



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	v2 (current)
This version publication date	30 April 2022
First version publication date	04 August 2021
Version creation reason	<ul style="list-style-type: none">• New data added to full data set Study results data have been updated based on final CSR.

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 January 2021
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 assess 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 was conducted in accordance with the principles and guidelines described in the study protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP R2, November 2016), Title 21 of the United States (US) Code of Federal Regulations, the European Union (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	30 May 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:

A total of 42 subjects were enrolled and treated. This study consisted of 3 treatment periods: Epoch 1 (E1), Epoch 2 (E2) and Epoch 3 (E3). Subject with anti-rHuPH20 antibody titer ≥ 160 during E1 or E2 and who experienced either a related serious or severe adverse event (AE) was followed to E3.

Pre-assignment

Screening details:

Subjects treated with HyQvia in E1 followed by E2 were referred as "HyQvia new starters" and who started directly in E2 were referred as "HyQvia pre-treated". 1 subject from "HyQvia new starters" discontinued E2, entered E3 due to a severe related AE and didn't receive HyQvia treatment in E3. No further safety and efficacy data were collected in E3

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	HyQvia New Starters

Arm description:

Subjects who were treated with non-HyQvia treatment by time of enrollment were enrolled in Epoch 1 (ramp-up) and treated with HyQvia subcutaneously (SC) with a dose or interval ramp-up period of up to 6 weeks. HyQvia dose was planned to be equivalent to 100% ($\pm 5\%$) of pre-study treatment. Dosage frequency was one treatment interval of one week, then one treatment interval of two weeks, then one treatment interval of three weeks (for subjects in whom treatment was expected to be every four weeks). The ramp-up period was followed by Epoch 2 with HyQvia SC treatment at every 3 or 4 weeks, depending on the subject's previous dosing schedule and the discretion of the investigator and subject, for up to 20 months.

Arm type	Experimental
Investigational medicinal product name	10% (Human) with Recombinant Human Hyaluronidase (IGI, 10% with rHuPH20)
Investigational medicinal product code	
Other name	HyQvia
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects treated with HyQvia subcutaneously with a dose or interval ramp-up period of up to 6 weeks in Epoch 1.

Arm title	HyQvia Pre-treated
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Arm description:

Subjects already treated with HYQVIA by the time of enrollment were directly enrolled in Epoch 2 and treated with HyQvia SC at every 3 or 4 weeks for up to 20 months. HyQvia dose was planned to be equivalent to 100% ($\pm 5\%$) of pre-study treatment with a dosage frequency of once every three or four weeks, based on the subject's previous dosing schedule and the discretion of the investigator and subject.

Arm type	Experimental
Investigational medicinal product name	10% (Human) with Recombinant Human Hyaluronidase (IGI, 10% with rHuPH20)
Investigational medicinal product code	
Other name	HyQvia
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects already treated with HYQVIA by the time of enrollment were directly enrolled in Epoch 2 and treated with HyQvia SC at every 3 or 4 weeks for up to 20 months.

Number of subjects in period 1	HyQvia New Starters	HyQvia Pre-treated
Started	23	19
Completed	22	17
Not completed	1	2
Consent withdrawn by subject	1	2

Baseline characteristics

Reporting groups

Reporting group title	HyQvia New Starters
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Reporting group description:

Subjects who were treated with non-HyQvia treatment by time of enrollment were enrolled in Epoch 1 (ramp-up) and treated with HyQvia subcutaneously (SC) with a dose or interval ramp-up period of up to 6 weeks. HyQvia dose was planned to be equivalent to 100% ($\pm 5\%$) of pre-study treatment. Dosage frequency was one treatment interval of one week, then one treatment interval of two weeks, then one treatment interval of three weeks (for subjects in whom treatment was expected to be every four weeks). The ramp-up period was followed by Epoch 2 with HyQvia SC treatment at every 3 or 4 weeks, depending on the subject's previous dosing schedule and the discretion of the investigator and subject, for up to 20 months.

Reporting group title	HyQvia Pre-treated
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Reporting group description:

Subjects already treated with HYQVIA by the time of enrollment were directly enrolled in Epoch 2 and treated with HyQvia SC at every 3 or 4 weeks for up to 20 months. HyQvia dose was planned to be equivalent to 100% ($\pm 5\%$) of pre-study treatment with a dosage frequency of once every three or four weeks, based on the subject's previous dosing schedule and the discretion of the investigator and subject.

Reporting group values	HyQvia New Starters	HyQvia Pre-treated	Total
Number of subjects	23	19	42
Age Categorical Units:			

Age Continuous Units: years			
arithmetic mean	10.3	11.7	
standard deviation	± 3.82	± 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
More than one race	0	0	0
Unknown or Not Reported	1	0	1
Ethnicity Units: Subjects			
Hispanic Or Latino	0	0	0
Not Hispanic Or Latino	23	19	42
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	HyQvia New Starters
Reporting group description: Subjects who were treated with non-HyQvia treatment by time of enrollment were enrolled in Epoch 1 (ramp-up) and treated with HyQvia subcutaneously (SC) with a dose or interval ramp-up period of up to 6 weeks. HyQvia dose was planned to be equivalent to 100% ($\pm 5\%$) of pre-study treatment. Dosage frequency was one treatment interval of one week, then one treatment interval of two weeks, then one treatment interval of three weeks (for subjects in whom treatment was expected to be every four weeks). The ramp-up period was followed by Epoch 2 with HyQvia SC treatment at every 3 or 4 weeks, depending on the subject's previous dosing schedule and the discretion of the investigator and subject, for up to 20 months.	
Reporting group title	HyQvia Pre-treated
Reporting group description: Subjects already treated with HYQVIA by the time of enrollment were directly enrolled in Epoch 2 and treated with HyQvia SC at every 3 or 4 weeks for up to 20 months. HyQvia dose was planned to be equivalent to 100% ($\pm 5\%$) of pre-study treatment with a dosage frequency of once every three or four weeks, based on the subject's previous dosing schedule and the discretion of the investigator and subject.	

Primary: Safety: Number of Subjects With Any Severe Related Treatment-emergent Adverse Events (TEAEs) per Infusion (Excluding Infections)

End point title	Safety: Number of Subjects With Any Severe Related Treatment-emergent Adverse Events (TEAEs) per Infusion (Excluding Infections) ^[1]
End point description: An Adverse Event (AE) 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. TEAEs are AEs with onset after date-time of first dose of IP, or any medical condition present prior to the start of IP but increased in severity or relationship after date-time of first dose of IP. TEAEs recorded as "possibly related" or "probably related" to HYQVIA are considered HYQVIA-related. The number of subjects with any severe related TEAEs 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	Primary
End point timeframe: From start of study drug administration up to 20 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 and comparison analysis were performed for this endpoint.	

End point values	HyQvia New Starters	HyQvia Pre-treated		
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: Safety: Rate of Any Severe Related TEAEs per Infusion (Excluding Infections)

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

An AE was defined as any untoward medical occurrence in a subject administered an 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 any medical conditions present prior to the start of IP but increased in severity or relationship after date-time of first dose of IP. Severe related TEAEs rate per infusion was calculated as number of severe related TEAEs/total number of infusions administered to subjects in the analysis set. Rate of any severe related TEAEs per infusion (excluding infections) 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	Primary
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End point timeframe:

From start of study drug administration up to 20 months

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 analysis were performed for this endpoint.

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Number of Severe Related TEAEs/Infusion				
number (not applicable)	0.004	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety: Number of Subjects With Any Related Serious TEAEs per Infusion (Excluding Infections)

End point title	Safety: Number of Subjects With Any 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, or any medical conditions present prior to the start of IP but increased in severity or relationship after date-time of first dose of IP. 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 was defined as AEs recorded in the study database as "possibly related" or "probably related" to IP. Number of subjects with any related serious 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	Primary
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End point timeframe:

From start of study drug administration up to 20 months

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 analysis were performed for this endpoint.

End point values	HyQvia New Starters	HyQvia Pre-treated		
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: Safety: Rate of Any Related Serious TEAEs per Infusion (Excluding Infections)

End point title	Safety: Rate of Any 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, or any medical conditions present prior to the start of IP but increased in severity or relationship after date-time of first dose of IP. 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 was defined as AEs recorded in the study database as "possibly related" or "probably related" to IP. Rate of related serious TEAEs per infusion was calculated as number of related serious TEAEs/total number of infusions administered to subjects in the analysis set. Rate of any related serious 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	Primary
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End point timeframe:

From start of study drug administration up to 20 months

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 analysis were performed for this endpoint.

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Number of Related Serious TEAEs/Infusion				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Change From Baseline in Total Serum Trough Levels of Immunoglobulin G (IgG) at Month 12

End point title	Efficacy: Change From Baseline in Total Serum Trough Levels of Immunoglobulin G (IgG) at Month 12
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End point description:

Change from baseline in total serum trough levels of IgG in Epoch 1 and 2 was reported. Baseline was defined as the last non-missing value before the initial dose of HYQVIA. Full analysis set included all

subjects who provided informed consent and met enrollment eligibility. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint.

End point type	Secondary
End point timeframe:	
Baseline, Month 12	

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	17		
Units: Gram per liter (g/L)				
arithmetic mean (standard deviation)	0.035 (± 1.6983)	-0.709 (± 2.6576)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Safety: Percentage of Subjects who Achieved a Treatment Interval of Three or Four Weeks in Epoch 2
End point description:	
Percentage of subjects who achieved a treatment interval of three or four weeks in Epoch 2 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:	
Up to 20 months	

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Percentage of subjects				
number (not applicable)				
Every 3 weeks treatment interval	39.1	15.8		
Every 4 weeks treatment interval	60.9	84.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Percentage of Subjects who Maintained a Treatment Interval of Three or Four Weeks in Epoch 2 up to 12 Months

End point title	Safety: Percentage of Subjects who Maintained a Treatment Interval of Three or Four Weeks in Epoch 2 up to 12 Months
End point description: Percentage of subjects who maintained a treatment interval of three or four weeks in Epoch 2 up to 12 months 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: Up to 12 Months	

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Percentage of subjects				
number (not applicable)	87.0	78.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Number of Subjects With Local TEAEs (Excluding Infections)

End point title	Safety: Number of Subjects With Local TEAEs (Excluding Infections)
End point description: TEAE was defined as AEs with onset after date-time of first dose of IP, or any medical conditions present prior to the start of IP but increased in severity or relationship after date-time of first dose of IP. Number of subjects with local TEAEs (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
End point timeframe: From start of study drug administration up to 20 months	

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	11	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Rate of Local TEAEs per Infusion (Excluding Infections)

End point title	Safety: Rate of Local TEAEs per Infusion (Excluding Infections)
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End point description:

Rate of local TEAEs per infusion was calculated as number of local adverse events/total number of infusions administered to subjects in the analysis set. Only events are included which start prior to subjects start date of non-response. Rate of local TEAEs per infusion (excluding infections) 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:

From start of study drug administration up to 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Number of local TEAEs/Infusion				
number (not applicable)	0.082	0.009		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Number of Subjects With Local Adverse Reactions (Excluding Infections)

End point title	Safety: Number of Subjects With Local Adverse Reactions (Excluding Infections)
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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. Number of subjects with local adverse reactions (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 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	11	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Rate of Local Adverse Reaction per Infusion (Excluding Infections)

End point title	Safety: Rate of Local Adverse Reaction per Infusion (Excluding Infections)
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End point description:

Rate of local adverse reaction per infusion was calculated as number of local adverse reaction events/total number of infusions administered to subjects in the analysis set. Rate of local adverse reactions per infusion (excluding infections) 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:

From start of study drug administration up to 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Number of Local AR events/Infusion				
number (not applicable)	0.080	0.009		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Number of Subjects With Systemic TEAEs (Excluding Infections)

End point title	Safety: Number of Subjects With Systemic TEAEs (Excluding Infections)
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End point description:

TEAE was defined as AEs with onset after date-time of first dose of IP, or any medical conditions present prior to the start of IP but increased in severity or relationship after date-time of first dose of IP. Number of subjects with systemic TEAEs (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 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	15	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Rate of Systemic TEAEs per Infusion (Excluding Infections)

End point title	Safety: Rate of Systemic TEAEs per Infusion (Excluding Infections)
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End point description:

Rate of systemic TEAEs per infusion was calculated as number of systemic adverse events/total number of infusions administered to subjects in the analysis set. Rate of systemic TEAEs per infusion was assessed 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	Secondary
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End point timeframe:

From start of study drug administration up to 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Number of systemic TEAEs/Infusion				
number (not applicable)	0.138	0.142		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Number of Subjects With Systemic Adverse Reactions (Excluding Infections)

End point title	Safety: Number of Subjects With Systemic Adverse Reactions (Excluding Infections)
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End point description:

Adverse reaction 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. Number of subjects with systemic adverse reactions (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
End point timeframe:	
From start of study drug administration up to 20 months	

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Rate of Systemic Adverse Reactions per Infusion (Excluding Infections)

End point title	Safety: Rate of Systemic Adverse Reactions per Infusion (Excluding Infections)
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End point description:

Rate of Systemic adverse reactions per infusion was calculated as number of systemic adverse reaction events/total number of infusions administered to subjects in the analysis set. Rate of systemic adverse reactions per infusion (excluding infections) 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:	
From start of study drug administration up to 20 months	

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Number of Systemic AR events/Infusion				
number (not applicable)	0.011	0.012		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Number of Subjects With Any TEAEs (Excluding Infections)

End point title	Safety: Number of Subjects With Any TEAEs (Excluding Infections)
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End point description:

TEAE was defined as AEs with onset after date-time of first dose of IP, or any medical conditions present prior to the start of IP but increased in severity or relationship after date-time of first dose of IP.

