measure was added to Epoch 1 and Epoch 2, and additional tertiary outcome measures were added to Epoch 2 to gain additional relevant information regarding outcome measures of efficacy. • The circumstances under which LDH isoenzyme testing would occur were clarified throughout the document. • In response to specific regulatory agency feedback, an additional inclusion criterion was added to ensure that participants were willing and able to sign an ICF. • Screening and Baseline Period was updated to clarify the use of previous EDX records during screening. • End of IV Treatment Period was updated to clarify that only participants who completed Epoch 1 may opt to participate in the open-label extension (Epoch 2). • Hand Grip Strength was updated as the instrument used to measure hand grip strength was changed from the JAMAR® PLUS + Hand Dynamometer to the Vigorimeter. • A new section was added to the protocol to clarify the ethical considerations of the trial. • Inclusion Criteria was updated by recommendation of the Canadian investigator to include males or females of age ≥18 at the time of screening. • Throughout the protocol, the minimal monthly maintenance dose of IGIV was decreased from 0.5 to 0.4 g/kg after discussion with the EU, US, and Canadian investigators and key opinion leaders. • Exclusion Criteria, Rescreening, and Section 10.5 Mediations and Non-drug Therapies were updated to allow for steroid treatment if administered >3 months prior to screening and within 3 months of screening allowing for a single steroid dose or Methylprednisolone Dose Pack for the treatment of AE and non-CIDP indications.

22 April 2016	Amendment 2 continued: • Overall Study Design and Schedule of Study Procedures and Assessments were updated to include unscheduled visits in Epoch 2 at any time during the treatment period. • The safety sections of the protocol (Serious Adverse Event Reporting, Safety Reporting, Untoward Medical Occurrences) were updated to include the reporting of all SAEs, including SUSARs, on the Serious Adverse Event Report Form and transmitted to the Sponsor within 24 hours after becoming aware of an event. Updated from eCRF reporting to SAE Report Form reporting. • Preparation and Storage of Pooled Products was updated to allow unblinded staff (nurse) to prepare the study drug, and ensure the infusions were stored and administered at the correct temperature. • Data Monitoring Committee was updated to state that the DMC may recommend to stop the trial if it finds toxicities or if the treatment was proven to be beneficial. • Inclusion Criteria (inclusion criterion 3) was updated to clarify the reasons participants may have received IgG treatment. • Withdrawal and Discontinuation was updated with language to specify that the participation in the Pregnancy Registry is based on whether it is available in the respective country. • Definitions was updated to include the definition of a TEAE. • Suspected and Unexpected Serious Adverse Reactions was added into the protocol. • Backup Samples/Biobanking was updated to include the clause "for no more than 2 years after the final study report has been completed" for the storage of serum samples. • Synopsis, Administration, Description of Treatment were updated to divide the mode of administration into 2 parts, 1 for bifurcated needle set, and 1 for trifurcated needle set.
30 January 2018	Amendment 3 • Overall Study Design, Schedule of Study Procedures and Assessments (Table 21-1, Table 21-2, Table 21-3), a reference point was added for Week 1 to ensure consistency from all sites on determining Week 1. • Duration of Study Periods and Participant Participation were updated to include new estimates of study completion and duration in line with the extended enrolment period. Inclusion Criteria was updated to remove the time limit on INCAT scores and replaced with documentation in medical records. • Inclusion Criteria, and Section 21.3 Schedule of Study Procedures and Assessments (Table 21-1, Table 21-2, Table 21-3) were updated to include the definition of stability in the inclusion criteria. • Inclusion Criteria was updated to include detail of INCAT scoring in inclusion criterion 4. • Exclusion Criteria was updated to include "MADSAM" in the list of hereditary demyelinating neuropathies for clarity for the investigators. • Background Information was updated to include a new reference to the sentence summarizing current publications on CIDP. • rHuPH20 was updated to include additional half-life information for rHuPH20. • Placebo control was updated to include the possible names of the placebo control in various countries. • Clinical Condition/Indication was updated to include 'Relapse of' in the clinical condition of Epoch 1 to align with the synopsis. • Population to be Studied, Brief Summary, Section 9.1 Inclusion Criteria, Screening and Baseline Period, and Rescreening were updated to clarify the description of the stable dosing regimen of IGIV therapy from 3 months to 12 weeks. • GGL/KIOVIG was updated to change the term "pharyngolaryngeal pain" to "laryngeal pain" in line with the current MedDRA PT

