

Efficacy, safety, tolerability and pharmacokinetics of a novel human immune globulin subcutaneous, 20%: a Phase 2/3 study in Europe in patients with primary immunodeficiencies

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Introduction

Primary immunodeficiency diseases (PIDD) are disorders that result in an increased susceptibility to recurrent infections, due to underlying genetic defects in antibody and/or cell-mediated immunity [1]. More than 300 different genetic defects leading to PIDD have been recognized [2]. Primary antibody deficiency with or without decreased levels of serum immunoglobulin (Ig) is the most common class of PIDD and includes syndromes such as common variable immunodeficiency (CVID), X-linked or autosomal

Summary

A highly concentrated (20%) immunoglobulin (Ig)G preparation for subcutaneous administration (IGSC 20%), would offer a new option for antibody replacement therapy in patients with primary immunodeficiency diseases (PIDD). The efficacy, safety, tolerability and pharmacokinetics of IGSC 20% were evaluated in a prospective trial in Europe in 49 patients with PIDD aged 2–67 years. Over a median of 358 days, patients received 2349 IGSC 20% infusions at monthly doses equivalent to those administered for previous intravenous or subcutaneous IgG treatment. The rate of validated acute bacterial infections (VASBIs) was significantly lower than 1 per year (0.022/patient-year, $P < 0.0001$); the rate of all infections was 4.38/patient-year. Median trough IgG concentrations were ≥ 8 g/l. There was no serious adverse event (AE) deemed related to IGSC 20% treatment; related non-serious AEs occurred at a rate of 0.101 event/infusion. The incidence of local related AEs was 0.069 event/infusion (0.036 event/infusion, when excluding a 13-year-old patient who reported 79 of 162 total related local AEs). The incidence of related systemic AEs was 0.032 event/infusion. Most related AEs were mild, none were severe. For 64.6% of patients and in 94.8% of IGSC 20% infusions, no local related AE occurred. The median infusion duration was 0.95 (range = 0.3–4.1) h using mainly one to two administration sites [median = 2 sites (range = 1–5)]. Almost all infusions (99.8%) were administered without interruption/stopping or rate reduction. These results demonstrate that IGSC 20% provides an effective and well-tolerated therapy for patients previously on intravenous or subcutaneous treatment, without the need for dose adjustment.

Keywords: 20% immunoglobulin, immunoglobulin replacement therapy, pharmacokinetics, primary immunodeficiency diseases, subcutaneous administration

recessive agammaglobulinaemia, hyper-immunoglobulin (Ig)M syndrome, deficiencies of specific antibodies and/or Ig isotype or IgG subclasses [3].

Antibody replacement therapy using highly purified human Ig preparations is the standard of care in immunodeficiencies with impaired antibody production [1]. Ig preparations, administered intravenously (IGIV) or subcutaneously (IGSC) to increase the serum IgG concentration to physiological levels with polyclonal broad-spectrum antibodies, provide protection against infection in PIDD patients [4,5].

Typically, effective treatment of PIDD with IGIV requires monthly doses of 0.3–0.8 g/kg body weight (BW) administered every 3–4 weeks by intravenous (i.v.) infusion over 2–4 h. The IGIV volumes delivered rapidly into the systemic circulation usually lead to serum IgG peaks within 24 h, decreasing gradually over the treatment interval. High peaks of serum IgG during IGIV therapy have been associated with an increased incidence of systemic adverse reactions. In contrast to IGIV, for subcutaneous (s.c.) therapy, the same dose is administered in smaller volumes at more frequent intervals (once a week or every other week) over 1–2 h. As Ig diffuses slowly from the s.c. space into the systemic circulation, weekly IGSC administration does not lead to peaks of serum IgG concentrations, unlike monthly i.v. infusions, and is associated with fewer systemic adverse reactions [6–8].

The s.c. route of administration may appeal particularly to patients interested in home-based therapy, as it can be self-administered more easily [5,9]. However, drawbacks exist, such as low infusion volumes and rates per site. Consequently, IGSC administration is often accomplished via several infusion sites per treatment. To improve the convenience of conventional IGSC infusion, highly concentrated IgG formulations are being developed that allow infusion of the same dose in smaller infusion volumes compared to less concentrated products [5].

An s.c. immunoglobulin product that can be infused at high rates and volumes per site provides a convenient alternative to currently available conventional s.c. preparations by decreasing infusion time and the number of infusion sites. Immune globulin subcutaneous (human) is a 20% concentrated, sterile liquid preparation of highly purified and functionally intact human Ig, developed specifically for s.c. administration (IGSC 20%) to provide patients with an additional treatment option. Presented here are the results of a multi-centre Phase 2/3 study that evaluated efficacy, safety, tolerability and pharmacokinetic (PK) characteristics of this new IGSC 20% treatment when administered to adult and paediatric patients with PIDD without dose adjustment relative to the previous i.v. or s.c. Ig product.

Material and methods

Study design

This prospective, non-controlled clinical trial in patients with PIDD was conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice in 16 clinical sites in seven countries in Europe (registered on clinicaltrialsregister.eu: EudraCT #: 2010-019459-23 and www.clinicaltrial.gov, identifier: NCT01412385). In period 1, patients received IGIV 10% for 13 weeks or IGSC 16% for 12 weeks to ensure a stable baseline serum IgG prior to IGSC 20% treatment. In

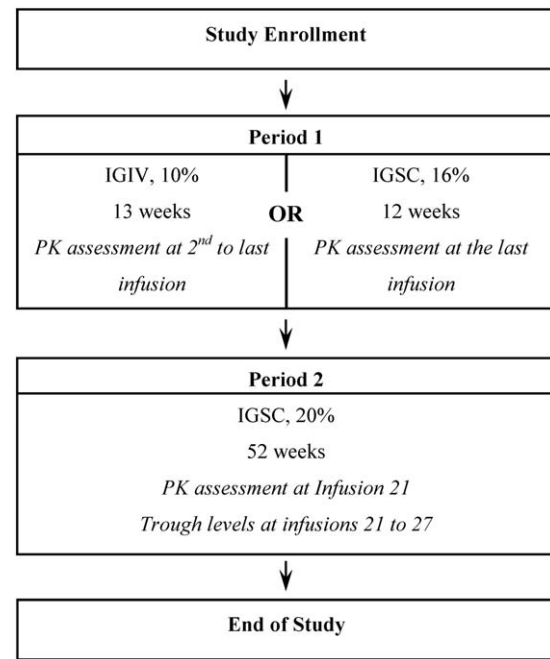


Fig. 1. Study design. i.v. = intravenous; s.c. = subcutaneous; IGIV 10% = 10% immunoglobulin (Ig) treatment administered i.v.; IGSC 16% = 16% Ig treatment administered s.c.; PK = pharmacokinetics.

period 2, patients were treated with IGSC 20% for 52 weeks (Fig. 1).

Study population

Patients aged ≥ 2 years qualified for participation in the study if they had a documented diagnosis of PIDD requiring IgG replacement therapy, as defined by the International Union of Immunological Societies (IUIS) Scientific Committee 2009 [10] and by diagnostic criteria according to Conley *et al.* [11]. Additionally, patients had to have received a stable monthly dose of IgG (i.v. or s.c.) of 0.3–1 g/kg BW/4 weeks for ≥ 3 months prior to first treatment in the study. Furthermore, they had to have serum IgG trough levels > 5 g/l at screening and have not had any serious bacterial infection within the 3 months prior to screening. Patients were ineligible if they had a history of hepatitis B or C or a positive human immunodeficiency virus test; if they had an infection and/or were receiving antibiotics; if they had abnormal alanine or aspartate aminotransferase values > 2.5 times the upper limit of normal for the testing laboratory, creatinine clearance value $< 60\%$ of normal according to their age and gender or severe neutropenia; and if they had a history of thrombotic episode, malignancy, protein loss, severe dermatitis, hypersensitivity to Ig treatment or selective IgA deficiency (IgA < 7 mg/dl) with anti-IgA antibodies and history of hypersensitivity. A complete list of eligibility criteria is available in the

Supporting information. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Study product

The production of IGSC 20%, a liquid concentrate of aggregate-free IgG derived from human plasma, follows the same manufacturing processes as IGI, 10% solution [Gam-magard Liquid[®] in the United States and Kiovig[®] in the European Union (EU); Baxalta Inc., now part of Shire Bannockburn, IL, USA] except for ultra-/diafiltration and final formulation at 20% (w/v) protein concentration. The manufacturing process of IGSC 20% includes three dedicated virus inactivation and reduction steps [12–15]. IGSC 20% contains glycine as stabilizer to minimize IgG dimerization. The final IGSC 20% product has a viscosity of 14.4 mPa.s, an osmolality of 280–292 mOsm/kg and contains trace amounts of IgA (average concentration: 80 µg/ml). Each lot of IGSC 20% is monitored for pro-coagulant activity using a thrombin generation assay to ensure that the final container is free of pro-coagulants.

Immunoglobulin treatments

During period 1, patients received either IGSC 16% (Subcuvia[®]) every week or every other week, or IGIV 10% (Kiovig[®]) every 3 or 4 weeks at the same dose as the pre-study dose. Administration, route and infusion frequency were dependent upon the prior treatment. During period 2, patients were administered IGSC 20% once a week at the same dose as in period 1 (adjusted to a weekly equivalent dose). IGSC 20% was infused using an electromechanical syringe-driver pump (CME T34L; Caesarea Medical Electronics, Caesarea, Israel) and 24-gauge needles (MarCal Medical Millersville, MD, USA). The needle sets used in the trial ranged from 6 to 12 mm in length at the discretion of the investigator; there was no specified needle length for infusion. If needed, the immunoglobulin dose was to be increased, to maintain IgG trough levels > 5 g/l in line with current treatment guidelines [16]. For patients with a BW of 40 kg or above, an infusion volume of up to 60 ml was to be administered per infusion site if well tolerated. For patients with BW below 40 kg, IGSC 20% infusion volumes were limited to 20 ml/site for the initial two infusions. Volumes could then be increased to a maximum of 60 ml/site as tolerated. Infusion rates were increased incrementally: the initial two infusions were started at 10 ml/h/site, and could be increased to a maximum of 20 ml/h/site. Subsequent IGSC 20% infusions could begin at the maximum tolerated rate, and as tolerated, the rate could be increased in a stepwise manner to a maximum of 60 ml/h/site. Multiple infusion

sites could be used simultaneously. Infusion sites were to be rotated to avoid any single infusion site being used repeatedly within a short time-interval. Infusion of IGSC 20% at home was possible after sufficient training of the patient/caregiver or with assistance of a health-care professional.

Efficacy assessment

Serious bacterial infections (e.g. bacteraemia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and visceral abscesses) caused by a recognized bacterial pathogen and diagnosed according to the Diagnostic Criteria for Serious Infection Types in the Food and Drug Administration (FDA) Guidance for Industry, June 2008 [17] were analysed. The primary efficacy assessment was the annualized rate of validated acute serious bacterial infections (VASBIs, defined as R_{VASBI} = mean number of VASBI/patient-year). Assessment of efficacy also included the annualized rate of all infections (i.e. VASBIs and all other events assessed clinically as infections), of fever episodes (body temperature $\geq 38^{\circ}\text{C}$), of days with fever and of days missed from school/work/daily activities due to illness/infection, the annualized rate of admissions to a hospital, duration of stay in the hospital as in-patient, as well as urgent/unscheduled physician visits due to illness/infection (apart from the regular investigator/study site visits scheduled every 8–12 weeks within the study).

Safety

Safety was evaluated through clinical and laboratory assessments. Safety data were collected throughout the study. The adverse events (AEs) that occurred during infusions at the study site (every 8–12 weeks) were recorded by the investigator. All investigators were trained specifically on symptoms of potential AEs. All patients received a diary to record home treatments, AEs and additional information continuously as they occurred. The investigator provided guidance for the patient/caregiver regarding identification and documentation of local and systemic AEs, including signs of haemolysis such as fever, chills, back pain, fatigue and dark urine. All patients were instructed to inform the investigator/site immediately in case of such an event. In addition, the patient was contacted by the investigator within 3–5 days after each infusion, either at the study site or at their home for follow-up to ensure appropriate documentation of AEs. The investigators reviewed patients' diary entries at every site visit. All AEs were assessed by the investigator using comprehensive data collection systems – including the patient's diary – for seriousness, severity, temporal association and possible causal relatedness to the immunoglobulin treatment.

Monitoring for potential cases of haemolysis included routine haematology screening and haemolysis screening as recommended by the FDA Guidance for Industry (June, 2008 [17]). If a decrease of haemoglobin ($\geq 2\text{g/dl}$) was

