Feasibility of Subcutaneous IgPro20 Administration Via Manual Push at High Flow Rates in Patients With Primary Immunodeficiency: Findings of the HILO Study

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Introduction

- IgPro20 (Hizentra®, CSL Behring, King of Prussia, PA, USA) is a ready-to-use 20% subcutaneous immunoglobulin G (SCIG) approved for treatment of primary immunodeficiency (PID)[1,2]
- Infusion of IgPro20 via manual push (also known as rapid push) is used in clinical practice but has not been approved by the US Food and Drug Administration[1]
- The safety and tolerability of IgPro20 manual push flow rates of 0.5–2.0 mL/min/injection site have not been systematically evaluated
- Assessment of increasing flow rates is important, as higher flow rates allow shorter infusion times[3,4]

Objectives

- The Hizentra® Label Optimization (HILO) study aimed to evaluate the safety and tolerability of IgPro20 flow rates of 0.5–2.0 mL/min/injection site administered via manual push in patients with PID

Methods

- The HILO study was a multicenter open-label trial (NCT03033745) using a forced upward titration design
- Patients with PID and previous experience with frequent manual push IgPro20 infusions at ~0.5 mL/min were eligible for inclusion in the manual push study cohort
- IgPro20 was administered in 2–7 manual push infusions/week at 0.5, 1.0, and 2.0 mL/min/site (or 30, 60, and 120 mL/h/site, respectively) over 12 weeks
  - Each flow rate was tested for 4 weeks
- Responder rates (percentage of patients who administered the minimum number of valid infusions) were evaluated for each flow rate
  - Valid infusions were those with ≥95% of planned volume/day and infusion duration not 1 minute or 10% longer than the calculated infusion duration (whichever was higher)
  - Only responders switched to the next flow rate after 4 weeks; non-responders continued at the highest tolerated rate
  - Flow rates were considered successful if the responder rate was ≥33%
- Treatment-emergent adverse events (TEAEs) up to a patient's non-response were summarized and tolerability under forced upward titration was evaluated (number of infusions without severe local reactions divided by total number of infusions)
- Infusion compliance and serum IgG levels were assessed

Results

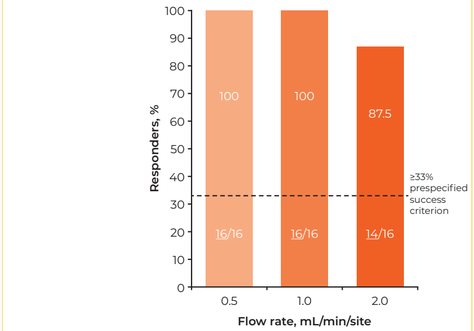
Patient disposition and demographics

- 16 patients were enrolled in this cohort, and 14 completed the study
  - 2 patients (12.5%) discontinued at the 1.0-mL/min infusion rate: 1 owing to an AE unrelated to study drug and 1 owing to a protocol deviation
  - Patient baseline demographics are reported in **Poster 097**

Responder analysis

- The percentage of responders at 0.5-, 1.0-, and 2.0-mL/min flow rates was 100%, 100%, and 87.5%, respectively (**Figure 1**)
- Mean weekly duration of infusions decreased compared with Week 1 as flow rates increased (**Figure 2**)
- Infusion compliance was high for all flow rates, with most patients achieving >90% compliance (**Table 1**)

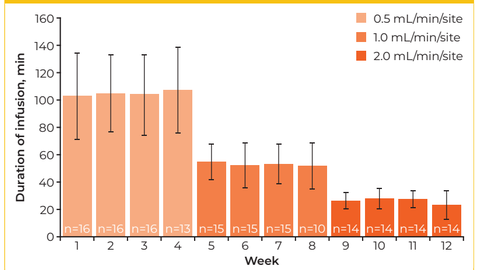
Figure 1. Responder analysis of increasing manual push flow rates (safety analysis set)



Number of patients with ≥1 infusion[a]	16	16	14
Number of infusions before non-response	220	208	198
Number (%) of valid infusions	219 (99.5)	208 (100)	195 (98.5)

Safety analysis set included all patients who received ≥1 dose or a partial dose of IgPro20 in the study.
[a]Prior to start date of non-response.
Number of responders shown in bars (underlined).

Figure 2. Mean weekly infusion duration with increasing manual push flow rates



Mean ± standard deviation values are presented.
n, number of patients with infusion duration data for each week.

Table 1. Infusion compliance (safety analysis set)

Flow rate	0.5 mL/min/site (N=16)	1.0 mL/min/site (N=16)	2.0 mL/min/site (N=14)
Overall compliance (administered dose/planned dose), %			
Mean (SD)	99.5 (10.1)	93.7 (11.8)	98.5 (3.5)
Median (min, max)	100.0 (82.9, 131.7)	99.8 (60.7, 100.5)	100.0 (90.0, 100.5)
Compliance level, n (%)			
<90%	2 (12.5)[a]	4 (25.0)[b]	0
≥90%	14 (87.5)	12 (75.0)	14 (100.0)

Safety analysis set included all patients who received ≥1 dose or a partial dose of IgPro20 in the study.
[a]2 patients had missing data records for some infusions at the 0.5-mL/min rate; therefore, compliance was <90%; [b]at the 1.0-mL/min rate, 1 patient received 9 of 12 planned infusions (to compensate for additional infusions at the 0.5-mL/min rate), 2 patients missed doses (one owing to a natural disaster and the other for an unknown reason), and 1 patient discontinued owing to an unrelated serious AE (suicide attempt) after receiving 5 of 8 planned infusions.
AE, adverse event; max, maximum; min, minimum; N, total number of patients per cohort; n, number of patients; SD, standard deviation.

Tolerability under forced upward titration conditions

- TEAE rates were low, with mostly mild local reactions (**Table 2**); TEAE rates were comparable across flow rates
- Tolerability was 100% for all flow rates
- Detailed safety and tolerability are reported in **Poster 097**

Table 2. Summary of TEAEs under forced upward titration conditions (safety analysis set)

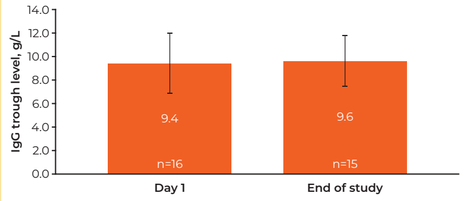
	Manual Push Flow Rate Cohort (N=16; Inf=626)	
	n (%)	E (rate)
Any TEAE	12 (75.0)	53 (0.085)
Treatment-related	6 (37.5)	33 (0.053)
Intensity of TEAEs		
Mild	11 (68.8)	49 (0.078)
Moderate	3 (18.8)	3 (0.005)
Severe	1 (6.3)[a]	1 (0.002)
Serious TEAEs	1 (6.3)[a]	1 (0.002)
Deaths	0	0
Study discontinuation due to TEAE	1 (6.3)[a]	1 (0.002)
Treatment-related	0	0
Local TEAEs	7 (43.8)	28 (0.045)
Treatment-related	6 (37.5)	27 (0.043)

Safety analysis set included all patients who received ≥1 dose or a partial dose of IgPro20 in the study.
[a]1 patient reported a severe, unrelated, serious TEAE (suicide attempt), which led to discontinuation.
E, number of events; inf, number of infusions; N, total number of patients per cohort; n, number of patients; rate, TEAE rate per infusion; TEAE, treatment-emergent adverse event.

Serum IgG trough levels

- Patient serum IgG concentrations were similar between the start and end of study (**Figure 3**)

Figure 3. Serum IgG trough levels at start and end of study



Mean ± standard deviation values are presented.
IgG, immunoglobulin G; n, number of patients with serum IgG concentration data at each time point.

Conclusions

- IgPro20 infusions via manual push at flow rates up to 2.0 mL/min/site were well tolerated in treatment-experienced PID patients
- Responder rates exceeded the prespecified success criterion at all flow rates
- Increasing flow rates did not impact the tolerability of IgPro20 manual push infusions
- Manual push IgPro20 administration at flow rates of 0.5–2.0 mL/min/site allows patients to individualize SCIG therapy by reducing infusion time

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