Clinical trial results:
Long-Term Tolerability and Safety of Immune Globulin Infusion 10% (Human) With Recombinant Human Hyaluronidase (HYQVIA/HyQvia) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

Summary

EudraCT number	2016-000374-37
Trial protocol	FR DK CZ GB ES NO GR SK DE PL HR IT
Global end of trial date	04 July 2023

Results information

Result version number	v1 (current)
This version publication date	17 July 2024
First version publication date	17 July 2024

Trial information

Trial identification

Sponsor protocol code	161505

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02955355
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	04 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the long-term safety, tolerability, and immunogenicity of HYQVIA/HyQvia.

Protection of trial subjects:

Each participant signed an informed consent form (ICF) before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Colombia: 2
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Serbia: 18
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Türkiye: 6
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	85
EEA total number of subjects	37

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)	65
From 65 to 84 years	19
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 39 investigative sites worldwide from 14 November 2016 to 04 July 2023.

Pre-assignment

Screening details:

A total of 85 participants with a diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) who completed Study 161403 (NCT02549170) without CIDP worsening were enrolled in this Extension Study to receive HYQVIA/HyQvia.

Period 1

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

Arms

Arm title	HYQVIA/HyQvia

Arm description:

Participants received HYQVIA/HyQvia (recombinant human hyaluronidase [rHuPH20] at a dose of 80 units per gram (U/g) immunoglobulin G [IgG], followed by subcutaneous [SC] immune globulin infusion [IGI] 10%) at the same monthly equivalent dose as the individual participant's IgG treatment in Study 161403, every 3 or 4 weeks in this Extension Study for 77.3 months or until relapse.

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

Dosage and administration details:

Participants received rHuPH20 SC at a dose of 80 U/g IgG, followed by SC IGI 10% at the same monthly equivalent dose as the individual participant's IgG treatment in Study 161403.

Number of subjects in period 1	HYQVIA/HyQvia
Started	85
Completed	0
Not completed	85
Adverse event, serious fatal	1
Physician decision	21
Consent withdrawn by subject	19
Adverse event, non-fatal	4
Reason Not Specified	5
Site Terminated by Sponsor	35

Baseline characteristics

Reporting groups	
Reporting group title	HYQVIA/HyQvia
Reporting group description:	
Participants received HYQVIA/HyQvia (recombinant human hyaluronidase [rHuPH20] at a dose of 80 units per gram (U/g) immunoglobulin G [IgG], followed by subcutaneous [SC] immune globulin infusion [IGI] 10%) at the same monthly equivalent dose as the individual participant's IgG treatment in Study 161403, every 3 or 4 weeks in this Extension Study for 77.3 months or until relapse.	

Reporting group values	HYQVIA/HyQvia	Total	
Number of subjects	85	85	
Age Categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 54.3 ± 13.11	 -	
Gender categorical Units: Subjects			
Female	39	39	
Male	46	46	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	81	81	
More than one race	0	0	
Unknown or Not Reported	3	3	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	14	14	
Not Hispanic or Latino	67	67	
Unknown or Not Reported	4	4	
Height Units: centimeters (cm) arithmetic mean standard deviation	 171.5 ± 10.98	 -	
Body Mass Index (BMI)			
BMI = weight (kg)/[height (m)^2]			
Units: kilograms per meter square (kg/m^2) arithmetic mean standard deviation	 27.42 ± 5.587	 -	
Weight Units: kilograms (kg)			

arithmetic mean standard deviation	80.89 ± 18.856	-	

End points

End points reporting groups

Reporting group title	HYQVIA/HyQvia

Reporting group description:

Participants received HYQVIA/HyQvia (recombinant human hyaluronidase [rHuPH20] at a dose of 80 units per gram (U/g) immunoglobulin G [IgG], followed by subcutaneous [SC] immune globulin infusion [IGI] 10%) at the same monthly equivalent dose as the individual participant's IgG treatment in Study 161403, every 3 or 4 weeks in this Extension Study for 77.3 months or until relapse.

Subject analysis set title	Placebo Then HYQVIA/HyQvia
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received placebo in the study 161403 and received HYQVIA/HyQvia (rHuPH20 at a dose of 80 U/g IgG, followed by SC IGI 10%) at the same monthly equivalent dose as the individual participant's IgG treatment in Study 161403, every 3 or 4 weeks in this Extension Study for 77.3 months or until relapse.