Table 1. Demographics and baseline characteristics of treated patients

Parameter	<i>n</i> = 49
Gender (<i>n</i> , %)	
Male	30 (61.2)
Female	19 (38.8)
Age (years)	
Median	17.0
Min; max	2; 67
Weight (kg)	
Median	63.00
Min; max	12.85; 140.00
Age group (years) (<i>n</i> , %)	
2 to < 6	5 (10.2)
6 to < 12	8 (16.3)
12 to < 18	12 (24.5)
18 to < 65	21 (42.9)
65 years and older	3 (6.1)
Primary immunodeficiency* (<i>n</i> , %)	
Common variable immunodeficiency	32 (65.3)
X-linked agammaglobulinaemia	9 (18.4)
Autosomal recessive hypogammaglobulinaemia	2 (4.1)
Hyper-IgM syndrome	2 (4.1)
Specific antibody deficiency	2 (4.1)
with IgG subclass deficiency	
Specific antibody deficiency	1 (2.0)
IgG and IgM deficiency	1 (2.0)

Ig = immunoglobulin. *Diagnosis of primary immunodeficiency disease (PIDD) involving defective antibody production and requiring IgG replacement as defined by the International Union of Immunological Societies (IUIS) Scientific Committee 2009 [10] and diagnostic criteria according to Conley *et al.* [11].

measured during either the haematology or haemolysis screening, the assessments to monitor for potential cases of haemolysis were to be performed within 48–72 h of being informed of the haemoglobin level, unless there was a clear alternative explanation. These assessments included: direct anti-globin (Coomb's) test, plasma-free haemoglobin, reticulocyte count, lactate dehydrogenase (LDH), serum haptoglobin and urine haemosiderin.

Pharmacokinetics

Serum IgG concentrations were determined at a central laboratory using a validated enzyme-linked immunosorbent assay (ELISA)-based assay. Pharmacokinetic (PK) assessments of IgG levels were performed in patients aged ≥ 12 years. In period 1, PK samples were collected between the penultimate and the last infusions for patients treated with IGIV 10% and after the last infusion prior to period 2 for patients receiving IGSC 16%. In period 2, PK samples were collected between IGSC 20% infusion 21 and infusion 22. All patients underwent regular IgG trough level assessment during period 1 at intervals of 3–4 weeks. During IGSC 20% treatment, serum IgG trough levels were

measured prior to infusion 1, and then every 8 weeks from infusion 5 to 21 and from infusion 27 until the end of study; between infusions 21 and 27 trough levels were measured weekly.

Statistical methods

Assuming $R_{VASBI} = 0.6$, a one-sided test and a type I error = 0.01, a sample size of 47 patients would have in excess of 84% power to test the null hypothesis that $R_{VASBI} \geq 1.0$ against the alternative hypothesis $R_{VASBI} < 1.0$. R_{VASBI} and the upper limit of 99% confidence interval (CI) were calculated using a Poisson model accounting for the variable length of observation periods. The area under the curve (AUC) between adjacent infusions was calculated by the trapezoidal rule. To allow for comparisons between treatments, AUC_{0– τ} was standardized for the infusion intervals (2, 3 or 4 weeks *versus* 1 week = AUC_{0– τ ;h}). The bioavailability of IGSC 20% relative to IGIV 10% was estimated from the ratio of AUC_{0– τ ;h} in period 2 over AUC_{0– τ ;h} in period 1 standardized to 1 week.

Measures of patient experience

Treatment burden related to Ig therapy was evaluated with the Life Quality Index questionnaire (LQI) for patients aged 2–13 years (observer: parent) and patients aged 14 years and older (observer: patient) [18,19]. The LQI covers four domains: treatment interference, therapy-related problems, therapy settings and treatment costs. Patients received free treatment during the study; thus, the cost domain is not reported. Quality of life was surveyed in patients aged 2–7 years (observer: parent) and aged 8–13 years (observer: patient) using the Pediatric Quality of Life InventoryTM (PEDS-QL) questionnaire [20] and in patients aged 14 years and older (observer: patient) using the SF-36 survey [21]. The EQ-5D Health Questionnaire [22] was used for all patients [aged 2–11 (observer: parents) and aged 12 years and older (observer: patient)]. Evaluations were performed at study start, at week 21 of period 2 and at the 'end-of-study' visit (or early termination visit). Score changes between the start of period 2 and the 'end-of-study' visit were analysed. In all questionnaires, higher scores indicated higher satisfaction.

Treatment preference outcomes were analysed separately for the patient age groups of 2–13 years (observer: parent) and 14 years and older (observer: patient) at the 'end-of-study' visit.