30 January 2018	Amendment 3 continued: Compliance Statement was updated to remove 'The Declaration of Helsinki (October 2013)' to align with the newest template language. • Screening and Baseline Period was updated to increase the dosing interval from 5 to 7 days. The section was also updated to include 'product name' as in the list of information captured for prerandomization IGIV infusion. • SC Infusion Visits, IV Infusion Visits were updated to clarify the window around the telephone follow-up visits. • Participant Diary and PROs was updated to clarify that the diary was the source records for patient reported data. The section was also updated to remove the text 'After reconciliation against eCRF, the data will be imported into the study database'. The study database would not be reconciled against the diary, the information would be reviewed by the investigator. • Participant Completion/Discontinuation was updated to include death as a reason for discontinuation. • R-ODS was updated to include additional information on eDiaries at screening. • SUSAR was updated to include text required by the Voluntary Harmonization Procedure. • Assessment of AEs was updated to include the qualifier of 30 days for SAE reported after study completion using the SAE Report Form. Additional text was added regarding the use of Council for International Organizations of Medical Sciences (CIOMS) forms or MedWatch forms after the 30 days from study completion. • Hematology and Clinical Chemistry, Table 21-1, Table 21-2, Table 21-3, Table 21-4, Table 21-5, Table 21-6, Table 21-7, and Table 21-8 were updated to include a window for Hgb and hematocrit, and specifications for when a reticulocyte count would be performed was added to the body text, removed from tables (21-1, 21-2, 21-3, 21-4, 21-5, 21-6, and 21-7) and added to Table 21-8.
30 January 2018	Amendment 3 continued: • Assessment of Abnormal Laboratory Values was updated to include specifications that investigators did not need to indicate if hyaluronidase antibody values constituted an AE. • Trough Serum IgG was updated to remove 'within 60 minutes' from the sentence regarding when the IgG sample must be collected. • Guidance on Reporting and Assessing rHuPH20 (hyaluronidase) antibody test results was updated to include guidance on reporting and assessing antibody results. • Updated to remove the following clause 'participant's electronic diary (as applicable)'. • Planned Interim Safety Analysis of the Study were updated to include details of a formal interim analysis for submission purposes. • Safety were updated to include a note to safety outcome measures: 'Note: Adverse events in this section refer to treatment-emergent AEs, if not specified'. • Blinding was updated that specifications that Epoch 1 was blinded and Epoch 2 was open-label were added, a definition of completion was also added for Epoch 1 participants. • Unblinding language was updated from the standard unblinding language to describe that treatment assignments were unblinded after Epoch 1. • Placebo Solution was updated to include additional text describing the placebo packaging, including coloration and dilution. • Epoch 2 was updated to specify maintenance infusions for GGL/KIOVIG and GAMUNEX-C. A maximum dose was also added. The clause 'every 3 weeks' was added to the mode of administration section for GGL/KIOVIG to emphasize that this was a fixed dose schedule. • Datasets and Analysis Cohorts, the definition of a PP analysis set was updated for consistency within the company and between the final and interim analyses.

30 January 2018	Amendment 3 continued: • In the Synopsis, the timing for subsequent doses for GAMMAGARD was updated from 1 to 2 days to 2 to 5 days. • Laboratory and Reader Standardization was updated to remove R-ODS from the list as it was not a participant reported outcome. • Schematics for Study Visits and Assessments Figure 21-1, Figure 21-2 were removed. References to these figures were removed throughout the protocol. •Schedule of Study Procedures and Assessments was updated. • Clinical Laboratory Assessments (Table 21-5, Table 21-6, Table 21-7, Table 21-8), a clause was added indicating that participants who met the criteria would have to return for additional testing. • Clinical Laboratory Assessments Table 21-5 was updated to add a footnote to the serum IgG to align with the protocol body text.