Subject analysis set title	HYQVIA/HyQvia Then HYQVIA/HyQvia
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received HYQVIA/HyQvia in the study 161403 and received HYQVIA/HyQvia (rHuPH20 at a dose of 80 U/g IgG, followed by SC IGI 10%) at the same monthly equivalent dose as the individual participant's IgG treatment in Study 161403, every 3 or 4 weeks in this Extension Study for 77.3 months or until relapse.

Primary: Number of Participants With any Treatment-emergent Serious Adverse Events (SAEs) and Adverse Events (AEs), Regardless of Causality

End point title	Number of Participants With any Treatment-emergent Serious Adverse Events (SAEs) and Adverse Events (AEs), Regardless of Causality[1]

End point description:

An AE was defined as any untoward medical occurrence in a participant administered an investigational product (IP) that did not necessarily have a causal relationship with the treatment. An SAE was defined as an untoward medical occurrence that at any dose met one or more of the following criteria: outcome was fatal/resulted in death, was life-threatening, required inpatient hospitalisation or resulted in prolongation of an existing hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. Treatment emergent adverse events (TEAEs) were defined as adverse events that occurred during or after administration of the first dose of IP in this Extension Study. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: participants				
Any TEAE	76			
Any Serious TEAE	20			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Causally Related Treatment-emergent SAEs and AEs

End point title	Number of Participants With Causally Related Treatment-emergent SAEs and AEs[2]

End point description:

An AE was defined as any untoward medical occurrence in a participant administered an IP that did not necessarily have a causal relationship with the treatment. An SAE was defined as an untoward medical occurrence that at any dose met one or more of the following criteria: outcome was fatal/resulted in death, was life-threatening, required inpatient hospitalisation or resulted in prolongation of an existing hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. TEAEs were defined as adverse events that occurred during or after administration of the first dose of IP in this Extension Study. Causality was used to determine whether there was a reasonable possibility that the IP was etiologically related to/associated with the AE. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[2] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: participants				
Any IP-related TEAE	51			
Any IP-related Serious TEAE	3			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Adverse Reactions (ARs) or Suspected Adverse Reactions (SARs) Categorised as Serious and Non-serious

End point title	Number of Participants With Adverse Reactions (ARs) or Suspected Adverse Reactions (SARs) Categorised as Serious and Non-serious[3]

End point description:

An AR plus SAR 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 hours following the end of IP infusion, or AE for which causality

assessment is missing or indeterminate. Serious AR/SAR=any AR/SAR that is an untoward medical occurrence which at any dose meets one or more of following criteria: outcome is fatal/results in death, is life-threatening, requires inpatient hospitalisation or results in prolongation of existing hospitalisation, results in persistent or significant disability/incapacity,is a congenital anomaly/birth defect,is a medically important event,thromboembolic events,hemolytic anemia. Nonserious AR/SAR=AR/SAR that does not meet the criteria. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[3] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: participants				
Any Serious AR/SAR	7			
Any Non-serious AR/SAR	57			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Causally Related Treatment-Emergent SAEs and AEs Associated With Infusions

End point title	Number of Causally Related Treatment-Emergent SAEs and AEs Associated With Infusions[4]

End point description:

An AE=any untoward medical occurrence in participant administered IP that did not necessarily have causal relationship with treatment. An SAE=an untoward medical occurrence that at any dose met one/more of following criteria: outcome was fatal/resulted in death, was life-threatening, required inpatient hospitalisation/resulted in prolongation of existing hospitalisation, resulted in persistent/significant disability/incapacity, was congenital anomaly/birth defect, was medically important event. TEAEs=AEs that occurred during or after administration of the first dose of IP in this Extension Study. AEs associated with an infusion are defined as AEs occurring after administration of IP (or any TEAE). Causality was used to determine whether there was a reasonable possibility that the IP was etiologically related to/associated with the AE. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[4] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: events in participants				
number (not applicable)				
IP-Related Serious TEAEs	3			
IP-Related TEAEs	798			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Treatment-Emergent SAEs and AEs Associated With Infusions, Regardless of Causality

End point title	Number of Treatment-Emergent SAEs and AEs Associated With Infusions, Regardless of Causality[5]

End point description:

An AE=any untoward medical occurrence in a participant administered an IP that did not necessarily have a causal relationship with the treatment. An SAE was defined as an untoward medical occurrence that at any dose met one or more of the following criteria: outcome was fatal/resulted in death, was life-threatening, required inpatient hospitalisation or resulted in prolongation of an existing hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. TEAEs were defined as adverse events that occurred during or after administration of the first dose of IP in this Extension Study. AEs associated with an infusion are defined as AEs occurring after administration of IP (or any TEAE). Participants can have more than one TEAE associated with infusion. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[5] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: events in participants				
number (not applicable)				
Serious TEAEs	30			
TEAEs	1406			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Treatment-Emergent Adverse Events That May be a Result of Immune-Mediated Responses

End point title	Percentage of Participants With Treatment-Emergent Adverse Events That May be a Result of Immune-Mediated Responses[6]

End point description:

Percentage of participants with TEAEs that may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other factors such as allergic reactions, immune complex-mediated reactions: local, complex-mediated reactions: systemic, thrombotic and embolic events were assessed. TEAEs were defined as adverse events that occurred during or after administration of the first dose of IP in this Extension Study. The percentage was rounded off to the nearest decimal. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[6] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: percentage of participants				
number (not applicable)	7.1			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Infusions Associated With One or More Systemic TEAEs

End point title	Number of Infusions Associated With One or More Systemic TEAEs[7]

End point description:

An AE was defined as any untoward medical occurrence in a participant administered an IP that did not necessarily have a causal relationship with the treatment. TEAEs were defined as adverse events that occurred during or after administration of the first dose of IP in this Extension Study. Systemic TEAEs were defined as AEs that were not included in the Medical Dictionary for Regulatory Activities (MedDRA) Higher Level Group Term "administration site reactions" and did not contain the phrase "injection site". Infusions associated with one or more AEs are defined as follows: if an AE occurs after an infusion but prior to the next infusion that infusion is associated with that AE. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[7] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: infusions				
number (not applicable)	50			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Serious and Non-Serious ARs or SARs Associated with Infusions

End point title	Number of Serious and Non-Serious ARs or SARs Associated with Infusions[8]

End point description:

AR/SAR=AE that meets any of following criteria:AE considered by investigator/sponsor to be possibly/probably related to IP administration,begins during/within 72 hours following end of IP infusion/AE for which causality assessment is missing/indeterminate. ARs/SARs associated with infusion=AEs considered by investigator to be occurring after IP administration.Serious AR/SAR=AR/SAR that is untoward medical occurrence which at any dose meets any of following criteria:outcome is fatal,life-threatening,requires inpatient hospitalisation/prolongation of existing hospitalisation,results in persistent/significant disability/incapacity,is a congenital anomaly/birth defect,is a medically important event,thromboembolic events,hemolytic anemia.Nonserious AR/SAR=AR/SAR that does not meet criteria. Participants can have >1 AR/SAR associated with infusion. Safety Analysis Set included all participants who were enrolled in this Extension Study & who received at least 1 dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[8] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: events in participants				
number (not applicable)				
Serious ARs/SARs	8			
Non-Serious ARs/SARs	913			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Infusions for Which the Infusion Rate Was Reduced and/or the Infusion was Interrupted or Stopped due to Intolerability and/or TEAEs

End point title	Number of Infusions for Which the Infusion Rate Was Reduced and/or the Infusion was Interrupted or Stopped due to

	Intolerability and/or TEAEs[9]

End point description:

An AE was defined as any untoward medical occurrence in a participant administered an IP that did not necessarily have a causal relationship with the treatment. TEAEs were defined as adverse events that occurred during or after administration of the first dose of IP in this Extension Study. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: infusions				
number (not applicable)	3			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Infusions Associated with One or More Local TEAEs

End point title	Number of Infusions Associated with One or More Local

End point description:

An AE was defined as any untoward medical occurrence in a participant administered an IP that did not necessarily have a causal relationship with the treatment. TEAEs were defined as adverse events that occurred during or after administration of the first dose of IP in this Extension Study. Local TEAEs were defined as AEs that were included in the MedDRA Higher Level Group Term "administration site reactions" or contained the phrase "injection site" or "infection site". Infusions associated with one or more AEs are defined as follows: if an AE occurs after an infusion but prior to the next infusion that infusion is associated with that AE. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[10] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: infusions				
number (not applicable)	17			

Statistical analyses

No statistical analyses for this end point

Primary: Number of TEAEs Temporally Associated With Infusions

End point title	Number of TEAEs Temporally Associated With Infusions[11]

End point description:

TEAEs that occurred during infusion or within 72 hours post-infusion were considered to be temporally associated with infusions. TEAEs were defined as adverse events that occurred during or after administration of the first dose of IP in this Extension Study. Participants can have more than one TEAE temporally associated with infusion. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: events in participants				
number (not applicable)	857			

Statistical analyses

No statistical analyses for this end point

Primary: Rate of TEAEs Categorised as Systemic and Local Regardless of Causality, Expressed as Number of Events Per Participant

End point title	Rate of TEAEs Categorised as Systemic and Local Regardless of Causality, Expressed as Number of Events Per Participant[12]

End point description:

TEAEs were defined as adverse events that occurred during or after administration of the first dose of IP in this Extension Study. Systemic TEAEs were defined as AEs that were not included in the MedDRA Higher Level Group Term "administration site reactions" and did not contain the phrase "injection site". Local TEAEs were defined as AEs that were included in the MedDRA Higher Level Group Term "administration site reactions" or contained the phrase "injection site" or "infection site". Events per participant was calculated by dividing number of events by total number of participants in the Safety Analysis Set. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[12] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: AEs/participant				
number (not applicable)				
Systemic TEAEs	10.38			
Local TEAEs	6.16			

Statistical analyses

No statistical analyses for this end point

Primary: Rate of TEAEs Categorised as Systemic and Local Regardless of Causality, Expressed as Number of Events Per Infusion

End point title	Rate of TEAEs Categorised as Systemic and Local Regardless of Causality, Expressed as Number of Events Per Infusion[13]

End point description:

TEAEs were defined as adverse events that occurred during or after administration of the first dose of IP in this Extension Study. Systemic TEAEs were defined as AEs that were not included in the MedDRA Higher Level Group Term "administration site reactions" and did not contain the phrase "injection site". Local TEAEs were defined as AEs that were included in the MedDRA Higher Level Group Term "administration site reactions" or contained the phrase "injection site" or "infection site". Events per infusion was calculated by dividing number of events by total number of infusions administered to participants in the Safety Analysis Set. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: AEs/infusion				
number (not applicable)				
Systemic TEAEs	0.25			
Local TEAEs	0.15			

Statistical analyses

No statistical analyses for this end point

Primary: Rate of TEAEs Categorised as Systemic and Local Regardless of Causality, Expressed as Number of Events Per 1000 Participant-year

End point title	Rate of TEAEs Categorised as Systemic and Local Regardless of Causality, Expressed as Number of Events Per 1000 Participant-year[14]

End point description:

TEAEs were defined as adverse events that occurred during or after administration of the first dose of IP in this Extension Study. Systemic TEAEs were defined as AEs that were not included in the MedDRA Higher Level Group Term "administration site reactions" and did not contain the phrase "injection site". Local TEAEs were defined as AEs that were included in the MedDRA Higher Level Group Term "administration site reactions" or contained the phrase "injection site" or "infection site". Events per participant-years was calculated as follows: 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). Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[14] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: AEs/1000 participant-year				
number (not applicable)				
Systemic TEAEs	4000.23			
Local TEAEs	2376.55			

Statistical analyses

No statistical analyses for this end point

Primary: Rate of IP-Related TEAEs Categorised as Systemic and Local, Expressed as Number of Events Per 1000 Participant-year

End point title	Rate of IP-Related TEAEs Categorised as Systemic and Local, Expressed as Number of Events Per 1000 Participant-year[15]

End point description:

TEAEs=AEs that occurred during or after administration of the first dose of IP in this Extension Study. Systemic TEAEs were defined as AEs that were not included in the MedDRA Higher Level Group Term "administration site reactions" and did not contain the phrase "injection site". Local TEAEs were defined as AEs that were included in the MedDRA Higher Level Group Term "administration site reactions" or contained the phrase "injection site" or "infection site". An adverse event that was “possibly related” or “probably related” to IP, or for which the relationship was unknown or missing, was considered as a “related AE”. Events per participant-years was calculated as follows: 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). Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: AEs/1000 participant-year				
number (not applicable)				
Systemic IP-Related TEAEs	1301.66			
Local IP-Related TEAEs	2317.59			

Statistical analyses

No statistical analyses for this end point

Primary: Rate of IP-Related TEAEs Categorised as Systemic and Local, Expressed as Number of Events Per Participant

End point title	Rate of IP-Related TEAEs Categorised as Systemic and Local, Expressed as Number of Events Per Participant[16]

End point description:

TEAEs were defined as adverse events that occurred during or after administration of the first dose of IP in this Extension Study. Systemic TEAEs were defined as AEs that were not included in the MedDRA Higher Level Group Term "administration site reactions" and did not contain the phrase "injection site". Local TEAEs were defined as AEs that were included in the MedDRA Higher Level Group Term "administration site reactions" or contained the phrase "injection site" or "infection site". An adverse event that was “possibly related” or “probably related” to IP, or for which the relationship was unknown or missing, was considered as a “related AE”. Events per participant was calculated by dividing number of events by total number of participants in the Safety Analysis Set. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[16] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: AEs/participant				
number (not applicable)				
Systemic IP-Related TEAEs	3.38			
Local IP-Related TEAEs	6.01			

Statistical analyses

No statistical analyses for this end point

Primary: Rate of IP-Related TEAEs Categorised as Systemic and Local, Expressed as Number of Events Per Infusion

End point title	Rate of IP-Related TEAEs Categorised as Systemic and Local, Expressed as Number of Events Per Infusion[17]

End point description:

TEAEs were defined as adverse events that occurred during or after administration of the first dose of IP in this Extension Study. Systemic TEAEs were defined as AEs that were not included in the MedDRA Higher Level Group Term "administration site reactions" and did not contain the phrase "injection site". Local TEAEs were defined as AEs that were included in the MedDRA Higher Level Group Term "administration site reactions" or contained the phrase "injection site" or "infection site". An adverse event that was "possibly related" or "probably related" to IP, or for which the relationship was unknown or missing, was considered as a "related AE". Events per infusion was calculated by dividing number of events by total number of infusions administered to participants in the Safety Analysis Set. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: AEs/infusion				
number (not applicable)				
Systemic IP-Related TEAEs	0.08			
Local IP-Related TEAEs	0.15			

Statistical analyses

No statistical analyses for this end point

Primary: Rate of ARs or SARs Categorised as Local and Systemic, Expressed as Reactions Per Infusion

End point title	Rate of ARs or SARs Categorised as Local and Systemic, Expressed as Reactions Per Infusion[18]

End point description:

An AR plus SAR 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 hours following the end of IP infusion, or AE for which causality assessment is missing or indeterminate. Systemic AEs were defined as AEs that were not included in the MedDRA Higher Level Group Term "administration site reactions" and did not contain the phrase "injection site". Local AEs were defined as AEs that were included in the MedDRA Higher Level Group Term "administration site reactions" or contained the phrase "injection site" or "infection site". Events per infusion was calculated by dividing number of events by total number of infusions administered to participants in the Safety Analysis Set. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[18] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: reactions/infusion				
number (not applicable)				
Systemic ARs/SARs	0.11			
Local ARs/SARs	0.15			

Statistical analyses

No statistical analyses for this end point

Primary: Rate of ARs or SARs Categorised as Local and Systemic, Expressed as Reactions Per 1000 Participant-year

End point title	Rate of ARs or SARs Categorised as Local and Systemic, Expressed as Reactions Per 1000 Participant-year[19]

End point description:

An AR+SAR is any AE that meets any of following criteria: AE considered by either investigator and/or sponsor to be possibly/probably related to IP administration/that begins during infusion of IP/within 72 hours following end of IP infusion/AE for which causality assessment is missing/indeterminate. Systemic AEs=AEs that were not included in MedDRA Higher Level Group Term "administration site reactions" & did not contain phrase "injection site". Local AEs=AEs that were included in the MedDRA Higher Level Group Term "administration site reactions" or contained the phrase "injection site" or "infection site". Events per participant-years was calculated as follows: 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). Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: reactions/1000 participant-year				
number (not applicable)				
Systemic ARs/SARs	1764.27			
Local ARs/SARs	2376.55			

Statistical analyses

No statistical analyses for this end point

Primary: Rate of ARs or SARs Categorised as Local and Systemic, Expressed as Reactions Per Participant

End point title	Rate of ARs or SARs Categorised as Local and Systemic, Expressed as Reactions Per Participant[20]

End point description:

An AR plus SAR 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 hours following the end of IP infusion, or AE for which causality assessment is missing or indeterminate. Systemic AEs were defined as AEs that were not included in the MedDRA Higher Level Group Term "administration site reactions" and did not contain the phrase "injection site". Local AEs were defined as AEs that were included in the MedDRA Higher Level Group Term "administration site reactions" or contained the phrase "injection site" or "infection site". Events per participant was calculated by dividing number of events by total number of participants in the Safety Analysis Set. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[20] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: reactions/participant				
number (not applicable)				
Systemic ARs/SARs	4.58			
Local ARs/SARs	6.16			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants That Experienced Treatment-Emergent Local Infusion Site Reactions

End point title	Number of Participants That Experienced Treatment-Emergent Local Infusion Site Reactions[21]

End point description:

TEAEs were defined as adverse events that occurred during or after administration of the first dose of IP in this Extension Study. AE=any untoward medical occurrence in participant administered an IP that does not have causal relationship with treatment. 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. All local infusion site treatment-emergent AEs were reported as adverse reactions. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: participants	30			

Statistical analyses

No statistical analyses for this end point

Primary: Rate of Moderate or Severe TEAEs That May be a Result of Immune-Mediated Responses, Expressed as Number of Events Per 100 Infusions

End point title	Rate of Moderate or Severe TEAEs That May be a Result of Immune-Mediated Responses, Expressed as Number of Events Per 100 Infusions[22]

End point description:

An AE was defined as any untoward medical occurrence in a participant administered an IP that did not necessarily have a causal relationship with the treatment. TEAEs were defined as adverse events that occurred during or after administration of the first dose of IP in this Extension Study. A moderate or severe AE could be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other concomitant medications. The severity of each AE was assessed by the investigator using clinical expertise. Rate per 100 infusions was calculated by dividing the number of events by the total number of infusions and multiplying that by 100. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[22] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: AEs/100 infusions				
number (not applicable)	0.0860			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Moderate or Severe TEAEs That may be a Result of Immune-Mediated Responses

End point title	Number of Participants With Moderate or Severe TEAEs That may be a Result of Immune-Mediated Responses[23]

End point description:

AE=any untoward medical occurrence in participant administered IP that did not necessarily have causal relationship with treatment. TEAEs=AEs that occurred during/after administration of first dose of IP in this Extension Study. Moderate/severe AE could be result of immune-mediated response to either immunoglobulin,rHuPH20/other factors like allergic reactions,immune complex-mediated reactions:local,complex-mediated reactions:systemic, thrombotic&embolic events.Severity of AEs was assessed by investigator using clinical expertise based on following description:moderate=AE produces limited impairment of function,may require therapeutic intervention&produces no sequela;severe=AE results in marked impairment of function&may lead to temporary inability to resume usual life pattern&produces sequela,which require prolonged therapeutic intervention. Safety Analysis Set included all participants who were enrolled in this Extension Study & who received at least 1 dose of study

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: participants	3			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With a TEAE That led to Discontinuation From Study

End point title	Number of Participants With a TEAE That led to Discontinuation From Study[24]

End point description:

An AE was defined as any untoward medical occurrence in a participant administered an IP that did not necessarily have a causal relationship with the treatment. TEAEs were defined as adverse events that

occurred during or after administration of the first dose of IP in this Extension Study. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[24] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: participants	4			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Whose Anti-Hyaluronidase Binding Antibody Titers Rose by ≥4-fold From Baseline

End point title	Number of Participants Whose Anti-Hyaluronidase Binding Antibody Titers Rose by ≥4-fold From Baseline[25]

End point description:

Number of participants whose anti-hyaluronidase antibody titers rose by ≥4 fold from the baseline value at any point during the study was assessed. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

Baseline, up to 6.6 years

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: participants	16			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Binding Antibodies to rHuPH20

End point title	Number of Participants With Binding Antibodies to rHuPH20[26]

End point description:

Binding antibodies were defined as anti-rHuPH20 titer ≥1:160. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication. Overall number analysed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[26] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: participants	14			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Treatment-Emergent Local Tolerability Events During Ramp-up

End point title	Number of Participants With Treatment-Emergent Local Tolerability Events During Ramp-up[27]

End point description:

Participants with local tolerability events=for which infusion rate was reduced and/or infusion was interrupted/stopped due to intolerability and/or AEs.These events were assessed during initial ramp-up for each participant i.e.,during first 8 weeks of open-label extension study 161505[NCT02955355]among participants originally randomised to placebo(as being in placebo arm,they had no ramp-up during the 161403[NCT02549170]study)versus during 8-week ramp-up for participants originally randomised to active HYQVIA in double-blind 161403 study.Thus, data for this endpoint are presented per bifurcation of participants in study 161403. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least 1 dose of study medication. As prespecified in SAP, comparative local tolerability data for ramp-up of 8 weeks from studies 161403 (for participants originally randomised to HYQVIA in double-blind) & 161505 were reported in results of study 161505.