Number of subjects with any TEAEs (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 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	18	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Rate of TEAEs per Infusion (Excluding Infections)

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

Rate of TEAEs per infusion was calculated as number of adverse events/total number of infusions administered to subjects in the analysis set. Rate of TEAEs per infusion (excluding infections) 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:

From start of study drug administration up to 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Number of TEAEs/Infusion				
number (not applicable)	0.220	0.151		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Number of Subjects With Any Adverse Reactions (Excluding Infections)

End point title	Safety: Number of Subjects With Any Adverse Reactions (Excluding Infections)
End point description:	
Adverse reaction 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. Number of subjects with any adverse reactions (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
End point timeframe:	
From start of study drug administration up to 20 months	

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	12	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Rate of Any Adverse Reaction per Infusion (Excluding Infections)

End point title	Safety: Rate of Any Adverse Reaction per Infusion (Excluding Infections)
End point description:	
Rate of all adverse reaction per infusion was calculated as number of adverse reaction events/total number of infusions administered to subjects in the analysis set. Rate of any adverse reactions per infusion (excluding infections) 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:	
From start of study drug administration up to 20 months	

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Adverse reaction event/Infusion				
number (not applicable)	0.091	0.021		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Number of Subjects With Any Temporally Associated TEAEs (Excluding Infections)

End point title	Safety: Number of Subjects With Any Temporally Associated TEAEs (Excluding Infections)
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End point description:

Temporally-associated TEAEs were defined as TEAEs which begin during infusion of IP or within 72 hours following the end of IP infusion. Number of subjects with any temporally associated TEAEs (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 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	13	6		

Statistical analyses

No statistical analyses for this end point

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

End point title	Safety: Rate of Any Temporally Associated TEAEs per Infusion (Excluding Infections)
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End point description:

Rate of any temporally associated TEAEs per infusion was calculated as number of temporally associated adverse events/total number of infusions administered to subjects in the analysis set. 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 temporally associated TEAEs per infusion (excluding infections) 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:

From start of study drug administration up to 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Temporally associated TEAEs/Infusion				
number (not applicable)	0.106	0.027		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Number of Subjects With Any Related (Causally) and/or Temporally Associated TEAEs (Excluding Infections)

End point title	Safety: Number of Subjects With Any Related (Causally) and/or Temporally Associated TEAEs (Excluding Infections)
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End point description:

Number of subjects with any related (causally) and/or temporally associated TEAEs (excluding infections) were reported. Temporally-associated TEAEs were defined as TEAEs which begin during infusion of IP or within 72 hours following the end of IP 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:

From start of study drug administration up to 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	13	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Rate of Any Related (Causally) and/or Temporally Associated TEAEs per Infusion (Excluding Infections)

End point title	Safety: Rate of Any Related (Causally) and/or Temporally Associated TEAEs per Infusion (Excluding Infections)
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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 subjects 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. 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 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Related Temporally TEAEs/Infusion				
number (not applicable)	0.112	0.033		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Number of Subjects With Any Serious TEAEs (Excluding Infections)

End point title	Safety: Number of Subjects With Any Serious TEAEs (Excluding Infections)
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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. Number of subjects with any serious TEAEs (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 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects	0	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Rate of Serious TEAEs per Infusion (Excluding Infections)

End point title	Safety: Rate of Serious TEAEs per Infusion (Excluding Infections)
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End point description:

Rate of serious TEAEs per infusion was calculated as number of serious adverse events/total number of infusions administered to subjects in the analysis set. Rate of serious TEAEs per infusion (excluding infections) 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:	
From start of study drug administration up to 20 months	

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Number of serious TEAEs/Infusion				
number (not applicable)	0	0.012		

Statistical analyses

No statistical analyses for this end point

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

End point title	Safety: 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:	
From start of study drug administration up to 20 months	

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Subjects				
Positive titer (≥ 160) of binding antibodies	0	0		
Neutralizing antibodies	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Other Analysis: Number of Infusions per Month

End point title	Other Analysis: Number of Infusions per Month
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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 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:

Up to 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Infusions per month				
median (full range (min-max))	1.30 (1.1 to 1.7)	1.20 (1.0 to 1.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Other Analysis: Number of Infusion Sites (Needle-Sticks) per Infusion

End point title Other Analysis: Number of Infusion Sites (Needle-Sticks) per Infusion

End point description:

Number of infusion sites (needle-sticks) per infusion was calculated as total number of infusion sites / total number of infusions. Only infusions with complete data available was included. 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:

Up to 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Infusion sites (needle sticks)/Infusion				
arithmetic mean (standard deviation)	1.65 (± 0.442)	1.25 (± 0.403)		

Statistical analyses

No statistical analyses for this end point

Secondary: Other Analysis: Duration of Infusion

End point title	Other Analysis: Duration of Infusion
End point description: The duration of infusion was defined as the difference between the end time and the start time of the HyQvia 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
End point timeframe: From start of study drug administration up to 20 months	

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Minutes				
median (full range (min-max))	75.0 (10 to 215)	101.0 (15 to 257)		

Statistical analyses

No statistical analyses for this end point

Secondary: Other Analysis: Maximum Infusion Rate per Site

End point title	Other Analysis: 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: Up to 20 months	

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Milliliter per hour per site (mL/h/site)				
arithmetic mean (standard deviation)	181.54 (\pm 77.772)	171.73 (\pm 90.203)		

Statistical analyses

No statistical analyses for this end point

Secondary: Other Analysis: Infusion Volume per Site

End point title	Other Analysis: Infusion Volume per Site
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End point description:

Infusion volume per site was calculated as actual IgG volume (milliliter [mL]) per total number of infusion sites (hour) 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
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End point timeframe:

Up to 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: milliliter per hour				
arithmetic mean (standard deviation)	112.39 (\pm 71.427)	178.23 (\pm 98.523)		

Statistical analyses

No statistical analyses for this end point

Secondary: Other Analysis: Number of Infusions That Were Interrupted or Stopped due to an AE

End point title	Other Analysis: Number of Infusions That Were Interrupted or Stopped due to an AE
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End point description:

Number of infusions that were interrupted or stopped 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:

Up to 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Infusions				
number (not applicable)				
Number of infusions interrupted	4	0		
Number of infusions Stopped	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Other Analysis: Number of Weeks to Reach Final 3 or 4-week Dose Interval in Epoch 1

End point title	Other Analysis: Number of Weeks to Reach Final 3 or 4-week Dose Interval in Epoch 1 ^[5]
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End point description:

Final dose interval was defined as three or four weeks infusion interval in Epoch 1 of treatment period was reported. Safety analysis set included all subjects in the full analysis set (enrolled Set) who received at least one dose of HyQvia. Here, "number analysed" signifies subjects who are evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Up to 20 months

Notes:

[5] - 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: As pre-specified in protocol, Data collection and analysis was not planned for HyQvia pre-treated.

End point values	HyQvia New Starters			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Weeks				
median (full range (min-max))	6.10 (3.0 to 7.0)			

Statistical analyses

No statistical analyses for this end point

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

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

TSQM-9 is a 9-item, validated, self-administered instrument to assess subjects satisfaction with medication. It consists of 3 sub-scales: effectiveness, convenience and global satisfaction. The scores were computed by adding items for each domain, i.e. 1 to 3 for effectiveness, 4 - 6 for convenience and 7 to 9 for global satisfaction. The lowest possible score (1 for each item and 3 for all 3 sub-scales) was subtracted from the composite score and divided by the greatest possible score range. The greatest range was $(7-1)*3$ items = 18 for the effectiveness and convenience, and $(5-1)*3$ items = 12 for global satisfaction. The item scores of each of the 3 domains are summed and transformed to create a score of 0 (extremely dissatisfied) to 100 (extremely satisfied). Higher score=greater satisfaction in that domain. A negative change from baseline indicates less satisfaction in that domain. Safety analysis set. Here, "number of subjects analysed"= subjects evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline up to 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	6		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Effectiveness: Change at 20 months	12.96 (\pm 32.552)	-0.92 (\pm 10.783)		
Convenience: Change at 20 months	14.81 (\pm 27.398)	4.63 (\pm 15.873)		
Global satisfaction: Change 20 months	11.90 (\pm 10.911)	-2.38 (\pm 19.518)		

Statistical analyses

No statistical analyses for this end point

Secondary: HRQoL: Change from Baseline in Pediatric Quality of Life Questionnaire (PedsQL)

End point title	HRQoL: Change from Baseline in Pediatric Quality of Life Questionnaire (PedsQL)
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End point description:

PedsQL Generic Core Scale (GCS) used for QOL assessment. It encompasses 4 dimensions (physical functioning [PF], emotional functioning [EF], social functioning [SF], school functioning [ScF]). Age groups: Toddler (2-4 years), Young child (5-7 years), Child (8-12 years) and Teens (13-<18 years). Depending on the subjects age, the questionnaire may be completed by either the subject or the parent/caregiver. For Toddler, PedsQL GCS as 21 items, using 5-point Likert scale (0 to 4); for all other, PedsQL as 23 items, with 3-point Likert scale (0, 2, 4) for young child, and 5-point Likert scale for child and teens. All scores were transformed on a scale from 0-100 where 0=100, 1=75, 2=50, 3=25 and 4=0. Higher scores= better quality of life. A negative change from baseline=worse quality of life. Safety analysis set. Here, "number of subjects analysed"= subjects evaluable for this endpoint and "n=number analysed" evaluable at specific timepoint. Here, '99999' = mean and SD was not estimated.

End point type	Secondary
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End point timeframe:

Baseline up to 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: Score on a scale				
arithmetic mean (standard deviation)				
PF in Toddler: Change up to 20 months (n=0,1)	99999 (\pm 99999)	-3.12 (\pm 99999)		
PF in Young child: Change up to 20 months (n=0,1)	99999 (\pm 99999)	-31.25 (\pm 99999)		
PF in Child: Change up to 20 months (n=2,1)	7.81 (\pm 6.626)	-71.88 (\pm 99999)		

PF in Teens: Change up to 20 months (n=3,5)	-12.65 (± 12.726)	13.75 (± 24.664)		
EF in Toddler: Change up to 20 months (n=0,1)	99999 (± 99999)	0.00 (± 99999)		
EF in Young child: Change up to 20 months (n=0,1)	99999 (± 99999)	-25.00 (± 99999)		
EF in Child: Change up to 20 months (n=2,1)	5.00 (± 14.142)	-20.00 (± 99999)		
EF in Teens: Change up to 20 months (n=3,5)	-13.33 (± 7.638)	1.25 (± 14.307)		
SF in Toddler: Change up to 20 months (n=0,1)	99999 (± 99999)	0.00 (± 99999)		
SF in Young child: Change up to 20 months (n=0,1)	99999 (± 99999)	-35.00 (± 99999)		
SF in Child: Change up to 20 months (n=2,1)	-20.00 (± 0.000)	-40.00 (± 99999)		
SF in Teens: Change up to 20 months (n=3,5)	1.67 (± 7.638)	8.00 (± 11.511)		
ScF in Toddler: Change up to 20 months (n=0,1)	99999 (± 99999)	25.00 (± 99999)		
ScF in Young child: Change up to 20 months (n=0,1)	99999 (± 99999)	-45.00 (± 99999)		
ScF in Child: Change up to 20 months (n=2,1)	-12.50 (± 10.607)	-65.00 (± 99999)		
ScF in Teens: Change up to 20 months (n=3,5)	1.67 (± 7.638)	-17.00 (± 24.135)		

Statistical analyses

No statistical analyses for this end point

Secondary: HRQoL: Change from Baseline in EuroQoL (Quality of Life)-5 Dimensions (EQ-5D)

End point title	HRQoL: Change from Baseline in EuroQoL (Quality of Life)-5 Dimensions (EQ-5D)
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End point description:

EQ-5D considered five attributes of QOL 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). The subjects rating of their current HRQoL state was recorded using a standard vertical 20-cm visual analog scale (EQ-VAS), which ranged from 0 to 100, where 0 indicated worst imaginable health state and 100 was best imaginable health state. Baseline was defined as the last non-missing value before the initial dose of HYQVIA. A negative change from baseline indicates worse health state. Safety analysis set. Here, "number of subjects analysed"= subjects evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline up to 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	7		
Units: Score on a scale				
arithmetic mean (standard deviation)	-8.60 (± 11.149)	-4.43 (± 15.447)		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Change From Baseline in Serum Trough Levels of IgG Subclasses at Month 12

End point title	Efficacy: Change From Baseline in Serum Trough Levels of IgG Subclasses at Month 12
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End point description:

Change from baseline in serum trough levels of IgG subclasses 1, 2, 3, and 4 in Epoch 1 and 2 was reported. Baseline was defined as the last non-missing value before the initial dose of HYQVIA. All subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia. Here, "number of subjects analysed" signifies subjects who were evaluable for endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Month 12

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: g/L				
arithmetic mean (standard deviation)				
IgG Subclass 1 : Changed at Month 12	-0.813 (± 1.1087)	-0.467 (± 1.5976)		
IgG Subclass 2 : Changed at Month 12	0.000 (± 0.8944)	-0.667 (± 1.3452)		
IgG Subclass 3 : Changed at Month 12	0.000 (± 0.3651)	0.133 (± 0.3519)		
IgG Subclass 4 : Changed at Month 12	0.094 (± 0.0854)	-0.027 (± 0.0799)		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Change From Baseline in Trough Levels of Specific Antibodies to Clostridium Tetani Toxoid IgG at Month 12

End point title	Efficacy: Change From Baseline in Trough Levels of Specific Antibodies to Clostridium Tetani Toxoid IgG at Month 12 ^[6]
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End point description:

Change from baseline in trough levels of specific antibodies in clostridium tetani toxoid IgG at Month 12 was reported. Baseline was defined as the last non-missing value before the initial dose of HYQVIA. Here, IU/ml was defined as "International units per milliliter". All subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia. Here, "number of subjects analysed" signifies subjects who were evaluable for endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Month 12

Notes:

[6] - 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: Specific antibody data were not scheduled to be collected at Epoch 2 Month 0, so for most subjects baseline could not be defined and change from baseline was not reported in HYQVIA Pre-treated arm.

End point values	HyQvia New Starters			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: IU/ml				
arithmetic mean (standard deviation)	-0.218 (\pm 0.9345)			

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Change From Baseline in Trough Levels of Specific Antibodies to Hepatitis B Virus (HBV) at Month 12

End point title	Efficacy: Change From Baseline in Trough Levels of Specific Antibodies to Hepatitis B Virus (HBV) at Month 12 ^[7]
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End point description:

Change from baseline in trough levels of specific antibodies in HBV at Month 12 was reported. Baseline was defined as the last non-missing value before the initial dose of HYQVIA. All subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia. Here, "number of subjects analysed" signifies subjects who were evaluable for endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Month 12

Notes:

[7] - 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: Specific antibody data were not scheduled to be collected at Epoch 2 Month 0, so for most subjects baseline could not be defined and change from baseline was not reported in HYQVIA Pre-treated arm.

End point values	HyQvia New Starters			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: International units per liter (IU/L)				
arithmetic mean (standard deviation)	167.875 (\pm 147.4887)			

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Change From Baseline in Trough Levels of Specific Antibodies to Haemophilus influenzae B IgG at Month 12

End point title	Efficacy: Change From Baseline in Trough Levels of Specific Antibodies to Haemophilus influenzae B IgG at Month 12 ^[8]
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End point description:

Change from baseline in trough levels of specific antibodies in Haemophilus influenzae B IgG at Month 12 was reported. Baseline was defined as the last non-missing value before the initial dose of HYQVIA. All subjects in the full analysis set (enrolled set) who received at least one dose of HyQvia. Here, "number of subjects analysed" signifies subjects who were evaluable for endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Month 12

Notes:

[8] - 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: Specific antibody data were not scheduled to be collected at Epoch 2 Month 0, so for most subjects baseline could not be defined and change from baseline was not reported in HYQVIA Pre-treated arm.

End point values	HyQvia New Starters			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Milligram per liter (mg/L)				
arithmetic mean (standard deviation)	-0.017 (\pm 0.9503)			

Statistical analyses

No statistical analyses for this end point

Secondary: Other Analysis: Number of Infusion Sites (Needle-Sticks) per Month

End point title	Other Analysis: Number of Infusion Sites (Needle-Sticks) per Month
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End point description:

Number of infusion sites per month was calculated as total number of infusion sites / duration of treatment (days) * 30.4 days. Only infusions with complete data available was included. 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:

Up to 20 months

End point values	HyQvia New Starters	HyQvia Pre-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	19		
Units: Infusion sites (needle sticks)/Month				
arithmetic mean (standard deviation)	1.96 (\pm 0.780)	1.33 (\pm 0.634)		

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 end of the study (up to 43 months)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	HyQvia New Starters
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Reporting group description:

Subjects who were treated with non-HyQvia treatment by time of enrollment were enrolled in Epoch 1 (ramp-up) and treated with HyQvia SC with a dose or interval ramp-up period of up to 6 weeks. HyQvia dose was planned to be equivalent to 100% ($\pm 5\%$) of pre-study treatment. Dosage Frequency was one treatment interval of one week, then one treatment interval of two weeks, then one treatment interval of three weeks (for subjects in whom treatment was expected to be every four weeks). The ramp-up period was followed by Epoch 2 (no ramp-up) with HyQvia SC treatment at every 3 or 4 weeks, depending on the subjects previous dosing schedule and the discretion of the investigator and subject, for up to 20 months.

Reporting group title	HyQvia Pre-treated
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Reporting group description:

Subjects already treated with HYQVIA by the time of enrollment were directly enrolled in Epoch 2 and treated with HyQvia SC at every 3 or 4 weeks for up to 20 months. HyQvia dose was planned to be equivalent to 100% ($\pm 5\%$) of pre-study treatment with a dosage frequency of once every three or four weeks, based on the subjects previous dosing schedule and the discretion of the investigator and subject.

Serious adverse events	HyQvia New Starters	HyQvia Pre-treated	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 23 (8.70%)	5 / 19 (26.32%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			

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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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	
Acute sinusitis			
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	

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

Non-serious adverse events	HyQvia New Starters	HyQvia Pre-treated	
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	0 / 23 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 23 (4.35%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Radius fracture			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 23 (8.70%)	0 / 19 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
Neutropenia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Application site pruritus			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	3 / 23 (13.04%)	1 / 19 (5.26%)	
occurrences (all)	3	2	

Infusion site erythema subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	0 / 19 (0.00%) 0	
Infusion site pain subjects affected / exposed occurrences (all)	6 / 23 (26.09%) 11	1 / 19 (5.26%) 1	
Infusion site pruritus subjects affected / exposed occurrences (all)	4 / 23 (17.39%) 6	0 / 19 (0.00%) 0	
Pyrexia subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 5	3 / 19 (15.79%) 7	
Eye disorders Conjunctival haemorrhage alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 1	
Eye pain subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	1 / 19 (5.26%) 1	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	1 / 19 (5.26%) 5	
Inflammatory bowel disease subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 19 (5.26%) 1	
Vomiting subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 4	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) Oropharyngeal pain subjects affected / exposed occurrences (all) Rhinorrhoea alternative assessment type: Systematic subjects affected / exposed occurrences (all)	0 / 23 (0.00%)	1 / 19 (5.26%)	
	0	1	
	8 / 23 (34.78%)	6 / 19 (31.58%)	
	13	12	
	2 / 23 (8.70%)	2 / 19 (10.53%)	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Solar urticaria subjects affected / exposed occurrences (all)	2	6	
	2 / 23 (8.70%)	2 / 19 (10.53%)	
	4	2	
	0 / 23 (0.00%)	1 / 19 (5.26%)	
	0	1	
Infections and infestations Acute sinusitis subjects affected / exposed occurrences (all) Bacterial infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all)	2 / 23 (8.70%)	0 / 19 (0.00%)	
	2	0	
	0 / 23 (0.00%)	1 / 19 (5.26%)	
	0	1	
	1 / 23 (4.35%)	1 / 19 (5.26%)	
	1	1	
	0 / 23 (0.00%)	1 / 19 (5.26%)	
	0	1	
	2 / 23 (8.70%)	0 / 19 (0.00%)	
	2	0	
	5 / 23 (21.74%)	0 / 19 (0.00%)	
	7	0	

Gastroenteritis viral		
subjects affected / exposed	2 / 23 (8.70%)	0 / 19 (0.00%)
occurrences (all)	2	0
Impetigo		
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	1
Lower respiratory tract infection		
subjects affected / exposed	2 / 23 (8.70%)	0 / 19 (0.00%)
occurrences (all)	3	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? Yes

Date	Amendment
07 October 2016	Amendment 1: <ul style="list-style-type: none">- To update the study termination/completion criteria for subjects entering Epoch 3.- To change the reference information for KIOVIG from IB to SmPC.- To match the dosing frequency suggestions of the SmPC for Cuvitru.- To update the study inclusion criteria.- To provide information on Cuvitru instead of SUBCUVIA.- To specify timelines for screening, to provide an option to treat the subject in the time period between signing the informed consent and first IP infusion, and to limit the number of re-screenings.- To define the timepoint for blood drawing for all trough level measurements.- To remove 'HRQoL assessments' from the Epoch 3 data under Table 6.- To define the timepoint for blood drawing for all trough level measurements.
04 December 2019	Amendment 2: <ul style="list-style-type: none">- To revise duration of study periods and subject participation till 2023 scenario in case 'last subject in' went until Epoch 2 Year 3 and then 1 year in Epoch 3.- To clarify that safety follow-up and the antibody testing were to continue for one year, not less, for all subjects who switched to Epoch 3.- To add 'planned interim analysis' for the study into the study protocol.- To update the HyQvia indication for the European region.- To add reference for the Cuvitru IB for countries where sites were open but Cuvitru was not registered.- To provide update on the study status during the protocol amendment 2.- To update to the latest version of GCP E6 guideline (Nov 2016) and to add 'Declaration of Helsinki' in the 'compliance statement' section.- To add a description to allow shorter infusion intervals (2 weeks, instead of 3 or 4 weeks) if preferable due to tolerability, at the discretion of the investigator.- To clarify in Table 8 that for some subjects Month 0 of Epoch 2 was to be considered as baseline for those subjects who did not have to participate in Epoch 2; therefore specific antibody tests also had to be performed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported