2 SYNOPSIS

<table>
<tr><td>Name of Sponsor:
CSL Behring</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 (Hizentra®)</td></tr>
<tr><td>Name of Active Ingredient:
IgPro20: Human normal immunoglobulin G (IgG), 20% liquid</td></tr>
<tr><td colspan="3">Name of Device: Investigational Wearable Infusor</td></tr>
<tr><td colspan="3">Title of Study:
Comparison of 2 Infusion Devices With Respect to Pharmacokinetics, Safety, and Tolerability of Hizentra®: An Investigational Wearable Infusor and the Crono S-PID-50 Infusion Pump</td></tr>
<tr><td colspan="3">Global Clinical Program PPD : PPD
CSL Behring</td></tr>
<tr><td colspan="3">Publication (reference): Not applicable.</td></tr>
<tr><td>Study Period:
First Subject Visit: 26 Jun 2018
Last Subject Visit: 19 Aug 2019</td><td colspan="2">Phase of Development: 1</td></tr>
<tr><td colspan="3">Objectives:

The primary objective in this study was to compare the area under curve from time 0 (pre-infusion) to 7 days after infusion ($AUC_{0\text{-}7\ days}$) of immunoglobulin G (IgG) during the last week of each study period (Weeks 4 and 8) after subcutaneous (SC) infusion of the same IgPro20 dose with the Investigational Wearable Infusor (IWI) vs Crono S-PID-50 Infusion Pump (CP) in primary immunodeficiency (PID) subjects.

The secondary objectives of the study were to:

• Compare other pharmacokinetic (PK) parameters of IgG after SC infusion of the same IgPro20 dose with the IWI vs the CP in PID subjects
o maximum observed IgG concentration (C_{max}) and serum IgG measured concentration at the end of a dosing interval (before the next administration) (C_{trough}) after IgPro20 infusion during the last weekly dosing interval for each period with the IWI vs the CP in PID subjects.
o C_{trough} before every infusion
• Evaluate the safety and local tolerability of IgPro20 infusions with the IWI in comparison to the CP in PID subjects</td></tr>
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The exploratory objectives of the study were:

- To assess dosing accuracy with each infusion device
- To assess flow rate with each infusion device
- To assess treatment satisfaction and convenience of IgPro20 infusions with the IWI in comparison to the CP
- To assess subject's preference of infusion device (IWI vs CP)
- To assess impact of side effects on treatment satisfaction (IWI vs CP)

Methodology:

This was a prospective, multicenter, randomized, open-label, controlled, crossover, 2-arm, phase 1 study to compare the PK, safety, and tolerability of therapeutic doses of IgPro20 between 2 different infusion devices: the IWI (the study device) and the CP (the comparator device).

The study consisted of a Screening Period (up to 5 weeks) and 2 treatment periods (Period 1 and Period 2) of 4 weeks each during which subjects were administered the same steady-state IgPro20 dose with both infusion devices sequentially. Subjects were randomly assigned in a 1:1 ratio to 1 of the following 2 treatment sequences:

- Sequence 1: IgPro20 administered with CP in Period 1 and with IWI in Period 2.
- Sequence 2: IgPro20 administered with IWI in Period 1 and with CP in Period 2.

In both treatment periods, PK, safety, and tolerability assessments were performed. In the last week of each treatment period, the PK of IgPro20 was assessed over a 7-day period to determine the primary endpoint $AUC_{0\text{-}7\ days}$ as well as other key PK parameters (C_{trough} and C_{max}). The End of Study (EOS) Visit occurred on the day of the last PK sampling time point (ie, the end of Week 8 in Period 2). After the EOS Visit, subjects switched back to their prestudy infusion device.

As the infusion devices could not be blinded due to the differences in physical appearance, the study was open-label.

No interim analysis was planned.

Number of Subjects:
Planned: 20
Actual: 23

Diagnosis and Criteria for Inclusion:

1. Capable of providing written informed consent / assent and willing and able to adhere to all protocol requirements. The subject's parent(s) or legally acceptable representative(s) capable of providing written informed consent / assent.
2. Male or female.
3. At least 12 years of age at the time of providing written informed consent / assent.
4. Diagnosis of PID as evidenced by the subject's medical records.
5. Previously receiving stable (within ± 10% of an average dose in the last 3 months) doses (mg/kg) of IgPro20 for at least 3 months prior to Day 1 at weekly intervals.
6. At least 1 historic IgG trough level of ≥ 5 g/L during the past 3 months before Day 1 (could be obtained at Screening).
7. At least 2 serum IgG trough levels within ± 10% of one another.
8. Investigator believed that the subject was willing and able to adhere to all protocol requirements. Investigator believed that the subject's parent(s) or legally acceptable representative(s) was / were willing and able to adhere to all protocol requirements.

