

Abstract

Introduction: A new formulation of immunoglobulin (Ig) was recently approved as a 20% ready-to-use liquid stabilized with L-proline (Hizentra®, CSL Behring) for subcutaneous (SC) infusion to treat subjects with primary immunodeficiency disease (PID). Local tolerability of SC infusions is important for long-term adherence to therapy.

Objective: To describe the local tolerability of Hizentra infusions as assessed by reports of injection-site reactions (ISRs) occurring during a pivotal clinical trial.

Methods: Subjects (N=49) aged 2–75 years received once-weekly SC infusions for up to 66 weeks (12-week baseline wash-in/wash-out + 12-month efficacy period) in a prospective, open-label, multicenter, single-arm, phase 3, efficacy and safety study (NCT00419341). Tolerability was assessed by evaluating ISRs. Individual symptoms of induration/edema, erythema, local heat, local pain, and itching were specifically assessed by investigators 15 to 45 minutes after the end of each clinic-based infusion. In addition, overall assessment of ISRs was done by subjects 24±3 hours after the end of each infusion. Intensity was scored as none=0, very slight=1, well-defined/slight=2, moderate=3 (moderate-severe=3 for erythema), and severe=4.

Results: Subjects received a total of 2264 Hizentra infusions. Although all subjects experienced ≥1 ISR during the study, 99.7% of ISRs were mild or moderate. Median time to onset of these reactions was 3.7 hours after the start of infusion and median duration was 1.5 days. Rates of ISRs assessed by investigators during the study were variable; the overall reaction incidence was ~75%, with reactions other than edema or erythema reported infrequently. For subject-reported ISRs, the overall rate was lower (~40%) and diminished over the duration of the study. Differences are most likely attributed to differences in the reporting period (15–45 min vs 24±3 h after infusion), different assessment criteria, and acclimation of subjects with repeat infusions. As expected for these volumes per injection site (15–25 mL), edema/induration and erythema were observed. Median edema/induration surface area, measured over the course of the study, ranged from 10.8 to 25.1 cm² (1.7–3.9 inches²). When present, all erythema ISRs were evaluated by investigators as “very slight” or “well defined.” The severity of ISR symptoms of heat, itching, and pain was described as none, slight, or very slight; no severe instances were noted. One subject withdrew because of severe ISRs (urticaria) that resolved after treatment with acetaminophen, prednisone, and hydroxyzine.

Conclusions: Typical of SCIG infusion, Hizentra infusion in subjects with PID was associated with ISRs, the majority of which were mild, with only 1 case leading to discontinuation. ISRs shortly following infusion appear to decrease with time and subsequent infusions. The ~50% difference in ISR rates reported by investigators compared with subjects suggests that the majority of reactions resolve within 24 hours. These data indicate that long-term SC administration of Hizentra is well tolerated.

Introduction

- Primary immunodeficiency diseases (PIDs) predispose patients to recurrent infections and require immunoglobulin (Ig) replacement therapy.¹
- Intravenous Ig (IVIg) is the most commonly used Ig replacement therapy in the United States, but adverse events (AEs), including headache and malaise, and the need for venous access, may be problematic for some patients.¹⁻³
- Subcutaneous Ig (SCIG) is an alternative to IVIg that is the preferred treatment in parts of Europe and has several advantages over IVIg.⁴
 - Self-administration at home
 - More uniform IgG levels^{4,5}
 - Low risk of systemic AEs^{1,2,5}
- The reported incidence of injection-site reactions (ISRs) after SCIG treatment varies widely among trials (44.7%–100%)^{6,7} possibly due to the lack of standard terminology for ISRs (ie, local tissue reactions, infusion-site reactions, local reactions, etc⁶⁻⁹), methods, time points, and evaluation scales.
 - Terminology and methods of assessing ISRs (ie, investigator vs subject, timing of assessment) are usually not well defined in publications, making it difficult to compare products based on their pivotal trials.⁸⁻⁸
 - Regulatory agency recommendations for defining local tolerability for IgG products do not currently exist.

- Hizentra is a 20% liquid SCIG product manufactured from human plasma and stabilized with L-proline.⁵
- Increased Ig concentration of Hizentra compared with lower concentration products allows for lower infusion volumes and potentially shorter infusion times. However, ensuring local tolerability is an important consideration for patients and health care providers.

Objective

- To describe the local tolerability of Hizentra infusions as assessed by clearly defined ISRs within a pivotal clinical trial

Methods

Study Design

- Prospective, open-label, multicenter, single-arm study of Hizentra SCIG therapy in subjects with PID who were previously on IVIg therapy
- The study consisted of a 12-week wash-in/wash-out period followed by a 12-month efficacy period.
 - Study visits occurred every 4 weeks for investigator assessments.
 - Hizentra infusions were predominantly home-based and performed by the subject after a training period at the study site.
 - Each infusion was performed using Cane Crono PCA-50 infusion pumps (Cane S.R.L., Turin, Italy) in up to 4 sites simultaneously (abdomen, thigh, upper arm, and/or lateral hip).
 - A bifurcated 27 gauge x 9-mm needle was used for every subject.
 - The initial volume per injection site was 15 mL and could be increased to a maximum of 25 mL per site after the fourth infusion, depending on patient tolerability.
- This study was conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki (1996). The study was conducted under an institutional review board reviewed and approved protocol with each subject (or parent/legal guardian) providing written informed consent.

Key Inclusion/Exclusion Criteria

- Subjects allowed to enter the study were males and females, 2–75 years of age, with either common variable immunodeficiency (CVID) or X-linked agammaglobulinemia (XLA) who had previously received IVIg therapy at regular 3- or 4-week intervals for at least 3 months prior to the study.
- Subjects were excluded if they were newly diagnosed with PID and had not received previous IVIg treatment.
- Additional exclusion criteria included hyperproliferation, hypoalbuminemia, protein-losing enteropathies, or proteinuria.

Local Tolerability of Subcutaneous Infusions With 20% Immunoglobulin: Results From a Phase 3 Study in Subjects With Primary Immunodeficiency

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Assessments

- Efficacy assessments have been previously published.⁸
- Injection-Site Reactions
 - Subjects rated and recorded their overall perception of ISRs as none, very slight, slight, moderate, or severe at 24±3 hours post-infusion in a daily diary.
 - Investigators assessed ISRs during each study visit at 15–45 minutes post-infusion for the following parameters:
 - For multiple injection sites, every site was judged but only the site with the strongest reaction was recorded.
 - Erythema was scored on a 5-point scale (none, very slight, well-defined, moderate to severe, and severe to slight eschar formation).
 - Edema/induration was determined by measuring the smallest and the largest diameter in millimeters and the surface area (S) calculated as $S = \frac{1}{4}ab$, where a and b are the smallest and greatest diameters, respectively.
 - Itching, local pain, and local heat were scored as none, very slight, slight, moderate, or severe.
 - Time to onset and duration of ISRs were provided from the aggregated (subject and investigator assessed) data.
- Adverse Events
 - AEs and their intensity were documented.
 - ISRs reported by the subjects and assessed by the investigator were aggregated to comprise ISR AEs; any assessment of an ISR other than “none” was automatically entered as an AE.
 - All symptoms of ISRs entered at the same time (if there was >1 symptom) were qualified as 1 ISR AE.

Statistical Analyses

- ISR analyses were conducted on the intention-to-treat population.
- Descriptive statistics were applied to continuous variables.
- Subgroup analyses of ISR AE rates by dose, age, and infusion rate were conducted.

Results

Subjects and Infusions

- Subject demographics are listed in **Table 1**. The majority of subjects were white, female, and 16–64 years of age, with a diagnosis of CVID.

Table 1. Subject Demographics

Parameter	ITT Population (N=49)
Sex, n (%)	
Female	27 (55.1)
Male	22 (44.9)
Age Group, n (%)	
2-<12 y	3 (6.1)
12-<16 y	7 (14.3)
16-<65 y	33 (67.3)
≥65 y	6 (12.2)
Race, n (%)	
White	46 (93.9)
Black	3 (6.1)
Ethnic Group, n (%)	
Hispanic or Latino	6 (12.2)
Mean weight (SD), kg	67.3 (21.24)
Primary Immunodeficiency, n (%)	
CVID	46 (93.9)
XLA	3 (6.1)

- A total of 2264 infusions of Hizentra were self-administered during the course of the study; 683 of them were self-administered by study subjects under the observation of study site personnel in the clinic during the required scheduled study visits.
- The mean individual weekly dose was 181.5 mg/kg during the wash-in/wash-out period and 213.2 mg/kg during the efficacy period, corresponding with 130% and 153% of previous IVIg doses, respectively.
- The mean (SD) infusion rate was 37.6 (13.5) mL/h and the median was 50 mL/h (total rate using ≤2 pumps in ≤4 infusion sites); median duration of infusion was 2 hours.

Subject and Investigator-Assessed ISRs

- All subjects experienced ≥1 ISR during the study.
- Overall median onset of ISRs was 3.7 hours from the start of infusion and the median duration was 1.5 days.
 - Onset and duration were not affected by infusion rate (**Table 2**).

Table 2. Onset and Duration of ISRs According to Infusion Rate*

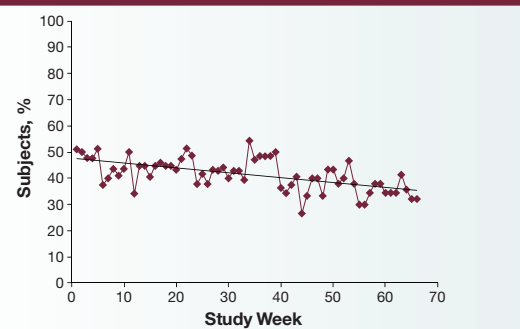
Median Infusion Rate, mL/h	Median Time to Onset of ISR, h (# of Infusions)	Median Duration of ISR, d (# of Infusions)
15–25	3.7 (561)	1.4 (252)
>25	3.8 (719)	1.5 (427)

ISR=injection-site reaction.
*1 subject received infusion at a rate <15 mL/h. Median time to onset of ISR was 1.9 hours; duration was not determined.

Subject-Reported ISRs

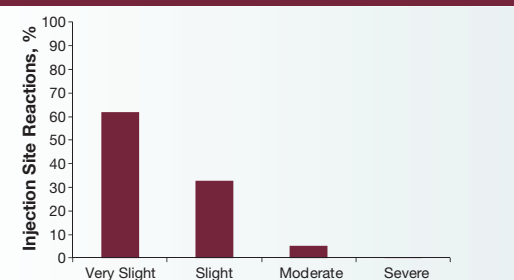
- Subjects reported an ISR for 41.9% of all infusions.
- The overall rate of subject-reported ISRs diminished over time (**Figure 1**).
- Of all subject-reported ISRs, 62.1%, 32.8%, 5.1%, and 0.1% were assessed as very slight, slight, moderate, and severe, respectively. Thus, 94.9% were assessed as very slight or slight (**Figure 2**).

Figure 1. Percentage of Subjects Reporting ISRs by Study Week



ISR=injection-site reaction.

Figure 2. Overall Severity of Subject-Reported ISRs



ISR=injection-site reaction.

Investigator-Assessed ISRs

- The rates of investigator-assessed ISRs are listed in **Table 3**.

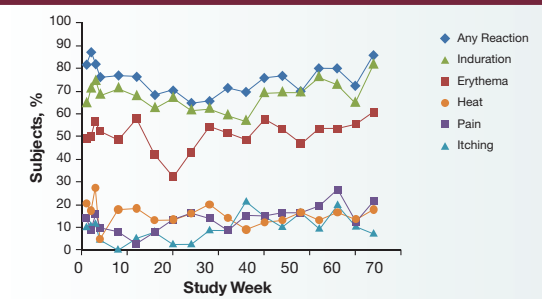
Table 3. Investigator Assessments* of ISRs by Infusion

Injection-Site Reaction	No.† (Rate)‡ of AEs (Infusions N=683§)
Any	516 (0.75)¶
Edema/induration	467 (0.68)
Erythema	346 (0.50)
Local heat	108 (0.16)
Local pain	88 (0.13)
Itching	64 (0.09)

AE=adverse event; ISR=injection-site reaction.
*Evaluated 15–45 minutes after the end of infusions.
†For multiple injection sites, every site was judged but only the site with the strongest reaction was recorded.
‡Rate of injection-site reactions per infusion.
§Number of infusions administered during regularly scheduled visits (every 4 weeks).
¶Subjects may have experienced more than 1 symptom of ISR; therefore, individual symptoms add up to more than “Any.”

- Overall, investigator-assessed ISRs occurred in 75.5% of infusions.
- Investigator-assessed ISRs did not show the same decrease during the study as compared with subject-reported ISRs, but remained stable and did not increase with time (**Figure 3**).

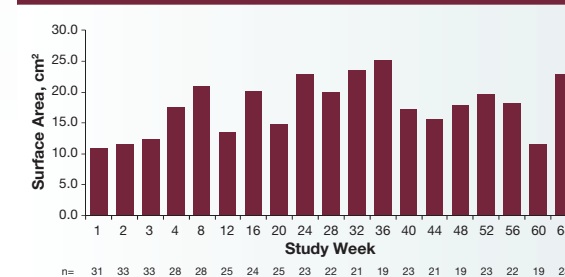
Figure 3. Percentage of Subjects With Investigator-Assessed ISRs by Study Week



ISR=injection-site reaction.

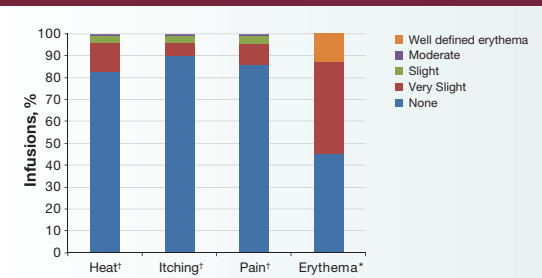
- Induration/edema and erythema were the most common individual symptoms, occurring in 68.4% and 50.7% of infusions, respectively.
 - Median surface area of edemas/indurations ranged from 10.8 to 25.1 cm² (1.7–3.9 inches²; **Figure 4**).
 - The median surface area increased after the first 3 weeks as the maximum infusion volume increased from 15 to 25 mL.
 - Most instances of erythema were scored as very slight or well-defined in severity (**Figure 5**).
 - Heat (15.8% of infusions), pain (12.9%), and itching (9.4%) were infrequent, and usually very slight or slight in severity (**Table 3** and **Figure 5**).

Figure 4. Median Investigator-Assessed Induration/Edema Surface Area



ISR=injection-site reaction.

Figure 5. Severity of Investigator-Assessed ISRs



ISR=injection-site reaction.*Investigator-assessed. None were assessed as severe.
†Assessed by questioning the subject during study visits. There were no erythema assessed as moderate to severe, or severe to slight eschar formations.

ISRs by Subgroup

- The rate of ISRs captured as AEs (comprising both investigator and subject-reported) was assessed for various treatment and demographic subgroups (**Table 4**).
 - The incidence and rate of ISRs were not affected by the infusion rate.
 - The ISR rates per infusion were comparable in the 100–150 mg/kg dose group and the >150 mg/kg dose group.
 - ISR rates by age were higher in the 2–11-year-olds compared with older age groups.

Table 4. Injection-Site Reactions Experienced by Patients According to Age and Treatment Delivery Characteristics

Treatment Delivery Characteristic	Total No. of Infusions	No. (Rate) of Infusions Resulting in Injection-Site Reactions
Any	2264	1314 (0.580)
Dose, mg/kg		
<100	118	70 (0.593)
100–150	423	235 (0.556)
>150	1703	1003 (0.589)
Unknown	20	6 (0.300)
Median infusion rate, mL/h*		
<15	1	1 (1.000)
15–25	913	572 (0.627)
>25	1331	736 (0.553)
Unknown	19	5 (0.263)
Age, y		
2–11	194	150 (0.773)
12–15	188	90 (0.479)
16–64	1637	955 (0.583)
≥65	245	119 (0.486)

*Total rate using ≤2 pumps in ≤4 infusion sites.

Discontinuation Due to ISRs

- One subject experienced a severe ISR that resulted in discontinuation from the study. The ISR was consistent with large urticaria and resolved after treatment with acetaminophen, prednisone, and hydroxyzine.

Discussion

- The discrepancy between subject-reported and investigator-assessed ISR rate may be due to differences in local reaction resolution at the time of assessment (24±3 h vs 15–45 min), different assessment criteria, and acclimation of subjects with repeat infusions.
- The difference in ISR rate in the age group 2–11 years of age may be due to the small number of subjects in this group (n=3) or the amount of subcutaneous tissue.
- It is important that health care providers and patients understand that ISRs are expected with SCIG infusions and are generally short in duration and predominantly mild in nature.
 - Infusion technique, site, and rate can be adjusted to maximize tolerability.⁹

Conclusions

- Nearly all ISRs (94.9%) reported by subjects or investigators were deemed to be very slight or slight in intensity. No ISRs were assessed as severe.
- No differences in ISRs were evident based on the infusion rate or the dose administered.
- The ~50% difference in ISR rates reported by investigators compared with those reported by subjects suggests that the majority of reactions resolve within 24 hours.
- Long-term weekly SC administration (up to 66 weeks) of Hizentra at a mean dose of 213.2 mg/kg body weight and a maximum infusion rate of 25 mL/h per site was well tolerated.

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