2 SYNOPSIS

<table>
<tr><td>Name of Sponsor:
CSL Behring LLC</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
IgPro20</td></tr>
<tr><td>Name of Active Ingredient:
Human normal immunoglobulin</td></tr>
<tr><td colspan="3">Title of Study:
An Open-label Multicenter Study to Evaluate the Safety and Tolerability of Higher Infusion Parameters of Immune Globulin Subcutaneous (Human), 20% Liquid (Hizentra®) in Subjects with Primary Immunodeficiency</td></tr>
<tr><td colspan="3">Global Clinical Program PPD: PPD
CSL Behring LLC
1020 1st Avenue
King of Prussia
PA 19406-1310, USA</td></tr>
<tr><td colspan="3">Publication (reference): Not applicable.</td></tr>
<tr><td colspan="2">Study Period:
First Subject Visit: 01 February 2017
Last Subject Visit: 14 December 2018</td><td>Phase of Development: Phase 4</td></tr>
<tr><td colspan="3">Objectives:
Primary Objective: To determine the responder rate at higher infusion parameters of IgPro20 under the following conditions:
Pump-Assisted: Volume per injection site of 25 mL, 40 mL, and 50 mL.
Pump-Assisted: Flow rate per injection site of 25 mL/h, 50 mL/h, 75 mL/h, and 100 mL/h.
Manual Push (manual infusion using syringe without a pump): Flow rate per injection site of 30 mL/h, 60 mL/h, and 120 mL/h (0.5 mL/min, 1 mL/min, and 2 mL/min, correspondingly).
Secondary Objectives:
To evaluate the safety of pump-assisted IgPro20 infusions at higher infusion parameters (volume and flow rate).
To evaluate the safety of manual push IgPro20 infusions.</td></tr>
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- To evaluate the tolerability of higher infusion parameters of IgPro20.

Exploratory Objective:

- To assess serum immunoglobulin G (IgG) concentrations at various IgPro20 infusion parameters for pump-assisted and manual push administration.

Methodology:

This was a multicenter, open-label, parallel-arm, nonrandomized study to evaluate safety and tolerability of higher infusion parameters of IgPro20 in subjects with primary immunodeficiency. A minimum of 15 subjects per cohort were enrolled in 3 cohorts, including a target of 14 subjects ≤ 17 years and a target of 9 subjects with body mass index (BMI) of ≥ 30 kg/m^2. These subjects were distributed across any or all cohorts without respect to balanced enrollment within the cohorts.

After a Screening Period of up to 28 days, subjects were allocated to 1 of the following 3 cohorts with IgPro20 infusions administered as follows:

- Pump-Assisted Volume Cohort (weekly infusions): Volume per injection site of 25 mL, 40 mL, and 50 mL.
- Pump-Assisted Flow Rate Cohort (weekly infusions): Flow rate per injection site of 25 mL/h, 50 mL/h, 75 mL/h, and 100 mL/h.
- Manual Push Flow Rate Cohort (2 to 7 infusions per week): Flow rate per injection site of 30 mL/h, 60 mL/h, and 120 mL/h (equivalent of 0.5 mL/min, 1 mL/min, 2 mL/min).

Each cohort tested 3 infusion parameter levels (4 infusion parameter levels in Pump-Assisted Flow Rate Cohort) for 4 weeks each. After 4 weeks on an infusion parameter level, subjects who were classified as responders switched to the next highest infusion parameter level.

Day 1 was the day on which the first IgPro20 infusion was administered at the study site. Subjects returned to the study sites on 3 occasions every 4 weeks (4 occasions in Pump-Assisted Flow Rate Cohort). After an active treatment period of 12 weeks (16 weeks in Pump-Assisted Flow Rate Cohort), subjects returned to the study site on Week 13 (Week 17 in Pump-Assisted Flow Rate Cohort) for an End of Study Visit.

Safety assessments were performed at all study site visits. Serum IgG trough concentrations were determined at Day 1 and at End of Study Visit at the study site. Treatment-emergent adverse events (TEAEs) and IgPro20 administrations were recorded on an ongoing basis.

Number of Subjects:

Planned: A minimum of 45 evaluable subjects (15 per cohort) based on an assumed response rate for reaching the top infusion parameter for each endpoint of 50%.

Actual: 49 subjects (Pump-Assisted Volume Cohort: 15 subjects; Pump-Assisted Flow Rate Cohort: 18 subjects; Manual Push Flow Rate Cohort: 16 subjects)

Diagnosis and Main Criteria for Inclusion:

Male or female subjects with primary immunodeficiency on a stable dose of IgPro20 with infusion parameters for each cohort specified as follows:

- Pump-Assisted Volume Cohort: Experience with pump-assisted infusions of IgPro20 at tolerated volumes of 25 mL per injection site for ≥ 1 month before Day 1. Total weekly IgPro20 dose of ≥ 50 mL (≥ 10 g).
- Pump-Assisted Flow Rate Cohort: Experience with pump-assisted infusions of IgPro20 at the tolerated flow rate of 25 mL/h per injection site for ≥ 1 month before Day 1.
- Manual Push Flow Rate Cohort: Experience with frequent (2 to 7 times per week) infusions of IgPro20 at the tolerated flow rate of approximately 0.5 mL/min (equivalent of 25 to 30 mL/h) per injection site for ≥ 1 month before Day 1. The dose (volume) per injection site should not have exceeded 25 mL.

Investigational Product, Dose and Mode of Administration, Batch Number(s):

IgPro20 was self-administered by the subjects under the supervision of the study staff during study site visits and at home without supervision.

All subjects administered IgPro20 doses that were prescribed by their healthcare provider prior to study entry.

IgPro20 infusions were administered as follows:

- Pump-Assisted Volume Cohort: Weekly infusions at volumes of 25 mL, 40 mL, and 50 mL per injection site.
- Pump-Assisted Flow Rate Cohort: Weekly infusions at flow rates of 25 mL/h, 50 mL/min, 75 mL/min, and 100 mL/h per injection site.
- Manual Push Flow Rate Cohort: Infusions 2 to 7 times per week at flow rates of 30 mL/h, 60 mL/h, and 120 mL/h (corresponding to 0.5 mL/min, 1 mL/min, and 2 mL/min) per injection site.

The following batches of IgPro20 were administered: 4355900009, 4355900010, 4355900012, 4363600002, 4363600003, and 4363600004.

Duration of Treatment:

The overall study duration (ie, First Subject First Visit to Last Subject Last Visit) was approximately 22.5 months. For the individual subject, the maximum study duration (excluding the Screening Period) was 12 weeks in the Pump-Assisted Volume Cohort and the Manual Push Flow Rate Cohort, and 16 weeks in the Pump-Assisted Flow Rate Cohort.

Criteria for Evaluation:

Primary Endpoint: Percentage of responders for each planned infusion parameter level in each cohort.

Secondary Endpoints:

- The rate of total TEAEs per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.
- The rate of local reactions per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.
- The time of onset of local reactions per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.
- Severity of local reactions per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.
- Duration of local reactions per subject and per infusion by cohort and by each of the infusion parameter levels within the cohort.
- Tolerability of a certain infusion parameter; ie, percentage of infusions per cohort by volume / flow rate subgroup experiencing no severe local reactions for each of the infusion parameter levels.

Statistical Methods:

Except for subject disposition (Screened Analysis Set), all analyses were performed in the Safety Analysis Set, which comprised all subjects who received ≥ 1 dose or a partial dose of IgPro20 in the study.

Efficacy Analysis

Serum IgG trough concentrations were summarized descriptively by cohort.

Safety Analysis – Responder Analysis

The number and percentage of responders, number of infusions, and number and percentage of valid infusions were calculated for each cohort and infusion parameter level. Only data collected until subject's non-response were used. Responder analyses were summarized by age (≤ 17 years, > 17 years) and BMI (< 30 kg/m^2, ≥ 30 kg/m^2). An infusion parameter level was considered successful if the percentage of responders was ≥ 33%. In the pump-assisted cohorts, a responder for a certain infusion parameter level was a subject who administered ≥ 3 valid infusions at that infusion parameter level. In the Manual Push Flow Rate Cohort, a responder for a certain infusion parameter level was a subject who administered the minimum prespecified number of valid infusions for that infusion parameter level. An infusion was considered valid if the subject completed the full dose per scheduled infusion parameter under test without interruptions or decrease during the infusion. In addition to the responder analysis as defined in the study protocol (main analysis), 2 sensitivity analyses

were conducted for the pump-assisted cohorts. Both sensitivity analyses considered infusions valid that were stopped or interrupted for technical reasons without related TEAEs (sensitivity analysis 1: infusion was valid if the field "Technical Problem" was ticked; sensitivity analysis 2: infusion was valid if "other" was selected, but any technical reason described).

Safety Analysis – Other Analyses

Local reactions (including their intensity, causality, seriousness, time of onset, and duration) and other TEAEs documented until subject's non-response were summarized descriptively by infusion parameter level. Tolerability data collected until subject's non-response and extent of exposure irrespective of subject's response status were summarized descriptively by infusion parameter level. Clinical laboratory evaluations (hematology, biochemistry) and vital signs were summarized descriptively by cohort. Tolerability was defined as the number of infusions without severe local reactions divided by the total number of infusions irrespective of their validity.

Results:

Subject Disposition

Of the 55 subjects screened, 49 subjects were enrolled and treated with IgPro20. Two subjects discontinued due to a TEAE (1 mild and related TEAE [Injection Site Pain], 1 severe and unrelated serious adverse event [Suicide Attempt]). One subject withdrew consent and another subject discontinued due to protocol deviation.

Demographics

Twenty subjects (40.8%) were male and 29 subjects (59.2%) were female. The majority of subjects were white (42 subjects [85.7%]) and ≥ 18 to ≤ 65 years (35 subjects [71.4%]). With respect to the age and BMI subgroups for responder analyses, the majority of all subjects were > 17 years (38 subjects [77.6%]) and had a BMI of < 30 kg/m^2 (35 subjects [71.4%]). Overall, the median age was 47.0 years, and the median body weight was 71.4 kg. More subjects ≤ 17 years were enrolled in the Pump-Assisted Flow Rate Cohort, resulting in lower age, height, weight, and BMI. There were no other clinically meaningful differences in demographic characteristics among the cohorts.

Efficacy

For all cohorts, IgG trough levels at End of Study were comparable with the baseline IgG trough levels measured on Day 1.

Safety – Extent of Exposure

The mean and median actual volumes and doses administered per week and infusion parameter level were consistent with the planned values for all infusion parameter levels in all cohorts. In the Pump-Assisted Volume Cohort, 0% to 15% of infusions were interrupted. Compared with Week 1, the median number of injection sites decreased with higher infusion volumes from 4 to 3 sites per infusion. In the Pump-Assisted Flow Rate Cohort, 1.8% to 12.9% of infusions were interrupted. Overall, median duration of infusion at Week 16 decreased by approximately 4 times compared with Week 1, from 47.0 minutes to 12.5 minutes. In the Manual Push Flow Rate Cohort, the median duration of infusion per week at Week 12 decreased by approximately 4 times compared with Week 1, from 100 minutes to 25 minutes.

Safety – Responder Analysis

The prespecified success criterion of ≥ 33% of responders was met for all infusion parameter levels in all cohorts. In the Pump-Assisted Volume Cohort, the percentage of responders was 86.7% at 25 mL and 73.3% at 40 mL and 50 mL. In the Pump-Assisted Flow Rate Cohort, the percentage of responders was 77.8% at 25 mL/h and 50 mL/h, 66.7% at 75 mL/h, and 61.1% at 100 mL/h. Sensitivity analyses, which included infusions that were interrupted for technical reasons without related TEAEs, confirmed the results of the main analysis. In the Manual Push Flow Rate Cohort, the percentage of responders was 100.0% at 30 mL/h (0.5 mL/min) and 60 mL/h (1 mL/min), and 87.5% at the 120 mL/h (2 mL/min). Age and BMI had no clinically meaningful effect on the responder analysis.

Safety – Adverse Events and Local Reactions

Excluding TEAEs that occurred after non-response, the TEAE rate per infusion was 0.138, 0.216, and 0.085 in the Pump-Assisted Volume Cohort, the Pump-Assisted Flow Rate Cohort, and the Manual Push Flow Rate Cohort, respectively. The TEAE rate per infusion for all TEAEs as well as for local reactions tended to decrease with increasing volume in the Pump-Assisted Volume Cohort and with increasing flow rate in the Pump-Assisted Flow Rate Cohort. Such a trend was not observed in the Manual Push Flow Rate Cohort.

The majority of TEAEs in all 3 cohorts and at all infusion parameter levels were mild or moderate. Except for 1 unrelated serious adverse event, all TEAEs were nonserious. Most TEAEs had the outcome of recovered / resolved. Except for 2 discontinuations, there were no IgPro20 dose changes for any TEAE during the study. The most frequent TEAEs across all cohorts were local reactions.

Most of the TEAEs related to IgPro20 were local reactions. In all 3 cohorts, most local reactions developed during the day of infusion and self-resolved within 24 hours. The number, type, intensity, or duration of local reactions did not increase with increasing infusion parameter levels in any of the study cohorts. Except for 2 events of Headache, other related TEAEs (Diarrhoea, Erythema, Gait Inability, Headache, Nausea, Pruritus, and Rash) were single occurrences.

There were no deaths. There was 1 serious adverse event (Suicide Attempt, not related) that led to study discontinuation.

One TEAE of Injection Site Pain related to IgPro20 led to discontinuation at 25 mL infusion parameter level in the Pump-Assisted Volume Cohort. The TEAE resolved in 3 days.

Safety – Tolerability

Tolerability was high; 999 of 1000 infusions were administered without severe local reactions. The 1 event of severe local reaction (Injection Site Pain) at the 100 mL/h flow rate resolved within 1 day.

Safety – Other Analyses

No safety concerns were observed in laboratory parameters and vital signs.

Conclusions:

Overall, IgPro20 infusions at higher infusion parameters tested in this study were well tolerated, with a clinically acceptable safety profile. There were no new safety concerns identified from this study.

In conclusion, for subjects who have previously tolerated volumes of 25 mL and flow rates of 25 mL/h administered via pump, volumes of up to 50 mL and flow rates up to 100 mL/h per injection site administered via pump as well as flow rates of up to 120 mL/h via manual push technique are viable options.
Date of Report: 23 May 2019