



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@csllbehring.com |
| Scientific contact | Trial Registration Co-ordinator, CSL Behring, clinicaltrials@csllbehring.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 \pm 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 \pm 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 (\pm 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) | 13 / 49 (26.53%) 40 | | |
| Migraine subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 5 | | |
| General disorders and administration site conditions Injection site reaction subjects affected / exposed occurrences (all) | 49 / 49 (100.00%) 1314 | | |
| Fatigue subjects affected / exposed occurrences (all) | 6 / 49 (12.24%) 6 | | |
| Injection site bruising subjects affected / exposed occurrences (all) | 5 / 49 (10.20%) 19 | | |
| Pain subjects affected / exposed occurrences (all) | 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) | 7 / 49 (14.29%) 8 | | |
| Abdominal pain upper | | | |

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