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

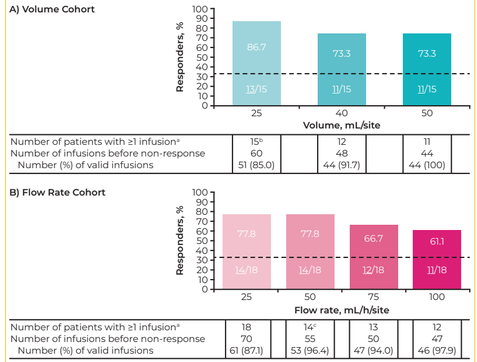
Patient disposition and demographics

- 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**)

Figure 1. Responder analysis (safety analysis set)

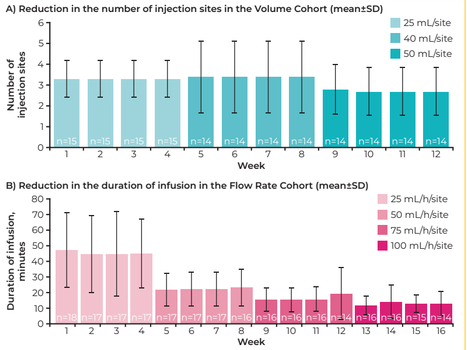


Safety analysis set included all patients who received ≥1 dose or a partial dose of IgPro20 in the study. Data labels indicate percentage of responders. Dashed line in the figure indicates ≥33% prespecified success criterion. Underlined numbers in the bars indicate the number of responders at a particular level.

[a]Before start date of non-response; [b]1 patient discontinued after completing the 25-mL volume level owing to a related TEAE of injection site pain. This patient fulfilled the criteria for 3 valid infusions, and data up to the discontinuation were included in the analysis; [c]1 patient had 3 valid infusions at the 50-mL/h flow rate level but returned to the 25-mL/h level owing to poor tolerability without trying the 75-mL/h level. This patient was classified as responder for the 50-mL/h flow rate level.

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

Figure 2. Change in number of injection sites and infusion duration in pump-assisted cohorts (safety analysis set)



Only infusions administered at the planned parameter level for the particular week were included, irrespective of the patient's response status. The duration of infusion per patient per week was calculated as the sum of all individual durations of single pump-assisted infusions given in the respective week, even if the infusions were overlapping.

SD, standard deviation.

- 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]

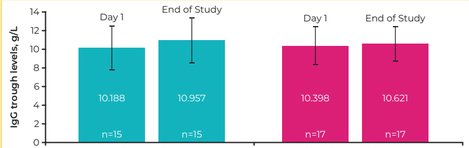
	Volume Cohort (N=15; Inf=152)		Flow Rate Cohort (N=18; Inf=222)	
	n (%)	E (rate)	n (%)	E (rate)
Any TEAE	7 (46.7)	21 (0.138)	12 (66.7)	48 (0.216)
Treatment-related	4 (26.7)	12 (0.079)	8 (44.4)	35 (0.158)
Intensity of TEAEs				
Mild	5 (33.3)	16 (0.105)	10 (55.6)	38 (0.171)
Moderate	4 (26.7)	5 (0.033)	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.
[a]Includes only events that occurred prior to patient's non-response; [b]1 patient reported 2 severe, related TEAEs (injection site pain and gait inability), which resolved within 24 hours; [c]1 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**)

Figure 3. IgG trough levels (safety analysis set)



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

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

1. Jolles S, et al. Adv Ther 2011;28(7):521.
2. CSL Behring. HIZENTRA®, Immune Globulin Subcutaneous (Human), 20% Liquid. US Prescribing Information, March 2018.
3. CSL Behring. HIZENTRA®, Immune Globulin Subcutaneous (Human), 20% Liquid. EU Summary of Product Characteristics, August 2019.

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