Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Hizentra

human normal immunoglobulin

Procedure no: EMEA/H/C/002127/P46/025

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.
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1. Introduction

On 05.03.2020, the MAH submitted a completed study for Hizentra (IgPro20) that included 23 PID patients thereof 2 paediatric patients (whereby 1 paediatric patient was excluded due to a protocol violation), in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

This study is a stand-alone study to compare 2 Infusion Devices with respect to pharmacokinetics (PK), safety, and tolerability of Hizentra: An Investigational Wearable Infusor (IWI) and the Crono S-PID-50 Infusion Pump (CP)

2.2. Information on the pharmaceutical formulation used in the study

Hizentra (IgPro20) is a ready-to-use 20% protein liquid formulation of a polyvalent human immunoglobulin G (IgG) preparation for subcutaneous administration (SCIG).

Commercially available Hizentra (IgPro20) was used for this study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- IgPro20_1001_CSR; 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

2.3.2. Clinical study IgPro20_1001_CSR

Description

This Phase 1, open-label, 2 device comparison, cross-over, post-marketing study, which in total lasted ~ 14 months, investigated the PK and safety of s.c. Hizentra in 23 PID patients using either the Investigational Wearable Infusor or the Crono S-PID-50 Infusion Pump

Methods

Objective(s)

Primary Objectives

The primary objective in this study was to compare the area under curve (AUC) of the same SC IgPro20 dose from time 0 (pre-infusion) to 7 days after infusion (AUC0-7 days) during the last week of each study period (Weeks 4 and 8) with a) the Investigational Wearable Infusor (IWI) vs b) Crono S-PID-50 Infusion Pump (CP) in primary immunodeficiency (PID) subjects.
Secondary objectives

• Compare other pharmacokinetic (PK) parameters of IgG after SC infusion of the same IgPro20 dose with the IWI vs the CP in PID subjects
  □ maximum observed IgG concentration (Cmax) and serum IgG measured concentration at the end of a dosing interval (before the next administration) (Ctrough) after IgPro20 infusion during the last weekly dosing interval for each period with the IWI vs the CP in PID subjects.
  □ Ctrough before every infusion

• Evaluate the safety and local tolerability of IgPro20 infusions with the IWI in comparison to the CP in PID subjects

Study design

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 AUC0-7 days as well as other key PK parameters (Ctrough and Cmax). The End of Study (EOS) Visit occurred on the day of the last PK sampling time point (i.e. the end of Week 8 in Period 2). After the EOS Visit, subjects switched back to their pre-study infusion device.
**Study population / Sample size**

23 PID patients

**Inclusion criteria**

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.

**Exclusion criteria**

Subjects meeting any of the following exclusion criteria could not be enrolled into the study:

1. Newly diagnosed PID; ie, subjects who had not previously received SCIG replacement therapy.

2. Ongoing active serious infection at the time of Screening (including but not limited to: pneumonia, bacteremia / septicemia, osteomyelitis/septic arthritis, bacterial meningitis, or visceral abscess).

3. Ongoing or history of concomitant malignancies of lymphoid cells, such as lymphocytic leukemia, non-Hodgkin’s lymphoma, or immunodeficiency with lymphoma.

4. Known hyperprolinemia.

5. Hypoalbuminemia, protein-losing enteropathies, and any proteinuria (defined by total urine protein concentration > 0.2 g/L) documented in medical history.

6. Allergic or other severe reactions to immunoglobulins or other blood products recorded in the past 3 months or at the time of Screening.

7. Female subject of reproductive potential (a nonmenopausal female who had not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition included a young woman who had not yet started menstruating, was not using or not willing to use a medically reliable method of contraception, not sexually abstinent during the study or for 30 days after receipt of the last infusion of investigational product, or not surgically sterile).

8. Intention to become pregnant during the course of the study.

9. Pregnancy or nursing mother.

10. A positive result at Screening of any of the following viral markers: human immunodeficiency virus-1 (HIV-1), Hepatitis C virus, or Hepatitis B virus.
11. Aspartate aminotransferase or alanine aminotransferase concentration > 2.5 times the upper limit of normal range (ULN) at Screening.

12. Creatinine concentration > 1.5 times the ULN at Screening.

13. Participated in another interventional clinical study within 3 months before the first administration of IgPro20 or at any time during the study. Exception was made for subjects who had participated in the IgPro20_4004 clinical study.

14. Subjects who were planning to donate blood during the study.

15. Study personnel who were involved in the development of IgPro20 and the IWI, subjects who were employees at the study site, or relatives or spouses of the study personnel.

16. Alcohol, drug, or medication abuse (based on the discretion of the investigator) within 1 year before the study.

17. Treatment with systemic immunosuppressants, except for stable corticosteroid treatment (oral and parenteral, daily ≤ 0.15 mg of prednisone equivalent/kg/day) required for preexisting conditions allowed at the discretion of the investigator.

18. Currently receiving a therapy not permitted during the study, as defined in Section 7.3 of the protocol (Appendix 16.1.1).

19. Mental condition rendering the subject (or the subject’s legally acceptable representative[s]) unable to understand the nature, scope, and possible consequences of the study.

20. Any condition likely to interfere with the evaluation of IgPro20 or the infusion devices, or with satisfactory conduct of the study.

21. Known or suspected hypersensitivity to the investigational product, to any excipients of the investigational product, or to materials of the infusion devices (polycarbonates, silicone and acrylics, or adhesive).

22. Any issue that, in the opinion of the investigator, would render the subject unsuitable for participation in the study.

**Treatments**

Hizentra via subcutaneous infusion either by IWI or CP

IWI
### Table 9-2  Characteristics of the Investigational Wearable Infusion

<table>
<thead>
<tr>
<th>Device description</th>
<th>IWI System – consisting of IWI and IWI filling base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reservoir volume</td>
<td>10 mL and 20 mL</td>
</tr>
<tr>
<td>Minimum fill volume</td>
<td>10 mL IWI = 5 mL</td>
</tr>
<tr>
<td></td>
<td>20 mL IWI = 10 mL</td>
</tr>
<tr>
<td>Residual volume</td>
<td>≤ 0.5 mL (excluding the syringe)</td>
</tr>
<tr>
<td>Needle</td>
<td>Length: 5 to 6 mm (10 mL device) and 7 to 8 mm (20 mL device)</td>
</tr>
<tr>
<td></td>
<td>Gauge: 31g for 10 mL device and 30g for 20 mL device</td>
</tr>
<tr>
<td>Flow rate(^a)</td>
<td>≤ 25 mL/h</td>
</tr>
<tr>
<td>Weight</td>
<td>25 g (10 mL IWI empty) and 35 g (20 mL IWI empty)</td>
</tr>
<tr>
<td></td>
<td>225 g (10 mL IWI filling base, empty) and 281 g (20 mL IWI filling base, empty)</td>
</tr>
<tr>
<td>Dimensions of IWI</td>
<td>57.15 x 19.05 mm (10 mL IWI, button down)</td>
</tr>
<tr>
<td>(Diameter x Height)</td>
<td>70.0 x 21.5 mm (20 mL IWI, button down)</td>
</tr>
<tr>
<td>Dimensions of Filling Base</td>
<td>127 x 127 x 76.2 mm (10 mL and 20 mL filling base including outer packaging)</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Enable Injections, Inc., Cincinnati, OH, US</td>
</tr>
</tbody>
</table>

\(^{a}\)The IWI flow rate is not pre-set; it is influenced by the needle size/length, elastomeric balloon pressure (within the device), fluid path tolerances, solution viscosity and tissue back-pressure. The flow rate parameter is an estimate based on open bench air tests, not in real human infusions conditions. Therefore, actual flow rate was expected to deviate due to contribution from tissue back-pressure and fluctuation in solution viscosity.
Table 9.3  Characteristics of the Crono S-PID-50 Infusion Pump

<table>
<thead>
<tr>
<th>Device description</th>
<th>Ambulatory syringe infusion pump</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>Crono S-PID-50</td>
</tr>
<tr>
<td>Syringe volume</td>
<td>Up to 50 mL</td>
</tr>
<tr>
<td>Flow rate</td>
<td>$\leq 50$ mL/h (programmable)$^a$</td>
</tr>
<tr>
<td>Flow rate accuracy</td>
<td>$\pm 3%$</td>
</tr>
<tr>
<td>Needle Length</td>
<td>9 mm (any dose)</td>
</tr>
<tr>
<td>Needle Gauge</td>
<td>26 g</td>
</tr>
<tr>
<td>Infusion set</td>
<td>Repro-med Systems (single or bifurcated)</td>
</tr>
<tr>
<td>Weight</td>
<td>140 g</td>
</tr>
<tr>
<td>Dimensions</td>
<td>3.3 x 2.15 x 1.65 inches / 84.5 x 55 x 42 mm</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Cané S.p.A., Turin, Italy</td>
</tr>
</tbody>
</table>

$^a$ For the purposes of this study, the flow rate was set to $\leq 25$ mL/h per injection site to match the approximate infusion parameters of the IWL. Treatment-naive IgPro20 users were not enrolled in this study and so the lower flow rate for naive users was not applicable.

<table>
<thead>
<tr>
<th>Administration Parameter</th>
<th>IgPro20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>SC</td>
</tr>
<tr>
<td>Anatomic location of injection sites</td>
<td>Abdominal area</td>
</tr>
<tr>
<td>Total infusion volume</td>
<td>Individual volume, based on the prescribed dose</td>
</tr>
<tr>
<td>Number of injection sites</td>
<td>Depending on the subject’s individual weekly dose (volume), not to exceed 4 injection sites for simultaneous infusions</td>
</tr>
<tr>
<td>Volume per injection site</td>
<td>$\leq 20$ mL</td>
</tr>
<tr>
<td>Flow rate per injection site</td>
<td>$\leq 25$ mL/h</td>
</tr>
</tbody>
</table>

SC=subcutaneous; $h=$hour

Outcomes/endpoints

Pharmacokinetics: primary endpoint: AUC0-7 days,

Cmax and serum IgG Ctrough
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 (AUC0-7 days and Cmax) 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

Recruitment/ Number analysed

The study enrolled 23 subjects with PID who were treated with steady-state IgPro20 doses before study entry.

Two of the 23 subjects were in the 12 to 16 years age range.

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 (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, including 1 paediatric subject) were excluded from the PK Analysis Set (PKS) because of major protocol deviations.

**Baseline data**

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 ≥30 kg/m².

A total of 17 subjects (73.9%) had common variable immunodeficiency. Congenital agammaglobulinemia, IgG deficiency, selective IgA deficiency, non-familial hypogammaglobulemia, dysgammaglobulinemia, and hypogammaglobulinemia were reported in 1 subject each.

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.

**PK**

<table>
<thead>
<tr>
<th>Table 11-1</th>
<th>Analysis Sets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sequence 1 CP / IWI</td>
</tr>
<tr>
<td></td>
<td>(N = 11) n (%)</td>
</tr>
<tr>
<td>Full Analysis Set</td>
<td>11 (100.0)</td>
</tr>
<tr>
<td>Safety Analysis Set</td>
<td>11 (100.0)</td>
</tr>
<tr>
<td>Pharmacokinetic Analysis Set</td>
<td>8 (72.7)</td>
</tr>
<tr>
<td>Pharmacokinetic Sensitivity Analysis Set</td>
<td>10 (90.9)</td>
</tr>
</tbody>
</table>

CP = Crono S-PID-50 Infusion Pump, IWI = Investigational Wearable Infusor (GoDisc) Source Table 14.1.1.2

The primary PK endpoint AUC0-7 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:

- **AUC0-7 days for**
  - IWI (1806 h*g/L) was 1% lower than for CP (1829 h*g/L).

- **Cmax for**
  - IWI (11.4 g/L) was 3% lower compared to CP (11.7 g/L).

- **mean Ctrough for**
  - for IWI (10.3 g/L) was ~ 5% lower compared to CP (10.9 g/L).
• median tmax for
  - IWI (50.3 h) was 30% lower compared to
  - CP (72.2 h)

Comparison of AUC0-7 days, Cmax, and Ctrough between the 2 devices, IWI and CP, was based on geometric mean ratio (GMR) and corresponding 90% CI. Log-transformed AUC0-7 days, Cmax, and Ctrough 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 AUC0-7 days (IWI / CP), Cmax (IWI / CP), Ctrough (IWI / CP) and corresponding 90% CI. Success for IWI was to be established if the 90% CI for the AUC0-7 days GMR fell entirely between the margins of 0.8 and 1.25.

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>GMR (90% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(IWI / CP)</td>
<td>Period</td>
</tr>
<tr>
<td>AUC0-7 days (h^2 g/L)</td>
<td>0.99 [0.96, 1.01]</td>
<td>0.4876</td>
</tr>
<tr>
<td>Cmax (g/L)</td>
<td>0.96 [0.91, 1.02]</td>
<td>0.2189</td>
</tr>
<tr>
<td>Ctrough (g/L)</td>
<td>0.94 [0.87, 1.00]</td>
<td>0.2177</td>
</tr>
</tbody>
</table>

Bioequivalence of IWI and CP was assumed as the 90% CI for the AUC0-7 days GMR fell between the predefined acceptance range of 0.8 and 1.25.

QoL

Standardized TSQ scale scores range from 0 to 100, 0 presenting the worst and 100 presenting the best result. TSQ was assessed at the end of the respective week.

Median TSQ scores for overall satisfaction and convenience were significantly higher for IWI than for CP.

<table>
<thead>
<tr>
<th>Parameter / Timepoint</th>
<th>Sequence 1 CP / IWI (N = 11)</th>
<th>Sequence 2 IWI / CP (N = 12)</th>
<th>Total (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convenience</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>8</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>41.668 (28.6393)</td>
<td>41.919 (18.9805)</td>
<td>41.813 (22.7845)</td>
</tr>
<tr>
<td>Median</td>
<td>47.225</td>
<td>50.000</td>
<td>50.000</td>
</tr>
<tr>
<td>Minimum, Maximum</td>
<td>-5.56, 72.22</td>
<td>0.00, 61.11</td>
<td>-5.56, 72.22</td>
</tr>
<tr>
<td>Overall Satisfaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>8</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>44.098 (37.3386)</td>
<td>42.676 (26.0075)</td>
<td>43.275 (30.3063)</td>
</tr>
<tr>
<td>Median</td>
<td>30.555</td>
<td>44.440</td>
<td>33.330</td>
</tr>
<tr>
<td>Minimum, Maximum</td>
<td>0.00, 100.00</td>
<td>0.00, 91.67</td>
<td>0.00, 100.00</td>
</tr>
</tbody>
</table>

CP = Credo S-PID-50 Infusion Pump, IWI = Investigational Wearable Infusor (GoDisc)
Note: Standardized TSQ scale score range from 0 to 100, 0 presenting the worst and 100 presenting the best result.
Difference between devices calculated as (Domain Score under IWI use - Domain score under CP use) by subject.
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 results**

**Exposure**

Majority of doses were within 100 to 200 mg/kg body weight

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). All subjects except 1 (withdrawn from study) received all 4 infusions per period.

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).

Device malfunction (1 subject) was reported for CP, leading to a dose interruption. Other errors (1 subject), use errors (1 subject), and device malfunction (5 subjects) were reported for IWI. There were 9 product technical complaints reported in the study (8 for IWI and 1 for CP).

**AEs**

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. Seventeen subjects (73.9%) experienced temporally associated (within 72 h post-infusion) TEAEs. 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 Injection Site Reactions- 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.

3. Overall conclusion and recommendation

This study in 23 PID patients (including 2 children) compared 2 infusion devices with respect to pharmacokinetics (PK), QoL, safety, and tolerability of Hizentra: Investigational Wearable Infusor (IWI) and the Crono S-PID-50 Infusion Pump (CP).

The primary objective was to compare the area under curve (AUC) of the same SC IgPro20 dose for the 2 devices. Secondary objectives encompassed Cmax and Ctrough: Bioequivalence (within the given acceptance range for the 90% CIs of 0.8 and 1.25) was sufficiently shown for the PK parameters AUC0-7, Cmax and Ctrough.

The overall QoL results indicated a preference for the IWI device.

The exposure (median weekly dose ~ 119 mg/kg) was the same in both Study Periods. Leakage was seen less with IWI and residual volume was also lower in IWI, however, there were more technical complaints/malfunctions with IWI than with CP.

No new or critical safety findings were revealed in this study. The most common related AEs injection site reactions in ~30% of the patients and mainly mild or moderate in intensity. Unrelated AEs were mainly URTI and sinusitis as would be expected in this PID population.

No conclusion regarding the paediatric population cannot be drawn as only 1 of 2 children stayed in the study.

No regulatory action required from the MAH.