



Clinical trial results:

Post-Authorization Safety, Tolerability and Immunogenicity Evaluation of HyQvia in Pediatric Subjects With Primary Immunodeficiency Diseases

Summary

EudraCT number	2016-003438-26
Trial protocol	GB SE DK CZ SK FR GR HU
Global end of trial date	15 January 2021

Results information

Result version number	v1
This version publication date	04 August 2021
First version publication date	04 August 2021

Trial information

Trial identification

Sponsor protocol code	161504
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03116347
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Baxalta Innovations GmbH
Sponsor organisation address	Industriestrasse 67, Vienna, Austria, 1220
Public contact	Study Director, Baxalta Innovations GmbH, ClinicalTransparency@takeda.com
Scientific contact	Study Director, Baxalta Innovations GmbH, ClinicalTransparency@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	Interim
Date of interim/final analysis	14 May 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety of HyQvia treatment in pediatric subjects with Primary Immunodeficiency Diseases (PIDD) who received immunoglobulin therapy prior to study enrollment.

Protection of trial subjects:

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, R2, November 2016), Title 21 of the US Code of Federal Regulations, the EU Directives 2001/20/EC and 2005/28/EC, the Declaration of Helsinki and applicable national and local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 June 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	Czechia: 7
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Slovakia: 9
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Hungary: 3
Worldwide total number of subjects	42
EEA total number of subjects	33

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)	21
Adolescents (12-17 years)	21
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 16 sites in Czech Republic, Denmark, France, Greece, Slovakia, Sweden, Hungary, and United Kingdom.

Pre-assignment

Screening details:

A total of 42 subjects were enrolled and treated in this study. Based on one year safety follow-up, subjects will be followed to Epoch 3 if anti-rHuPH20 antibody titer ≥ 160 , and who experience either a related SAE or a related severe AE during Epoch 1 or Epoch 2. Data was reported based on interim analysis cut-off date (14-May-2020).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Epoch 1

Arm description:

Pediatric subjects with PIDD who were on non-HyQvia intravenous (IV) or subcutaneous (SC) treatment with immunoglobulin (IV-pretreated, SC-pretreated) were enrolled and treated with HyQvia (Immune Globulin Infusion 10% [Human] with Recombinant Human Hyaluronidase) SC with a dose or interval ramp-up period of up to 6 weeks. HyQvia was administered at a starting dose of 5 milliliter per hour per site (mL/h/site) to maximum tolerated dose of 80 mL/h/site (for subject with body weight [BW] < 40 kilogram [kg]) or starting dose of 10 mL/h/site to maximum tolerated dose of 240 mL/h/site (for subject with BW greater than or equal to $\geq$ 40 kg).

Arm type	Experimental
Investigational medicinal product name	Immune Globulin Infusion
Investigational medicinal product code	
Other name	HyQvia
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Pediatric subjects treated with HyQvia subcutaneously with a dose or interval ramp-up period of up to 6 weeks.

Arm title	Epoch 2
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Arm description:

Pediatric subjects who were treated with HyQvia prior to this study and those who completed the ramp-up period (Epoch 1) are followed by Epoch 2 with HyQvia treatment. After one year in Epoch 2, subjects with anti-rHuPH20 antibody titer <160 at all time-points during the study will complete the study termination/completion visit at the next possible occasion. Subjects with anti-rHuPH20 antibody titer ≥ 160 during the study and/or at the last measurement will continue for an additional two years of HyQvia treatment and observation. HyQvia was administered at a starting dose of 10 mL/h/site to maximum tolerated dose of 160 mL/h/site (for subject with body weight [BW] <40kg) or starting dose of 10 mL/h/site to maximum tolerated dose of 300 mL/h/site (for subject with BW $\geq$ 40kg).

Arm type	Experimental
Investigational medicinal product name	Immune Globulin Infusion
Investigational medicinal product code	
Other name	HyQvia
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects who were treated with HyQvia prior to this study, and those who completed the ramp up period (Epoch 1) is followed by Epoch 2 with HyQvia treatment.