End point type	Primary

End point timeframe:

During the ramp-up (8 weeks)

Notes:

[27] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Placebo Then HYQVIA/HyQvia	HYQVIA/HyQvia Then HYQVIA/HyQvia		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	43		
Units: participants	6	13		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Local Infusion Reactions, as a Function of Dosing Interval, Infusion Rate per Site, and Infusion Volume per Site

End point title	Number of Participants With Local Infusion Reactions, as a Function of Dosing Interval, Infusion Rate per Site, and Infusion Volume per Site[28]

End point description:

Local infusion reactions were defined as local (administration site-related) adverse events. Median infusion rate per site was derived as the median value across all participants, per participant's average infusion rate, by site: actual volume infused / duration in hours of infusion / number of sites. Median infusion volume per site was derived as the median value across all participants, per participant's average actual volume infused, by site: actual volume infused / number of sites. Number of participants with local infusion reactions as a function of each of these categories are presented below. Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[28] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: participants				
3 Week Dosing Interval	8			
4 Week Dosing Interval	22			
< Median Infusion Rate per Site	15			
≥ Median Infusion Rate per Site	15			
< Median Infusion Volume per Site	15			
≥ Median Infusion Volume per Site	15			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Neutralising Antibodies Binding to rHuPH20

End point title	Number of Participants With Neutralising Antibodies Binding to rHuPH20[29]

End point description:

Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication. Overall number analysed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: participants	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With a Decline of Anti-rHuPH20 Binding Antibody Titers to the Antibody Titer Level at Baseline in Study 161403 or to <1:160 Antibody Titer Level at the Study Completion or Early Discontinuation

End point title	Number of Participants With a Decline of Anti-rHuPH20 Binding Antibody Titers to the Antibody Titer Level at Baseline in Study 161403 or to <1:160 Antibody Titer Level at the Study Completion or Early Discontinuation[30]

End point description:

Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[30] - 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 planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: participants	12			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants who Had >1:10,000 Anti-rHuPH20 Binding Antibody Titers With Neutralising Antibodies

End point title	Number of Participants who Had >1:10,000 Anti-rHuPH20 Binding Antibody Titers With Neutralising Antibodies[31]

End point description:

Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication. Overall number analysed is the number of participants who had >1:10,000 anti-rHuPH20 antibody titers.

End point type	Primary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

Notes:

[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: participants				
Neutralizing Antibodies	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Had >1:10,000 Anti-rHuPH20 Binding Antibody Titers Showing Cross Reactivity With Hyaluronidase (Hyal)-1,2 and 4

End point title	Number of Participants Who Had >1:10,000 Anti-rHuPH20 Binding Antibody Titers Showing Cross Reactivity With Hyaluronidase (Hyal)-1,2 and 4

End point description:

Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication. Overall number analysed is the number of participants who had >1:10,000 anti-rHuPH20 antibody titers.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to end of study (up to 6.6 years)

End point values	HYQVIA/HyQvia			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug up to end of study (up to 6.6 years)

Adverse event reporting additional description:

Safety Analysis Set included all participants who were enrolled in this Extension Study and who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	HYQVIA/HyQvia

Reporting group description:

Participants received HYQVIA/HyQvia (rHuPH20 at a dose of 80 U/g IgG, followed by SC IGI 10%) at the same monthly equivalent dose as the individual participant's IgG treatment in Study 161403, every 3 or 4 weeks in this Extension Study for 77.3 months or until relapse.

Serious adverse events	HYQVIA/HyQvia		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 85 (23.53%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Mantle cell lymphoma			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Ventricular fibrillation			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus tachycardia			

subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Conus medullaris syndrome			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Papilloedema			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	2 / 85 (2.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Abdominal pain			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal polyp			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoventilation			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Systemic lupus erythematosus			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Rotator cuff syndrome			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc degeneration			

subjects affected / exposed	1 / 85 (1.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fibromyalgia				
subjects affected / exposed	1 / 85 (1.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	1 / 85 (1.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	1 / 85 (1.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tuberculosis				
subjects affected / exposed	1 / 85 (1.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	1 / 85 (1.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary tuberculosis				
subjects affected / exposed	1 / 85 (1.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary tuberculoma				
subjects affected / exposed	1 / 85 (1.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	HYQVIA/HyQvia		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 85 (74.12%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 85 (5.88%)		
occurrences (all)	5		
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 85 (9.41%)		
occurrences (all)	8		
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 85 (27.06%)		
occurrences (all)	123		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	17 / 85 (20.00%)		
occurrences (all)	66		
Infusion site pruritus			
subjects affected / exposed	5 / 85 (5.88%)		
occurrences (all)	15		
Fatigue			
subjects affected / exposed	12 / 85 (14.12%)		
occurrences (all)	17		
Infusion site erythema			
subjects affected / exposed	13 / 85 (15.29%)		
occurrences (all)	336		
Infusion site pain			

subjects affected / exposed	5 / 85 (5.88%)		
occurrences (all)	11		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 85 (8.24%)		
occurrences (all)	13		
Diarrhoea			
subjects affected / exposed	11 / 85 (12.94%)		
occurrences (all)	13		
Nausea			
subjects affected / exposed	11 / 85 (12.94%)		
occurrences (all)	18		
Vomiting			
subjects affected / exposed	8 / 85 (9.41%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	5 / 85 (5.88%)		
occurrences (all)	8		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	5 / 85 (5.88%)		
occurrences (all)	43		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 85 (7.06%)		
occurrences (all)	8		
Arthralgia			
subjects affected / exposed	12 / 85 (14.12%)		
occurrences (all)	26		
Pain in extremity			
subjects affected / exposed	6 / 85 (7.06%)		
occurrences (all)	18		
Myalgia			
subjects affected / exposed	5 / 85 (5.88%)		
occurrences (all)	5		

Infections and infestations			
Urinary tract infection			
subjects affected / exposed	7 / 85 (8.24%)		
occurrences (all)	9		
Upper respiratory tract infection			
subjects affected / exposed	7 / 85 (8.24%)		
occurrences (all)	10		
Influenza			
subjects affected / exposed	8 / 85 (9.41%)		
occurrences (all)	10		
COVID-19			
subjects affected / exposed	18 / 85 (21.18%)		
occurrences (all)	19		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2016	The following changes were made as per Amendment 1: 1) Specified that eligible participants may also be recruited from Study 161601 (NCT02955355). 2) The maximum treatment duration was clarified to extend up to 3 years if mandated by regulations. 3) Text was added to clarify the determination of infusion rate based on participant weight, and to specify the differences for administration with single, bifurcated, or trifurcated SC needle sets. 4) The number of potential participants was increased from 124 to 149. 5) A description of Study 161403 was added. 6) The planned statistical analysis was updated. Subgroup analysis was removed and changed to single group analysis. 7) The maximum infusion volume was defined as 1200 milliliters per day (mL/d). 8) Clarified that each participant should be kept on the same infusion schedule as in the parent study.
13 November 2018	The following changes were made as per Amendment 2: 1) All references to Study 161601 was deleted. 2) Planned duration of participant participation was revised. 3) Revised text for dose and mode of administration of IP. 4) Revised rHuPH20 administration text to clarify that the initial infusion rate is to carry over from Study 161403. 5) Planned final analysis of the study was updated. 6) A new section was added on guidance on reporting and assessing rHuPH20 (hyaluronidase) antibody test results. 7) Text was revised for sample size and power calculations.
05 August 2019	The following changes were made as per Amendment 3: 1) Updated primary outcome measures section to include local infusion site reactions to be reported as AEs. 2) Added that an interim analysis is planned to be performed 6 months after unblinding of Study 161403 (unblinding of Epoch 1).
10 January 2022	The following changes were made as per Amendment 4: 1) Target accrual was updated to 88 throughout the protocol. 2) Changed the description for safety/ tolerability outcome measures. 3) Clarified that analyses will be presented by actual treatment received in Study 161403 Epoch 1 and overall. 4) Updated the planned interim analysis timing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported