Clinical trial results:
Efficacy, Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HYQVIA in Pediatric Subjects with Primary Immunodeficiency Diseases

Summary

EudraCT number	2022-003501-29
Trial protocol	Outside EU/EEA
Global end of trial date	20 July 2022

Results information

Result version number	v1 (current)
This version publication date	07 February 2023
First version publication date	07 February 2023

Trial information

Trial identification

Sponsor protocol code	161503

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03277313
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to assess the efficacy of HYQVIA treatment in pediatric participants with primary immunodeficiency disease (PIDD) who received prior intravenous (IV) or subcutaneous (SC) immunoglobulin therapy before enrollment into the study.

Protection of trial subjects:

All study participants and/or their legally authorised representative had to sign an informed consent form (ICF) before entering into the study. Assent was also obtained from the participant as applicable.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 44
Worldwide total number of subjects	44
EEA total number of subjects	0

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)	32
Adolescents (12-17 years)	12
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 19 investigative sites in the United States from 25 September 2017 to 20 July 2022. Pediatric participants with a diagnosis of primary immunodeficiency diseases (PIDD) were enrolled in this study.

Pre-assignment

Screening details:

Pediatric participants who received IV or non-HYQVIA SC immunoglobulin therapy prior to enrollment received ramp-up doses of HYQVIA in Epoch 1 and at 3- or 4-week intervals in Epoch 2. Epoch 3 was planned for safety follow-up if needed, however no participants continued in Epoch 3. Data is reported only for Epoch 1 and 2.

Period 1

Period 1 title	Epoch 1 (Six-week Ramp-up Period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Epoch 1

Arm description:

Pediatric participants with PIDD who were on IV or non-HYQVIA SC treatment with immunoglobulin were enrolled and treated with HYQVIA SC with a dose or interval ramp-up period of up to six weeks. HYQVIA dose was planned to be equivalent to 100% (± 5%) of pre-study treatment. Dose frequency was one treatment interval of one week, then one treatment interval of two weeks for participants who were planned to be treated every three weeks, and one more treatment interval of three weeks for participants who were planned to be treated every four weeks.

Arm type	Experimental
Investigational medicinal product name	HYQVIA
Investigational medicinal product code	
Other name	IGI 10% with rHuPH20
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (IGI, 10% with rHuPH20)

Number of subjects in period 1	Epoch 1
Started	44
Completed	43
Not completed	1
Adverse event, non-fatal	1

Period 2

Period 2 title	Epoch 2 (36 Months After Epoch 1)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Epoch 2

Arm description:

Epoch 1 was followed by Epoch 2 with HYQVIA treatment infusions given once every 3 or 4 weeks, depending on the participant's previous IV dosing schedule (for IV pretreated participants) and at the discretion of the investigator and participant (for SC-pretreated participants) up to approximately 36 months.

Arm type	Experimental
Investigational medicinal product name	HYQVIA
Investigational medicinal product code	
Other name	IGI 10% with rHuPH20
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (IGI, 10% with rHuPH20)

Number of subjects in period 2	Epoch 2
Started	43
Completed	34
Not completed	9
Physician decision	1
Consent withdrawn by subject	6
Adverse event, non-fatal	1
Reason not Specified	1

Baseline characteristics

Reporting groups	
Reporting group title	Epoch 1
Reporting group description:	
Pediatric participants with PIDD who were on IV or non-HYQVIA SC treatment with immunoglobulin were enrolled and treated with HYQVIA SC with a dose or interval ramp-up period of up to six weeks. HYQVIA dose was planned to be equivalent to 100% (± 5%) of pre-study treatment. Dose frequency was one treatment interval of one week, then one treatment interval of two weeks for participants who were planned to be treated every three weeks, and one more treatment interval of three weeks for participants who were planned to be treated every four weeks.	

Reporting group values	Epoch 1	Total	
Number of subjects	44	44	
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	9.0		
standard deviation	± 3.63	-	
Gender categorical Units: Subjects			
Female	18	18	
Male	26	26	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	2	2	
White	40	40	
More than one race	1	1	
Unknown or Not Reported	1	1	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	5	
Not Hispanic or Latino	39	39	
Unknown or Not Reported	0	0	
Region of Enrollment Units: Subjects			
United States United States	44	44	
Weight Units: kg			
arithmetic mean	37.78		
standard deviation	± 19.858	-	
Height Units: cm			
arithmetic mean	133.60		

standard deviation	± 24.024	-	

Subject analysis sets

Subject analysis set title	Epoch 1 + Epoch 2
Subject analysis set type	Full analysis

Subject analysis set description:

Pediatric participants with PIDD who were on IV or non-HYQVIA SC treatment with immunoglobulin were enrolled and treated with HYQVIA SC with a dose or interval ramp-up period of up to six weeks. HYQVIA dose was planned to be equivalent to 100% (± 5%) of pre-study treatment. Dose frequency was one treatment interval of one week, then one treatment interval of two weeks for participants who were planned to be treated every three weeks, and one more treatment interval of three weeks for participants who were planned to be treated every four weeks. Epoch 1 was followed by Epoch 2 with HYQVIA treatment infusions given once every 3 or 4 weeks, depending on the participant's previous IV dosing schedule (for IV pretreated participants) and at the discretion of the investigator and participant (for SC-pretreated participants) up to approximately 36 months.

Reporting group values	Epoch 1 + Epoch 2		
Number of subjects	44		
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	0		
standard deviation	±		
Gender categorical Units: Subjects			
Female	0		
Male	0		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	0		
More than one race	0		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	0		
Unknown or Not Reported	0		
Region of Enrollment Units: Subjects			
United States United States	0		
Weight Units: kg			
arithmetic mean	0		

standard deviation	±		
Height			
Units: cm			
arithmetic mean	0		
standard deviation	±		

End points

End points reporting groups

Reporting group title	Epoch 1

Reporting group description:

Pediatric participants with PIDD who were on IV or non-HYQVIA SC treatment with immunoglobulin were enrolled and treated with HYQVIA SC with a dose or interval ramp-up period of up to six weeks. HYQVIA dose was planned to be equivalent to 100% (± 5%) of pre-study treatment. Dose frequency was one treatment interval of one week, then one treatment interval of two weeks for participants who were planned to be treated every three weeks, and one more treatment interval of three weeks for participants who were planned to be treated every four weeks.

Reporting group title	Epoch 2

Reporting group description:

Epoch 1 was followed by Epoch 2 with HYQVIA treatment infusions given once every 3 or 4 weeks, depending on the participant's previous IV dosing schedule (for IV pretreated participants) and at the discretion of the investigator and participant (for SC-pretreated participants) up to approximately 36 months.

Subject analysis set title	Epoch 1 + Epoch 2
Subject analysis set type	Full analysis

Subject analysis set description:

Pediatric participants with PIDD who were on IV or non-HYQVIA SC treatment with immunoglobulin were enrolled and treated with HYQVIA SC with a dose or interval ramp-up period of up to six weeks. HYQVIA dose was planned to be equivalent to 100% (± 5%) of pre-study treatment. Dose frequency was one treatment interval of one week, then one treatment interval of two weeks for participants who were planned to be treated every three weeks, and one more treatment interval of three weeks for participants who were planned to be treated every four weeks. Epoch 1 was followed by Epoch 2 with HYQVIA treatment infusions given once every 3 or 4 weeks, depending on the participant's previous IV dosing schedule (for IV pretreated participants) and at the discretion of the investigator and participant (for SC-pretreated participants) up to approximately 36 months.

Primary: Rate Represented as Mean Number of Acute Serious Bacterial Infections (ASBI) per Participant-year

End point title	Rate Represented as Mean Number of Acute Serious Bacterial Infections (ASBI) per Participant-year[1]

End point description:

The rate of ASBI was defined as the mean number of ASBI per participant-year based on the United States (U.S.) Food and drugs Administration (FDA) guidance for industry to support marketing of human immune globulin intravenous (IGIV) as replacement therapy for primary humoral immunodeficiency and the European Medicines Agency (EMA) guideline on the clinical investigation of human normal immunoglobulin for SC and /or intramuscular administration. ASBI included bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess, diagnosed according to the Diagnostic Criteria for Acute Serious Bacterial Infections. Full Analysis Set (FAS) included all participants who provided informed consent, and met enrollment eligibility.

End point type	Primary

End point timeframe:

From first dose of study drug up to end of Study Epoch 2 (up to approximately 37.2 months)

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: No statistical comparison was performed between arms (as this is a single arm study), the ASBI rate was compared to a fixed threshold (1.0) defined by an FDA Guideline.

End point values	Epoch 1 + Epoch 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: ASBI per participant-year				
arithmetic mean (standard error)	0.04 (± 0.027)			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate Represented as Mean Number of All Infections per Participant-year

End point title	Rate Represented as Mean Number of All Infections per Participant-year

End point description:

The rate of all infections was defined as the mean number of all infections per participant-year. Number of all infections was calculated as number of infections per participant-year. FAS included all participants who provided informed consent, and met enrollment eligibility.

End point type	Secondary

End point timeframe:

From first dose of study drug up to end of Study Epoch 2 (up to approximately 37.2 months)

End point values	Epoch 1 + Epoch 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: infections per participant-year				
arithmetic mean (standard error)	3.12 (± 0.450)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Trough Levels of Immunoglobulin G (IgG) Total and IgG Subclasses

End point title	Epoch 2: Trough Levels of Immunoglobulin G (IgG) Total and IgG Subclasses

End point description:

FAS=all participants who provided informed consent, and met enrollment eligibility. Only FAS participants in Epoch 2 were analysed for this outcome measure. Number of subjects analysed=number of participants with data available for analyses. Number analysed(n)=number of participants with data available for analysis at specified timepoint. 9999=Standard deviation (SD) was not estimable for 1 participant. 99999=Data was not estimable for 0 participants.

End point type	Secondary

End point timeframe:

Study Epoch 2, Year 1: Months 0, 6, and 12; Year 2: Months 18, 24 and 36

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: grams per liter (g/L)				
arithmetic mean (standard deviation)				
IgG Total: Month 0 (n=40)	10.381 (± 2.9191)			
IgG Total: Month 6 (n=33)	9.199 (± 1.9577)			
IgG Total: Month 12 (n=36)	9.214 (± 1.9800)			
IgG Total: Month 18 (n=1)	13.80 (± 9999)			
IgG Total: Month 24 (n=1)	10.80 (± 9999)			
IgG Total: Month 36 (n=1)	13.50 (± 9999)			
IgG Subclass 1: Month 0 (n=39)	5.888 (± 2.7193)			
IgG Subclass 1: Month 6 (n=39)	5.317 (± 1.4887)			
IgG Subclass 1: Month 12 (n=36)	5.284 (± 1.2103)			
IgG Subclass 1: Month 18 (n=1)	7.590 (± 9999)			
IgG Subclass 1: Month 24 (n=1)	7.710 (± 9999)			
IgG Subclass 1: Month 36 (n=0)	99999 (± 99999)			
IgG Subclass 2: Month 0 (n=39)	3.311 (± 0.6833)			
IgG Subclass 2: Month 6 (n=39)	3.156 (± 0.6694)			
IgG Subclass 2: Month 12 (n=36)	3.106 (± 0.5839)			
IgG Subclass 2: Month 18 (n=1)	3.480 (± 9999)			
IgG Subclass 2: Month 24 (n=1)	3.510 (± 9999)			
IgG Subclass 2: Month 36 (n=0)	99999 (± 99999)			
IgG Subclass 3: Month 0 (n=39)	0.534 (± 0.2838)			
IgG Subclass 3: Month 6 (n=39)	0.508 (± 0.2545)			
IgG Subclass 3: Month 12 (n=36)	0.507 (± 0.2799)			
IgG Subclass 3: Month 18 (n=1)	0.360 (± 9999)			
IgG Subclass 3: Month 24 (n=1)	0.430 (± 9999)			
IgG Subclass 3: Month 36 (n=0)	99999 (± 99999)			
IgG Subclass 4: Month 0 (n=39)	0.2998 (± 0.26802)			
IgG Subclass 4: Month 6 (n=39)	0.3161 (± 0.32899)			
IgG Subclass 4: Month 12 (n=36)	0.3118 (± 0.32790)			
IgG Subclass 4: Month 18 (n=1)	0.9380 (± 9999)			
IgG Subclass 4: Month 24 (n=1)	1.4560 (± 9999)			

IgG Subclass 4: Month 36 (n=0)	99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Trough Levels of Specific Antibodies to Clinically Relevant Pathogens Categorised as Clostridium Tetani Toxoid and Hepatitis B Virus

End point title	Epoch 2: Trough Levels of Specific Antibodies to Clinically Relevant Pathogens Categorised as Clostridium Tetani Toxoid and Hepatitis B Virus

End point description:

FAS=all participants who provided informed consent, and met enrollment eligibility. Only FAS participants in Epoch 2 were analysed for this outcome measure. Number of subjects analysed=number of participants with data available for analyses. Number analysed=number of participants with data available for analysis at specified timepoint. IU/mL international units per milliliters. CTT=Clostridium Tetani Toxoid. Ab=Antibody. HBV=Hepatitis B Virus.

End point type	Secondary

End point timeframe:

Study Epoch 2, Year 2: Months 6, 24, and 36

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: IU/mL				
arithmetic mean (standard deviation)				
CTT Ab:Month 6(n=36)	1.685 (± 0.6793)			
CTT Ab:Month 24(n=1)	2.450 (± 99999)			
CTT Ab:Completion/Termination(Month 36)(n=37)	1.598 (± 0.5889)			
HBV Ab:Month 6(n=36)	199.6 (± 122.97)			
HBV Ab:Month 24(n=1)	146.0 (± 99999)			
HBV Ab:Completion/Termination(Month 36)(n=37)	256.7 (± 219.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Trough Levels of Specific Antibodies to Clinically Relevant Pathogen Haemophilus Influenzae B

End point title	Epoch 2: Trough Levels of Specific Antibodies to Clinically Relevant Pathogen Haemophilus Influenzae B

End point description:

FAS=all participants who provided informed consent, and met enrollment eligibility. Only FAS participants in Epoch 2 were analysed for this outcome measure. Number of subjects analysed=number of participants with data available for analyses. Number analysed=number of participants with data available for analysis at specified timepoint.

End point type	Secondary

End point timeframe:

Study Epoch 2, Year 2: Months 6, 24, and 36

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: milligrams per liter (mg/L)				
arithmetic mean (standard deviation)				
Month 6(n=36)	1.839 (± 1.5222)			
Month 24(n=1)	1.810 (± 99999)			
Completion/Termination(Month 36)(n=39)	1.678 (± 0.8009)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Area Under the Curve Normalised for Week (AUCweek)

End point title	Epoch 2: Area Under the Curve Normalised for Week (AUCweek)

End point description:

Pharmacokinetic analysis set (PKAS) included all participants in the Safety Analysis Set who have at least 1 evaluable post-dose concentration data for PK assessments without major protocol deviations or events affecting the PK results. Number of subjects analysed is the number of participants with data available for analyses. As pre-specified in statistical analysis plan (SAP), this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2, Month 6: Day 0 pre-infusion, and at Days 2, 4, 10, 21 and 28 post-infusion

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: grams*day per liter (g*day/L)				
geometric mean (geometric coefficient of variation)	74.57 (± 19.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Area Under the Curve Over the Infusion Interval (AUCTau)

End point title	Epoch 2: Area Under the Curve Over the Infusion Interval (AUCTau)

End point description:

PKAS included all participants in the Safety Analysis Set who have at least 1 evaluable post-dose concentration data for PK assessments without major protocol deviations or events affecting the PK results. Number of subjects analysed is the number of participants with data available for analyses. As pre-specified in SAP, this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2, Month 6: Day 0 pre-infusion, and at Days 2, 4, 10, 21 and 28 post-infusion

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: g*day/L				
geometric mean (geometric coefficient of variation)	288.8 (± 21.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Apparent Clearance (CL/F)

End point title	Epoch 2: Apparent Clearance (CL/F)

End point description:

PKAS included all participants in the Safety Analysis Set who have at least 1 evaluable post-dose concentration data for PK assessments without major protocol deviations or events affecting the PK results. Number of subjects analysed is the number of participants with data available for analyses. As pre-specified in SAP, this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2, Month 6: Day 0 pre-infusion, and at Days 2, 4, 10, 21 and 28 post-infusion

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: milliliters per day (mL/day)				
geometric mean (geometric coefficient of variation)	56.45 (± 61.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Minimum Concentration (Cmin)

End point title	Epoch 2: Minimum Concentration (Cmin)

End point description:

PKAS included all participants in the Safety Analysis Set who have at least 1 evaluable post-dose concentration data for PK assessments without major protocol deviations or events affecting the PK results. Number of subjects analysed is the number of participants with data available for analyses. As pre-specified in SAP, this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2, Month 6: Day 0 pre-infusion, and at Days 2, 4, 10, 21 and 28 post-infusion

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: g/L				
geometric mean (geometric coefficient of variation)	8.571 (± 25.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Maximum Concentration (Cmax)

End point title	Epoch 2: Maximum Concentration (Cmax)

End point description:

PKAS included all participants in the Safety Analysis Set who have at least 1 evaluable post-dose concentration data for PK assessments without major protocol deviations or events affecting the PK results. Number of subjects analysed is the number of participants with data available for analyses. As pre-specified in SAP, this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2, Month 6: Day 0 pre-infusion, and at Days 2, 4, 10, 21 and 28 post-infusion

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: g/L				
geometric mean (geometric coefficient of variation)	12.94 (± 17.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Time to Maximum Concentration (Tmax)

End point title	Epoch 2: Time to Maximum Concentration (Tmax)

End point description:

PKAS included all participants in the Safety Analysis Set who have at least 1 evaluable post-dose concentration data for PK assessments without major protocol deviations or events affecting the PK results. Number of subjects analysed is the number of participants with data available for analyses. As pre-specified in SAP, this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2, Month 6: Day 0 pre-infusion, and at Days 2, 4, 10, 21 and 28 post-infusion

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: days				
median (full range (min-max))	4.20 (0.0 to 26.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Terminal Half-life (T 1/2)

End point title	Epoch 2: Terminal Half-life (T 1/2)

End point description:

PKAS included all participants in the Safety Analysis Set who have at least 1 evaluable post-dose concentration data for PK assessments without major protocol deviations or events affecting the PK results. Number of subjects analysed is the number of participants with data available for analyses. As pre-specified in SAP, this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2, Month 6: Day 0 pre-infusion, and at Days 2, 4, 10, 21 and 28 post-infusion

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: days				
geometric mean (geometric coefficient of variation)	44.98 (± 45.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Serious Adverse Events (SAEs) Excluding Infections, Related and not Related

End point title	Number of Participants With Serious Adverse Events (SAEs) Excluding Infections, Related and not Related

End point description:

An SAE is defined as an untoward medical occurrence that at any dose is fatal, life-threatening, requires inpatient hospitalisation 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. Number of participants who experienced SAEs, related or not related, was reported. Safety Analysis Set (SAS) included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From first dose of study drug up to EOS (up to 4 years 9 months)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: participants				
SAE: Related	0	0		
SAE: Not Related	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of SAEs Excluding Infections, Related and not Related, per Infusion

End point title	Rate of SAEs Excluding Infections, Related and not Related, per Infusion

End point description:

Rate of SAEs per infusion was calculated as number of serious adverse events/total number of infusions administered to participants in the analysis set. Rate of SAEs per infusion (excluding infections) was reported. SAS included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From first dose of study drug up to EOS (up to 4 years 9 months)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: SAEs per infusion				
number (not applicable)				
SAE: Related	0.0	0.0		
SAE: Not Related	0.0	0.002		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With all Treatment Emergent Adverse Events (TEAEs) Excluding Infections, Related and not Related

End point title	Number of Participants With all Treatment Emergent Adverse Events (TEAEs) Excluding Infections, Related and not Related

End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A TEAE is defined as an adverse event with an onset that occurs after receiving study drug. Number of participants who experienced TEAEs, related or not related, was reported. SAS included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From first dose of study drug up to EOS (up to 4 years 9 months)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: participants				
TEAE: Related	25	31		
TEAE: Not Related	16	36		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of all TEAEs Excluding Infections, Related and not Related, per Infusion

End point title	Rate of all TEAEs Excluding Infections, Related and not Related, per Infusion

End point description:

Rate of all TEAEs per infusion was calculated as number of any adverse reaction events/total number of infusions administered to participants in the analysis set. Rate of any adverse reactions per infusion (excluding infections) was reported. SAS included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From first dose of study drug up to EOS (up to 4 years 9 months)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: adverse reaction event per infusion				
number (not applicable)				
TEAE: Related	0.675	0.397		
TEAE: Not Related	0.270	0.262		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Local TEAEs Excluding Infections, Related and not Related

End point title	Number of Participants With Local TEAEs Excluding Infections, Related and not Related

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A TEAE is defined as an adverse event with an onset that occurs after receiving study drug. Number of participants who experienced local TEAEs, related or not related, was reported. SAS included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From first dose of study drug up to EOS (up to 4 years 9 months)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: participants				
Local TEAE: Related	22	28		
Local TEAE: Not Related	2	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Local TEAEs Excluding Infections, Related and not Related, per Infusion

End point title	Rate of Local TEAEs Excluding Infections, Related and not Related, per Infusion

End point description:

Rate of local TEAEs per infusion was calculated as number of local TEAEs/total number of infusions administered to participants in the analysis set. Rate of local TEAEs per infusion (excluding infections) was reported. SAS included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From first dose of study drug up to EOS (up to 4 years 9 months)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: local TEAEs per infusion				
number (not applicable)				
Local TEAE: Related	0.460	0.212		
Local TEAE: Not Related	0.016	0.013		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Systemic TEAEs Excluding Infections, Related and not Related

End point title	Number of Participants With Systemic TEAEs Excluding Infections, Related and not Related

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A TEAE is defined as an adverse event with an onset that occurs after receiving study drug. Number of participants who experienced systemic TEAEs, related or not related, was reported. SAS included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From first dose of study drug up to EOS (up to 4 years 9 months)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: participants				
Systemic TEAE: Related	12	20		
Systemic TEAE: Not Related	16	33		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Systemic TEAEs Excluding Infections, Related and not Related, per Infusion

End point title	Rate of Systemic TEAEs Excluding Infections, Related and not Related, per Infusion

End point description:

Rate of systemic TEAEs per infusion was calculated as number of systemic TEAEs/total number of infusions administered to participants in the analysis set. Rate of systemic TEAEs per infusion (excluding infections) was reported. SAS included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From first dose of study drug up to EOS (up to 4 years 9 months)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: systemic TEAEs per infusion				
number (not applicable)				
Systemic TEAE: Related	0.214	0.185		
Systemic TEAE: Not Related	0.254	0.250		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of all Temporally Associated TEAEs Excluding Infections per Infusion

End point title	Rate of all Temporally Associated TEAEs Excluding Infections per Infusion

End point description:

Rate of all temporally associated TEAEs per infusion was calculated as number of all temporally associated TEAEs/total number of infusions administered to participants in the analysis set. Rate of all temporally associated TEAEs per infusion (excluding infections) was reported. SAS included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From beginning of infusion up to 72 hours post infusion

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: temporally associated TEAEs per infusion				
number (not applicable)	0.722	0.460		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With all Temporally Associated TEAEs Excluding Infections

End point title	Number of Participants With all Temporally Associated TEAEs Excluding Infections

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. TEAE is defined as an adverse event with an onset that occurs after receiving study drug. Number of participants who experienced all temporally associated TEAEs, related or not related, was reported. SAS included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From beginning of infusion up to 72 hours post infusion

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: participants	27	35		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With all Related (Causally) and/or Temporally Associated TEAEs Excluding Infections

End point title	Number of Participants With all Related (Causally) and/or Temporally Associated TEAEs Excluding Infections

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A TEAE is defined as an adverse event with an onset that occurs after receiving study drug. Number of participants with any related (causally) and/or temporally associated TEAEs (excluding infections) was reported. Temporally-associated TEAEs were defined as TEAEs which begin during infusion of IP or within 72 hours following the end of IP infusion. SAS included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From beginning of infusion up to 72 hours post infusion

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: participants	27	35		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Participants With all Related (Causally) and/or Temporally Associated TEAEs Excluding Infections per Infusion

End point title	Rate of Participants With all Related (Causally) and/or Temporally Associated TEAEs Excluding Infections per Infusion

End point description:

Rate of any related (causally) and/or temporally associated TEAEs per infusion was calculated as number of related and/or temporally associated adverse events/ total number of infusions administered to participants in the analysis set. TEAEs recorded in the study database as "possibly related" or "probably related" to HYQVIA are considered HYQVIA-related adverse events. Temporally-associated TEAEs were defined as TEAEs which begin during infusion of IP or within 72 hours following the end of IP infusion. Rate of any related (causally) and/or temporally associated TEAEs per infusion (excluding infections) was reported. SAS included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From beginning of infusion up to 72 hours post infusion

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: related temporally TEAEs per infusion				
number (not applicable)	0.762	0.482		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With any TEAEs Excluding Infections

End point title	Percentage of Participants With any TEAEs Excluding Infections

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A TEAE is defined as an adverse event with an onset that occurs after receiving study drug. Percentages are rounded off to whole number at the nearest decimal. SAS included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From first dose of study drug up to EOS (up to 4 years 9 months)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: percentage of participants				
number (not applicable)	65.9	93.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Developed Positive Titer (≥160) of Binding or Neutralising Antibodies to rHuPH20

End point title	Percentage of Participants who Developed Positive Titer (≥160) of Binding or Neutralising Antibodies to rHuPH20

End point description:

Percentage of participants who developed positive titer (rHuPH20 titer ≥160) of binding antibodies to rHuPH20 was reported. Neutralising antibodies were only tested if the participant had a titer of ≥160 of binding antibodies. Participants with multiple assessments of titer of ≥160 of binding antibodies are counted only once. Percentages are rounded off to whole number at the nearest decimal. FAS included all participants who provided informed consent, and met enrollment eligibility.

End point type	Secondary

End point timeframe:

From first dose of study drug up to EOS (up to 4 years 9 months)

End point values	Epoch 1 + Epoch 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: percentage of participants				
number (not applicable)	2.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Developed Positive Titer (≥160) of Binding or Neutralising Antibodies to rHuPH20

End point title	Number of Participants who Developed Positive Titer (≥160) of Binding or Neutralising Antibodies to rHuPH20

End point description:

Number of participants who developed positive titer (rHuPH20 titer ≥160) of binding antibodies to rHuPH20 was reported. Neutralising antibodies were only tested if the participant had a titer of ≥160 of binding antibodies. Participants with multiple assessments of titer of ≥160 of binding antibodies are counted only once. FAS included all participants who provided informed consent, and met enrollment eligibility.

End point type	Secondary

End point timeframe:

From first dose of study drug up to EOS (up to 4 years 9 months)

End point values	Epoch 1 + Epoch 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: participants	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Number of Infusion Sites (Needle Sticks) per Infusion

End point title	Epoch 2: Number of Infusion Sites (Needle Sticks) per Infusion

End point description:

SAS included all participants who received at least one dose of HyQvia. As pre-specified in SAP, this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2: Up to 36 months

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: infusion sites per infusion				
arithmetic mean (standard deviation)	1.83 (± 0.366)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Number of Infusions per Month

End point title	Epoch 2: Number of Infusions per Month

End point description:

SAS included all participants who received at least one dose of HyQvia. As pre-specified in SAP, this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2: Up to 36 months

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: infusions per month				
median (full range (min-max))	1.10 (1.0 to 1.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Number of Infusion Sites (Needle Sticks) per Month

End point title	Epoch 2: Number of Infusion Sites (Needle Sticks) per Month

End point description:

SAS included all participants who received at least one dose of HyQvia. As pre-specified in SAP, this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2: Up to 36 months

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: infusion sites per month				
median (full range (min-max))	2.17 (1.1 to 2.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Maximum Infusion Rate per Site

End point title	Epoch 2: Maximum Infusion Rate per Site

End point description:

HYQVIA treatment infusions in Epoch 2 were given at a rate of 10 milliliters per hour per site (mL/h/site) to 160 ml/h/site (body weight [BW] of <40 kg) and 10 mL/h/site to 300 mL/h/site (BW of ≥40 kg). SAS included all participants who received at least one dose of HyQvia. As pre-specified in SAP, this outcome measure was planned only for Epoch 2. mL/h/site= milliliters per hour per site.

End point type	Secondary

End point timeframe:

Study Epoch 2: Up to 36 months

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: mL/h/site				
arithmetic mean (standard deviation)	173.5 (± 81.32)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Duration of Infusion

End point title	Epoch 2: Duration of Infusion

End point description:

Duration of infusion is the time from the start of rHuPH20 infusion until the stop time of immunoglobulin infusion. SAS included all participants who received at least one dose of HyQvia. As pre-specified in SAP, this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2: Up to 36 months

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: minutes (mins)				
median (full range (min-max))	85.0 (45 to 215)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Infusion Volume per Site

End point title	Epoch 2: Infusion Volume per Site

End point description:

SAS included all participants who received at least one dose of HyQvia. As pre-specified in SAP, this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2: Up to 36 months

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: mL/site				
arithmetic mean (standard deviation)	101.3 (± 51.69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Infusions Which Were Discontinued, Slowed, or Interrupted due to an AE

End point title	Epoch 2: Infusions Which Were Discontinued, Slowed, or Interrupted due to an AE

End point description:

SAS included all participants who received at least one dose of HyQvia. As pre-specified in SAP, this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2: Up to 36 months

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: infusions				
number (not applicable)				
Infusions That Were Discontinued	0			
Infusions That Were Slowed	0			
Infusions That Were Interrupted	17			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Percentage of Infusions Which Were Discontinued, Slowed, or Interrupted due to an AE

End point title	Epoch 2: Percentage of Infusions Which Were Discontinued, Slowed, or Interrupted due to an AE

End point description:

Percentages are rounded off to whole number at the nearest decimal. SAS included all participants who received at least one dose of HyQvia. As pre-specified in SAP, this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2: Up to 36 months

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: percentage of infusions				
number (not applicable)				
Infusions That Were Discontinued	0			
Infusions That Were Slowed	0			
Infusions That Were Interrupted	30.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Percentage of Participants who Achieved a Treatment Interval of Three or Four Weeks in Epoch 2

End point title	Epoch 2: Percentage of Participants who Achieved a Treatment Interval of Three or Four Weeks in Epoch 2

End point description:

Percentages are rounded off to whole number at the nearest decimal. SAS included all participants who received at least one dose of HyQvia. As pre-specified in SAP, this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2: Up to 36 months

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: percentage of participants				
number (not applicable)				
Every 3 Weeks	18.6			
Every 4 Weeks	83.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 1: Number of Weeks to Reach Final Dose Interval

End point title	Epoch 1: Number of Weeks to Reach Final Dose Interval

End point description:

SAS included all participants who received at least one dose of HyQvia. Number of subjects analysed is the number of participants with data available for analyses. As pre-specified in SAP, this outcome measure was planned only for Epoch 1.

End point type	Secondary

End point timeframe:

Epoch 1 (up to 6 weeks)

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: weeks				
median (full range (min-max))	6.14 (3.0 to 6.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epoch 2: Percentage of Participants who Maintained a Treatment Interval of Three or Four Weeks in Epoch 2 for 12 Months

End point title	Epoch 2: Percentage of Participants who Maintained a Treatment Interval of Three or Four Weeks in Epoch 2 for 12 Months

End point description:

Percentages are rounded off to whole number at the nearest decimal. SAS included all participants who received at least one dose of HyQvia. As pre-specified in SAP, this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2: Up to 12 months

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: percentage of participants				
number (not applicable)	74.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Health-related Quality of Life (HRQoL): Change From Baseline in Pediatric Quality of Life Inventory (Peds-QL) Score

End point title	Health-related Quality of Life (HRQoL): Change From Baseline in Pediatric Quality of Life Inventory (Peds-QL) Score

End point description:

Peds-QL=generic questionnaire developed,validated measuring HRQoL in pediatric population.4domains measured:physical,emotional,social,school functioning.Age groups:Toddler(2-4years[y]),Young child(5-7y),Child(8-12y),Teens(13-<18y).Depending on participant age,questionnaire completed by participant/parent/caregiver as appropriate.Toddler group,PedsQL Generic Core Scale(GCS):21 items,using 5-point Likert scale(0-4);all other groups,PedsQL:23 items,3-point Likert scale(0,2,4)young child, 5-point Likert scale for child,teens groups.Scores were transformed on scale 0-100;0=100,1=75,2=50,3=25,4=0.Total score,domain scores calculated with higher scores indicating better health.End of Epoch2=participant's data for last epoch2 visit(not including participant discontinuing epoch1).SAS=participants receiving atleast 1dose of HyQvia.Number of subjects analysed=participants with data for analyses,n=participants with data at specified timepoint.CFB=Change From Baseline.C/T=completion/termination.

End point type	Secondary

End point timeframe:

Epoch 1: Baseline (First Infusion); Study Epoch 2: Up to Month 36

End point values	Epoch 1 + Epoch 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline:2-4 Years(n=8)	72.67 (± 12.969)			
Baseline:5-7 Years(n=8)	77.29 (± 18.908)			
Baseline:8-12 Years(n=8)	75.42 (± 17.227)			
Baseline:13-<16 Years(n=8)	76.09 (± 7.894)			
CFB at Epoch 2 Month 12:2-4 Years(n=7)	4.57 (± 17.134)			
CFB at Epoch 2 Month 12:5-7 Years(n=9)	-3.74 (± 15.170)			
CFB at Epoch 2 Month 12:8-12 Years(n=13)	0.84 (± 21.050)			
CFB at Epoch 2 Month 12:13-<16 Years(n=5)	-6.09 (± 8.750)			
CFB at C/T (Month 36):2-4 Years(n=3)	8.73 (± 18.799)			
CFB at C/T (Month 36):5-7 Years(n=1)	-26.09 (± 9999)			
CFB at C/T (Month 36):8-12 Years(n=8)	-5.16 (± 19.735)			
CFB at C/T (Month 36):13-<16 Years(n=3)	3.62 (± 5.471)			
CFB at End of Epoch 2:2-4 Years(n=8)	8.16 (± 17.730)			
CFB at End of Epoch 2:5-7 Years(n=9)	-4.59 (± 16.266)			
CFB at End of Epoch 2:8-12 Years(n=17)	-1.98 (± 14.027)			
CFB at End of Epoch 2:13-<16 Years(n=8)	-2.45 (± 8.807)			

Statistical analyses

No statistical analyses for this end point

Secondary: HRQoL: Change From Baseline in EuroQol Five Dimensions Questionnaire (EQ-5D) Score

End point title	HRQoL: Change From Baseline in EuroQol Five Dimensions Questionnaire (EQ-5D) Score

End point description:

EQ-5D=validated,self-administered assessment of overall health consisting of 5 dimensions(mobility,self-care,usual activities,pain/discomfort,anxiety/depression).Participants were asked to describe health state that day by choosing 1 of 3 responses reflecting levels of severity for 5 dimensions:no problems,some or moderate problems,extreme problems.Total score,domain scores calculated with higher scores indicating worsening health status.EQ-5D includes standard vertical 20cm visual analogue scale (VAS) for recording participant’s rating of current HRQoL state,ranging from 0-100,0 indicated worst imaginable health state,100 was best imaginable health state.End of Epoch2=participant's data for last epoch2 visit (not including participant discontinuing in epoch1).SAS=participants who received at least one dose of HyQvia.Number of subjects analysed=participants with data available for analyses.n=participants with data available for analysis at

End point type	Secondary

End point timeframe:

Epoch 1: Baseline (First Infusion); Study Epoch 2: Up to Month 36

End point values	Epoch 1 + Epoch 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline: Index Score(n=43)	0.8912 (± 0.16457)			
Baseline: VAS Score(n=43)	82.84 (± 16.806)			
Baseline: Mobility(n=43)	1.07 (± 0.258)			
Baseline: Self-care(n=43)	1.16 (± 0.485)			
Baseline: Usual Activities(n=43)	1.14 (± 0.413)			
Baseline: Pain/Discomfort(n=43)	1.28 (± 0.454)			
Baseline: Anxiety/Depression(n=43)	1.28 (± 0.549)			
CFB, Epoch2 Month12:Index Score(n=33)	0.0033 (± 0.14177)			
CFB, Epoch2 Month12:VAS Score(n=33)	0.64 (± 23.504)			
CFB, Epoch2 Month12:Mobility(n=33)	-0.09 (± 0.292)			
CFB, Epoch2 Month12:Self-care(n=33)	-0.12 (± 0.415)			
CFB, Epoch2 Month12:Usual Activities(n=33)	0.03 (± 0.394)			
CFB, Epoch2 Month12:Pain/Discomfort(n=33)	0.18 (± 0.528)			
CFB, Epoch2 Month12:Anxiety/Depression(n=33)	-0.06 (± 0.556)			
CFB, C/T (Month36):Index Score(n=15)	0.0445 (± 0.14426)			
CFB, C/T (Month36):VAS Score(n=15)	-8.93 (± 26.993)			
CFB, C/T (Month36):Mobility(n=15)	0.00 (± 0.00)			
CFB, C/T (Month36):Self-care(n=15)	0.00 (± 0.00)			
CFB, C/T (Month36):Usual Activities(n=15)	0.00 (± 0.535)			
CFB, C/T (Month36):Pain/Discomfort(n=15)	-0.07 (± 0.594)			
CFB, C/T (Month36):Anxiety/Depression(n=15)	-0.27 (± 0.594)			
CFB, End of Epoch2:Index Score(n=41)	0.0169 (± 0.13099)			
CFB, End of Epoch2:VAS Score(n=41)	-2.83 (± 24.895)			
CFB, End of Epoch2:Mobility(n=41)	-0.07 (± 0.264)			
CFB, End of Epoch2:Self-care(n=41)	-0.10 (± 0.374)			
CFB, End of Epoch2:Usual Activities(n=41)	0.00 (± 0.387)			

CFB, End of Epoch2:Pain/Discomfort(n=41)	0.07 (± 0.565)			
CFB, End of Epoch2:Anxiety/Depression(n=41)	-0.10 (± 0.539)			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Preference and Satisfaction: Change From Baseline in Assessment of Life Quality Index (LQI) Score

End point title	Treatment Preference and Satisfaction: Change From Baseline in Assessment of Life Quality Index (LQI) Score

End point description:

The LQI is a validated questionnaire assessing participant perceptions of their HRQoL and their treatment specifically among participants who use IgG therapy. This questionnaire covers 4 domains: treatment interferences, therapy-related problems, therapy setting, and treatment costs. The LQI domains are scored from 0 to 100, with higher scores associated with better IgG treatment satisfaction. End of Epoch 2 summarises all participant's data for their last epoch 2 visit (so not including the participant that discontinued in epoch 1). SAS included all participants who received at least one dose of HyQvia. Number of subjects analysed is the number of participants with data available for analyses. Number analysed (n) is the number of participants with data available for analysis at a specified timepoint.

End point type	Secondary

End point timeframe:

Epoch 1: Baseline (First Infusion); Study Epoch 2: Up to Month 36

End point values	Epoch 1 + Epoch 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline: Treatment Interferences(n=43)	69.77 (± 17.518)			
Baseline: Therapy-related Problems(n=43)	65.21 (± 17.080)			
Baseline: Therapy Setting(n=43)	85.66 (± 14.610)			
Baseline: Treatment Costs(n=43)	60.85 (± 27.310)			
CFB, Epoch2 Month12:Treatment Interferences(n=33)	4.71 (± 18.419)			
CFB, Epoch2 Month12:Therapy-related Problems(n=33)	4.67 (± 17.670)			
CFB, Epoch2 Month12:Therapy Setting(n=33)	-6.23 (± 23.189)			
CFB, Epoch2 Month12:Treatment Costs(n=33)	4.55 (± 36.330)			
CFB, C/T (Month36):Treatment Interferences(n=14)	-10.52 (± 23.850)			
CFB, C/T (Month36):Therapy-related Problems(n=14)	-13.39 (± 31.656)			

CFB, C/T (Month36):Therapy Setting(n=14)	-15.87 (± 27.808)			
CFB, C/T (Month36):Treatment Costs(n=14)	-1.19 (± 32.826)			
CFB, End of Epoch2:Treatment Interferences(n=41)	1.49 (± 20.908)			
CFB, End of Epoch2:Therapy-related Problems(n=41)	0.41 (± 24.399)			
CFB, End of Epoch2:Therapy Setting(n=41)	-10.16 (± 24.718)			
CFB, End of Epoch2:Treatment Costs(n=41)	4.27 (± 35.164)			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Preference and Satisfaction: Change From Baseline in Assessment of Treatment Satisfaction and Medication Questionnaire (TSQM-9) Score

End point title	Treatment Preference and Satisfaction: Change From Baseline in Assessment of Treatment Satisfaction and Medication Questionnaire (TSQM-9) Score

End point description:

The TSQM-9 is a 9-item, validated, self-administered instrument to assess subject satisfaction with medication, which assesses 3 domains: effectiveness, convenience, and global satisfaction. The TSQM-9 domain scores range from 0 to 100 with higher scores representing higher satisfaction. End of Epoch 2 summarises all participant's data for their last epoch 2 visit (so not including the participant that discontinued in epoch 1). SAS included all participants who received at least one dose of HyQvia. Number of subjects analysed is the number of participants with data available for analyses. Number analysed (n) is the number of participants with data available for analysis at a specified timepoint.

End point type	Secondary

End point timeframe:

Epoch 1: Baseline (First Infusion); Study Epoch 2: Up to Month 36

End point values	Epoch 1 + Epoch 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline: Effectiveness(n=43)	74.81 (± 15.494)			
Baseline: Convenience(n=43)	66.15 (± 16.436)			
Baseline: Global Satisfaction(n=43)	79.07 (± 16.525)			
CFB at Epoch 2, Month 12:Effectiveness(n=33)	6.40 (± 16.204)			
CFB at Epoch 2, Month 12:Convenience(n=33)	2.19 (± 19.834)			
CFB at Epoch 2,Month 12:Global Satisfaction(n=33)	4.76 (± 18.529)			

CFB at C/T (Month 36):Effectiveness(n=14)	-12.70 (± 33.577)			
CFB at C/T (Month 36):Convenience(n=14)	-7.14 (± 20.375)			
CFB at C/T (Month 36):Global Satisfaction(n=14)	-17.35 (± 36.283)			
CFB at End of Epoch 2:Effectiveness(n=41)	3.52 (± 20.591)			
CFB at End of Epoch 2:Convenience(n=41)	-0.81 (± 20.244)			
CFB at End of Epoch 2:Global Satisfaction(n=41)	-0.17 (± 24.406)			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Preference and Satisfaction: Number of Participants Who Completed Treatment Preference Questionnaire

End point title	Treatment Preference and Satisfaction: Number of Participants Who Completed Treatment Preference Questionnaire

End point description:

The treatment preference questionnaire, internally developed by the study sponsor, is a self-administered, non-validated scale assessing participant preference for various attributes of immunoglobulin G (IgG) therapy.End of Epoch 2 summarises all participant's data for their last epoch 2 visit (so not including the participant that discontinued in epoch 1). SAS included all participants who received at least one dose of HyQvia. As pre-specified in SAP, this outcome measure was planned only for Epoch 2.

End point type	Secondary

End point timeframe:

Study Epoch 2: Up to Month 36

End point values	Epoch 2			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: participants				
Month 12	34			
Completion/ Termination (Month 36)	14			
End of Epoch 2	42			

Statistical analyses

No statistical analyses for this end point

Secondary: Health Resource Utilisation: Days not Able to go to School or Work, or to Perform Normal Daily Activities

End point title	Health Resource Utilisation: Days not Able to go to School or Work, or to Perform Normal Daily Activities

End point description:

Days not able to go to school or work, or to perform normal daily activities due to infection or other illnesses were calculated as days not able to go to school or work, or to perform normal daily activities due to infection or other illnesses per participant-year. Per participant-years = number or days reported / total number of years of study duration, i.e., the sum of study duration for all subjects in the analysis set, divided by 365.25. SAS included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From first dose of study drug up to EOS (up to 4 years 9 months)

End point values	Epoch 1 + Epoch 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: days per participant-year				
number (not applicable)	4.28			

Statistical analyses

No statistical analyses for this end point

Secondary: Health Resource Utilisation: Days on Antibiotics

End point title	Health Resource Utilisation: Days on Antibiotics

End point description:

Days on antibiotics were calculated as days on antibiotics per participant-year. Per participant-years = number or days reported / total number of years of study duration, i.e., the sum of study duration for all subjects in the analysis set, divided by 365.25. SAS included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From first dose of study drug up to EOS (up to 4 years 9 months)

End point values	Epoch 1 + Epoch 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: days per participant-year				
number (not applicable)	26.77			

Statistical analyses

No statistical analyses for this end point

Secondary: Health Resource Utilisation: Number of Hospitalisations

End point title	Health Resource Utilisation: Number of Hospitalisations

End point description:

Number of hospitalisations, indication for the hospitalisation (infection or non-infection) were calculated as number of hospitalisations, indication for the hospitalisation (infection or non-infection) per participant-year. Per participant-years = number or days reported / total number of years of study duration, i.e., the sum of study duration for all subjects in the analysis set, divided by 365.25. SAS included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From first dose of study drug up to EOS (up to 4 years 9 months)

End point values	Epoch 1 + Epoch 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: hospitalisations per participant-year				
number (not applicable)	0.08			

Statistical analyses

No statistical analyses for this end point

Secondary: Health Resource Utilisation: Number of Days Hospitalised per Participant-Year

End point title	Health Resource Utilisation: Number of Days Hospitalised per Participant-Year

End point description:

Number of days hospitalised were calculated as number of days hospitalised per participant-year. Per participant-years = number or days reported / total number of years of study duration, i.e., the sum of study duration for all subjects in the analysis set, divided by 365.25. SAS included all participants who received at least one dose of HyQvia.

End point type	Secondary

End point timeframe:

From first dose of study drug up to EOS (up to 4 years 9 months)

End point values	Epoch 1 + Epoch 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: days per participant-year				
number (not applicable)	0.21			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to EOS (up to 4 years 9 months)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of AE and abnormal laboratory findings. Any event spontaneously reported by the participant via the participant diary or observed by the investigator was recorded, irrespective of the relation to study treatment. SAS included all participants who received at least one dose of HYQVIA.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Epoch 2

Reporting group description:

Epoch 1 was followed by Epoch 2 with HYQVIA treatment infusions given once every 3 or 4 weeks, depending on the participant's previous IV dosing schedule (for IV pretreated participants) and at the discretion of the investigator and participant (for SC-pretreated participants) up to approximately 36 months.

Reporting group title	Epoch 1

Reporting group description:

Pediatric participants with PIDD who were on IV or non-HYQVIA SC treatment with immunoglobulin were enrolled and treated with HYQVIA SC with a dose or interval ramp-up period of up to six weeks. HYQVIA dose was planned to be equivalent to 100% (± 5%) of pre-study treatment. Dose frequency was one treatment interval of one week, then one treatment interval of two weeks for participants who were planned to be treated every three weeks, and one more treatment interval of three weeks for participants who were planned to be treated every four weeks.

Serious adverse events	Epoch 2	Epoch 1	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 43 (6.98%)	1 / 44 (2.27%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Tonsillar hypertrophy			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Adenovirus infection			

subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Epoch 2	Epoch 1	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 43 (93.02%)	28 / 44 (63.64%)	
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	3 / 43 (6.98%)	0 / 44 (0.00%)	
occurrences (all)	3	0	
Infusion related reaction			
subjects affected / exposed	4 / 43 (9.30%)	2 / 44 (4.55%)	
occurrences (all)	6	2	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 43 (37.21%)	7 / 44 (15.91%)	
occurrences (all)	71	13	
Dizziness			
subjects affected / exposed	4 / 43 (9.30%)	0 / 44 (0.00%)	
occurrences (all)	5	0	
General disorders and administration site conditions			
Chills			

subjects affected / exposed	3 / 43 (6.98%)	0 / 44 (0.00%)	
occurrences (all)	3	0	
Fatigue			
subjects affected / exposed	2 / 43 (4.65%)	5 / 44 (11.36%)	
occurrences (all)	5	5	
Infusion site erythema			
subjects affected / exposed	10 / 43 (23.26%)	5 / 44 (11.36%)	
occurrences (all)	26	11	
Infusion site extravasation			
subjects affected / exposed	10 / 43 (23.26%)	2 / 44 (4.55%)	
occurrences (all)	19	2	
Infusion site pain			
subjects affected / exposed	15 / 43 (34.88%)	10 / 44 (22.73%)	
occurrences (all)	36	12	
Infusion site pruritus			
subjects affected / exposed	10 / 43 (23.26%)	3 / 44 (6.82%)	
occurrences (all)	17	5	
Infusion site swelling			
subjects affected / exposed	9 / 43 (20.93%)	3 / 44 (6.82%)	
occurrences (all)	14	4	
Injection site pain			
subjects affected / exposed	1 / 43 (2.33%)	7 / 44 (15.91%)	
occurrences (all)	2	11	
Pyrexia			
subjects affected / exposed	12 / 43 (27.91%)	0 / 44 (0.00%)	
occurrences (all)	18	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 43 (6.98%)	2 / 44 (4.55%)	
occurrences (all)	3	2	
Abdominal pain upper			
subjects affected / exposed	3 / 43 (6.98%)	1 / 44 (2.27%)	
occurrences (all)	3	1	
Diarrhoea			
subjects affected / exposed	5 / 43 (11.63%)	4 / 44 (9.09%)	
occurrences (all)	5	5	

Nausea			
subjects affected / exposed	6 / 43 (13.95%)	2 / 44 (4.55%)	
occurrences (all)	7	2	
Vomiting			
subjects affected / exposed	8 / 43 (18.60%)	2 / 44 (4.55%)	
occurrences (all)	10	2	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	5 / 43 (11.63%)	1 / 44 (2.27%)	
occurrences (all)	11	1	
Cough			
subjects affected / exposed	4 / 43 (9.30%)	1 / 44 (2.27%)	
occurrences (all)	5	1	
Epistaxis			
subjects affected / exposed	5 / 43 (11.63%)	0 / 44 (0.00%)	
occurrences (all)	10	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	5 / 43 (11.63%)	1 / 44 (2.27%)	
occurrences (all)	5	1	
Rash			
subjects affected / exposed	5 / 43 (11.63%)	0 / 44 (0.00%)	
occurrences (all)	7	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 43 (6.98%)	0 / 44 (0.00%)	
occurrences (all)	3	0	
Pain in extremity			
subjects affected / exposed	3 / 43 (6.98%)	2 / 44 (4.55%)	
occurrences (all)	3	2	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	5 / 43 (11.63%)	0 / 44 (0.00%)	
occurrences (all)	7	0	
Bronchitis			

subjects affected / exposed	3 / 43 (6.98%)	0 / 44 (0.00%)	
occurrences (all)	5	0	
Ear infection			
subjects affected / exposed	4 / 43 (9.30%)	0 / 44 (0.00%)	
occurrences (all)	5	0	
Gastroenteritis viral			
subjects affected / exposed	3 / 43 (6.98%)	1 / 44 (2.27%)	
occurrences (all)	4	2	
Influenza			
subjects affected / exposed	6 / 43 (13.95%)	0 / 44 (0.00%)	
occurrences (all)	6	0	
Otitis media			
subjects affected / exposed	5 / 43 (11.63%)	2 / 44 (4.55%)	
occurrences (all)	12	2	
Otitis externa			
subjects affected / exposed	3 / 43 (6.98%)	0 / 44 (0.00%)	
occurrences (all)	3	0	
Pharyngitis			
subjects affected / exposed	3 / 43 (6.98%)	0 / 44 (0.00%)	
occurrences (all)	3	0	
Pharyngitis streptococcal			
subjects affected / exposed	6 / 43 (13.95%)	1 / 44 (2.27%)	
occurrences (all)	10	1	
Sinusitis			
subjects affected / exposed	16 / 43 (37.21%)	4 / 44 (9.09%)	
occurrences (all)	21	4	
Upper respiratory tract infection			
subjects affected / exposed	8 / 43 (18.60%)	1 / 44 (2.27%)	
occurrences (all)	9	1	
Viral upper respiratory tract infection			
subjects affected / exposed	8 / 43 (18.60%)	2 / 44 (4.55%)	
occurrences (all)	11	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 July 2017	Following changes were implemented with Protocol Amendment 1: -Included word "efficacy" in study title, short study title, and wherever applicable. -Clarified that latest approved version of prescribing Information for United States (US) would be applicable. -Updated study status from planned to ongoing. -Updated study purpose and objectives. -Revised and rearranged secondary and tertiary objectives. -Provided information on testing and characterisation of neutralising anti-rHuPH20. -Updated overall study design. -Clarified time point and location of study completion visit. -Updated blood sample collection information for PK assessments. -Updated study outcome measures. -Revised stopping rules. -Moved GAMMAGARD LIQUID administration instructions to applicable section of protocol. -Provided additional guidance on administration of HYQVIA. -Provided additional clarification that treatment with GAMMAGARD LIQUID will follow guidance of product information and site´s standard of care. -Widened range of potential source data documents. -Update text to define exclusion criterion. -Clarified definition of "enrollment" for informed consent. -Updated text to define screening and clarified screening/re-screening procedures and time limit. -Provided additional information regarding timepoints of administration of QoL questionnaires and treatment preference and satisfaction assessments. -Removed redundant information about PK assessments. -Reflected an operational change. -Clarified of data collection method to match secondary outcome measures, and to add LQI to allow for collection of additional QoL data. -Limited investigator´s responsibility to report SAEs after study completion. -Deleted requirement of a Non-Medical Complaints (NMC) form, and updated term used for safety monitoring committee. -Updated clinical laboratory sections (hematology, chemistry, anti-rHuPH20 antibodies) and related tables. -Updated statistical section. -Updated schedule of assessments.
24 March 2019	Following changes were implemented with Protocol Amendment 2: -Clarified that the safety follow-up and antibody testing were to continue for 1 year, not less, for all participants who were switched to Epoch 3. -Allowed shorter infusion intervals (e.g., 2 weeks) in Epoch 2 to provide increased flexibility for pediatric participants. -Clarified that for pediatric participants, the full vial of rHuPH20 will not always be needed. -Clarified when rHuPH20 dose adjustments were required. -Clarified the study procedures that were to be performed at scheduled site visits and those that were to be performed outside of scheduled site visits. The schedule of study procedures and assessments was also updated accordingly. -Clarified that blood and urine collection were to occur pre-infusion but may be performed outside the specified time to accommodate the needs of young children. -Confirmed the IgG trough level at study entry without additional blood sampling for the pediatric participants. The clinical laboratory assessments tables were updated to better distribute the blood samples and ensure a baseline IgG trough level and IgG subclasses samples were taken. -Included two additional domains (a Life Quality Index domain and a Global Satisfaction domain) in the HRQoL statistical hypothesis testing. -Included additional descriptive statistics for the healthcare resource utilisation assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported