Clinical trial results:
A Phase III Open-Label, Prospective, Multicenter Study of the Efficacy, Tolerability, Safety, and Pharmacokinetics of Immune Globulin Subcutaneous (Human), IgPro20 in Subjects With Primary Immunodeficiency (PID)

Summary

EudraCT number	2014-003607-30
Trial protocol	Outside EU/EEA
Global end of trial date	27 October 2008

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	ZLB04_009CR

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00419341
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring, LLC
Sponsor organisation address	1020 First Avenue, King of Prussia, PA, United States, 19406-0901
Public contact	Trial Registration Co-ordinator, CSL Behring, clinicaltrials@cslbehring.com
Scientific contact	Trial Registration Co-ordinator, CSL Behring, clinicaltrials@cslbehring.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	26 November 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 October 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to assess the efficacy, tolerability, safety and pharmacokinetics of IgPro20 in patients with primary humoral immunodeficiency (PID).

Protection of trial subjects:

This study was conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki (version of 1996), and standard operating procedures for clinical research and development at CSL Behring and the Clinical Research Organizations involved. Compliance with these requirements also constitutes conformity with the ethical principles of the Declaration of Helsinki. The study was conducted under a protocol reviewed and approved by an IRB; the study was conducted by scientifically and medically qualified persons; the benefits of the study were in proportion to the risks; the rights and welfare of the subjects were respected; the physicians conducting the study did not find the hazards to outweigh the potential benefits; the results reported are accurate; and each subject or subject's parent or legal guardian gave his or her written informed consent before any protocol-driven tests or evaluations were performed.
A properly executed, written informed consent in compliance with the Declaration of Helsinki (version of 1996), ICH, GCP, and local regulations was obtained for each subject prior to entering the subject into the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 November 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 49
Worldwide total number of subjects	49
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	3
Adolescents (12-17 years)	14
Adults (18-64 years)	26
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 12 centers in the United States enrolled subjects for this study.

Pre-assignment

Screening details:

A total of 52 subjects were screened, and 49 subjects were enrolled into the study and treated with IgPro20.

Period 1

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

Arms

Arm title	IgPro20

Arm description:

IgPro20 is a liquid formulation of normal human IgG at a concentration of 20% administered as a subcutaneous (SC) infusion at weekly intervals.

Arm type	Experimental
Investigational medicinal product name	IgPro20
Investigational medicinal product code	
Other name	Human Normal Immunoglobulin for Subcutaneous Administration (IGSC), Hizentra
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IgPro20 is a liquid formulation of normal human IgG at a concentration of 20% administered as a SC infusion at weekly intervals. The initial weekly dose was determined based on subjects' previous treatment. Dose adjustments could be performed during the wash-in/wash-out period at the discretion of the investigator.

Number of subjects in period 1	IgPro20
Started	49
Wash in/Wash Out Period	49
Efficacy Period	38
Completed	28
Not completed	21
Lost to follow-up (efficacy period)	1
Consent withdrawn by subject	8
Adverse event, non-fatal	2
Protocol deviation (efficacy period)	1
Termination of study site (efficacy period)	1

Disqualifying laboratory results	1
Consent withdrawn by subject (efficacy period)	6
Non-compliance (efficacy period)	1

Baseline characteristics

Reporting groups	
Reporting group title	IgPro20
Reporting group description:	
IgPro20 is a liquid formulation of normal human IgG at a concentration of 20% administered as a subcutaneous (SC) infusion at weekly intervals.	

Reporting group values	IgPro20	Total	
Number of subjects	49	49	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	3	3	
Adolescents (12-17 years)	14	14	
Adults (18-64 years)	26	26	
From 65-84 years	6	6	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	34.4		
standard deviation	± 20.09	-	
Gender categorical Units: Subjects			
Female	27	27	
Male	22	22	
Race Units: Subjects			
Black or African American	3	3	
White	46	46	
Type of Primary Immunodeficiency Units: Subjects			
Common variable immunodeficiency (CVID)	46	46	
X-linked agammaglobulinemia (XLA)	3	3	

End points

End points reporting groups

Reporting group title	IgPro20

Reporting group description:

IgPro20 is a liquid formulation of normal human IgG at a concentration of 20% administered as a subcutaneous (SC) infusion at weekly intervals.

Subject analysis set title	IgPro20 (PK Substudy)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

IgPro20 is a liquid formulation of normal human IgG at a concentration of 20% administered as a SC infusion at weekly intervals. The Per Protocol Pharmacokinetic (PPK) population included all subjects with the disease under study who fulfilled the requirements of the PK substudy, including PK sampling in a preceding study with IVIG (Privigen, CSL Behring), and fulfilling IgPro20 dosing requirements and providing adequate PK blood samples in the current study.

Subject analysis set title	IVIG (Privigen; Previous Study)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Privigen is a liquid formulation of normal human IgG at a concentration of 10% administered as an intravenous infusion every 3 or 4 weeks. The Per Protocol Pharmacokinetic (PPK) population included all subjects with the disease under study who fulfilled the requirements of the PK substudy, including PK sampling in a preceding study with IVIG (Privigen, CSL Behring), and fulfilling IgPro20 dosing requirements and providing adequate PK blood samples in the current study.

Subject analysis set title	IgPro20 - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention To Treat (ITT) population included all subjects who were treated with IgPro20 during any study period.

Primary: Annualized Rate of Clinically Documented Serious Bacterial Infections (SBIs) (MITT Population)

End point title	Annualized Rate of Clinically Documented Serious Bacterial Infections (SBIs) (MITT Population)[1]

End point description:

The annualized rate was based on the total number of SBIs and the total number of subject study days during the efficacy period for all subjects in the specified analysis population and adjusted to 365 days. Potential SBIs included pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess. If an adverse event (AE) was identified as a potential SBI, the AE was adjudicated by a review committee to determine if the event fulfilled the predefined criteria for SBIs. The modified intention-to-treat (MITT) population included all subjects who were treated with IgPro20 during the efficacy period (starting with Week 13) who had the disease under study.

End point type	Primary

End point timeframe:

Efficacy period: up to 12 months (week 13 to the completion visit)

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: End point data analysis consisted of a comparison of the annualized rate 99% upper confidence interval limit to 1 (in accordance with the US Food and Drug Administration Guidance for Industry on "Safety, efficacy, and pharmacokinetic studies to support marketing of immune globulin intravenous (human) as replacement therapy for primary humoral immunodeficiency" [June 2008]).

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	38[2]			
Units: SBIs per subject year				
number (not applicable)	0			

Notes:

[2] - Number of Efficacy Period Subject Study Days Analyzed = 12697
MITT population

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration-time Curve (AUC) of Total Serum Immunoglobulin G (IgG)

End point title	Area Under the Concentration-time Curve (AUC) of Total Serum Immunoglobulin G (IgG)

End point description:

Evaluate non-inferiority of steady-state IgG area under the concentration-time curves standardized to a 7-day period (sAUCs) for subcutaneous immunoglobulin (SCIG) (IgPro20) versus the sAUC under intravenous immunoglobulin (IVIG) (Privigen) treatment. The sAUC under IVIG was taken from the same subjects in a preceding study (either ZLB03_002CR [NCT00168025] or ZLB05_006CR [NCT00322556, 2014-003772-23]).

End point type	Primary

End point timeframe:

Measured during a single dosing interval after at least 12 weeks of stable subcutaneous (SC) dosing with IgPro20 treatment

End point values	IgPro20 (PK Substudy)	IVIG (Privigen; Previous Study)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18[3]	18[4]		
Units: days*g/L				
arithmetic mean (standard deviation)	105.6 (± 31.56)	103.2 (± 20)		

Notes:

[3] - PPK population

[4] - PPK population

Statistical analyses

Statistical analysis title	AUC of IgG: IgPro20 vs IVIG

Statistical analysis description:

Individual sAUC values (standardized to a 7-day period) of the IV and adjusted SC sampling periods in each individual subject were log transformed and a parametric 2-sided 90% confidence interval (CI) for the mean of the individual differences was obtained. Back-transformation of the mean and its CI produced the geometric mean ratio (GMR) and its respective 90% CI.

Comparison groups	IgPro20 (PK Substudy) v IVIG (Privigen; Previous Study)

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Method	t-test, 2-sided
Parameter estimate	Geometric mean ratio (GMR)
Point estimate	1.002
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.951
upper limit	1.055

Notes:

[5] - Non-inferiority of SCIG:IVIG treatment was concluded if the lower GMR confidence limit was 0.8 or more. With 18 evaluable subjects, the power to show this non-inferiority was calculated to be 85% based on the assumptions of an intra-individual variability with a coefficient of variation (CV) = 25% and a GMR equal to or greater than 1.

Secondary: Annualized Rate of Clinically Documented SBIs (ITT Population)

End point title	Annualized Rate of Clinically Documented SBIs (ITT Population)

End point description:

The annualized rate was based on the total number of SBIs and the total number of subject study days during the study for all subjects in the specified analysis population and adjusted to 365 days.

Potential SBIs included pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess. If an AE was identified as a potential SBI, the AE was adjudicated by a review committee to determine if the event fulfilled the predefined criteria for SBIs.

End point type	Secondary

End point timeframe:

For the duration of the study, up to 15 months

End point values	IgPro20 - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	49[6]			
Units: SBIs per subject year				
number (not applicable)	0			

Notes:

[6] - ITT population
Number of Subject Study Days Analyzed: 16234

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Clinically Documented SBIs (PPE Population)

End point title	Annualized Rate of Clinically Documented SBIs (PPE Population)

End point description:

The annualized rate was based on the total number of SBIs and the total number of subject study days during the efficacy period for all subjects in the specified analysis population and adjusted to 365 days. Potential SBIs included pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess. If an AE was identified as a potential SBI, the AE was adjudicated by a review committee to determine if the event fulfilled the predefined criteria for SBIs.

The Per Protocol Efficacy (PPE) population included all subjects who completed the 12-month efficacy period according to the protocol-defined requirements.

End point type	Secondary

End point timeframe:

Efficacy period: up to 12 months (week 13 to the completion visit)

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	25[7]			
Units: SBIs per subject year				
number (not applicable)	0			

Notes:

[7] - PPE population
Number of Efficacy Period Subject Study Days Analyzed = 9543

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Infection Episodes

End point title	Annualized Rate of Infection Episodes

End point description:

The annualized rate was based on the total number of infection episodes occurring during the efficacy period (N = 96) divided by the total number of subject study days for all subjects in the specified analysis population and adjusted to 365 days.
The MITT population included all subjects who were treated with IgPro20 during the efficacy period (starting with Week 13) who had the disease under study.

End point type	Secondary

End point timeframe:

Efficacy period: up to 12 months (week 13 to completion visit)

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	38[8]			
Units: infection episodes per subject year				
number (confidence interval 95%)	2.76 (2.235 to 3.37)			

Notes:

[8] - MITT population
Number of Subject Study Days Analyzed = 12697

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Infection Episodes (Serious and Non-serious)

End point title	Number of Infection Episodes (Serious and Non-serious)

End point description:

Total number of infections for the specified analysis population.
The MITT population included all subjects who were treated with IgPro20 during the efficacy period (starting with week 13) who had the disease under study.

End point type	Secondary

End point timeframe:

Efficacy period: up to 12 months (week 13 to the completion visit)

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	38[9]			
Units: infections	96			

Notes:

[9] - MITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Days Out of Work / School / Kindergarten / Day Care or Unable to Perform Normal Daily Activities Due to Infections

End point title	Annualized Rate of Days Out of Work / School / Kindergarten / Day Care or Unable to Perform Normal Daily Activities Due to Infections

End point description:

The annualized rate was based on the total number of days out of work / school / kindergarten / day care or inability to perform normal activities due to infection (N = 71), and the total number of subject study days for all subjects in the specified analysis population and adjusted to 365 days.
The MITT population included all subjects who were treated with IgPro20 during the efficacy period (starting with Week 13) who had the disease under study.

End point type	Secondary

End point timeframe:

Efficacy period: up to 12 months (week 13 to the completion visit)

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	38[10]			
Units: days per subject year				
number (not applicable)	2.06			

Notes:

[10] - MITT population
Number of Exposure Days Analyzed = 12605

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days Out of Work / School / Kindergarten / Day Care or

Unable to Perform Normal Daily Activities Due to Infections

End point title	Number of Days Out of Work / School / Kindergarten / Day Care or Unable to Perform Normal Daily Activities Due to Infections

End point description:

Total number of days out of work / school / kindergarten / day care or unable to perform normal daily activities due to infections, for the specified analysis population.
The MITT population included all subjects who were treated with IgPro20 during the efficacy period (starting with week 13) who had the disease under study.

End point type	Secondary

End point timeframe:

Efficacy period: up to 12 months (week 13 to the completion visit)

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	38[11]			
Units: Days	71			

Notes:

[11] - MITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Hospitalization Due to Infection

End point title	Annualized Rate of Hospitalization Due to Infection

End point description:

The annualized rate was based on the total number of days of hospitalization due to infection (N = 7) and the total number of subject study days for all subjects in the specified analysis population and adjusted to 365 days.
The MITT population included all subjects who were treated with IgPro20 during the efficacy period (starting with week 13) who had the disease under study.

End point type	Secondary

End point timeframe:

Efficacy period: up to 12 months (week 13 to the completion visit)

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	38[12]			
Units: days per subject year				
number (not applicable)	0.2			

Notes:

[12] - MITT population
Number of Exposure Days Analyzed = 12605

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days of Hospitalization Due to Infections

End point title	Number of Days of Hospitalization Due to Infections

End point description:

Total number of days of hospitalization due to infections for the specified analysis population.
The MITT population included all subjects who were treated with IgPro20 during the efficacy period (starting with week 13) who had the disease under study.

End point type	Secondary

End point timeframe:

Efficacy period: up to 12 months (week 13 to the completion visit)

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	38[13]			
Units: days	7			

Notes:

[13] - MITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Use of Antibiotics for Infection Prophylaxis and Treatment

End point title	Use of Antibiotics for Infection Prophylaxis and Treatment

End point description:

Annualized rate of days with antibiotics for infection prophylaxis and treatment. The annualized rate was based on the total number of days of antibiotic use for infection prophylaxis and treatment in the efficacy period, and the total number of subject study days for all subjects in the specified analysis population, and adjusted to 365 days.
The MITT population included all subjects who were treated with IgPro20 during the efficacy period (starting with week 13) who had the disease under study.

End point type	Secondary

End point timeframe:

Efficacy period: up to 12 months (week 13 to the completion visit)

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	38[14]			
Units: days per subject year				
number (not applicable)	48.52			

Notes:

[14] - MITT population
Number of Exposure Days Analyzed = 12697

Statistical analyses

No statistical analyses for this end point

Secondary: Total Serum IgG Trough Levels

End point title	Total Serum IgG Trough Levels

End point description:

The IgG trough values per subject were aggregated to a median value, and then median values across subjects were summarized using descriptive statistics.
The MITT population included all subjects who were treated with IgPro20 during the efficacy period (starting with week 13) who had the disease under study.

End point type	Secondary

End point timeframe:

Every 4 weeks, throughout the 12-month efficacy period

End point values	IgPro20			
Subject group type	Reporting group			
Number of subjects analysed	38[15]			
Units: g/L				
arithmetic mean (standard deviation)	12.53 (± 3.21)			

Notes:

[15] - MITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Total Serum IgG at Steady State

End point title	Maximum Concentration (Cmax) of Total Serum IgG at Steady State

End point description:

The PPK population included all subjects with the disease under study who fulfilled the requirements of the PK substudy, including PK sampling in a preceding study with IVIG (Privigen, CSL Behring), and fulfilling IgPro20 dosing requirements and providing adequate PK blood samples in the current study.

End point type	Secondary

End point timeframe:

Week 28 ± 1 week of the treatment period

End point values	IgPro20 (PK Substudy)			
Subject group type	Subject analysis set			
Number of subjects analysed	18[16]			
Units: g/L				
arithmetic mean (standard deviation)	16.16 (± 4.93)			

Notes:

[16] - PPK population

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax at Steady State

End point title	Tmax at Steady State

End point description:

Timepoint of maximum concentration (Cmax).
The PPK population included all subjects with the disease under study who fulfilled the requirements of the PK substudy, including PK sampling in a preceding study with IVIG (Privigen, CSL Behring), and fulfilling IgPro20 dosing requirements and providing adequate PK blood samples in the current study.

End point type	Secondary

End point timeframe:

Week 28 ± 1 week of the treatment period

End point values	IgPro20 (PK Substudy)			
Subject group type	Subject analysis set			
Number of subjects analysed	18[17]			
Units: days				
median (full range (min-max))	3.118 (0 to 6.97)			

Notes:

[17] - PPK population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Minimum Concentration (Cmin) of Total Serum IgG at Steady State

End point title	Minimum Concentration (Cmin) of Total Serum IgG at Steady State

End point description:

The PPK population included all subjects with the disease under study who fulfilled the requirements of the PK substudy, including PK sampling in a preceding study with IVIG (Privigen, CSL Behring), and fulfilling IgPro20 dosing requirements and providing adequate PK blood samples in the current study.

End point type	Other pre-specified

End point timeframe:

Week 28 ± 1 week of the treatment period

End point values	IgPro20 (PK Substudy)			
Subject group type	Subject analysis set			
Number of subjects analysed	18[18]			
Units: g/L				
arithmetic mean (standard deviation)	13.7 (± 4.39)			

Notes:
[18] - PPK population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Rate of All AEs by Relatedness and Seriousness

End point title	Rate of All AEs by Relatedness and Seriousness

End point description:

The rate of AEs was the number of AEs over the number of infusions administered. At least possibly related AEs included possibly related AEs, probably related AEs, and related AEs.

End point type	Other pre-specified

End point timeframe:

For the duration of the study, up to 15 months

End point values	IgPro20 - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	49[19]			
Units: AEs per infusion				
number (not applicable)				
All	0.773			
At least possibly related	0.634			
Serious	0.004			
At least possibly related and serious	0			

Notes:
[19] - ITT population
Number of infusions analyzed: 2264

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Rate of Mild, Moderate, or Severe Local Reactions

End point title	Rate of Mild, Moderate, or Severe Local Reactions

End point description:

In addition to the standard MedDRA System Organ Class (SOC) AE assignments, the category of 'local reactions' was defined to provide the possibility for a combined analysis of local reactions and included AEs of injection site reaction, injection site bruising, infusion site scab, injection site cyst, injection site eczema, injection site irritation, injection site nodule, and injection site pain.

Mild AE: Did not interfere with routine activities; Moderate AE: Interfered somewhat with routine activities; Severe AE: Impossible to perform routine activities.

End point type	Other pre-specified

End point timeframe:

For the duration of the study, up to 15 months

End point values	IgPro20 - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	49[20]			
Units: local reactions per infusion				
number (not applicable)				
All	0.592			
Mild	0.553			
Moderate	0.038			
Severe	0.002			

Notes:

[20] - ITT population
Number of Infusions Analyzed = 2264

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 15 months (including the 3 month wash in/wash out period and the 12 month efficacy period).

Adverse event reporting additional description:

For the serious AEs (SAEs), treatment-emergent SAEs are provided.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	IgPro20

Reporting group description:

IgPro20 is a liquid formulation of normal human IgG at a concentration of 20% administered as a SC infusion at weekly intervals.

Serious adverse events	IgPro20		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 49 (14.29%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Small intestinal obstruction			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth abscess			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	IgPro20		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 49 (100.00%)		
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 4		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all)	 13 / 49 (26.53%) 40 4 / 49 (8.16%) 5		
General disorders and administration site conditions Injection site reaction subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Injection site bruising subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	 49 / 49 (100.00%) 1314 6 / 49 (12.24%) 6 5 / 49 (10.20%) 19 4 / 49 (8.16%) 5		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	 3 / 49 (6.12%) 3		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	 3 / 49 (6.12%) 3		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain upper	 7 / 49 (14.29%) 8 		

subjects affected / exposed	5 / 49 (10.20%)		
occurrences (all)	5		
Nausea			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 49 (16.33%)		
occurrences (all)	9		
Epistaxis			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	6		
Pharyngolaryngeal pain			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	6		
Asthma			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences (all)	7		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences (all)	11		
Arthralgia			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	5		

Pain in extremity subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 7		
Myalgia subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 4		
Infections and infestations Sinusitis subjects affected / exposed occurrences (all)	14 / 49 (28.57%) 20		
Nasopharyngitis subjects affected / exposed occurrences (all)	11 / 49 (22.45%) 15		
Bronchitis subjects affected / exposed occurrences (all)	6 / 49 (12.24%) 9		
Acute sinusitis subjects affected / exposed occurrences (all)	5 / 49 (10.20%) 7		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 49 (10.20%) 6		
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 3		
Viral infection subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 7		
Influenza subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 3		
Otitis media subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 November 2006	A health-related quality of life assessment was incorporated as Appendix 6, references to the subject diary as an electronic tool were removed, and minor changes to the schedule of assessments were incorporated. This amendment was implemented before any subject had received the first infusion of study drug.
17 January 2007	The design of the health-related quality of life assessment was changed from comparative to single group longitudinal and the assessment of local tolerability was clarified. This amendment was implemented after 2 subjects had received their first infusion of study drug.
23 April 2007	Changes associated with the switch from the electronic to the paper diary used for collecting subject information were described, references to the health-related quality of life substudy were removed, and entry criteria for new subjects regarding the number of required serum IgG Ctrough values measured prior to study entry were clarified to match the current USA standard of care. This amendment was implemented after 23 subjects had received their first infusion of study drug.
30 April 2008	The maximum number of injection sites to be infused simultaneously and maximum total body flow rate of IgPro20 were described, additional timepoints for vital signs evaluation during visits to the study site were added, several statistical concepts were clarified, completion visit procedures were updated, and the lower limit of polysorbate 80 concentration in IgPro20 was specified. In addition, a set of tests to follow a newly positive Direct Coombs' test result was specified. This amendment was implemented after 25 subjects had received their first infusion of study drug.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/20454851

http://www.ncbi.nlm.nih.gov/pubmed/21553933