12 February 2019	Amendment 4 •The overall duration of the study was extended to 68 months and the enrollment period was extended to 61 months. • A reference to GAMUNEX-C prescribing instruction (for storage conditions) was included in the synopsis. • The mode of administration of GAMUNEX-C was amended. • Inclusion criteria, inclusion criterion 5 was corrected to include a cross-reference • Exclusion criteria were updated to improve the instructions to the investigators for clearer directions on participant eligibility and include an exclusion criterion for thrombophilic disorders. • Unblinding was updated to include unblinding language from protocol amendment 2 (dated 22 Apr 2016) and provide additional information • Placebo solution was updated to include the storage temperature of LR solution. • Epoch 1 was updated to include "for both rHuPH20 and IGI,10%/placebo solution" to improve clarity in the protocol. • HYQVIA/HyQvia, Section 9.3 Withdrawal and Discontinuation, SAEs, Assessment of AEs were updated as enrolment in the Pregnancy Registry had been closed. • Hematology and Clinical Chemistry was updated to clarify the description of sampling time points as per the US FDA's recommendation. • Hemolytic Panel was updated to improve clarity/readability and reflect the same instructions previously provided to sites in memos. • Schedule of Assessments was updated to improve assessments and clarity of the protocol, and to change the frequency of the assessment of the INCAT disability score in response to regulatory requirements.
10 May 2019	Amendment 5 • Exclusion Criteria, Screening and Baseline Period, and Medications and Non-drug Therapies were updated preclude use of any corticosteroids within 8 weeks prior to screening, regardless of indication. • Methods of Analysis, and Trough Serum IgG were updated to include the following outcome measure: In addition, potential correlation between serum IgG trough levels on or after Day 120 or at the time of CIDP symptom relapse and relapse status (relapse, no relapse) will be assessed as an exploratory analysis. • Compliance Statement was updated to clarify the study would be conducted in accordance with EU Directives (2001/20/EC; 2005/28/EC). • Source Data was updated to clarify that all data entered in to the CRF should be able to be verified by a corresponding source document. • INCAT disability Scale and MRC sum score were updated to clarify that the same individual should administer the hand grip Strength, INCAT and MRC tests. • were updated at the request of the US FDA to include that infusion site swelling following SC infusion would be captured and reported as AEs. • Safety was updated at the request of the US FDA to include that the incidence of local infusion site reactions would be reported by geographic region (US, non-US) and overall. • Schedule of Study Procedures and Assessments was updated to remove the collection of BMI at several visits. • Schedule of Study Procedures and Assessments and Clinical Laboratory Assessments were updated to correct footnotes as per protocol amendment 4.

20 May 2021	Amendment 6 • Duration of Study Periods and Participant Participation were updated; the maximum overall duration of the study was changed from 68 to 72 months, and the enrollment period was changed from 61 to 64 months. • Tertiary Objectives, and Other Assessments were updated to include additional tertiary objective for Epoch 1 to better assess treatment benefit in participants. • Tertiary Objectives was updated to include an additional tertiary objective for Epoch 2 to better assess treatment effects. • Study Stopping Rules, Sample Size and Power Calculations, and Power Calculation were updated to include further detail related to stopping randomization in Epoch 1. • Synopsis was updated to add the requirement to collect trough serum IgG levels and PRO measures. • Study Design were updated with details related to administration of IP at the sire, infusion related data to be recorded and participant/caregiver's training. • Efficacy were updated to add tertiary outcome measures for Epoch 1. • Efficacy were updated to add tertiary outcome measured for Epoch 2.
20 May 2021	Amendment 6 continued: • Study Design, Administration, and Epoch 2, details related to the mode of administration and specifications of infusion pump were revised due to the pump recall in the US of the body guard. • Tertiary Outcome Measures were updated to include details related to statistical analysis of R-ODS score and DAs based on EDX studies (tertiary outcome measures). • Synopsis was updated to remove a footnote relating to the pump occlusion alarm. • Background Information was updated to include literature references describing therapeutic efficacy and safety of IGSC treatment and impact of COVID-19 pandemic on ongoing drug development efforts. • Unblinding was updated to reflect updated study procedures. • Study Stopping Rules and Section 8.6.1 Operational Procedures for Study Stopping were updated to reflect updated study stopping rules. • Trial Integrity was added. • Alternative Approaches to Study Procedures and Data collection due to COVID-19 Related Factors was added to reflect changes made in response to the COVID-19 pandemic. • R-ODS was updated to introduce patient-centric endpoint. • EDX Studies (electromyography) was added to describe EDX studies. • Handling of Missing, Unused, and Spurious Data was updated to clarify rules for handling missing data would be described in the SAP. • Primary Outcome Measure were updated to include a sensitivity analysis with an alternative relapse definition.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported