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Long-term efficacy, safety, and tolerability of Hizentra® for treatment of primary immunodeficiency disease

Stephen Jolles[a,*], Michael Borte[b], Robert P. Nelson Jr.[c], Mikhail Rojavin[d], Martin Bexon[e], John-Philip Lawo[f], Richard L. Wasserman[g]

[a] University Hospital of Wales, Cardiff, UK
[b] Hospital St. Georg GmbH Leipzig, Academic Teaching Hospital of the University of Leipzig, Leipzig, Germany
[c] Indiana University School of Medicine and the IU-Simon Cancer Center, Indianapolis, IN, USA
[d] CSL Behring, LLC, King of Prussia, PA, USA
[e] CSL Behring AG, Berne, Switzerland
[f] CSL Behring, Marburg, Germany
[g] Medical City Children's Hospital, Dallas, TX, USA

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Abstract Hizentra® (20% subcutaneous immunoglobulin [SCIG]) was administered to subjects with primary immunodeficiency disease in two extension studies in the EU and US to assess long-term efficacy and tolerability. Subjects (aged 4–69 years) were treated for 148 weeks in the EU (N = 40; 5405 infusions) and 87 weeks in the US (N = 21; 1735 infusions). Weekly doses were 116.0 mg/kg (EU) and 193.2 mg/kg (US); IgG levels were 7.97 g/L (EU) and 11.98 g/L (US). Annualized rates of serious bacterial infections were 0.05 infections/subject/year (EU) and 0.06 infections/subject/year (US). Rates of any infection were 3.33 infections/subject/year (EU) and 2.38 infections/subject/year (US). The rate of bronchopulmonary infections was higher in the EU study. No treatment-related serious AEs occurred; no subject discontinued because of treatment-related AEs. Self-administered Hizentra afforded sustained effective protection from infections and favorable tolerability during an extended treatment period of up to 3 years.

* Corresponding author at: Department of Immunology, University Hospital of Wales, Heath Park, Cardiff CF14 4XW, UK. Fax: +44 29 2074 8383.
E-mail addresses: jollessr@cardiff.ac.uk (S. Jolles), Michael.Borte@sanktgeorg.de (M. Borte), ronelson@iu.edu (R.P. Nelson), Mikhail.Rojavin@cslbehring.com (M. Rojavin), Martin.Bexon@cslbehring.com (M. Bexon), John-Philip.Lawo@cslbehring.com (J.-P. Lawo), drrichwasserman@gmail.com (R.L. Wasserman).

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1. Introduction

Primary immunodeficiency disease (PIDD) is a group of more than 200 inherited disorders in which patients are predisposed to recurrent infections, autoimmune disease, and malignancy [1,2]. Some of the most common forms of PIDD are associated with deficient antibody production capacity and include common variable immunodeficiency disease (CVID) and X-linked agammaglobulinemia (XLA). The mainstay of treatment for patients with antibody deficiency is lifelong treatment with immunoglobulin (Ig) replacement therapy, which is known to reduce the risk of infections and their sequelae [3]. Although the administration of IgG via the intravenous route (IVIG) has been the predominant treatment for the past 25 years, patients are increasingly receiving treatment via the subcutaneous route (SCIG) for reasons of fewer systemic side effects, improved adherence, manageable self-administration, or personal choice [4–7]. SCIG is absorbed more slowly into the bloodstream and is given more frequently than IVIG; thus, a less variable steady-state IgG level is maintained, which eliminates the peaks and troughs that occur with monthly IVIG therapy [7]. Maintenance of steady-state Ig levels may reduce the "wear-off" effects that have been reported toward the end of an IVIG dosing cycle [3,6,8].

Hizentra® (CSL Behring, King of Prussia, PA), a 20% Ig replacement product specifically formulated for lower-volume subcutaneous administration (compared with 10% and 16% Ig products), was assessed in 2 pivotal clinical trials in the European Union (N = 51) and in the United States (N = 49) [9,10]. These trials, which lasted more than 40 weeks and 60 weeks, respectively, demonstrated the safety and efficacy of Hizentra. Patients with genetic defects resulting in PIDD usually require Ig replacement therapy throughout their lifetime; therefore, long-term studies are necessary to establish that protection from infections can be sustained. In addition, long-term studies are needed to demonstrate that repeated self-administration of SCIG, often with multiple infusion sites, remains acceptable, practical, and well tolerated for patients over extended periods. Currently, published studies of Ig products approved for subcutaneous use report efficacy and safety for up to 15 months only [9–12]. Consequently, the long-term efficacy, safety, and tolerability of Hizentra were examined in 2 extension studies that collected data from subjects who took part in the aforementioned EU and US pivotal studies, for a treatment duration of up to 3 years (ClinicalTrials.gov identifiers: NCT00751621 [EU], NCT00719680 [US]).

2. Subjects and methods

2.1. Subjects

Subjects who had enrolled in the preceding pivotal studies of Hizentra conducted in the European Union and the United States [9,10] were offered the opportunity to participate in the extension studies. Subjects in both extension studies had either CVID or XLA as defined by the Pan-American Group for Immunodeficiency and the European Society for Immunodeficiency [13]. Subjects with autosomal recessive agammaglobulinemia (ARAG) were also eligible for the EU extension study. Subjects in both extension studies were excluded if they had hypoalbuminemia, protein-losing enteropathies, or proteinuria. The US extension study also excluded subjects with an ongoing serious bacterial infection (SBI) at the time of screening.

The extension studies were conducted in accordance with the International Conference on Harmonisation, Good Clinical Practice guidelines, and the Declaration of Helsinki (1996 version). Study protocols and informed consent documents were reviewed and approved by the appropriate institutional review boards or independent ethics committees. Written informed consent was obtained for each subject.

2.2. Study design

These were prospective, open-label, single-arm, phase 3 extension studies in the European Union (13 sites, between August 2008 and December 2011) and the United States (4 sites, between June 2008 and June 2010) in patients with PIDD who had previously been treated with Hizentra in pivotal studies [9,10]. Starting doses of Hizentra were the same as the last dose for each subject in the preceding pivotal study and could be adjusted if medically indicated or if a subject's weight changed by more than ±5% at any time during the study. In addition, doses in the US study could be adjusted if the trough level fell outside individual limits carried over from the pivotal study. Subjects in the EU study were allowed to have their weekly dose distributed over several days, whereas in the US study, doses were given once or twice per week according to subject preference and the clinical judgment of the investigator. Regardless of dosing frequency, the total weekly dose remained unchanged. The studies were planned to continue until the product became commercially available.

The number of injection sites for each subject was determined by the total volume to be administered. The initial volume per injection site was equal to that administered at the subject's last infusion during the pivotal study but could be increased to a maximum of 40 mL/site if preferred by the subject or recommended by the investigator. The initial infusion rate was the same as the rate of last administration of the pivotal studies and could be increased to a maximum total infusion rate of 35 mL/h in the EU extension study or 70 mL/h in the US extension study (if using 2 pumps simultaneously), depending on the subject's tolerability and investigator recommendation. Training in self-administration of Hizentra was conducted during the pivotal trial; retraining could be conducted if necessary.

Premedications such as prophylaxis against infusion reactions on the day of infusion were not permitted. Oral and parenteral steroids were permitted in the US extension study if the average daily dose was <0.15 mg of prednisone equivalent/kg per day.

2.3. Efficacy and safety assessments

The annual rate of SBIs was assessed in both studies (as defined by the US Food and Drug Administration [FDA]: bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, visceral abscess [14]). Additional efficacy outcomes captured from subject diaries included the number of any infectious episodes

("infection" designated at the discretion of the investigators); the number of days missed from work/school/kindergarten/day care or unable to perform normal daily activities due to infections; the number of days of infection-related hospitalization; and the number of days of antibiotic usage for infection prophylaxis and treatment. Total serum and selected specific IgG levels for bacterial and viral pathogens were measured prior to infusion at the first visit and then at months 6, 12, 18, 24, 30, 36, and 42 in the EU study, while only total serum IgG levels were measured in the US study at the first visit and at weeks 24, 48, 72, 96, and 120 (Table S1).

Safety evaluation included assessment of adverse events (AEs) and local tolerability. A schedule of safety evaluations is shown in Table S1. In both extension studies, local tolerability was evaluated by subjects, and comments were recorded in diaries. Injection sites in the US extension study were assessed by subjects 24 ± 3 h following every Hizentra administration and reactions were classified as none, very slight, slight, moderate, or severe. In addition, local reactions could be reported via standard AE reporting methods at any time during the study. No specific time point for assessment of local reactions was designated in the EU extension study; however, local reactions were identified manually from AE listings during each study visit. "Local reaction" included, but was not limited to, infusion-site edema, infusion-site reaction, injection-site pain, injection-site rash, and injection-site reaction. Systemic AEs were recorded by subjects and observed by investigators at study visits. Vital signs were evaluated at screening and before and after each infusion at the study site during both studies (Table S1). Routine laboratory parameters were determined pre-infusion at visits 3, 5, 7, 9, 11, 13, and 15 and completion visit of the EU study and at weeks 1, 24, 48, 72, 96, and 120 and the completion visit of the US study (Table S1).

2.4. Statistical methodology

Sample size for the extension studies was determined by the number of subjects agreeing to continue from the respective short-term pivotal studies. Efficacy analysis in the EU extension study was performed in the all-treated (AT) population (all subjects treated with Hizentra), and in the US extension study, efficacy was assessed in the intent-to-treat (ITT; all subjects treated with Hizentra for whom any efficacy data was available) and per-protocol efficacy (PPE; all subjects who completed $\geq$48 weeks of the efficacy period that started with the first Hizentra dose in this study) populations. The results of the PPE analysis were similar to those of the ITT analysis and are not presented here. Safety assessment was performed in the AT population in both extension studies. The annualized rate of SBIs was calculated along with the upper 1-sided 99% confidence limit (CL) using a chi-square distribution. No imputation was made for subjects who discontinued the study. The annualized rate of all infections was calculated with a 2-sided 95% confidence interval (CI). Annualized rates and descriptive statistics were calculated for days missed from school/work/kindergarten/day care, days hospitalized, and days of antibiotic use. Serum IgG levels were analyzed using descriptive statistics. Bronchopulmonary AE rates, including the preferred terms bronchitis, bronchitis acute, bronchitis bacterial, bronchitis chronic, bronchitis pneumococcal, bronchitis viral, influenza, mycoplasma infection, pneumonia, pneumonia bacterial, productive cough, pulmonary tuberculosis, and tracheitis, were analyzed and compared between studies post hoc using a 95% CI for the difference of exposure-adjusted rates [15]. To assess potential enrollment bias based on tolerability, rates per infusion were compared post hoc using a Wilcoxon test between subjects who did and did not enter the US extension study from the pivotal trial.

3. Results

3.1. Subjects

Baseline characteristics for subjects in both extension studies are presented in Table 1. In the EU extension study, 40 of 43 subjects who completed the pivotal study were screened, enrolled, and treated with Hizentra. All 40 subjects were included in the efficacy analysis. Four subjects discontinued during the study (1 non-treatment-related death, 1 withdrew consent, 1 moved to another country, and 1 was excluded for lack of adherence to anti-inflammatory therapy for asthma) and 36 (90%) completed the study. The mean age of subjects was 21.6 years and the study included 15 children (37.5%) and 4 adolescents (10.0%). Most subjects (57.5%) had CVID, 40.0% had XLA, and 1 had ARAG. The median disease duration at enrollment was 6 years.

In the US extension study, 21 of 28 subjects who completed the pivotal study were screened, enrolled, and treated with Hizentra. All 21 subjects were included in the efficacy analysis. In a post hoc analysis to determine enrollment bias, there was no difference in AE rates between the 7 subjects who

Table 1 Demographic and baseline characteristics at enrollment into the extension study.

Characteristic	EU study (N = 40)	US study (N = 21)
Gender, n (%)		
Female	12 (30.0)	15 (71.4)
Male	28 (70.0)	6 (28.6)
Age (years)		
Mean (SD)	21.6 (15.31)	42.4 (18.53)
Median (range)	16.0 (4–52)	42.0 (11–69)
Age group, n (%)		
2 to <12 years	15 (37.5)	1 (4.8)
12 to <16 years	4 (10.0)	1 (4.8)
16 to <65 years	21 (52.5)	16 (76.2)
≥65 years	0	3 (14.3)
Race, n (%)		
White	40 (100)	21 (100)
Body mass index (kg/m^2)		
Mean (SD)	20.5 (4.67)	26.4 (6.46)
Median (range)	20.5 (14–31)	26.2 (18–43)
Primary disease, n (%)		
CVID	23 (57.5)	21 (100)
XLA	16 (40.0)	0
ARAG	1 (2.5)	0

ARAG = autosomal recessive agammaglobulinemia; CVID = common variable immunodeficiency; SD = standard deviation; XLA = X-linked agammaglobulinemia.

discontinued after completion of the US pivotal study and the 21 subjects who continued Hizentra treatment in the US extension study (median, min–max: 0.32, 0.11–0.89 for those who discontinued and 0.65, 0.08–1.36 for those who continued; $P = 0.4175$). Five subjects discontinued during the study (3 withdrew consent, 1 was lost to follow-up, 1 discontinued because of thyroid cancer, a non-treatment-related serious AE [SAE]) and 16 subjects (76.2%) completed the study. The mean age of subjects was 42.4 years, and the study included 1 child (4.8%) and 1 adolescent (4.8%). All subjects in the US study had CVID, with a disease duration of >5 years at the time of enrollment.

3.2. Study drug administration

A total of 5405 infusions were administered in the EU study. The median of individual median doses was 116.0 mg/kg body weight. Weekly doses ranged from 54 mg/kg to 406 mg/kg. The median treatment period was 148 weeks (range, 9–166 weeks).

A total of 1735 infusions were administered in the US extension study. All subjects received weekly doses, except one subject who received 50 weekly doses divided into 2 infusions/week. The median of individual median weekly doses was 193.2 mg/kg body weight, and doses ranged from 97 mg/kg to 354 mg/kg per week. The median total infusion rate was 50 mL/h (range, 15–70 mL/h). The median treatment period was 87 weeks (range, 11–104 weeks).

3.3. Efficacy

3.3.1. EU extension study

There were 5 reported SBIs in 5 (12.5%) subjects (Table 2), which is equivalent to an annualized rate of 0.05 (upper 99% CL, 0.13) infections per subject. All SBIs were acute bacterial pneumonia and required hospitalization (thus also classified as SAEs); no subjects discontinued the study because of SBIs. One subject, a 6-year-old female, had a known ongoing history of recurrent severe pneumonia; 3 days after infusion 5 in the extension study, she developed an acute exacerbation and died of respiratory failure 41 days later. This SAE was not related to study medication.

Thirty-eight subjects (95.0%) had at least 1 infection during the study, resulting in an annualized rate of infection of 3.33 infections/subject/year (95% CI 2.99, 3.70). Bronchitis

Table 2 Efficacy outcomes, including infections occurring in ≥10% of subjects.

Endpoint	EU study AT population (N = 40)		US study ITT population (N = 21)	
	Number (%) of subjects	Number of events or days (annualized rate per subject)	Number (%) of subjects	Number of events or days (annualized rate per subject)
Serious bacterial infections [a]	5 (12.5)	5 (0.048)	2 (9.5)	2 (0.06)
[Upper 99% CL]		[0.1252]		[0.257]
All infection episodes [a]	38 (95.0)	349 (3.33)	20 (95.2)	78 (2.38)
[95% CI]		[2.993–3.703]		[1.883–2.973]
Bronchitis	21 (52.5)	51 (0.487)	5 (23.8)	7 (0.21)
Upper respiratory tract infection	18 (45.0)	49 (0.468)	6 (28.6)	6 (0.18)
Sinusitis	13 (32.5)	31 (0.296)	13 (61.9)	23 (0.70)
Cough	8 (20.0)	26 (0.248)	0	0
Nasopharyngitis	12 (30.0)	19 (0.182)	4 (19.0)	5 (0.15)
Rhinitis	9 (22.5)	15 (0.143)	0	0
Febrile infection	6 (15.0)	10 (0.096)	0	0
Pharyngitis	5 (12.5)	10 (0.096)	2 (9.5)	2 (0.06)
Acute sinusitis	5 (12.5)	5 (0.048)	0	0
Pneumonia bacterial	5 (12.5)	5 (0.048)	0	0
Viral upper respiratory tract infection	4 (10.0)	5 (0.048)	2 (9.5)	2 (0.06)
Influenza	4 (10.0)	4 (0.038)	1 (4.8)	1 (0.03)
Viral infection	4 (10.0)	4 (0.038)	2 (9.5)	4 (0.12)
Days missed from work/school/kindergarten/day care or unable to perform normal activities due to infections	27 (67.5)	706 (6.77)	9 (49.2)	140 (4.28)
Days hospitalized due to infections	7 (17.5)	110 (1.06)	2 (9.5)	18 (0.55)
Days with antibiotics for infection prophylaxis or treatment	36 (90.0)	7551 (72.13)	19 (90.5)	2746 (83.87)
Serum Ig concentration, mean (SD), g/L	7.97 (1.17)		11.98 (3.65)	

CI = confidence interval; CL = confidence limit.

[a] The total number of days in the EU study was 38,208 and in the US study was 11,950.

was the most frequently occurring infection (51 events), followed by upper respiratory tract infection (49 events), sinusitis (31 events), and cough (26 events). Twenty-seven subjects (67.5%) missed work/school, totaling 706 days (annualized rate, 6.77 days/subject). Seven subjects (17.5%) were hospitalized due to infections, totaling 110 days (annualized rate, 1.06 days/subject).

Immunoglobulin G levels were measured before each infusion every 6 months for 42 months, with mean values ranging from 7.5 to 8.8 g/L (Fig. 1). The mean (SD) of the individual median IgG values was 7.97 g/L (1.17). One subject with celiac disease had a pre-infusion IgG level <5 g/L at several visits. Mean levels of specific antibodies against *Haemophilus influenzae* B, *Streptococcus pneumoniae*, and cytomegalovirus in the EU study population were stable throughout, whereas antibody titers against measles virus and tetanus toxin declined moderately over the course of the study (data not shown).

3.3.2. US extension study

There were 2 reported SBIs in 2 subjects (9.5%; Table 2), giving an annualized rate of 0.06 (upper 99% CL, 0.26) infections per subject. Both SBIs were bacterial pneumonia. No deaths occurred.

Twenty subjects (95.2%) had at least 1 infection during the study period, amounting to an annualized rate of infection of 2.38 infections/subject/year (95% CI 1.88, 2.97). Sinusitis was the most frequently occurring infection (23 events), followed by bronchitis (7 events), and upper respiratory tract infection (6 events). Nine subjects (42.9%) missed work/school because of infection, totaling 140 days (annualized rate, 4.28 days/subject). Two subjects (9.5%) were hospitalized because of infections, totaling 18 days (annualized rate, 0.55 days/subject).

Immunoglobulin G levels were measured before each infusion every 24 weeks for 96 weeks, with mean values ranging from 11.7 to 12.8 g/L (Fig. 1). The mean (SD) of the individual median IgG values was 11.98 g/L (3.65). No subjects had an IgG level <5 g/L during the study.

3.4. Safety

3.4.1. EU extension study

The majority of AEs in this study were considered mild (370 of 506 AEs, 73.1%) or moderate (125 of 506 AEs, 24.7%) in intensity. A total of 39 subjects (97.5%) experienced at least 1 AE (Table 3). Eight subjects (20.0%) experienced AEs that were considered treatment-related by the investigator (Table 3). A total of 7 local injection-site reactions (abscess, induration, nodule, pain, pruritus, and scar) were reported in 6 subjects (15%), resulting in a rate of 0.13% per infusion; local reactions were the only treatment-related AEs occurring in ≥10% of subjects. Overall, 506 AEs were reported among a total of 5405 infusions, resulting in an AE rate of 9.4% per infusion. The most common event, excluding infections, was arthralgia (Table 4), which was not considered related to the study drug by the investigator, as it is a recognized side effect of treatment. Excluding infections, there were 195 AEs, resulting in an AE rate of 3.6% per infusion.

Eighteen SAEs occurring entirely within the time frame of the extension study were reported in 14 subjects (35.0%), none of which were considered related to the study drug (Table 3). An additional SAE began during the pivotal study and continued into the extension study. Ten of the SAEs were moderate and 2 were mild. Seven SAEs (in 5 subjects) were severe in intensity (pneumonia [n = 3], septic shock [n = 1], agranulocytosis [n = 1], diarrhea [n = 1], and dyspnea [n = 1]). Most SAEs resolved without sequelae; 2 exceptions included the subject with recurrent pneumonia described above, and a subject with transient dyspnea associated with signs of bronchiolitis obliterans and mild interstitial thickening.

No clinically relevant changes over time were observed in vital signs or median values of hematology and serum chemistry analytes. One subject, who had a history of ongoing hemolytic anemia, had a positive direct Coombs' test at screening and changes in hemoglobin, haptoglobin, and lactate dehydrogenase levels that were considered unrelated to treatment.

3.4.2. US extension study

The majority of AEs were considered mild (87.0%) or moderate (11.5%) in intensity, although all 21 subjects (100.0%) experienced at least 1 event (Table 3). Overall, 1147 AEs were reported among a total of 1735 infusions, resulting in an AE rate of 66% per infusion. The majority of events were local reactions (Table 4). Excluding infections, there were 1068 AEs, resulting in an AE rate of 62% per infusion. Excluding local reactions and infections, the most common AE was oropharyngeal pain (Table 4). The incidence of any AE per infusion was similar for the different total body infusion rates: <35 mL/h (0.703), 35 to 50 mL/h (0.680), and >50 to 70 mL/h (0.584).

Excluding local reactions, 47.6% of subjects experienced an AE that was considered treatment-related by the investigator. A total of 868 local reactions were reported in 19 subjects (90.5%), resulting in a rate of 50% per infusion (868 per 1735 infusions). Nearly all local reactions (99.3%) were assessed by subjects as "very slight" or "slight." No subjects discontinued from the extension study because of local reactions. None were considered "severe" and only 6 (0.7%) were considered "moderate."

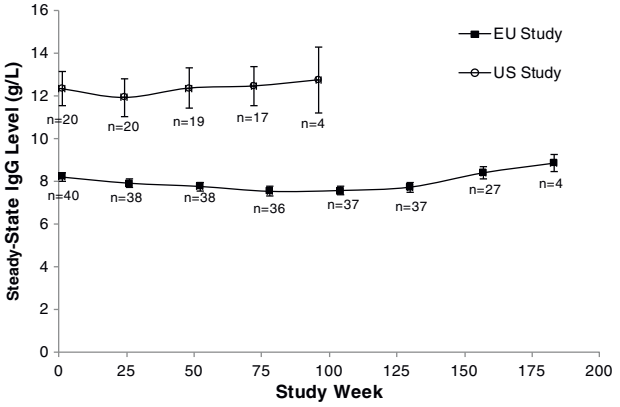

Figure 1 Mean steady-state IgG levels. Mean and standard errors of the serum IgG concentrations measured during the EU (closed squares) and US (open circles) extension studies. For the sake of comparison between the EU and US studies, visits in the EU study were converted from every 6 months to every 26 weeks (1 month = 4.35 weeks).

Table 3 Summary of subjects with adverse events and adverse event rates per infusion.

AE category	EU study		US study	
	No. (%) of subjects (N = 40)	No. (rate) of events (N = 5405)	No. (%) of subjects (N = 21)	No. (rate) of events (N = 1735)
AEs	39 (97.5)	506 (0.094)	21 (100)	1147 (0.661)
Mild AEs	39 (97.5)	370 (0.069)	21 (100)	998 (0.575)
Moderate AEs	25 (62.5)	125 (0.023)	18 (85.7)	132 (0.076)
At least possibly related AEs	8 (20.0)	14 (0.003)	21 (100)	909 (0.524)
SAEs	14 (35.0)	18 (0.003)	4 (19.0)	5 (0.003)
At least possibly related SAEs	0	0	0	0
Treatment-related AEs leading to discontinuation	0	0	0	0
AEs leading to death	1 (2.5)	1 (0.0002)	0	0

AE = adverse event; SAE = serious adverse event.

Five SAEs were reported in 4 subjects (19.0%), none of which were considered treatment-related. These SAEs were cellulitis (n = 1), pneumonia (n = 1), thyroid cancer (n = 1; 2 events, 1 of which started during the pivotal study, and the second resulted in discontinuation from the extension study), and diarrhea (n = 1). The thyroid cancer and diarrhea were considered severe, whereas the cellulitis and pneumonia were moderate in intensity. All SAEs resolved without sequelae, except for the thyroid cancer. No deaths occurred during the study.

No clinically relevant changes over time were observed in vital signs or median values of hematology and serum chemistry analytes. Seven subjects had positive direct Coombs' test results during the extension study, but none were assessed as clinically significant, and there were no indications of hemolysis in any subjects. Two of the 7 subjects also had positive Coombs' tests before the first Hizentra administration in the pivotal trial.

3.4.3. Rates of bronchopulmonary AEs

In the EU extension study, 79 bronchopulmonary AEs were reported during the 38,208 study days, resulting in an exposure adjusted rate of 0.0021. In the US extension study, 11 bronchopulmonary AEs were reported during the 11,950 study days, resulting in an exposure adjusted rate of 0.0009. The exposure-adjusted rate of bronchopulmonary AEs was statistically significantly higher in the EU extension study than in the US extension study (ratio: 2.25, 95% CI 1.21, 4.18) as determined in a post hoc analysis.

4. Discussion

The extension studies presented here support the conclusion that long-term repeated self-administration of Hizentra is effective and safe, with up to 3 years of observation in subjects with PIDD. These are the first published reports of efficacy and safety from an extension study of any SCIG product. Evidence of long-term efficacy and safety is important for all Ig products used to treat PIDD. Robust protection from infections is important to avoid long-term complications, as well as leading a full and active life. Long-term tolerability is of particular concern to those with chronic diseases such as PIDD, as treatment is expected to extend throughout a patient's lifetime. Serum IgG levels remained generally stable throughout each of these 2 extension studies, indicating that long-term, weekly subcutaneous administration of Hizentra maintains IgG at levels sufficient to prevent most SBIs [16].

The ability to capture information on SBIs was not unexpected within the time frame of these extension studies, as patients who receive adequate IgG therapy (with serum IgG levels well within the normal range) may still occasionally experience serious infections because of chronic preexisting conditions such as chronic lung disease, particularly bronchiectasis [17,18]. The observed upper 1-sided 99% confidence limits of annualized SBI rates in both extension studies were well below the accepted US FDA and European Medicines Agency threshold of 1.0 [14,19].

The combined pivotal and extension studies demonstrate the sustained activity of Hizentra in limiting the number of SBIs experienced by patients with PIDD. However, because SBIs are a relatively rare occurrence in clinical trials of SCIG therapy, the use of this outcome as a measure of treatment efficacy may not be fully reflective of the efficacy of SCIG [9–12]. Potentially useful outcomes for future study may include the rate of total infections, or the rate of specific, or types, of infections (e.g., sinopulmonary infections). The rate of any infection was slightly higher in the EU extension study (3.33 infections/subject/year) compared with the US extension study (2.38 infections/subject/year), but was lower than in the EU pivotal study (5.18 infections/subject/year). The reason for this difference in infection rates between the pivotal and extension studies may simply be that the longer observation period in the extension studies (including seasonal periods of low and high infection rates) permitted a more precise assessment, as the EU pivotal study was less than 1 year and required extrapolation to determine the annualized rate. Furthermore, the longer duration of the extension studies may have allowed the disease to stabilize in some subjects, or the pivotal study may have had a more rigorous detection process. Differences in infection rates between the 2 extension studies may be due to differences in the patient population. For example, the greater percentage of children in the EU extension study (37.5%) compared with the US extension study (4.8%), and differences in the proportion of subjects with CVID versus XLA, may be relevant to understanding the difference in infection rates. Another contributing factor may have been the difference in Hizentra doses and corresponding IgG

levels in the 2 extension studies. Although subjects in both extension studies began at the last dose of the corresponding pivotal study, the average dose conversion factors when transitioning from IVIG to SCIG in the pivotal study were 1:1 in the European Union [9] and 1:1.53 in the United States [10]. Thus, Hizentra doses were, in general, higher in the US extension study and therefore explain the higher steady-state serum IgG levels observed in the US study. Higher serum IgG concentrations during IVIG therapy have been associated with lower rates of infections [20,21], a finding which is corroborated by these 2 extension studies. However, despite the differences in IgG levels in the studies, the rate of infections converged toward that observed in the US pivotal study. Given the key impact of primary antibody deficiency on sinopulmonary infections, a post hoc analysis of the exposure-adjusted rate of bronchopulmonary AEs was performed and was found to be statistically significantly higher in the EU extension study than in the US extension study (ratio: 2.25, 95% CI 1.21, 4.18), suggesting a possible clinical benefit of higher IgG levels.

Although the rate of local site reactions was higher in the US study than in the EU study, nearly all injection-site reactions were assessed by the subject as slight or very slight and did not lead to treatment discontinuation. No single set of terms, grading scales, or mandatory evaluation time points have been established for consistent use across studies of SCIG, which points out a significant problem with definitions of AEs for studies of SCIG administration. The local site reactions experienced by the majority of subjects in the extension studies described here were expected physiological results of simply injecting fluid into the subcutaneous tissue. Therefore, differences between the rates of local site reactions in the two studies may, in part, be explained by methodological differences in the definition of a "reaction," in particular by the timing of mandatory assessment, and by the scales or terminology employed. The results presented here reiterate that local site reaction rates cannot be compared between studies unless the methods for defining local site reactions are fully described and are exactly the same. Local site reactions following administration of SCIG are typically transient and resolve within 24–72 h [10,22,23]. Infusion technique, site location, needle length, site volume, and flow rate can be adjusted to maximize tolerability [24,25]. Because Hizentra is formulated with L-proline, the viscosity of this product (14.7 mPa·s) is similar to that of the 16% Ig product (Vivaglobin®; 14.4 mPa·s) [26]. In addition, osmolality is not expected to be a causative factor in the occurrence of local site reactions [27]. For these reasons, real-world local site reactions that are troublesome or need special management may be expected to occur at lower rates than were seen in some studies.

In addition to the safety and efficacy data presented here, health-related quality of life (HRQoL) and treatment satisfaction for the US extension study were reported by Jones et al. [28]. High HRQoL levels were maintained throughout the study as measured by a number of standard and disease-specific questionnaires. All but 1 domain in the Short-Form 36 questionnaire were within US norms; General Health was lower than the average norm. For most visits, subjects scored at or within US norms in the EuroQol 5D index score. Subjects also indicated a high degree of treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication Short Form and a specific questionnaire for IgG therapy. Together, these data indicate that extended use of Hizentra is efficacious, well tolerated and helps patients maintain a high quality of life.

Potential limitations of these extension studies may include a self-selection bias of subjects who enrolled in the extension studies; patients who were doing well might have been more likely to commit to a longer observation period. The possibility that the occurrence of AEs during the pivotal studies may have, in part, determined a subject's willingness to volunteer for the extension study was examined in a post hoc analysis of safety data from the US pivotal study. This analysis indicated that there was no statistically significant difference in AE rates between those who discontinued after completion of the pivotal study and those who continued into the extension study. This suggests that an individual's decision to participate in the extension study was influenced by factors other than AE rates. Additional limitations included the lack of a testable hypothesis and the limited

Table 4 Most common adverse events, excluding infections (experienced by ≥10% of subjects).

Adverse event	EU study		US study	
	No. (%) of subjects (N = 40)	No. (rate) of events (N = 5405)	No. (%) of subjects (N = 21)	No. (rate) of events (N = 1735)
Any adverse event	39 (97.5)	506 (0.094)	21 (100)	1147 (0.661)
Local reactions [a]	6 (15.0)	7 (0.001)	19 (90.5)	868 (0.5)
Arthralgia	6 (15.0)	7 (0.001)	5 (23.8)	5 (0.003)
Abdominal pain upper	4 (10.0)	9 (0.002)	2 (9.5)	6 (0.003)
Abdominal pain	0	0	3 (14.3)	4 (0.002)
Diarrhea	4 (10.0)	6 (0.001)	3 (14.3)	4 (0.002)
Pyrexia	4 (10.0)	6 (0.001)	2 (9.5)	2 (0.001)
Back pain	3 (7.5)	3 (0.001)	3 (14.3)	10 (0.006)
Headache	2 (5.0)	6 (0.001)	3 (14.3)	10 (0.006)
Fatigue	1 (2.5)	1 (0.0002)	5 (23.8)	33 (0.019)
Oropharyngeal pain	1 (2.5)	2 (0.0004)	6 (28.6)	12 (0.007)
Anxiety	0	0	3 (14.3)	3 (0.002)
Nausea	0	0	4 (19.0)	4 (0.002)

[a] A group of preferred terms in the system organ class of "General disorders and administration site conditions."

number of subjects available for subgroup analyses. Although the number of subjects was not large, the combined number of total infusions (7140) was the most administered and assessed in any clinical trial of SCIG to date. Additional strengths of the study were the age range of the subjects and the wide geographic area encompassed.

In conclusion, the EU and US extension studies represent the longest clinical observation of any SCIG product and demonstrate the prolonged efficacy, safety, and tolerability of Hizentra in the treatment of PIDD.

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Conflict of interest statement

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