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RESEARCH ARTICLE

Long-term safety of hyaluronidase-facilitated subcutaneous immunoglobulin 10%: a European post-authorization study

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ABSTRACT

Aim: To assess the long-term safety of hyaluronidase-facilitated subcutaneous immunoglobulin (fSCIG) 10% in European routine clinical practice.

Materials & methods: This prospective, noninterventional, open-label, post-authorization safety study (EUPAS5812) sourced data on adverse events, immunogenicity, treatment regimens and product administration for 106 adult patients prescribed fSCIG 10% across 17 sites in six European countries from July 2014 to February 2020.

Results: In total, 1171 treatment-emergent adverse events were reported in 94 patients (88.7%); 25.5% of these events were considered related to fSCIG 10%. Positive binding antibody titers developed in three patients; no neutralizing antibodies to recombinant human hyaluronidase were detected.

Conclusion: This real-world study of fSCIG 10% is the longest to date and confirms its long-term safety and tolerability in adults with antibody deficiency diseases.

PLAIN LANGUAGE SUMMARY

One way that the immune system fights infection is by making proteins known as antibodies, also called immunoglobulins. In conditions known as primary immunodeficiency diseases or secondary immunodeficiency diseases, the immune system may not work properly and so treatment with immunoglobulins might be needed. This study looked at the use of an antibody treatment called hyaluronidase-facilitated subcutaneous immunoglobulin (or fSCIG) in European adults mostly with primary immunodeficiency diseases in the real world. Details of adverse events and how fSCIG was used was taken from patient medical records and other documents, and information provided by patients. Of 106 patients, 94 (88.7%) reported 1171 adverse events which started during fSCIG treatment, and 25.5% of these events were considered related to patients receiving fSCIG. For the 105 patients who had information available, 66 patients (62.9%) were treated with fSCIG every 4 weeks. The study results support that fSCIG has a beneficial safety profile in adults with primary or secondary immunodeficiency diseases.

ARTICLE HISTORY
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KEYWORDS
antibody deficiency; human; immunodeficiency diseases; immunoglobulins; inborn errors of immunity (IEI)

1. Background

Primary immunodeficiency diseases (PID), also known as inborn errors of immunity, encompass a diverse range of >480 disorders; the majority are characterized by abnormal antibody formation with or without reduced levels of serum antibodies [1–3]. While PID typically result from intrinsic genetic factors, secondary immunodeficiency diseases (SID) can arise owing to other underlying conditions or medication use, and may also result in antibody deficiencies [4]. Patients with antibody defects or deficiencies characteristically experience recurring bacterial infections, particularly of the sinopulmonary tract [2–5]. In clinically more severe PID with impaired

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antibody-mediated immunity, long-term plasma-derived immunoglobulin G (IgG) replacement therapy represents the standard-of-care; intravenous and subcutaneous immunoglobulin therapies also offer beneficial patient outcomes in several autoimmune and inflammatory conditions [6–8]. IgG administered subcutaneously (SCIG) for the treatment of PID effectively reduces the risk of infections, is associated with fewer systemic adverse events (AEs) when compared with intravenous administration and can be self-infused at home [6,9]. However, the limited volume of IgG that can be administered with conventional SCIG often necessitates multiple infusion sites and frequent administration, usually once per week [10].

Hyaluronidase-facilitated SCIG 10% (fSCIG 10% [HyQvia; Baxalta US, Inc. a member of the Takeda group of companies, MA, USA]) is a dual-vial unit of IgG 10% and recombinant human hyaluronidase PH20 (rHuPH20). rHuPH20 depolymerizes hyaluronan in the subcutaneous tissue, transiently increasing tissue permeability to IgG [11]. This results in enhanced dispersion and absorption of IgG, facilitating the infusion of larger volumes per site compared with conventional SCIG, and permits treatment every 3–4 weeks [10,12]. fSCIG 10% is approved in the EU as immunoglobulin replacement therapy for adults and children (aged 0–18 years) with PID or SID [11], and is also approved for the treatment of PID in adults and children aged 2 years and above in the USA [13]. Since the completion of the current study, fSCIG 10% has also received approval for use as maintenance therapy in adults and children with chronic inflammatory demyelinating polyradiculoneuropathy following stabilization with intravenous immunoglobulin (IVIG) in the EU, and as maintenance therapy in the USA for adults with the disease [11,13]. fSCIG 10% has demonstrated a safety profile similar to conventional SCIG and also offers the flexibility for home infusion [10,14]. To date, clinical trials in PID have shown that fSCIG 10% infusions are well tolerated in most patients, with approximately 97% of individuals receiving the infusions at the recommended dose without the need for a reduction in infusion rate or treatment discontinuation [14]. Given that many patients with PID will require lifelong treatment with IgG replacement therapy, it is important to understand the long-term safety profile of fSCIG 10%.

This post-authorization safety study assessed the long-term safety of fSCIG 10% and collected data on immunogenicity, prescribed treatment regimens and treatment administration in routine clinical practice in Europe, in addition to health-related quality of life (HRQoL) and health resource utilization (HRU) assessments.

2. Materials & methods

2.1. Study design

This was a prospective, noninterventional, open-label, uncontrolled, multicenter post-authorization safety study conducted in Europe (EUPAS5812), designed and carried out in line with European Medicine Agency pharmacovigilance guidelines, the study protocol and applicable national and local pharmacovigilance requirements (Figure 1) [15]. Institutional review board approval was obtained centrally, and locally at each site prior to site initiation.

Patients were recruited over an approximately 3-year period, with the first patient enrolled on 17 July 2014 and the last patient on 23 February 2017. Patients participated in the study for approximately 3–6 years depending on the time of enrollment, unless they prematurely discontinued, with the last study visit taking place on 26 February 2020. Patients with a final regular visit at the treatment center before the end of the first quarter of 2020 were considered to have completed the study according to the protocol. The reasons for premature study discontinuation were recorded, and all patient data up to the time of discontinuation were included for analysis.

Patients were eligible for inclusion if they required IgG treatment and were receiving or were prescribed fSCIG 10% prior to enrollment, were aged $\geq$18 years and were able to provide informed consent. fSCIG 10% dosage regimens and treatment schedules were chosen by the attending physician in accordance with routine clinical practice. Patients were excluded if they had known hypersensitivity to any of the components of the medicinal product, had previously participated in an interventional clinical study involving a medicinal product or device within 30 days prior to enrollment, were scheduled to participate in an interventional clinical study involving a medical product or device during the course of the study, or were a family member or employee of the investigator.

2.2. Study variables

2.2.1. Treatment & safety data

Data on variables, including treatment regimens, product administration details and safety data regarding AEs and serious AEs (SAEs) were retrieved from patient medical records and associated documentation throughout the study, as well as voluntary paper or electronic patient diaries that were offered at enrollment for completion during the study. Details of dose according to body weight per 4 weeks, infusion interval and incidence of all and treatment-related SAEs were recorded, in

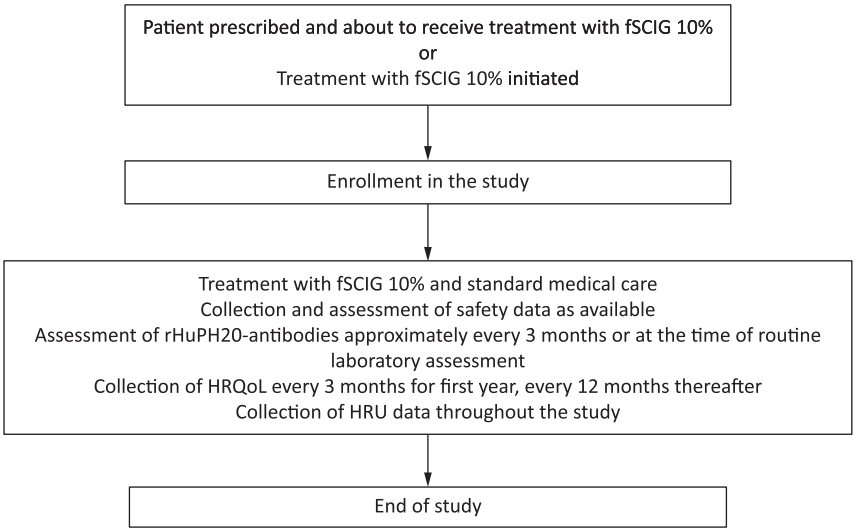

Figure 1. Study design.
fSCIG 10%: Hyaluronidase-facilitated subcutaneous immunoglobulin 10%; HRQoL: Health-related quality of life; HRU: Health resource utilization; rHuPH20: Recombinant human hyaluronidase PH20.

addition to the incidence of treatment-related and non-treatment related non-serious AEs, incidence of local suspected immunological AEs and temporally and/or causally associated systemic allergic AEs. For an event to be considered temporally related to fSCIG 10% therapy, the AE must have occurred during fSCIG 10% infusion or within 72 h of the end of the infusion. The presence of a causal relationship between fSCIG 10% and an AE was assessed by the investigator using their clinical expertise and judgment. For events assessed as not related to fSCIG 10%, or unlikely to be related to fSCIG 10%, the investigator provided an alternative etiology. In addition, the incidence of the new onset of other potentially immunologically mediated AEs and gastrointestinal AEs were also evaluated.

2.2.2. Anti-rHuPH20 antibodies

Participants had additional blood samples drawn on a voluntary basis at the time of routine laboratory assessments approximately every 3 months, but not more often than four times a year, for the measurement of anti-rHuPH20 antibodies. The clinical immunogenicity of rHuPH20 was assessed by the presence of anti-rHuPH20-binding antibodies using a validated electrochemiluminescence-based bridging immunoassay for binding antibodies. A modified rHuPH20 activity assay was used to assess the presence of neutralizing antibodies in anti-rHuPH20-positive antibody samples [16]. Further details on the methodology used for assessment of anti-rHuPH20 antibodies have been published previously [16]. A positive binding anti-rHuPH20 antibody titer was defined as a titer of $\geq$1:160, as used in previous studies with fSCIG 10% [10,17]. Neutralizing antibodies were also measured in patients with an anti-rHuPH20 binding antibody titer of $\geq$160.

2.2.3. HRQoL & HRU

All HRQoL and HRU questionnaires and assessments were optional. The Short Form-36 version 2 (SF-36v2) [18] physical and mental health component summary scores were assessed, with higher scores indicating better HRQoL, along with change from baseline at Month 12 and at the completion visit. The EuroQoL 5-dimension-3L (EQ-5D-3L) [19] visual analog scale (VAS) score of the current HRQoL state and index score were also evaluated, with increasing scores representing better health status, and change from baseline at Month 12 and at the completion visit measured. Finally, the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) [20] was completed, with three domain scores (effectiveness, convenience and global satisfaction) recorded. Higher scores indicate greater satisfaction with respect to that domain. All HRQoL questionnaires were completed at the screening/enrollment visit, approximately every 3 months during the first year of the study, then annually thereafter and at the study termination visit.

In addition, HRU assessments, which included hospitalizations, length of inpatient stay, acute care visits, emergency room visits and days missed/worked from work/school, were performed at each study visit throughout the study and at study termination site visits.

2.3. Statistical analyses

2.3.1. Sample size

No minimum sample size was specified for this study, although it was anticipated that between 80 and 120 patients would be included.

2.3.2. Analysis populations

The safety analysis population was used for all statistical analyses, and was defined as all patients in the enrolled population (all patients who provided informed consent and met enrollment eligibility criteria) who received at least one dose of fSCIG 10% that was recorded in the study database.

2.3.3. Analysis of variables

2.3.3.1. Safety end point analysis. The number and proportion of patients experiencing treatment-emergent AEs (TEAEs) and SAEs were calculated, and terms were coded using MedDRA version 16.1 and summarized by system organ class and preferred term. The incidence of AEs was also calculated as the rate per infusion and rate per patient-year, and was analyzed for changes in frequency and for changes in severity over time.

In addition, these analyses were performed overall and by age group (18–<30, 30–<40, 40–<50, 50–<60, 60–<65 and ≥65 years), gender and indication. Analysis was also performed for the incidence and titer of binding and neutralizing antibodies to rHuPH20 and the changes in titers over time.

2.3.3.2. Treatment regimen, HRQoL & HRU end point analysis. Data for all other study end points, including details of prescribed treatment regimens, product administration and HRQoL and HRU, were summarized descriptively.

2.3.4. Summary measures

All computations were performed using SAS® version 9.4 or higher (SAS Institute, NC, USA). Missing data were not imputed, and data were analyzed and presented as recorded in the database. Missing items on the questionnaires were handled according to questionnaire scoring guidelines for missing data.

Summaries of categorical variables included frequencies and percentages, and summaries of continuous variables included the sample size, mean, standard deviation (SD), median, 25th percentile (Q1), 75th percentile (Q3), minimum and maximum, as appropriate.

3. Results

3.1. Study population

Overall, 111 patients were enrolled at 17 sites in six European countries (Czechia, Denmark, Germany, Ireland, Italy and The Netherlands). Each site enrolled between 1 and 20 patients. Data were reported on at least one fSCIG 10% dose for 106 patients, who were included in the safety analysis population.

The mean (SD) age of patients was 46.2 (14.7) years (median [range] 45 [18–86] years), and 14.2% (n = 15) of the patients were ≥65 years. The largest proportion of patients were aged between 40 and <50 years (n = 28; 26.4%), followed by 30–<40 years (n = 22; 20.8%) and 50–<60 years (n = 22; 20.8%). In total, 12.3% (n = 13) and 5.7% (n = 6) of patients were aged between 18–<30 years and 60–<65 years, respectively. Overall, 56.6% of patients (n = 60) were female, of whom 56.7% (n = 34) were of childbearing potential, and most patients were Caucasian (n = 104; 98.1%) and of non-Hispanic or Latino ethnicity (n = 99; 93.4%; ethnicity could not be recorded for the remaining patients). All patients but one (n = 105) had a history of IgG treatment. All patients were prescribed fSCIG 10% before enrollment, and fSCIG 10% represented the most common immunoglobulin therapy received prior to the study (n = 63). Pre-study fSCIG 10% treatment was reported as ongoing at enrollment in 38 patients, and the most common pre-study fSCIG 10% treatment interval was every 4 weeks, followed by every 3 weeks. Most patients received fSCIG 10% for treatment of PID (n = 97; 91.5%). A small number of patients received treatment for SID (n = 7; 6.6%) and two patients received fSCIG 10% for treatment of a disease that could not be classified as either PID or SID. For patients receiving fSCIG 10% for the treatment of PID, the most common diagnosis recorded was common variable immunodeficiency (n = 63; 59.4%), followed by IgG subclass deficiency (n = 14; 13.2%). In total, six patients (5.7%) had a diagnosis of primary immunodeficiency 'not otherwise specified'. Diagnoses of agammaglobulinemia and specific antibody deficiency (n = 4; each 3.8%) were reported, as well as hypoglobulinemia 'not otherwise specified' (n = 3; 2.8%), combined immunodeficiency, regulatory T-cell defects (cytotoxic T-lymphocyte antigen 4 deficiency) and severe combined immune deficiency (n = 1; each 0.9%).

In total, 56 out of 111 patients discontinued prematurely and thus did not receive fSCIG 10% over the entire duration of the study. Reasons for discontinuation were as follows: patient withdrawal of consent to participate in the study (n = 18/56; 32.1%); patient lost to follow-up (n = 14/56; 25.0%); AEs (n = 13/56; 23.2%); physician decision (n = 4/56; 7.1%); pregnancy (n = 2/56; 3.6%); and other (n = 5/56; 8.9%). For all 56 patients who

discontinued, the mean duration of study participation was 1.9 years. The mean durations of study participation for affected patients by reason for discontinuation were: 1.8 years for patients who withdrew consent; 3.7 years for patients lost to follow-up; and 0.7, 0.6, 2.00 and 1.3 years for patients who discontinued owing to an AE, physician decision, pregnancy and other, respectively.

3.2. Treatment characteristics

The total duration of fSCIG 10% exposure across the safety analysis population was 302.4 person-years (PYs), with a mean (SD) duration of fSCIG 10% exposure of 2.9 (1.5) years (range: 0.02–5.22 years). During the study, a total of 3363 infusions were administered. Patients used a mean (SD) of 1.1 (0.4) infusion sites, with the most common site being the abdomen (n = 2952; 91.5% of infusions), and had a mean (SD) maximum infusion rate of 238.7 (65.5) ml/h and a mean (SD) IgG dose of 362.1 (216.5) mg/kg body weight per 4 weeks (Table 1). The mean (SD) duration of all reported infusions was 2.7 (0.70) h. As the study progressed, the proportion of fSCIG 10% infusions administered at home increased, with 72.9%, 92.6%, 94.8%, 96.8% and 94.9% (n = 70, 990, 837, 645 and 389 infusions, respectively) at initial treatment, in the first, second and third year, and after the third year, respectively (Figure 2). Most fSCIG 10% infusions (n = 3348 infusions; 99.6%) were administered without the need for infusion rate change or infusion interruption due to an AE, and in year 3 and beyond, no infusion rate changes or interruptions were reported (Figure 3). The most common fSCIG 10% treatment interval was every 4 weeks (n = 66; 62.9% of patients; Table 1), with a total observation time of 114 PYs. Less than half of patients (n = 46; 43.8%) received fSCIG 10% infusions every 3 weeks representing the next most common infusion interval, and 31.4% (n = 33) of patients received infusions every 2 weeks. Patients may have had more than one fSCIG 10% treatment interval during the study.

3.3. Safety analysis

3.3.1. Overall

Overall, including infections, 1171 TEAEs were reported in 94 patients (88.7%; 95% confidence interval [CI]: 81.1, 94.0; Table 2), an event rate of 0.348 per infusion. Of the total TEAEs, 925 were mild (n = 26 patients; 24.5%), 201 were moderate (n = 40 patients; 37.7%) and 45 were severe (n = 28 patients; 26.4%). Approximately one-quarter of the TEAEs (n = 299; 25.5%) were related to fSCIG 10%, with most events classified as mild (n = 280; 93.6%). Infusion site pain, headache and pyrexia were the most common treatment-related AEs reported in 12.3% (n = 13), 8.5% (n = 9) and 5.7% (n = 6) of patients, respectively (Table 3). Treatment-related gastrointestinal AEs (n = 17 events) were reported in 9.4% (n = 10) of patients, with diarrhea (n = 10) and nausea (n = 4) being the two most common gastrointestinal AEs.

In total, 82 treatment-emergent SAEs were reported in 36 patients, in whom one treatment-emergent SAE was considered probably related to fSCIG 10%. The affected patient was a 50-year-old man with PID who experienced a toxic skin eruption of the abdomen skin during the first year of follow-up after multiple uneventful doses of study treatment. The event was coded as a toxic skin eruption of the abdominal skin. Immunological investigations, including measurement of C3 and C4 levels, did not reveal any abnormality, and anti-rHuPH20 antibody titers were repeatedly negative. Prednisolone was administered once intravenously at a dose of 250 mg for treatment of toxic skin eruption. A skin biopsy was performed which indicated toxic vasculopathy without any sign of increased complement deposition or complement activity. The initially reported diagnosis was erysipelas for the patient's skin lesion and joint pain, which was considered by the investigator potentially to have been a co-factor that more plausibly explained the event. The event of toxic skin eruption resolved with sequelae of skin fibrosis. One death occurred, which was assessed as not related to fSCIG 10% (an 86-year-old female patient with multiple comorbidities).

In total, 724 non-serious TEAEs (excluding infections) were reported in 84 patients (79.2%). Of these individuals, 42 patients (39.6%) had 297 non-serious AEs (excluding infections) related to fSCIG 10%, with an incidence of 0.98 events per PY (95% CI: 0.87, 1.10), all of which were non-serious AEs that were mild or moderate in severity.

3.3.2. Infections

The incidence of treatment-emergent infections was 1.3 events per PY (398 events in 77 patients). The most common infection events were bronchitis, sinusitis and nasopharyngitis in 22.6% (n = 24), 21.7% (n = 23) and 19.8% (n = 21) of patients, respectively (Table 4). A large proportion of infection events were mild or moderate (381 events in 67 patients). Of the 867 non-treatment related systemic AEs, 397 were infections, with one local moderate infection event (infusion site abscess) deemed to be treatment related.

3.3.3. Local & systemic TEAEs

The incidence of local and systemic TEAEs related to fSCIG 10% were 0.57 events per PY (0.051 per infusion) and 0.42 events per PY (0.037 per infusion), respectively (Table 5). The most common fSCIG 10% related local TEAEs were infusion site irritation, infusion site mass and infusion site pain (n = 51, 49 and 23 events, respectively; Table 6).

Table 1. Treatment characteristics (safety population; N = 106).

Characteristic	First treatment (n = 96)	1st year (n = 85)	2nd year (n = 66)	3rd year (n = 49)	After 3rd year (n = 31)	Unknown (n = 16)	Overall (N = 106)
Type of infusions[†]	96	1069	883	666	410	239	3363
Number of home treatments (%)	70 (72.9)	990 (92.6)	837 (94.8)	645 (96.8)	389 (94.9)	236 (98.7)	3167 (94.2)
Number of site administrations (%)	26 (27.1)	79 (7.4)	46 (5.2)	21 (3.2)	21 (5.1)	3 (1.3)	196 (5.8)
Infusion duration							
Number of patients (%)[‡]	38 (39.6)	46 (54.1)	27 (40.9)	18 (36.7)	10 (32.3)	1 (6.3)	51 (48.1)
Number of infusions[†]	38	431	332	199	61	19	1080
Hours, median (range)	3.0 (2.0, 4.0)	3.0 (2.0, 5.0)	3.0 (1.0, 4.0)	3.0 (1.0, 5.0)	3.0 (2.0, 4.0)	4.0 (3.0, 5.0)	3.0 (1.0, 5.0)
Planned IgG dose							
Number of patients (%)[‡]	95	79	64	52[§]	22	2	69
g/kg/4 weeks, mean (SD)	0.5 (0.17)	0.4 (0.16)	0.5 (0.16)	0.5 (0.15)	0.5 (0.16)	0.6 (0.22)	0.5 (0.16)
Administered IgG dose							
Number of patients (%)[‡]	53 (55.2)	53 (62.4)	48 (72.7)	40 (81.6)	25 (80.6)	4 (25.0)	53 (50.0)
Number of infusions[†]	53	740	687	552	383	20	2435
mg/kg/4 weeks, mean (SD)	334.1 (218.03)	339.5 (213.60)	353.0 (203.42)	381.5 (201.09)	405.4 (251.95)	221.4 (244.53)	362.1 (216.46)
Maximum IgG infusion rate							
Number of patients (%)[‡]	88 (91.7)	83 (97.6)	66 (100.0)	48 (98.0)	31 (100.0)	13 (81.3)	99 (93.4)
Number of infusions[†]	88	1039	880	654	408	194	3263
mL/h, mean (SD)	236.5 (68.5)	248.3 (58.6)	241.7 (63.6)	244.6 (72.4)	219.2 (68.7)	195.2 (50.6)	238.7 (65.53)
Administered IgG dose							
Number of patients (%)[‡]	88 (91.7)	83 (97.6)	66 (100.0)	49 (100.0)	31 (100.0)	15 (93.8)	99 (93.4)
Number of infusions[†]	88	1051	883	666	410	237	3335
mL/site, mean (SD)	271.6 (109.3)	295.3 (93.1)	300.5 (95.7)	302.3 (103.4)	294.1 (98.4)	226.4 (63.4)	292.4 (97.1)
Infusion interval, number of patients (%)[¶]							
1 week	–	–	–	–	–	–	18 (17.1)
2 weeks	–	–	–	–	–	–	33 (31.4)
3 weeks	–	–	–	–	–	–	46 (43.8)
4 weeks	–	–	–	–	–	–	66 (62.9)
>4 weeks	–	–	–	–	–	–	17 (16.2)
Other	–	–	–	–	–	–	31 (29.5)

[†]Number of fSCIG 10% treatments with treatment information during the study period.
[‡]Number of patients with non-missing treatment data for at least one reported infusion.
[§]A total of 52 patients reported relevant data for this period.
[¶]Overall, 105 patients had infusion interval data. Unless explicitly stated otherwise, all fSCIG 10% administrations during the study period are counted. 1 week and 2 weeks include ramp-up periods. A patient may have more than one fSCIG 10% treatment interval. Category 'other' includes intervals specified as free-text by the investigator and it includes intervals of >4 weeks.
fSCIG 10%: Hyaluronidase-facilitated subcutaneous immunoglobulin 10%; IgG: Immunoglobulin G; SD: Standard deviation.

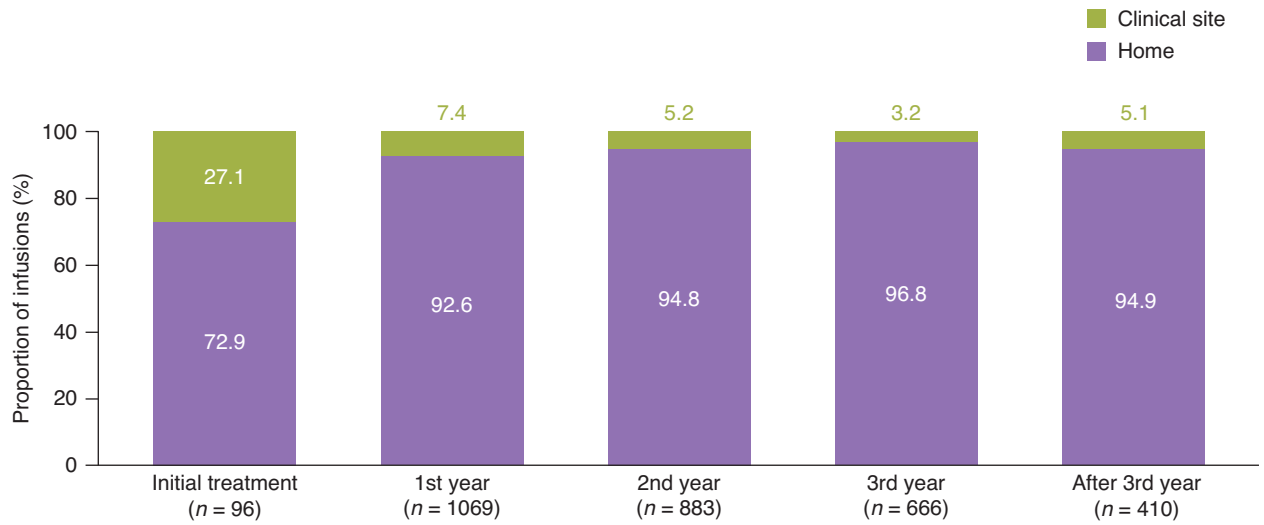

Figure 2. Location of fSCIG 10% treatment. Follow-up years are from the date of first fSCIG 10% treatment; n is the number of all fSCIG 10% treatments during each study period.
fSCIG 10%: Hyaluronidase-facilitated subcutaneous immunoglobulin 10%.

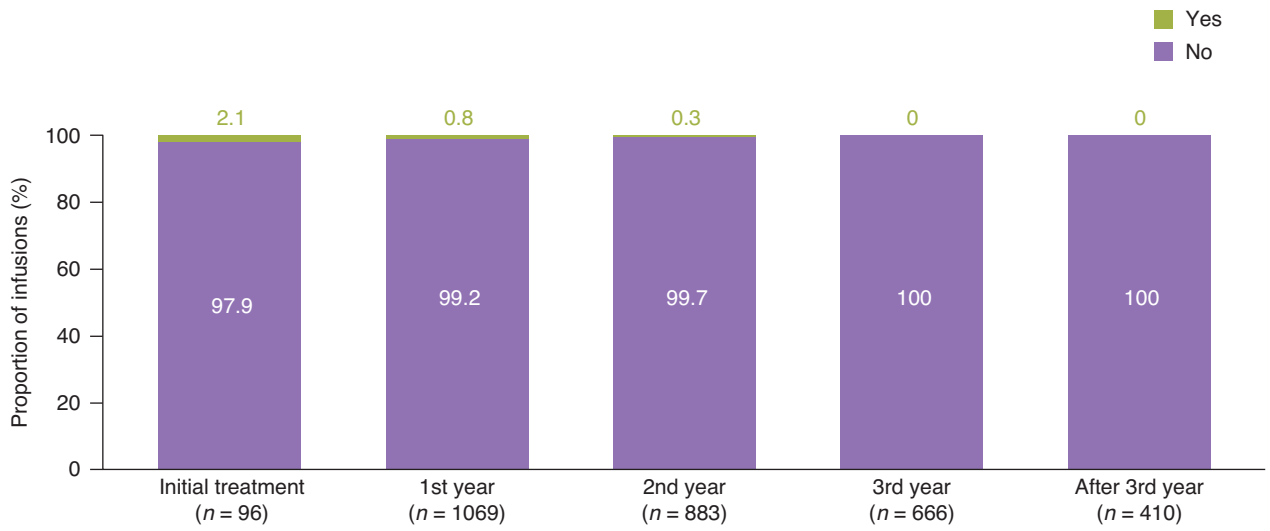

Figure 3. Changes in infusion rate or infusion interruptions due to an adverse event. Follow-up years are from the date of first fSCIG 10% treatment; n is the number of all fSCIG 10% treatments during each study period.
fSCIG 10%: Hyaluronidase-facilitated subcutaneous immunoglobulin 10%.

Table 2. Summary of treatment-emergent adverse events (safety population; N = 106).

Event	Patients, n (%)	Events, n
Any TEAE	94 (88.7)	1171
Related	43 (40.6)	299
Unrelated	51 (48.1)	872
Any serious TEAE	36 (34.0)	82
Related	1 (0.9)	1
Unrelated	35 (33.0)	81
Any local TEAE	32 (30.2)	178
Related	29 (27.4)	173
Unrelated	5 (4.7)	5
Any systemic TEAE	93 (87.7)	993
Related	25 (23.6)	126
Unrelated	91 (85.8)	867

TEAE: Treatment-emergent adverse event.

Table 3. Summary of most common adverse events (safety population; N = 106).

Event	Total, all causality			Treatment-related		
	Events, n	Patients, n (%)	Rate per patient/ rate per infusion	Events, n	Patients, n (%)	Rate per patient/ rate per infusion
Adverse events (≥15 total events)						
Bronchitis	79	24 (22.6)	0.745/0.023	0	0	–
Infusion site irritation	51	1 (0.9)	0.481/0.015	51	1 (0.9)	0.481/0.015
Infusion site mass	49	2 (1.9)	0.462/0.015	49	2 (1.9)	0.462/0.015
Fatigue	38	14 (13.2)	0.358/0.011	25	2 (1.9)	0.236/0.007
Sinusitis	35	23 (21.7)	0.330/0.010	0	0	–
Upper respiratory tract infection	34	16 (15.1)	0.321/0.010	0	0	–
Nasopharyngitis	32	21 (19.8)	0.302/0.010	0	0	–
Pyrexia	31	16 (15.1)	0.292/0.009	11	6 (5.7)	0.104/0.003
Headache	30	21 (19.8)	0.283/0.009	10	9 (8.5)	0.094/0.003
Diarrhea	27	17 (16.0)	0.255/0.008	10	4 (3.8)	0.094/0.003
Infusion site pain	24	13 (12.3)	0.226/0.007	23	13 (12.3)	0.217/0.007
Respiratory tract infection	22	11 (10.4)	0.208/0.007	0	0	–
Pneumonia	21	16 (15.1)	0.198/0.006	0	0	–
Lacrimation increased	20	1 (0.9)	0.189/0.006	0	0	–
Influenza like illness	18	16 (15.1)	0.170/0.005	3	3 (2.8)	0.028/0.001
Cough	17	12 (11.3)	0.160/0.005	0	0	–
Peripheral coldness	15	1 (0.9)	0.142/0.004	15	1 (0.9)	0.142/0.004

Adverse events were captured from the first treatment throughout the follow-up period and are coded using the MedDRA dictionary, version 18.0. Percentages are based on the number of patients in the safety population. All events of infusion site mass were reported as resolved at study completion.

Table 4. Summary of infection adverse events (safety population; N = 106).

Event	Total, all causality			Treatment-related		
	Events, n	Patients, n (%)	Rate per patient/ rate per infusion	Events, n	Patients, n (%)	Rate per patient/ rate per infusion
Infection Adverse events (>15 total events)						
Bronchitis	79	24 (22.6)	0.745/0.023	0	0	–
Sinusitis	35	23 (21.7)	0.330/0.010	0	0	–
Upper respiratory tract infection	34	16 (15.1)	0.321/0.010	0	0	–
Nasopharyngitis	32	21 (19.8)	0.302/0.010	0	0	–
Respiratory tract infection	22	11 (10.4)	0.208/0.007	0	0	–

Adverse events were captured from the first treatment throughout the follow-up period and are coded using the MedDRA dictionary, version 18.0. Percentages are based on the number of patients in the safety population.

Table 5. Treatment-emergent adverse events per infusion, per patient and per patient-year.

Event	Events per infusion	Events per patient	Events per patient-year
Any serious TEAE	0.024	0.77	0.27
Any fSCIG 10%-related serious TEAE	<0.001	<0.01	<0.01
Any fSCIG 10%-related local TEAE	0.051	1.63	0.57
Any fSCIG 10%-related systemic TEAE	0.037	1.19	0.42

fSCIG 10%: Hyaluronidase-facilitated subcutaneous immunoglobulin 10%; TEAE: Treatment-emergent adverse event.

Table 6. Summary of most common systemic and local adverse events (safety population; N = 106).

Event	Total, all causality			Treatment-related		
	Events, n	Patients, n (%)	Rate per patient/ rate per infusion	Events, n	Patients, n (%)	Rate per patient/ rate per infusion
Systemic adverse events (>15 total events)						
Bronchitis	79	24 (22.6)	0.745/0.023	0	0	–
Fatigue	38	14 (13.2)	0.358/0.011	25	2 (1.9)	0.236/0.007
Headache	30	21 (19.8)	0.283/0.009	10	9 (8.5)	0.094/0.003
Sinusitis	35	23 (21.7)	0.330/0.010	0	0	–
Upper respiratory tract infection	34	16 (15.1)	0.321/0.010	0	0	–
Nasopharyngitis	32	21 (19.8)	0.302/0.010	0	0	–
Pyrexia	31	16 (15.1)	0.292/0.009	11	6 (5.7)	0.104/0.003
Diarrhea	27	17 (16.0)	0.255/0.008	10	4 (3.8)	0.094/0.003
Respiratory tract infection	22	11 (10.4)	0.208/0.007	0	0	–
Pneumonia	21	16 (15.1)	0.198/0.006	0	0	–
Lacrimation increased	20	1 (0.9)	0.189/0.006	0	0	–
Influenza like illness	18	16 (15.1)	0.170/0.005	3	3 (2.8)	0.028/0.001
Cough	17	12 (11.3)	0.160/0.005	0	0	–
Peripheral coldness	15	1 (0.9)	0.142/0.004	15	1 (0.9)	0.142/0.004
Local adverse events (≥15 total events)						
Infusion site irritation	51	1 (0.9)	0.481/0.015	51	1 (0.9)	0.481/0.015
Infusion site mass	49	2 (1.9)	0.462/0.015	49	2 (1.9)	0.462/0.015
Infusion site pain	24	13 (12.3)	0.226/0.007	23	13 (12.3)	0.217/0.007

Adverse events were captured from the first treatment throughout the follow-up period and are coded using the MedDRA dictionary, version 18.0. Percentages are based on the number of patients in the safety population. All events of infusion site mass were reported as resolved at study completion.

The most common fSCIG 10% related systemic TEAEs were fatigue, peripheral coldness, pyrexia and headache (n = 25, 15, 11 and 10 events, respectively).

The annual per-patient rates of fSCIG 10% related local AEs per-patient were substantially lower in the second half of the follow-up period, with an event rate of 0.00 per 100 patients in Year 5. The annual per-patient event rates of fSCIG 10% related systemic AEs decreased annually from a high of 42.05 per 100 patients in Year 1 to 10.71 per 100 patients in Year 4 and 0.00 per 100 patients in Year 5, although the overall change was not significant over the first 3 years.

3.3.4. Allergic events

One temporally and/or causally associated systemic allergic AE (mild reaction; tingling of the tongue and throat) was observed (incidence of <0.01 per PY (95% CI: 0.00, 0.02]). No local immunologic TEAEs were reported.

3.3.5. Anti-rHuPH20 antibodies

Of the 74 patients tested for anti-rHuPH20 binding antibodies, three patients (4.1%) developed positive binding antibodies to rHuPH20, with a maximum titer of 1:1280 and an incidence of 4.05 (95% CI: 1.39, 11.25). After 3 years of fSCIG 10% treatment, no positive titers were reported. In addition, no neutralizing antibodies to rHuPH20 were detected throughout the study.

3.4. HRQoL outcomes

The SF-36v2 was completed by 61 patients at baseline. During follow-up, the time point with the highest number of respondents was Year 2 (n = 56) and the lowest was Year 5 (n = 3). SF-36v2 data were reported by 19–48 patients at all other time points, including the completion visit (n = 24). No notable differences in the domains over the course of the study were observed. The highest mean (SD) physical health component score was observed at the Year 5 time point (49.0 [14.88]; n = 3), followed by Year 4 (46.7 [12.30]; n = 19) and Month 6 (46.6 [10.41]; n = 48). The lowest mean (SD) physical health component score was 41.6 (11.62; n = 37) at Month 3. For mental health component scores, the highest mean (SD) scores were observed at Year 5 (50.2 [5.47]; n = 3), followed by Month 6 (47.2 [10.40]; n = 48) and Month 9 (46.2 [11.96]; n = 32). The lowest mean (SD) mental health component score was observed at Year 4 (40.7 [13.24]; n = 19). Mean (SD) change from baseline in SF-36v2 scores at Month 12 was 0.4 (5.46) for the physical health component score (n = 23) and 2.5 (10.07) for the mental health component score (n = 23). At study completion, mean (SD) change from baseline was 1.9 (8.56) and −1.5 (8.10) for physical and mental health component scores, respectively (both n = 14).

The EQ-5D was completed by 58 patients at baseline, with the highest number of responses received at Year 2 (n = 51) and the lowest at Year 5 (n = 2); 17–44 patients had data at all other time points, including the completion visit (n = 15). Most patients across all domains experienced no change in their reported problems from baseline to Year 1 and the completion visit. Mean index scores ranged from 0.8 to 1.0, with no change from baseline reported at Month 12 or at study completion. Slightly more variation was seen in EQ VAS scores, with the highest mean (SD) EQ VAS score observed at Year 5 (90.0 [0.00]; n = 2), followed by Month 12 (71.8 [18.23]; n = 33) and Year 4 (70.8 [14.67]; n = 17). The lowest mean (SD) EQ VAS score observed was 64.7 (21.17; n = 38) at the Month 3 time point. Mean (SD) change from baseline in EQ VAS scores was 3.0 (16.56; n = 24) and −5.4 (13.07; n = 7) at Month 12 and at study completion, respectively.

For the TSQM-9 questionnaire, at baseline 56 patients separately reported effectiveness and convenience score data, while 57 patients reported global satisfaction score data. During follow-up, the time point with the highest number of respondents was Year 2 (range: 57–58 patients) and the lowest was Year 5 (n = 2) across all domains. At all other time points, 18–46 patients had effectiveness score data, 17–45 patients had convenience score data and 18–45 patients had satisfaction score data. There were 19 respondents at the completion visit across all domains, and mean effectiveness, convenience and global satisfaction scores did not differ substantially over the course of the study. The highest mean (SD) score observed for the effectiveness domain was seen at the Month 9 time point (77.4 [16.25]; n = 33), followed by Year 3 (74.4 [21.06]; n = 33) and Month 12 (72.4 [19.55]; n = 35), while the lowest score was 60.0 (23.71; n = 38) at Month 3. For the convenience domain, the highest mean (SD) scores were observed at Year 5 (83.3 [23.57]; n = 2), Month 12 (72.1 [18.46]; n = 33) and Month 9 (71.0 [15.25]; n = 32), with the lowest convenience domain score recorded at Month 3 (66.8 [15.63]; n = 38). For the global satisfaction domain, highest mean (SD) scores were 100.00 (0.00; n = 2), 79.1 (16.87; n = 33) and 76.9 (22.43; n = 18), recorded at Year 5, Year 3 and Year 4, respectively. The lowest global satisfaction domain score was recorded at study completion as 71.6 (18.61; n = 19).

3.5. Health resource utilization

The average annualized per-person rates for hospitalizations, acute care visits and emergency room visits were all <1; the event rate for days in hospital was 2.59 days per PY (Table 7). Of the 33 patients hospitalized (a total of 69 all-cause hospitalization events, at an event rate of 0.22 per PY), 32 hospitalization events were due to infections. In total, 1996 days were missed from work/school, as reported by 27 patients, with an event rate of 6.41 missed days per PY.

4. Discussion

This European post-authorization study assessed the long-term (up to 5.2 years) safety and tolerability of fSCIG 10% in a real-world population, observing adult patients mostly with PID in a predominantly home setting rather than under clinical trial conditions. To the best of the authors' knowledge, the present study has the longest overall follow-up of any subcutaneous IgG replacement treatment for PID to date, with 302.4 PYs of exposure to fSCIG 10% observed in total. The patient population in the current study had a mean (SD) duration of fSCIG 10% exposure of 2.9 (1.5) years (range 0.02–5.22 years), and a higher median age (45 years) than in previous analyses of fSCIG 10% [10,12,14]. fSCIG 10% appeared

Table 7. Healthcare resource use (safety population; N = 106).

Healthcare resource use	Patients with ≥1 event, n	Events, n	Event rate	95% CI
Hospitalization	33	69	0.22	0.17, 0.28
Days in hospital	32	807	2.59	2.42, 2.78
Acute care visits	33	195	0.63	0.54, 0.72
Emergency room visits	19	35	0.11	0.08, 0.16
Days missed from school/work	27	1996	6.41	6.13, 6.70

Data are for a total of 311.3 person-years, the sum of time for all patients from enrollment to the earliest date of end of study participation.
CI: 95% exact Poisson confidence interval; Event rate: Number of events/person-year.

to have a favorable long-term safety profile with a rare occurrence of binding antibodies to rHuPh20. No neutralizing antibodies, which potentially could have led to secondary loss of efficacy, were observed.

During the study, the most common dosing interval for participants receiving fSCIG 10% was 4 weeks, with 3 weeks being the next most common interval, in line with the associated European prescribing information [11]. This reflects the half-life of circulating IgG antibodies in humans, although this appears to differ between individuals [11,21]. However, 2-weekly administrations were also used in the study, even in the third year of fSCIG 10% treatment (n = 142; 21.3% of the infusions), which could not be explained by the ramp-up periods after initiation of fSCIG 10% treatment. These data show that, even though fSCIG 10% was designed to be administered every 3 or 4 weeks, some participating centers preferred to administer fSCIG 10% more frequently. The preferences for using different administration schedules vary between countries and sites. These shorter dosing intervals may have been driven by patient and doctor preferences, consideration of tolerability of larger volume injections or circulating antibody half-lives, or may be reflective of the standard-of-care in treatment centers. Data from another post-marketing study with fSCIG 10%, which was also conducted in Europe, showed that the patients predominantly received fSCIG 10% every 3–4 weeks with only about 9% of patients with PID receiving fSCIG 10% every 2 weeks at 1-year follow-up [22]. These findings demonstrate that treatment with fSCIG 10% lends itself to treatment individualization and shared decision-making between physicians and patients, because it is easily adjustable to their preferences.

The safety findings from this study are similar to those previously observed [10]. In total, 88.7% (n = 94) of patients reported AEs, with 40.6% (n = 43) of patients experiencing treatment-related AEs (93.6% [n = 280/299] of which were mild), which is perhaps unsurprising given the substantial duration of follow-up in this study. Overall, patient withdrawal and loss to follow-up were the most common reasons for study discontinuation, again potentially owing to the study duration, followed by AEs. Overall, the annual per-patient rates of related local and systemic AEs (local: 0.57 events per PY; systemic: 0.42 events per PY) were substantially lower in the second half of follow-up, which is supported by several observations that the frequency of local reactions lessen over time with continued SCIG therapy. Rates of related AEs were similar to those observed in an associated pivotal, phase 3 study at the 3rd year of follow-up (local: 0.37 events per PY; systemic: 0.63 events per PY), although the differences in study type must be considered [10]. Importantly, the safety findings also suggest that recurrent injections of hyaluronidase do not damage the skin. When considering adverse events, the years-long treatment with fSCIG 10% in the current study did not cause long-term changes to skin integrity such as infusion site mass, infusion site discoloration, atrophy or lipodystrophy at the infusion sites. This finding is also supported by the observation that subcutaneous tissue echogenicity after 1 year of fSCIG 10% treatment did not change compared with baseline [23]. One serious AE (toxic erythema) was reported, resolved with sequelae of skin fibrosis and was considered probably related to treatment, although the investigator deemed that the patient's bacterial erysipelas may have been a cofactor that more plausibly explained the SAE. Although the study was not designed to investigate efficacy, it is worth noting that the rate of collected treatment-emergent infections (1.3 events per PY) was low [10]. The development of antibodies against rHuPH20 was rare (3/74 patients), and even rarer than in the pivotal study [14]. No neutralizing antibodies were detected during the study period and no resulting secondary loss of efficacy was observed, which is consistent with previous studies with fSCIG 10% in patients with PID [10,14,17]. Finally, HRQoL measures remained stable over the course of the study, and rates of hospitalizations, acute care visits and emergency room visits in patients receiving fSCIG 10% were low.

The strengths of this study include the substantial number of patient-years of exposure to fSCIG 10%, with the longest follow-up of any subcutaneous IgG replacement treatment of PID to date, in addition to the observation of patients in real-world practice rather than clinical trial conditions. However, as is common with

long-term observational studies, there are some study limitations that must be considered. The mean duration of exposure to fSCIG 10% was long, which could have led to reporting 'fatigue' of AEs over the study. Overall, 94.2% (n = 3167) of fSCIG 10% infusions were self-administered by patients at home during the study, and it is likely that they missed reporting some infusion data. Owing to the structured nature of data reporting in post-authorization safety studies, safety data are likely to be more complete than for spontaneous reporting in a real-world setting; accordingly, this may lead to potentially higher reported rates of AEs. To mitigate this, all sites underwent standardized training and used standardized documentation for completing the case report forms; these forms were also designed to limit out-of-range data at the point of data entry. This study relied on patient self-reported outcomes, which were optional for all patients; results are therefore limited to patients willing to provide responses. In addition, patient retention through the end of the follow-up period was a concern, with 25.0% (n = 14) of patients in the safety population lost to follow-up. It is possible that the patients who discontinued or were lost to follow-up may have differed from those remaining in the study; if so, this may have resulted in selection bias, which could limit the generalizability of our findings. Finally, unmeasured patient and clinical variables related to fSCIG 10% treatment may have confounded the results.

5. Conclusion

The present study is the longest observational analysis of fSCIG 10% therapy to date and provides valuable insights into safety and treatment administration data of fSCIG 10% in Europe. The study also offered an opportunity to collect data for fSCIG 10% at a relatively early stage in its product lifecycle. The analysis of prospectively collected data confirms the long-term (up to 5.2 years) safety and tolerability of fSCIG 10% in a real-world population of adult patients with antibody deficiencies in a predominantly home setting and demonstrates safety and tolerability profiles consistent with previous studies.

Summary points

- This European post-authorization safety study (EUPAS5812) assessed the long-term safety of hyaluronidase-facilitated subcutaneous immunoglobulin (fSCIG) 10% in routine clinical practice in the longest observational analysis of fSCIG 10% to date (up to 5.2 years).
- Overall, 106 patients had data reported for at least one fSCIG 10% dose, primarily indicated for primary immunodeficiency (91.5% of patients), with a total duration of exposure of 302.4 person-years (mean [standard deviation, SD] duration of 2.9 [1.5] years [range: 0.02–5.22 years]).
- Patients used a mean (SD) of 1.1 (0.4) infusion sites, most commonly the abdomen (91.5%).
- Over the course of the study, the proportion of fSCIG 10% infusions administered at home increased from 72.9% at initial treatment to 94.9% after the 3rd year.
- In total, 1171 treatment-emergent adverse events were reported in 94 patients (88.7%), at an event rate of 0.348 per infusion (similar to prior studies of subcutaneous immunoglobulin); 25.5% of treatment-emergent adverse events were considered related to fSCIG 10%, of which most were mild in severity (93.6%).
- Low rates of positive anti-recombinant human hyaluronidase (rHuPH20) binding antibody titers (≥1:160) were observed during the study, and no neutralizing anti-rHuPH20 antibodies were detected.
- Most fSCIG 10% infusions (99.6%) were administered without the need for changes to infusion rate or infusion interruption due to an AE, and from Year 3 of the study and onwards no infusion rate changes or interruptions were reported.
- The analysis of prospectively collected data confirms the long-term safety and tolerability profiles of fSCIG 10% in a real-world population of adult patients with immunodeficiency diseases in a predominantly home setting.

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Author contributions

B McCoy and L Yel contributed to the conceptualization of the study. V Lougaris curated the study data, and V Lougaris and J Chen performed the data analysis. K Fielhauer, B McCoy and L Yel designed the study methodology and V Lougaris, K Fielhauer, B McCoy and L Yel conducted the investigation process. K Fielhauer, B McCoy and L Yel provided study resources and A Nagy supported project administration. L Yel acquired study funding, and study validation and visualization of the manuscript were performed by T Witte, K Fielhauer, B McCoy and L Yel. L Yel supported study supervision, and all authors contributed to preparation of the original draft, and review and editing of the manuscript.

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Competing interests disclosure

PM Ellerbroek is a local investigator of studies funded by the Takeda group of companies. LG Hanitsch has nothing to disclose. T Witte has received honoraria for lectures as well as research support from Takeda Pharmaceuticals. V Lougaris has nothing to disclose. PM Hagen is a member of the Plasma Protein Therapeutics Association European Immunoglobulin Advisory Group. P Paassen has nothing to disclose. J Chen is an employee of Takeda Development Center Americas, Inc. and a Takeda shareholder. B McCoy, A Nagy, and K Fielhauer are employees of Baxalta Innovations GmbH, a Takeda company, and are Takeda shareholders. L Yel was an employee of Takeda

Development Center Americas, Inc. at the time of the study, and is a Takeda shareholder. This study was funded by Baxalta Innovations GmbH, a Takeda company. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

Medical writing assistance was provided by Alexandra Kisbey-Ascott, MPharm, of Oxford PharmaGenesis, Oxford, UK and was funded by Takeda Development Center Americas, Inc. and Takeda Pharmaceuticals International AG.

Ethical conduct of research

Prior to patient enrollment, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided were reviewed and approved by independent ethics committees, institutional review boards and applicable regulatory authorities. Ethics committee approval was obtained centrally, and locally at each site prior to site initiation. The regional and local institutional review boards providing approval were: Ethics Committee of the University of Freiburg (EK Freiburg: 173/14, EC Freiburg: 173/14_160446), Ethics Committee of Hannover Medical School (Approval 2290-2014) and Saxon State Medical Association Ethics Committee (EK-BR-34/14-1; Germany); University Medical Center Groningen (METc2014/348), Medical-Ethical Review Committee of the University Hospital Maastricht and Maastricht University (METC 14-4-196/ivb), University Medical Center Utrecht (WAG/om/15/000584 and METC 14–669/C) and Erasmus University Medical Center (MEC-2014-508 and FS/hl/226363; Netherlands); the Scientific Medical Ethics Committees (1-10-72-144-14; Denmark); Cork Ethics Committee (Ref ECM 5(5) 19/11/14) and Adelaide & Meath Hospital (REC Reference: 2015 List 27 (3)/ 2015-09 List 33 (6); Ireland); Provincial Ethics Committee of the Province of Brescia (NP 2345 – HyQvia/161302 Study; Italy); Faculty Ethics Committee Hospital at St. Anne v Brno (24JS/2016), Ethics Commission of the Region T. Bati Hospital A.S. and the Ethics Committee for Multicenter Clinical Evaluation Faculty Hospital Motola (Czechia). All patients and/or their legally authorized representative signed an informed consent form before study entry according to applicable regulatory requirements. Please see the patient consent section for more details.

Data availability statement

The data sets, including the redacted study protocol, redacted statistical analysis plan and individual participant data supporting the results reported in this article will be made available within 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.

Patient consent

All patients and/or their legally authorized representative signed and dated an informed consent form before entering into the study, according to applicable regulatory requirements. Any patient could voluntarily withdraw consent for continued participation and data collection.

Clinical trial registration

This trial is registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EU PAS Register Number: EUPAS5812). Details of this registration may be found here: https://catalogues.ema.europa.eu/node/2767/administrative-details.

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