

The HILO Study: High Volumes and Flow Rates of Subcutaneous IgPro20 Pump-assisted Infusions in Patients With Primary Immunodeficiency

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Introduction

- Hizentra® (IgPro20, CSL Behring, King of Prussia, PA, USA) is a ready-to-use formulation of polyvalent subcutaneous immunoglobulin (SCIG) with 20% highly purified (≥98% purity) immunoglobulin G (IgG) content, approved for the treatment of primary immunodeficiency (PID)¹⁻³
- The safety and tolerability of pump-assisted IgPro20 infusion volumes of >25 mL/injection site and flow rates of >25 mL/h/injection site have not been systematically evaluated

Objective

- The Hizentra® Label Optimization (HILO) study aimed to evaluate the safety and tolerability of IgPro20 infusion volumes of 25–50 mL/injection site or flow rates of 25–100 mL/h/injection site administered by pump in patients with PID

Methods

- HILO (NCT03033745) was the first multicenter, open-label, parallel-arm, non-randomized study of IgPro20 using a forced upward titration design
- Eligible patients included in the pump cohorts were experienced with pump-assisted infusions at volumes of 25 mL/injection site or flow rates of 25 mL/h/injection site
- Patients received weekly IgPro20 infusions at a constant dose
- Increasing volumes (25–50 mL/injection site) or flow rates (25–100 mL/h/injection site) were evaluated for 12 weeks in the Volume Cohort and for 16 weeks in the Flow Rate Cohort
 - Each level was tested for 4 weeks before switching to the next parameter level
- Responder rates (percentage of patients who successfully completed ≥75% of planned infusions) were evaluated
 - An infusion parameter level was considered successful if the response rate was ≥33% for that level
- Tolerability was defined as the number of infusions achieved without severe local reactions divided by the total number of infusions irrespective of infusion validity
- Safety under forced upward titration conditions was evaluated by summarizing treatment-emergent adverse events (TEAEs) up to a patient's non-response at a particular parameter level
- Compliance rates and serum IgG trough levels were also evaluated

Results

Patient disposition and demographics

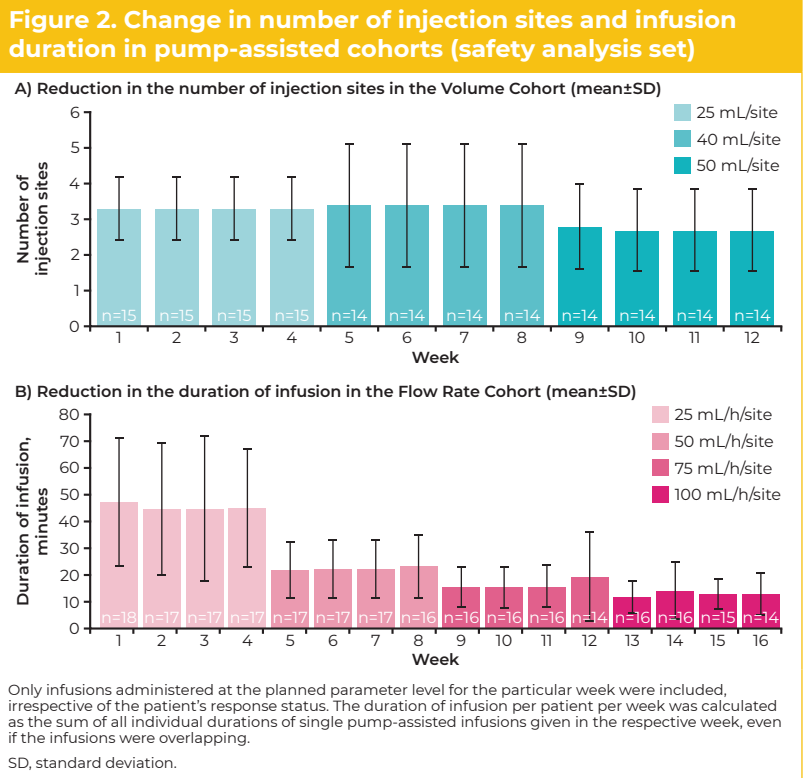
- Volume Cohort: 15 patients were included, of whom 14 completed the study; 1 patient discontinued because of a TEAE at the 25-mL level
- Flow Rate Cohort: 18 patients were included, of whom 17 completed the study; 1 patient was withdrawn at the 25-mL/h level
- Patient baseline demographics are reported in **Poster 097**

Responder analysis

- Volume Cohort: responder rates were 86.7% at the 25-mL level and 73.3% at both 40-mL and 50-mL levels (**Figure 1A**)
- Flow Rate Cohort: responder rates were 77.8% at the 25-mL/h and 50-mL/h levels, 66.7% at the 75-mL/h level, and 61.1% at the 100-mL/h level (**Figure 1B**)



- High infusion parameters reduced the number of injection sites or infusion time during the study compared with Week 1 (**Figure 2**)



- Infusion compliance rates were ≥90% for all patients in the Volume Cohort and for 83.3% of patients in the Flow Rate Cohort, with overall compliance of <90% in 3 patients (**Table 1**)

Table 1. Infusion compliance (safety analysis set)

Volume Cohort	25 mL/site (N=15)	40 mL/site (N=12)	50 mL/site (N=11)
Overall compliance (administered dose/planned dose, %)			
Mean (SD)	100.33 (1.16)	100.41 (1.30)	100.42 (1.36)
Median (min, max)	100.00 (99.8, 104.5)	100.05 (99.8, 104.5)	100.0 (99.8, 104.5)
Compliance level, n (%)			
<90%	0	0	0
≥90%	15 (100.0)	12 (100.0)	11 (100.0)

Flow Rate Cohort	25 mL/h/site (N=18)	50 mL/h/site (N=14)	75 mL/h/site (N=13)	100 mL/h/site (N=12)
Overall compliance (administered dose/planned dose, %)				
Mean (SD)	97.32 (10.69)	98.13 (6.75)	95.98 (8.79)	98.47 (16.82)
Median (min, max)	100.00 (54.5, 100.3)	100.00 (74.7, 100.3)	100.00 (75.0, 100.4)	100.00 (50.1, 124.7)
Compliance level, n (%)				
<90%	1 (5.6)	1 (7.1)	2 (15.4)	1 (8.3)
≥90%	17 (94.4)	13 (92.9)	11 (84.6)	11 (91.7)

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

Tolerability of high infusion parameters

- Volume Cohort: 100% for all volume levels
- Flow Rate Cohort: 100% for 25 mL/h, 50 mL/h, and 75 mL/h and 98% for 100 mL/h
 - One 6-year-old patient experienced a severe TEAE (injection site pain) immediately after starting an infusion at 100 mL/h; the TEAE resolved within 3 hours

Safety under forced upward titration conditions

- Volume Cohort: the overall TEAE rate per infusion was 0.138 (0.079 for related TEAEs; **Table 2**)
- Flow Rate Cohort: the overall TEAE rate per infusion was 0.216 (0.158 for related TEAEs; **Table 2**)
- The most common TEAEs in both cohorts were injection site pain, injection site erythema, and injection site swelling
- No deaths or serious adverse events were reported in either cohort
- Overall safety and tolerability are reported in **Poster 097**

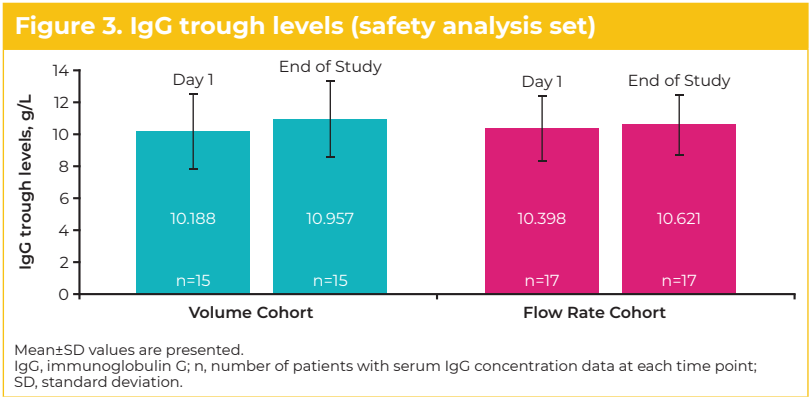
Table 2. Summary of TEAEs under forced upward titration conditions (safety analysis set)^a

	Volume Cohort (N=15; Inf=152)		Flow Rate Cohort (N=18; Inf=222)	
	n (%)	E (rate)	n (%)	E (rate)
Any TEAE	7 (46.7)	21 (0.138)	12 (66.7)	48 (0.216)
Treatment-related	4 (26.7)	12 (0.079)	8 (44.4)	35 (0.158)
Intensity of TEAEs				
Mild	5 (33.3)	16 (0.105)	10 (55.6)	38 (0.171)
Moderate	4 (26.7)	5 (0.033)	5 (27.8)	8 (0.036)
Severe	0	0	1 ^b (5.6)	2 (0.009)
Serious TEAEs	0	0	0	0
Deaths	0	0	0	0
Study discontinuation due to TEAE	1 ^c (6.7)	1 (0.007)	0	0
Treatment-related	1 ^c (6.7)	1 (0.007)	0	0
Study drug withdrawal due to TEAE	1 (6.7)	2 (0.013)	0	0
Treatment-related	1 (6.7)	2 (0.013)	0	0
Local TEAEs	4 (26.7)	12 (0.079)	8 (44.4)	31 (0.140)
Treatment-related	4 (26.7)	12 (0.079)	8 (44.4)	29 (0.131)

Rate=number of events/total number of infusions prior to patient's start date of non-response.
^aIncludes only events that occurred prior to patient's non-response; ^b1 patient reported 2 severe, related TEAEs (injection site pain and gait inability), which resolved within 24 hours; ^c1 patient discontinued because of a mild, related TEAE (injection site pain) after completing the 25-mL level.
E, number of events; TEAE, treatment-emergent adverse event.

Serum IgG trough levels

- Serum IgG trough levels (g/L) were similar between Day 1 and end of the study in both the Volume Cohort and Flow Rate Cohort (**Figure 3**)



Conclusions

- IgPro20 infusion volumes of up to 50 mL/injection site and flow rates of up to 100 mL/h/injection site were tolerated well in ≥98% of treatment-experienced patients with PID
- Responder rates exceeded the prespecified success criterion in both pump cohorts
- Increasing the infusion parameters did not negatively impact the tolerability of IgPro20

References

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