Number of subjects in period 1	Epoch 1	Epoch 2
Started	23	19
Completed	11	11
Not completed	12	8
Consent withdrawn by subject	1	1
Ongoing	11	6
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Epoch 1
Reporting group description:	
Pediatric subjects with PIDD who were on non-HyQvia intravenous (IV) or subcutaneous (SC) treatment with immunoglobulin (IV-pretreated, SC-pretreated) were enrolled and treated with HyQvia (Immune Globulin Infusion 10% [Human] with Recombinant Human Hyaluronidase) SC with a dose or interval ramp-up period of up to 6 weeks. HyQvia was administered at a starting dose of 5 milliliter per hour per site (mL/h/site) to maximum tolerated dose of 80 mL/h/site (for subject with body weight [BW] < 40 kilogram [kg]) or starting dose of 10 mL/h/site to maximum tolerated dose of 240 mL/h/site (for subject with BW greater than or equal to [$\geq$] 40 kg).	
Reporting group title	Epoch 2
Reporting group description:	
Pediatric subjects who were treated with HyQvia prior to this study and those who completed the ramp-up period (Epoch 1) are followed by Epoch 2 with HyQvia treatment. After one year in Epoch 2, subjects with anti-rHuPH20 antibody titer <160 at all time-points during the study will complete the study termination/completion visit at the next possible occasion. Subjects with anti-rHuPH20 antibody titer $\geq$ 160 during the study and/or at the last measurement will continue for an additional two years of HyQvia treatment and observation. HyQvia was administered at a starting dose of 10 mL/h/site to maximum tolerated dose of 160 mL/h/site (for subject with body weight [BW] <40kg) or starting dose of 10 mL/h/site to maximum tolerated dose of 300 mL/h/site (for subject with BW $\geq$ 40kg).	

Reporting group values	Epoch 1	Epoch 2	Total
Number of subjects	23	19	42
Age Categorical Units:			

Age Continuous Units: years			
arithmetic mean	10.3	11.7	
standard deviation	$\pm$ 3.82	$\pm$ 4.33	-
Gender Categorical Units: Subjects			
Female	5	3	8
Male	18	16	34
Race Units: Subjects			
American Indian Or Alaska Native	0	0	0
Asian	0	0	0
Black Or African American	0	0	0
Native Hawaiian Or Other Pacific Islander	0	0	0
White	22	19	41
Unknown/Not Available/Not Reported	0	0	0
Not Collected Per Local Regulations	1	0	1
Other	0	0	0
Ethnicity Units: Subjects			
Hispanic Or Latino	0	0	0
Not Hispanic Or Latino	23	19	42
Not Reported	0	0	0

Unknown	0	0	0
Decline To Provide	0	0	0

End points

End points reporting groups

Reporting group title	Epoch 1
Reporting group description:	
Pediatric subjects with PIDD who were on non-HyQvia intravenous (IV) or subcutaneous (SC) treatment with immunoglobulin (IV-pretreated, SC-pretreated) were enrolled and treated with HyQvia (Immune Globulin Infusion 10% [Human] with Recombinant Human Hyaluronidase) SC with a dose or interval ramp-up period of up to 6 weeks. HyQvia was administered at a starting dose of 5 milliliter per hour per site (mL/h/site) to maximum tolerated dose of 80 mL/h/site (for subject with body weight [BW] < 40 kilogram [kg]) or starting dose of 10 mL/h/site to maximum tolerated dose of 240 mL/h/site (for subject with BW greater than or equal to [$\geq$] 40 kg).	
Reporting group title	Epoch 2
Reporting group description:	
Pediatric subjects who were treated with HyQvia prior to this study and those who completed the ramp-up period (Epoch 1) are followed by Epoch 2 with HyQvia treatment. After one year in Epoch 2, subjects with anti-rHuPH20 antibody titer <160 at all time-points during the study will complete the study termination/completion visit at the next possible occasion. Subjects with anti-rHuPH20 antibody titer $\geq$ 160 during the study and/or at the last measurement will continue for an additional two years of HyQvia treatment and observation. HyQvia was administered at a starting dose of 10 mL/h/site to maximum tolerated dose of 160 mL/h/site (for subject with body weight [BW] <40kg) or starting dose of 10 mL/h/site to maximum tolerated dose of 300 mL/h/site (for subject with BW $\geq$ 40kg).	

Primary: Number of Subjects with All Severe Related Treatment-emergent Adverse Events (TEAEs) per Infusion (Excluding Infections)

End point title	Number of Subjects with All Severe Related Treatment-emergent Adverse Events (TEAEs) per Infusion (Excluding Infections) ^[1]
End point description:	
An Adverse Events (AEs) was defined as any untoward medical occurrence in a subject administered an investigational product (IP) that does not necessarily have a causal relationship with the treatment. TEAE was defined as AEs with onset after date-time of first dose of IP, or medical conditions present prior to the start of IP but increased in severity or relationship after date-time of first dose of IP. Related AEs was defined as an AE that was recorded as "possibly related" or "probably related" to IP was considered "related AE", and AE recorded as "unlikely related" or "not related" was considered "unrelated" AE. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.	
End point type	Primary
End point timeframe:	
From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)	

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 and comparison analyses were performed for this endpoint.

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Rate of All Severe Related TEAEs per Infusion (Excluding Infections)

End point title	Rate of All Severe Related TEAEs per Infusion (Excluding Infections) ^[2]
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End point description:

An Adverse Events (AEs) was defined as any untoward medical occurrence in a subject administered an investigational product (IP) that does not necessarily have a causal relationship with the treatment. TEAE was defined as AEs with onset after date-time of first dose of IP in Epoch 1, or medical conditions present prior to the start of IP but increased in severity or relationship after date-time of first dose of IP in Epoch 1. Severe Related adverse events rate per infusion = number of adverse events/total number of infusions prior to subject's start date of non-response. Severe related TEAEs per Infusion was calculated based on events per 1000 subject years, Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.

End point type	Primary
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End point timeframe:

From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)

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: No statistical and comparison analyses were performed for this endpoint.

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Events per infusion				
number (not applicable)	0.1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Related Serious TEAEs per Infusion (Excluding Infections)

End point title	Number of Subjects with Related Serious TEAEs per Infusion (Excluding Infections) ^[3]
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End point description:

TEAE was defined as AEs with onset after date-time of first dose of IP in Epoch 1, or medical conditions present prior to the start of IP but increased in severity or relationship after date-time of first dose of IP in Epoch 1. A serious TEAE was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged in-patient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. Related TEAE = AEs recorded in the study database as "possibly related" or "probably related" to IP. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.

End point type	Primary
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End point timeframe:

From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)

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: No statistical and comparison analyses were performed for this endpoint.

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Rate of Related Serious TEAEs per Infusion (Excluding Infections)

End point title	Rate of Related Serious TEAEs per Infusion (Excluding Infections) ^[4]
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End point description:

TEAE was defined as AEs with onset after date-time of first dose of IP in Epoch 1, or medical conditions present prior to the start of IP but increased in severity or relationship after date-time of first dose of IP in Epoch 1. A serious TEAE was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged in-patient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. Related TEAE = AEs recorded in the study database as "possibly related" or "probably related" to IP. Related serious adverse events rate per infusion = number of adverse events/total number of infusions prior to subject's start date of non-response. Related serious TEAEs per Infusion was calculated based on events per infusion. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.

End point type	Primary
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End point timeframe:

From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)

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: No statistical and comparison analyses were performed for this endpoint.

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Events per infusion				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Serum Trough Levels of Immunoglobulin G (IgG)

End point title	Total Serum Trough Levels of Immunoglobulin G (IgG)
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End point description:

Total serum trough levels of IgG in Epoch 1 and 2 were reported. Full analysis set included all participants who provide informed consent and meet enrollment eligibility.

End point type	Secondary
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End point timeframe:

Months 6 and 12

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[5]	0 ^[6]		
Units: Milligram per deciliter (mg/dL)				
arithmetic mean (standard deviation)	()	()		

Notes:

[5] - Data will be reported from the final analysis.

[6] - Data will be reported from the final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Achieved a Treatment Interval of Three or Four weeks in Epoch 2

End point title	Percentage of Subjects who Achieved a Treatment Interval of Three or Four weeks in Epoch 2
End point description: Percentage of subjects who achieve a treatment interval of three or four weeks in Epoch 2 will be reported.	
End point type	Secondary
End point timeframe: up to Month 12	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[7]	0 ^[8]		
Units: Percentage of subjects				
number (not applicable)				

Notes:

[7] - Data will be reported from the final analysis.

[8] - Data will be reported from the final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Maintained a Treatment Interval of Three or Four Weeks in Epoch 2

End point title	Percentage of Subjects who Maintained a Treatment Interval of Three or Four Weeks in Epoch 2
End point description: Percentage of subjects who maintained a treatment interval of three or four weeks in Epoch 2 will be reported.	
End point type	Secondary

End point timeframe:
up to Month 12

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[9]	0 ^[10]		
Units: Percentage of subjects				
number (not applicable)				

Notes:

[9] - Data will be reported from the final analysis.

[10] - Data will be reported from the final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Local TEAEs

End point title	Number of Subjects with Local TEAEs
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End point description:

TEAE was defined as AEs with onset after date-time of first dose of IP, or medical conditions present prior to the start of IP but increased in severity or relationship after date-time of first dose of IP. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.

End point type	Secondary
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End point timeframe:

From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	9	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Local TEAEs Per Infusion

End point title	Rate of Local TEAEs Per Infusion
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End point description:

Local adverse event rate per infusion = number of local adverse events/total number of infusions prior to subject's start date of non-response. Local Adverse Events: comprises all events reported within the MedDRA high level terms "administration site reactions NEC (Not Elsewhere Classified)", "infusion site reactions", and "injection site reactions". Only events are included which start prior to subject's start date of non-response. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.

End point type	Secondary
End point timeframe:	
From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Events per infusion				
number (not applicable)	0.1	0.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Local Adverse Reactions

End point title	Number of Subjects with Local Adverse Reactions
End point description:	
Local Adverse reactions was defined as any TEAE that meets any of the following criteria: 1) A TEAE considered by either the investigator and/or the sponsor to be possibly or probably related to IP administration, or; 2) A TEAE that begins during infusion of IP or within 72 hours following the end of IP infusion, or; 3) A TEAE for which causality assessment is missing or indeterminate. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.	
End point type	Secondary
End point timeframe:	
From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	9	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Local Adverse Reaction per Infusion

End point title	Rate of Local Adverse Reaction per Infusion
End point description:	
Local adverse reaction per infusion = number of local adverse events/total number of infusions prior to subject's start date of non-response. Safety analysis set included all subjects in the full analysis set (enrolled Set) who received at least one dose of HyQvia.	
End point type	Secondary

End point timeframe:

From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Events per infusion				
number (not applicable)	0.1	0.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Systemic TEAEs

End point title	Number of Subjects with Systemic TEAEs
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End point description:

TEAE was defined as AEs with onset after date-time of first dose of IP in Epoch 1, or medical conditions present prior to the start of IP but increased in severity or relationship after date-time of first dose of IP in Epoch 1. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.

End point type	Secondary
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End point timeframe:

From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	13	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Systemic TEAEs Per Infusion

End point title	Rate of Systemic TEAEs Per Infusion
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End point description:

Systemic TEAEs per infusion = number of local adverse events/total number of infusions prior to subject's start date of non-response. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.

End point type	Secondary
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End point timeframe:

From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Events per infusion				
number (not applicable)	0.2	0.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Systemic Adverse Reactions

End point title	Number of Subjects with Systemic Adverse Reactions
End point description:	Number of subjects with systemic adverse reactions were reported. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.
End point type	Secondary
End point timeframe:	From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	6	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Systemic Adverse Reactions Per Infusion

End point title	Rate of Systemic Adverse Reactions Per Infusion
End point description:	Systemic adverse reactions rate per infusion = number of local adverse events/total number of infusions prior to subject's start date of non-response. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.
End point type	Secondary
End point timeframe:	From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Events per infusion				
number (not applicable)	0.1	0.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with All TEAEs

End point title	Number of Subjects with All TEAEs
End point description: TEAE was defined as AEs with onset after date-time of first dose of IP in Epoch 1, or medical conditions present prior to the start of IP but increased in severity or relationship after date-time of first dose of IP in Epoch 1. Safety analysis set included all subjects in the full analysis set (Enrolled set) who received at least one dose of HyQvia.	
End point type	Secondary
End point timeframe: From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	16	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of TEAEs per Infusion

End point title	Rate of TEAEs per Infusion
End point description: Rate of TEAEs per infusion = number of adverse events/total number of infusions prior to subject's start date of non-response. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.	
End point type	Secondary
End point timeframe: From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Events per infusion				
number (not applicable)	0.3	0.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with All Adverse Reactions

End point title	Number of Subjects with All Adverse Reactions
End point description:	
Adverse reactions was defined as any TEAE that meets any of the following criteria: 1) A TEAE considered by either the investigator and/or the sponsor to be possibly or probably related to IP administration, or; 2) A TEAE that begins during infusion of IP or within 72 hours following the end of IP infusion, or; 3) A TEAE for which causality assessment is missing or indeterminate. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.	
End point type	Secondary
End point timeframe:	
From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	12	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Adverse Reaction per Infusion

End point title	Rate of Adverse Reaction per Infusion
End point description:	
Rate of adverse reaction per infusion = number of adverse events/total number of infusions prior to subject's start date of non-response. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.	
End point type	Secondary
End point timeframe:	
From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Events per infusion				
number (not applicable)	0.1	0.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with all Temporally Associated TEAEs per infusion (Excluding Infections)

End point title	Number of Subjects with all Temporally Associated TEAEs per infusion (Excluding Infections)
End point description: Temporally associated TEAEs were all AEs which occur during the infusion or within 72 hours of completion of infusion.	
End point type	Secondary
End point timeframe: From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[11]	0 ^[12]		
Units: Subjects				

Notes:

[11] - Data will be reported from the final analysis.

[12] - Data will be reported from the final analysis.

Statistical analyses

No statistical analyses for this end point

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

End point title	Rate of all Temporally Associated TEAEs per Infusion (Excluding Infections)
End point description: Rate of Temporally associated TEAEs per infusion = number of adverse events/total number of infusions prior to subject's start date of non-response. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.	
End point type	Secondary
End point timeframe: From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[13]	0 ^[14]		
Units: Events per infusion				
number (not applicable)				

Notes:

[13] - Data will be reported from the final analysis.

[14] - Data will be reported from the final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with all Causally Related TEAEs per Infusion (Excluding Infections)

End point title	Number of Subjects with all Causally Related TEAEs per Infusion (Excluding Infections)
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End point description:

Related TEAEs were defined as causally related TEAEs. Number of Subjects with all causally related TEAEs per infusion (excluding infections) were reported. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.

End point type	Secondary
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End point timeframe:

From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	10	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Causally Related TEAEs per Infusion (Excluding Infections)

End point title	Rate of Causally Related TEAEs per Infusion (Excluding Infections)
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End point description:

Rate of causally related TEAEs per infusion = number of causally related adverse events/total number of infusions prior to subject's start date of non-response. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.

End point type	Secondary
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End point timeframe:

From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Events per infusion				
number (not applicable)	0.1	0.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with all Serious TEAEs

End point title	Number of Subjects with all Serious TEAEs
End point description: Serious TEAE was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged in-patient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.	
End point type	Secondary
End point timeframe: From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Serious TEAEs per Infusion

End point title	Rate of Serious TEAEs per Infusion
End point description: Rate of Serious TEAEs per infusion = number of local adverse events/total number of infusions prior to subject's start date of non-response. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.	
End point type	Secondary
End point timeframe: From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Events per infusion				
number (not applicable)	0.1	0.1		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects who Developed Positive Titer (≥ 160) of Binding or Neutralizing Antibodies to rHuPH20
End point description: Number of Subjects who developed positive titer (≥ 160) of binding or neutralizing antibodies to rHuPH20 were reported. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.	
End point type	Secondary
End point timeframe: Epoch 1 (up to 6 weeks) and Epoch 2 (up to 35 months)	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Infusions per Month per Subject

End point title	Number of Infusions per Month per Subject
End point description: Number of infusions per month was calculated as total number of infusions per duration of treatment (days) * 30.4 days per month. Number of infusions per month per subject was reported. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.	
End point type	Secondary
End point timeframe: Epoch 1 (up to 6 weeks) and Epoch 2 (up to 35 months)	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Infusions per month				
arithmetic mean (standard deviation)	1.62 ($\pm$ 1.423)	1.11 ($\pm$ 0.517)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Infusion Sites per Infusion per Month per Subject

End point title	Number of Infusion Sites per Infusion per Month per Subject
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End point description:

Number of infusion sites per infusion per month was calculated as total number of infusion sites per total number of infusions per duration of treatment (days) * 30.4 days per month. Mean number of infusion sites per infusion per month per subject was reported. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.

End point type	Secondary
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End point timeframe:

Epoch 1 (up to 6 weeks) and Epoch 2 (up to 35 months)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Infusion sites per infusion/Month				
arithmetic mean (standard deviation)	0.43 ($\pm$ 0.824)	0.31 ($\pm$ 0.622)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Infusion

End point title	Duration of Infusion
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End point description:

Duration of infusion was defined as time from the start of rHuPH20 infusion until the stop time of immunoglobulin infusion. Duration of infusion was calculated as stop time of infusion – start time of infusion. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.

End point type	Secondary
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End point timeframe:

Epoch 1 (up to 6 weeks) and Epoch 2 (up to 35 months)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Minutes				
arithmetic mean (standard deviation)	77.6 ($\pm$ 28.41)	104.1 ($\pm$ 37.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Infusion Rate per Site

End point title	Maximum Infusion Rate per Site
End point description: Maximum infusion rate per site was reported. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.	
End point type	Secondary
End point timeframe: Epoch 1 (up to 6 weeks) and Epoch 2 (up to 35 months)	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Milliliter per hour (mL/h)				
arithmetic mean (standard deviation)	253.84 ($\pm$ 113.952)	181.61 ($\pm$ 98.932)		

Statistical analyses

No statistical analyses for this end point

Secondary: Infusion Volume per Site

End point title	Infusion Volume per Site
End point description: Infusion volume per site was calculated as actual IgG volume (milliliter [mL]) per total number of infusion sites used. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.	
End point type	Secondary
End point timeframe: Epoch 1 (up to 6 weeks) and Epoch 2 (up to 35 months)	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: milliliter per site				
arithmetic mean (standard deviation)	101.99 ($\pm$ 66.388)	162.00 ($\pm$ 93.988)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Infusions that are Discontinued, Slowed, or Interrupted due to an AE

End point title	Number of Subjects with Infusions that are Discontinued, Slowed, or Interrupted due to an AE
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End point description:

Number of subjects with infusions that are discontinued, slowed, or interrupted due to an AE were reported. Safety analysis set included all subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia.

End point type	Secondary
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End point timeframe:

Epoch 1 (up to 6 weeks) and Epoch 2 (up to 35 months)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	8	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Weeks to Reach Final Dose Interval

End point title	Number of Weeks to Reach Final Dose Interval ^[15]
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End point description:

Final dose interval was defined as three or four weeks infusion interval. Safety analysis set included all subjects in the full analysis set (enrolled Set) who received at least one dose of HyQvia.

End point type	Secondary
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End point timeframe:

Epoch 1 (up to 6 weeks) and Epoch 2 (up to 35 months)

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was not planned to be collected and analysed for EPOCH 2 group.

End point values	Epoch 1			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Weeks				
arithmetic mean (standard deviation)	5.19 ($\pm$ 1.625)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health Related Quality of Life (HR QoL): Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9)

End point title	Health Related Quality of Life (HR QoL): Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9)
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End point description:

TSQM-9 was a 9-item, validated, self-administered instrument to assess subjects satisfaction with medication. The 3 domains assessed are effectiveness, convenience, and global satisfaction. The score of each of the 3 domains is based on an algorithm to create a score of 0 to 100. Higher score indicated greater satisfaction in that domain.

End point type	Secondary
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End point timeframe:

Epoch 1 (up to 6 weeks) and Epoch 2 (up to 35 months)

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[16]	0 ^[17]		
Units: Score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[16] - Data will be reported from the final analysis.

[17] - Data will be reported from the final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: HRQoL: Pediatric Quality of Life Questionnaire (PedsQL)

End point title	HRQoL: Pediatric Quality of Life Questionnaire (PedsQL)
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End point description:

The Peds-QL was a generic HR QoL instrument designed specifically for a pediatric population. It captures the following domains: general health/activities, feelings/emotional, social functioning, school

functioning. For this study, the Peds-QL for 8 to 18-year-old subjects was used. Higher scores indicate better quality of life (QOL) for all domains of the Peds-QL. This modular instrument uses a 5-point scale: from 0 (never) to 4 (almost always). Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0. 4 dimensions (physical, emotional, social, & school functioning) are scored.

End point type	Secondary
End point timeframe:	
Epoch 1 (up to 6 weeks) and Epoch 2 (up to 35 months)	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[18]	0 ^[19]		
Units: Score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[18] - Data will be reported from the final analysis.

[19] - Data will be reported from the final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQoL (Quality of Life)-5 Dimensions (EQ-5D)

End point title	EuroQoL (Quality of Life)-5 Dimensions (EQ-5D)
End point description:	
EQ-5D considered five attributes of quality of life evaluation, that is, mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension had five possible levels: 1 (no problems); 2 (slight problems); 3 (moderate problems); 4 (severe problems), and; 5 (extreme problems). EQ-5D also included an additional visual analogic scale (EQ-VAS), which ranged from 0 to 100, where 0 indicated worst imaginable health state and 100 was best imaginable health state.	
End point type	Secondary
End point timeframe:	
Epoch 1 (up to 6 weeks) and Epoch 2 (up to 35 months)	

End point values	Epoch 1	Epoch 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[20]	0 ^[21]		
Units: Score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[20] - Data will be reported from the final analysis.

[21] - Data will be reported from the final analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration up to 35 months (Data cut-off date: 14-May-2020)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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Reporting groups

Reporting group title	Epoch 1
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Reporting group description:

Pediatric subjects with PIDD who were on non-HyQvia intravenous (IV) or subcutaneous (SC) treatment with immunoglobulin (IV-pretreated, SC-pretreated) were enrolled and treated with HyQvia (Immune Globulin Infusion 10% [Human] with Recombinant Human Hyaluronidase) SC with a dose or interval ramp-up period of up to 6 weeks. HyQvia was administered at a starting dose of 5 milliliter per hour per site (mL/h/site) to maximum tolerated dose of 80 mL/h/site (for subject with body weight [BW] < 40 kilogram [kg]) or starting dose of 10 mL/h/site to maximum tolerated dose of 240 mL/h/site (for subject with BW greater than or equal to [$\geq$] 40 kg).

Reporting group title	Epoch 2
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Reporting group description:

Pediatric subjects who were treated with HyQvia prior to this study and those who completed the ramp-up period (Epoch 1) are followed by Epoch 2 with HyQvia treatment. After one year in Epoch 2, subjects with anti-rHuPH20 antibody titer <160 at all time-points during the study will complete the study termination/completion visit at the next possible occasion. Subjects with anti-rHuPH20 antibody titer $\geq$ 160 during the study and/or at the last measurement will continue for an additional two years of HyQvia treatment and observation. HyQvia was administered at a starting dose of 10 mL/h/site to maximum tolerated dose of 160 mL/h/site (for subject with body weight [BW] <40kg) or starting dose of 10 mL/h/site to maximum tolerated dose of 300 mL/h/site (for subject with BW $\geq$ 40kg).

Serious adverse events	Epoch 1	Epoch 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 23 (8.70%)	4 / 19 (21.05%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
Idiopathic orbital inflammation			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammatory bowel disease			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pharyngitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (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 1	Epoch 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 23 (95.65%)	14 / 19 (73.68%)	
Investigations			

Blood immunoglobulin G decreased subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Haemangioma subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 1	
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) Radius fracture subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1 0 / 23 (0.00%) 0	1 / 19 (5.26%) 1 1 / 19 (5.26%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 3	0 / 19 (0.00%) 0	
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 1	
General disorders and administration site conditions Application site pruritus subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Infusion site erythema subjects affected / exposed occurrences (all) Infusion site pain subjects affected / exposed occurrences (all) Infusion site pruritus	0 / 23 (0.00%) 0 3 / 23 (13.04%) 3 2 / 23 (8.70%) 2 6 / 23 (26.09%) 11	1 / 19 (5.26%) 1 1 / 19 (5.26%) 2 0 / 19 (0.00%) 0 1 / 19 (5.26%) 1	

subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	4 / 23 (17.39%) 6 3 / 23 (13.04%) 5	0 / 19 (0.00%) 0 3 / 19 (15.79%) 7	
Eye disorders Conjunctival haemorrhage subjects affected / exposed occurrences (all) Eye pain subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0 1 / 23 (4.35%) 1	1 / 19 (5.26%) 1 1 / 19 (5.26%) 1	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Inflammatory bowel disease subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1 0 / 23 (0.00%) 0 2 / 23 (8.70%) 4	1 / 19 (5.26%) 5 1 / 19 (5.26%) 1 1 / 19 (5.26%) 2	
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 1	
Respiratory, thoracic and mediastinal disorders Bronchiectasis subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0 8 / 23 (34.78%) 13 2 / 23 (8.70%) 2	1 / 19 (5.26%) 1 6 / 19 (31.58%) 12 2 / 19 (10.53%) 6	

Oropharyngeal pain subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 4	2 / 19 (10.53%) 2	
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 1	
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	0 / 19 (0.00%) 0	
Solar urticaria subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 1	
Infections and infestations			
Acute sinusitis subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	1 / 19 (5.26%) 1	
Bacterial infection subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 1	
Bronchitis subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	0 / 19 (0.00%) 0	
Gastroenteritis subjects affected / exposed occurrences (all)	5 / 23 (21.74%) 7	0 / 19 (0.00%) 0	
Gastroenteritis viral subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	0 / 19 (0.00%) 0	
Impetigo subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 1	
Lower respiratory tract infection subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 3	0 / 19 (0.00%) 0	
Nasopharyngitis			

subjects affected / exposed	5 / 23 (21.74%)	1 / 19 (5.26%)
occurrences (all)	6	1
Otitis media		
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	1
Pharyngotonsillitis		
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	1
Pneumonia		
subjects affected / exposed	0 / 23 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	2
Respiratory tract infection		
subjects affected / exposed	0 / 23 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	2
Rhinitis		
subjects affected / exposed	3 / 23 (13.04%)	6 / 19 (31.58%)
occurrences (all)	4	12
Sinusitis		
subjects affected / exposed	1 / 23 (4.35%)	1 / 19 (5.26%)
occurrences (all)	1	1
Upper respiratory tract infection		
subjects affected / exposed	0 / 23 (0.00%)	3 / 19 (15.79%)
occurrences (all)	0	3
Viral infection		
subjects affected / exposed	3 / 23 (13.04%)	0 / 19 (0.00%)
occurrences (all)	4	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported