Safety Profile of High IgPro20 Infusion Parameters in Patients With Primary Immunodeficiency (PID): Results From the Forced Upward Titration HILO Study

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Introduction

- Patients with primary immunodeficiency (PID) usually require lifelong immunoglobulin G (IgG) replacement therapy administered via intravenous (IVIG) or subcutaneous (SCIG) routes[1,2]
- SCIG can be self-administered using an infusion pump or by manual push (also known as rapid push) using a syringe[3-6]
  - Administration by pump allows higher infusion volumes and less frequent (weekly) infusions vs manual push
  - Administration by manual push allows shorter infusion times, more frequent (≥2 times weekly) infusions, and fewer injection sites per dosing session vs pump-assisted infusions
- IgPro20 (Hizentra®, CSL Behring, King of Prussia, PA, USA) is a ready-to-use 20% formulation of polyvalent SCIG approved since 2010 for the treatment of patients with PID aged ≥2 years[7]
- In the United States, the approved maximal pump-assisted IgPro20 infusion parameters are volumes of ≤25 mL/injection site and flow rates of ≤25 mL/h/injection site[7]
- Results from clinical trials and real-world studies suggest that higher volumes and flow rates are well tolerated,[8-11] yet no prospective studies have evaluated higher infusion parameters

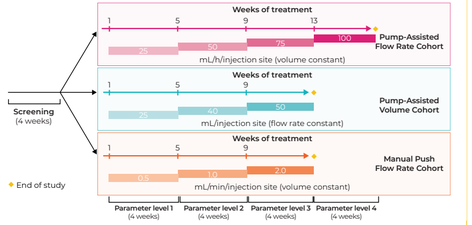
Objective

To evaluate the safety and tolerability of IgPro20 infusion volumes of up to 50 mL/injection site (pump) and flow rates of up to 100 mL/h/injection site (pump) or 2 mL/min/injection site (push) in patients with PID

Methods

- The Hizentra® Label Optimization (HILO) study (NCT03033745) was a multicenter, open-label, parallel-arm, non-randomized Phase 4 study in patients with PID
  - Details of the forced upward titration study design have been reported previously[12]
- Eligible patients had PID, were receiving a stable dose of IgPro20 therapy, and had experience with pump-assisted or manual push infusions of IgPro20 at the approved maximal infusion parameters for ≥1 month prior to Day 1 (first IgPro20 infusion)
  - Patients with hypersensitivity to IgPro20, ongoing serious bacterial infection at the time of screening, or other serious medical conditions were excluded

Figure 1. Study design



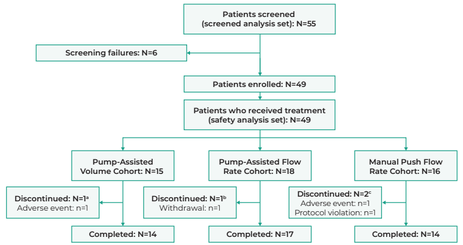
Flow rate was constant for each patient in the Pump-Assisted Volume Cohort, but differed between patients. Volume was constant for each patient in the Pump-Assisted Flow Rate and Manual Push Flow Rate Cohorts, but differed between patients. An infusion was considered valid if the patient completed the full dose per the scheduled infusion parameter (volume or flow rate) without interruption or decrease during infusion. Responders in the Pump-Assisted Flow Rate and Volume Cohorts were patients who received ≥3 valid infusions for an infusion parameter level. Responders in the Manual Push Flow Rate Cohort were patients who received the predetermined minimum number of valid infusions for an infusion parameter level. Each infusion parameter level was tested for 4 weeks, after which responders were switched to the next level. The weekly dose remained unchanged during the study. The last IgPro20 infusion was administered at Week 16 in the Pump-Assisted Flow Rate Cohort and at Week 12 in the other cohorts.

- 49 patients were enrolled and assigned to 1 of 3 cohorts (**Figure 1**):
  - **Pump-Assisted Volume Cohort:** n=15; 25–50 mL/injection site; weekly infusions
  - **Pump-Assisted Flow Rate Cohort:** n=18; 25–100 mL/h/injection site; weekly infusions
  - **Manual Push Flow Rate Cohort:** n=16; 30–120 mL/h/injection site; 2–7 infusions/week
- Safety was assessed by the frequency and severity of treatment-emergent adverse events (TEAEs), by cohort, and by infusion parameter level in all patients who received ≥1 dose of IgPro20 or a partial dose of IgPro20 (safety analysis set)

Results

Patient population

Figure 2. Patient disposition



[a]1 patient discontinued at infusion parameter level 25 mL because of mild injection site pain; [b]1 patient withdrew at infusion parameter level 25 mL/h because their caregiver was uncomfortable with IgPro20 administration; [c]1 patient discontinued because of a suicide attempt and 1 patient discontinued because of a diagnosis of secondary immunodeficiency (protocol violation), both at infusion parameter level 60 mL/h.

- Patient disposition is presented in **Figure 2**
- There were no clinically meaningful differences in demographic characteristics between the Pump-Assisted Volume Cohort and the Manual Push Flow Rate Cohort (**Table 1**)
- As more patients aged ≤17 years were enrolled in the Pump-Assisted Flow Rate Cohort, mean and median age, weight, and BMI were lower in this cohort (**Table 1**)
- Further demographic data are presented in **Posters 697** and **699**

Safety overall

- Mean and median patient duration of exposure and total duration of exposure are presented in **Table 2**
- For the total study population irrespective of responder status, the rate of TEAEs/infusion was low across cohorts: 0.145, 0.228, and 0.085 in the Pump-Assisted Volume Cohort, the Pump-Assisted Flow Rate Cohort, and the Manual Push Flow Rate Cohort, respectively (**Table 3**)
- There were no clinically meaningful differences in the frequency, type, intensity, or duration of TEAEs between cohorts
- There were no trends indicating an increase in the frequency or intensity of TEAEs with increasing flow rate or volume per injection site in any cohort
- The majority of treatment-related TEAEs were mild or moderate injection site reactions (ISRs) (**Table 3**)
- No serious related TEAEs were reported, and no patients died (**Table 3**)

Table 1. Demographics and clinical characteristics at baseline (safety analysis set)

Parameter	Pump-Assisted Volume Cohort (N=15)	Pump-Assisted Flow Rate Cohort (N=18)	Manual Push Flow Rate Cohort (N=16)	Total (N=49)
Age, years				
Mean (SD)	49.1 (14.2)	26.7 (24.5)	47.9 (13.3)	40.5 (21.0)
Median (min, max)	50.0 (19, 75)	15.0 (2, 75)	49.5 (17, 65)	47.0 (2, 75)
Age ≤17 years, n (%)	0	10 (55.6)	1 (6.3)	11 (22.4)
Male, n (%)	6 (40.0)	8 (44.4)	6 (37.5)	20 (40.8)
Race, n (%)				
White	14 (93.3)	16 (88.9)	12 (75.0)	42 (85.7)
American Indian or Alaska Native	0	1 (5.6)	0	1 (2.0)
Black or African American	0	1 (5.6)	1 (6.3)	2 (4.1)
Other	0	0	1 (6.3)	1 (2.0)
Multiple	1 (6.7)	0	2 (12.5)	3 (6.1)
Weight, kg				
Mean (SD)	80.1 (21.0)	52.6 (26.1)	81.8 (15.7)	70.6 (25.3)
Median (min, max)	71.4 (55.8, 143.1)	59.0 (11.3, 88.8)	81.1 (52.3, 107.0)	71.4 (11.3, 143.1)
BMI, kg/m²				
Mean (SD)	30.1 (8.6)	22.6 (5.8)	29.3 (6.7)	27.1 (7.7)
Median (min, max)	27.7 (23.2, 58.1)	22.3 (13.4, 31.4)	26.7 (19.2, 40.0)	26.1 (13.4, 58.1)
BMI <30 kg/m², n (%)	11 (73.3)	15 (83.3)	9 (56.3)	35 (71.4)
Immunodeficiency disease, n (%)				
Common variable immunodeficiency	11 (73.3)	8 (44.4)	14 (87.5)	33 (67.3)
Congenital agammaglobulinemia	1 (6.7)	1 (5.6)	0	2 (4.1)
Other immunodeficiency[a]	3 (20.0)	9 (50.0)	2 (12.5)	14 (28.6)
Time since first PID diagnosis, years				
Mean (SD)	11.1 (13.0)	5.2 (6.0)	12.5 (13.8)	9.4 (11.5)
Median (min, max)	5.0 (0.8, 45.0)	2.3 (0.2, 23.0)	4.8 (0.1, 46.0)	3.1 (0.1, 46.0)
Pre-study IgG trough levels, g/L				
N	15	18	15	48
Mean (SD)	11.2 (2.8)	9.6 (3.0)	9.1 (1.9)	9.9 (2.7)
Median (min, max)	11.6 (6.9, 16.1)	9.9 (1.5, 14.2)	9.1 (5.7, 13.3)	9.8 (1.5, 16.1)

[a]Other immunodeficiency category includes combined immunodeficiency, specific antibody deficiency, hypogammaglobulinemia, IgG deficiency, Bruton's agammaglobulinemia, polysaccharide non-response immunodeficiency, and zap 70 immunodeficiency.
BMI, body mass index; IgG, immunoglobulin G; max, maximum; min, minimum; PID, primary immunodeficiency; SD, standard deviation.

Table 2. Extent of exposure

Parameter	Pump-Assisted Volume Cohort (N=15)	Pump-Assisted Flow Rate Cohort (N=18)	Manual Push Flow Rate Cohort (N=16)
Patient duration of exposure, weeks			
Mean (SD)	11.8 (2.1)	16.2 (2.0)	11.8 (1.8)
Median (min, max)	12.1 (4.3, 13.3)	16.1 (9.4, 19.1)	12.1 (6.6, 14.1)
Total duration of exposure, patient-years	3.4	5.6	3.6

max, maximum; min, minimum; SD, standard deviation.

Table 3. Summary of TEAEs overall (safety analysis set)[a]

Parameter	Pump-Assisted Volume Cohort (N=15; Inf=172)		Pump-Assisted Flow Rate Cohort (N=18; Inf=272)		Manual Push Flow Rate Cohort (N=16; Inf=626)	
	n (%)	E (rate)	n (%)	E (rate)	n (%)	E (rate)
Any TEAE	8 (53.3)	25 (0.145)	12 (66.7)	62 (0.228)	12 (75.0)	53 (0.085)
Treatment-related	4 (26.7)	12 (0.070)	8 (44.4)	49 (0.180)	6 (37.5)	33 (0.053)
Intensity of TEAEs						
Mild	6 (40.0)	20 (0.116)	10 (55.6)	52 (0.191)	11 (68.8)	49 (0.078)
Moderate	4 (26.7)	5 (0.029)	5 (27.8)	8 (0.029)	3 (18.8)	3 (0.005)
Severe	0	0	1[c] (5.6)	2 (0.007)	1[d] (6.3)	1 (0.002)
Serious TEAEs	0	0	0	0	1[d] (6.3)	1 (0.002)
Deaths	0	0	0	0	0	0
Study discontinuation due to TEAE	1[b] (6.7)	1 (0.006)	0	0	1[d] (6.3)	1 (0.002)
Treatment-related	1[b] (6.7)	1 (0.006)	0	0	0	0
Study drug withdrawal due to TEAE	1 (6.7)	2 (0.012)	0	0	1 (6.3)	1 (0.002)
Treatment-related	1 (6.7)	2 (0.012)	0	0	0	0
Local TEAEs	4 (26.7)	12 (0.070)	8 (44.4)	44 (0.162)	7 (43.8)	28 (0.045)
Treatment-related	4 (26.7)	12 (0.070)	8 (44.4)	42 (0.154)	6 (37.5)	27 (0.043)

Rate=number of events/total number of infusions.
[a]Adverse events starting on or after the date (and time if available) of the first administration of IgPro20 treatment were considered TEAEs. Includes TEAEs occurring before and after non-response; [b]1 patient discontinued because of a mild, related TEAE (injection site pain); [c]1 patient reported 2 severe related TEAEs (injection site pain and gait inability), which resolved within 24 hours; [d]1 patient reported a severe, unrelated, serious TEAE (suicide attempt), which led to discontinuation.
E, number of events; Inf, infusions; N, total number of patients per cohort; n, number of patients with event; TEAE, treatment-emergent adverse event.

Safety under forced upward titration conditions

- The rate of TEAEs/infusion under forced upward titration conditions was low across cohorts: 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
- In the Pump-Assisted Volume Cohort, 4 patients (26.7%) had 12 related TEAEs (0.079/infusion), all of which were ISRs
- In the Pump-Assisted Flow Rate Cohort, 8 patients (44.4%) had 35 related TEAEs (0.158/infusion), of which 29 were ISRs
- In the Manual Push Flow Rate Cohort, 6 patients (37.5%) had 33 related TEAEs (0.053/infusion), of which 27 were ISRs
- Further details are provided in **Posters 697** and **699**

Conclusions

- In treatment-experienced patients with PID:
  - IgPro20 volumes of up to 50 mL/injection site and flow rates of up to 100 mL/h/injection site administered via pump were well tolerated
  - IgPro20 flow rates of up to 120 mL/h/injection site administered via manual push were well tolerated
- There were no trends indicating an increase in the frequency or intensity of TEAEs with increasing flow rate or volume per injection site
- No new safety signals for IgPro20 were reported

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MAR, MP, and **JH:** employees of CSL Behring; own CSL Behring shares. **CH:** none. **JA:** speaker, consultant, and clinical research principal site investigator for CSL Behring and Takeda. **VRB:** speaker for CSL Behring and Takeda. **JC:** research funding from CSL Behring and Octapharma; clinical trial investigator for Takeda. **PLL:** clinical trial site investigator for CSL Behring and Takeda. **PJM:** research funding from the National Institutes of Health, the AAAAI Foundation, Boston University, Takeda, and Horizon Pharma. **SSM:** speaker for CSL Behring, Genentech, Teva, AstraZeneca, and Regeneron; research funding from CSL Behring, Shire, and Regeneron. **NCP:** speaker for CSL Behring and Takeda; research funding from CSL Behring and Takeda; advisory board member for Horizon Therapeutics. **JMR:** principal site investigator for CSL Behring; independent contractor for Takeda. **PS:** publication research grant from CSL Behring. **DCV:** research funding from Fonds de la recherche en santé du Quebec, Canadian Institutes of Health Research, U.S. Department of Defense, Jeffrey Modell Foundation, La Fondation du Grand Défi Pierre Lavoie, and CSL Behring; speaker for CSL Behring and Avir Pharma; clinical trial funding from CSL Behring and Cidara Therapeutics.

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