Investigational Product, Dose and Mode of Administration, Batch Number(s):
Ready-to-use 20% liquid formulation of polyvalent human IgG via subcutaneous infusion.
IWI System (consisting of IWI and IWI filling base)
Majority of IgPro20 dose within 100 to 200 mg/kg body weight

Duration of Treatment:
4 weeks per treatment period

Criteria for Evaluation:
Pharmacokinetics: $AUC_{0\text{-}7\ days}$, C_{max}, C_{trough}, and serum IgG C_{trough}
Quality of Life: Treatment satisfaction, device preference, and self-injection assessment
Safety: Adverse Events (AEs): frequency, intensity, causal relationship (to study product/device/both), temporal association, seriousness, and action taken with respect to study drug; time to onset and duration of injection site reactions, clinical laboratory tests: biochemistry; hematology; vital signs; and physical examinations.

Statistical Methods:
Demographics: The number of subjects screened, enrolled into the study, completing each study period, and completing the study were presented in summary tables by device group (IWI and CP), treatment sequence, and overall. The reasons for withdrawing a subject from the study was presented in summary tables (by device group, treatment sequence, and overall) and also listed by subject.

Pharmacokinetics: The PK parameters ($AUC_{0\text{-}7\ days}$ and C_{max}) were derived using standard non-compartmental analysis. For each of the PK parameters, the following summary statistics were calculated for each study device: n, median, geometric mean, geometric mean standard deviation, minimum, and maximum, geometric percent coefficient of variation.

Quality of Life: Derived domains (side effects, convenience and overall satisfaction) from the modified Treatment Satisfaction Questionnaire for Medication, were summarized and listed by device and overall for Weeks 1 and 4 of each study period. Device preference and the three most important ranked reasons for preference as well as intent to switch to a preferred device were summarized by treatment sequence and in total. Derived domains for Self-injection Assessment Questionnaire (SIAQ) were summarized by treatment sequence and time point for safety analysis set.
Safety: AEs were coded using the Medical Dictionary for Regulatory Activities version 21.1. An AE was regarded as treatment-emergent, if it either started on or after the first infusion of study treatment. Summary tables with number and percentage of subject with injection site reactions (ISRs) and number and percentage of infusions with ISRs in general and by preferred term were provided by device and overall. Extent of exposure, laboratory parameters, infusion data, vital signs, physical examination, and viral safety were summarized.
Changes in Planned Analyses: In addition to the planned analysis, an exploratory analysis of differences in dosing accuracy (%), leakage adjusted dosing accuracy (%), residual volume (mL), residual volume (%), residual volume (g), and leakage (g) comparing CP and IWI using a paired t-test and presenting the mean, 95% confidence interval (CI) of the mean and the resulting p-value was planned.

Results:

Subject Disposition

The study enrolled 23 subjects with PID who were treated with steady-state IgPro20 doses before study entry. A total of 11 subjects were randomized to Sequence 1 (CP in Study Period 1 and IWI in Study Period 2) and 12 subjects were randomized to Sequence 2 (IWI in Study Period 1 and CP in Study Period 2).

One subject PPD (randomized to CP / IWI sequence) had a major protocol deviation related to violation of inclusion criterion and was withdrawn from the study during Study Period 1. Three subjects (all randomized to Sequence 1- CP / IWI) were excluded from the PK Analysis Set (PKS) because of major protocol deviations.

Demographics

Of the 23 subjects enrolled in this study, 18 subjects (78.3%) were female. All subjects were white. All subjects except 1 were not Hispanic or Latino. Only 2 of the 23 subjects were in the 12 to 16 years age range (1 pediatric subject was excluded from PKS). The body mass index (BMI) of subjects ranged from 17.2 to 57.1 kg/m2, with 9 of the 23 subjects having BMIs $\geq$30 kg/m2.

Overall dose compliance was high and ranged from 92.49 to 108.36% in the 23 subjects randomized to Sequence 1 and 90.83 to 97.35% in the 22 subjects randomized to Sequence 2.

The median study duration was 57.0 days (6 to 71 days). The mean and median actual volumes and doses administered per week and infusion parameter level were consistent with the planned values. The median weekly dose in Study Period 1 was 119.58 mg/kg bw (78.6 to 197.3 mg/kg bw). The median weekly dose in Study Period 2 was 119.20 mg/kg bw (72.2 to 203.2 mg/kg bw).

Mean (SD) dose accuracy (%) was significantly higher with IWI (97.97 [0.418]%) than CP (96.63 [1.945]%) ($p = 0.0025$). Majority of the infusions with IWI were without any leakage (73 [83.0%]). Mean (SD) leakage (g) was significantly lower for IWI (0.008 [0.0166] g) than for CP (0.071 [0.0844] g) ($p = 0.0009$).

Mean (SD) residual volume (mL) was significantly lower for IWI (1.099 [0.3626] mL) for IWI than for CP (1.695 [0.7448] mL) ($p < 0.0001$). Mean (SD) residual amount (g) was significantly lower for IWI (1.166 [0.3847] g) than for CP (1.798 [0.7903] g) ($p < 0.0001$).

Pharmacokinetics

The primary PK endpoint $AUC_{0\text{-}7\ days}$ was selected as the most appropriate endpoint to assess the ability of the IWI to deliver IgPro20 to achieve equivalent IgG levels and systemic exposure over a weekly dosing interval compared to the CP. The overall geometric mean for $AUC_{0\text{-}7\ days}$ for IWI (1806 h*g/L) was only 1% lower than the corresponding value for CP (1829 h*g/L). The overall geometric mean C_{max} was 3% lower for IWI (11.4 g/L) compared to CP (11.7 g/L). The overall geometric mean C_{trough} was approximately 5% lower for IWI (10.3 g/L) compared to CP (10.9 g/L). The overall median t_{max} was 30% lower for IWI (50.3 h) compared to CP (72.2 h). There were nominal differences in the PK parameters between devices and sequences following weekly SC infusions of IgPro20. Comparison of $AUC_{0\text{-}7}$ days, C_{max}, and C_{trough} between the 2 devices, IWI and CP, was based on geometric mean ratio (GMR) and corresponding 90% CI. Log-transformed $AUC_{0\text{-}7}$ days, C_{max}, and C_{trough} were analyzed with a mixed model for repeated measures with fixed factors of period, device, and period-by-device interaction, and a random factor for subject.

The corresponding results were used to determine the GMR of $AUC_{0\text{-}7}$ days (IWI / CP), C_{max} (IWI / CP), C_{trough} (IWI / CP) and corresponding 90% CI. Success for IWI was to be established if the 90% CI for the $AUC_{0\text{-}7}$ days GMR fell entirely between the margins of 0.8 and 1.25. The GMRs for IWI versus CP for $AUC_{0\text{-}7}$ days, C_{max}, and C_{trough} were 0.99 (90% CI: 0.96, 1.01), 0.96 (90% CI: 0.91, 1.02), and 0.94 (90% CI: 0.87, 1.00), respectively. Bioequivalence of IWI and CP was assumed as the 90% CI for the $AUC_{0\text{-}7}$ days GMR fell entirely between the predefined acceptance range of 0.8 and 1.25.

Quality of Life

Median TSQ scores for overall satisfaction and convenience were significantly higher for IWI than for CP. An improvement in SIAQ scores for self-confidence, feelings about injections, and satisfaction with self-injection was observed for IWI in comparison to CP. All subjects (randomized to any sequence) except 1 (missing preference) preferred IWI over CP. All subjects, except 1 (missing preference) indicated a preference to switch to IWI in the future.

Safety

There were no deaths or serious AEs in this study. No subject discontinued/withdrew from the study due to treatment-emergent AEs (TEAEs). Nineteen subjects (82.6%) experienced at least 1 TEAE during the study. Ten subjects (43.5%) experienced at least 1 TEAE moderate in intensity and 2 subjects (8.7%) experienced a severe TEAE.

The most common System Organ Class (excluding ISRs) was Infections and Infestations (9 subjects [39.1%]). The most common TEAEs (excluding ISRs) reported were Upper Respiratory Tract Infection (4 subjects [17.4%]) and Sinusitis (3 subjects [13.0%]), all of which were unrelated to IgPro20 and/or both study devices. Two events of Hepatic Enzymes Increased and Migraine were reported as severe. Both events were unrelated to IgPro20 and/or both study devices.

In this study, unlike previous studies with IgPro20, ISRs were evaluated at each injection site. Overall, ISRs were observed in 7 subjects (30.4%) after a total of 40 infusions (22.6%). Injection site induration was the most frequently reported event observed in 5 subjects (21.7%) after 34 infusions (19.2%). The majority of the ISRs reported were mild or moderate in intensity. Injection site pain was reported as severe in 1 subject (4.5%) after infusion 3 with IWI.

Overall, the rates of most TEAEs per infusion, including ISRs, were numerically lower when IgPro20 infusions were performed using IWI compared to CP. No new previously unreported AEs were observed in this study with either device. Overall rates of AEs per infusion were similar to or lower than those recorded in previous IgPro20 studies.

The changes in hematology and biochemistry parameters from baseline to EOS Visit were not clinically relevant in any subject. Except for 1 unrelated TEAE of hepatic enzyme increased, none of the other biochemistry parameters outside the normal range were associated with a TEAE. No consistent or clinically relevant changes in vital signs were reported. No positive virology results were observed in any subject.

Conclusions:

The data from this study indicate that administration of IgPro20 with IWI ensures similar systemic IgG exposure for the same weekly dose compared to CP, as evidenced by GMR of IWI:CP AUCs at 0.99. In the same time, IWI provides better dosing accuracy and less leakage, leads to a more favorable safety profile, and maintains a better quality of life. All the study subjects who answered device preference questions indicated that they would prefer infusions with IWI due to such major reasons as easier use, higher mobility with device during infusion, less time required to set the device, and lower pain during injection.

Date of Report: 11 February 2020