Results

Study population

Forty-nine patients with PIDD started period 1 (30 male, 19 female; age range = 2–67 years, Table 1). The majority of patients had either CVID (65.3%) or

Table 2. Efficacy of protection against infections

Parameters	Total number of events and annualized rate per patient*		
	IGIV 10%	IGSC 16%	IGSC 20%
	<i>n</i> = 33 (8.42 PY) [†]	<i>n</i> = 16 (3.70 PY) [†]	<i>n</i> = 48 (45.66 PY) [†]
Validated acute bacterial infections (upper limit 99% CI)	0 (0.0) (0.547)	1 (0.270) (0.851)	1 (0.022) [‡] (0.049)
All infections [§]			
<i>n</i>	53	33	200
Point estimate	6.29	8.92	4.38
95% CI	4.20–8.99	6.36–12.09	3.38–5.56
Number of fever episodes			
<i>n</i>	8	8	40
Point estimate	0.95	2.16	0.88
Days with fever			
<i>n</i>	22	34	150
Point estimate	2.61	9.19	3.29
Days off school or work			
<i>n</i>	90	187	710
Point estimate	10.69	50.42	15.55
95% CI	5.34–18.78	19.64–103.37	10.06–22.75
Days on antibiotics			
<i>n</i>	165	201	827
Point estimate	19.59	54.34	18.11
95% CI	12.59–28.80	31.44–86.32	13.01–24.41
Days in hospital			
<i>n</i>	1	9	76
Point estimate	0.12	2.43	1.66
95% CI	0.04–0.26	0.69–5.94	0.74–3.16
Number of hospitalizations			
<i>n</i>	1	2	7
Point estimate	0.12	0.54	0.15
95% CI	0.04–0.26	0.16–1.31	0.08–0.26
Number of acute physician visits			
<i>n</i>	43	28	172
Point estimate	5.11	7.57	3.77
95% CI	2.97–8.08	3.57–13.81	2.56–5.30

*Rate = number of infections divided by the total number of patient-years (PY) under treatment. [†]Patient-years = number of patient-years under treatment. [‡]For the null hypothesis of one or more validated acute bacterial infections (VASBIs) per year, *P*-value < 0.0001. [§]VASBIs and all other events assessed clinically as infections during the study. CI = confidence interval; *n* = number of treated patients. IGIV = intravenous immunoglobulin; IGSC = subcutaneous immunoglobulin.

agammaglobulinaemia (22.4% congenital and autosomal recessive combined, Table 1). All patients had received antibody replacement therapy until just prior to study entry (67.3% i.v.; 32.7% s.c.); the administration route in period 1 stayed the same as in the pre-study period. Forty-eight patients continued into period 2 and received IGSC 20%; 45 (93.8%) patients completed period 2 (Supporting information, Fig. S1). One patient withdrew prematurely during period 1 after becoming pregnant. In period 2, 3 patients discontinued prematurely: one 13-year-old patient (patient B) reported pain during and after administration and chose to stop participation and two patients withdrew consent for reasons unrelated to an AE (Supporting information, Fig. S1).

Efficacy

The rate of VASBIs during IGSC 20% treatment was significantly lower than 1 ($R_{VASBI} = 0.022$ event/patient-year, upper limit of 99% CI = 0.049; *P* < 0.0001) across all age groups (Table 2). Two VASBIs of bacterial pneumonia occurred in an 11-year-old patient who had X-linked agammaglobulinaemia: one occurred during IGSC 16% treatment and one occurred approximately 1 year after the first case, during IGSC 20% treatment. Both pneumonia episodes were treated with parenteral antibiotics in the hospital.

The annualized rate of any infection was 4.38 events/patient during IGSC 20% treatment (Table 2). One 39-year old patient with CVID experienced two severe non-

Table 3. Summary of adverse event (AE) analysis

AE categories	Treatments					
	IGIV 10%		IGSC 16%		IGSC 20%	
	Number (%) of patients (n = 33)	Number (rate)* of AEs (n = 139)	Number (%) of patients (n = 16)	Number (rate)* of AEs (n = 181)	Number (%) of patients (n = 48)	Number (rate)* of AEs (n = 2349)
Non-serious AEs (excluding infections)						
All	24 (72.7)	99 (0.712)	12 (75.0)	35 (0.193)	41 (85.4)	524 (0.223)
Mild	23 (69.7)	85 (0.612)	10 (62.5)	25 (0.138)	39 (81.3)	438 (0.186)
Moderate	7 (21.2)	14 (0.101)	7 (43.8)	10 (0.055)	18 (37.5)	84 (0.036)
Severe	0	0	0	0	2 (4.2)	2 (0.001)
Causally related non-serious AEs (excluding infections)						
All	7 (21.2)	24 (0.173)	5 (31.3)	11 (0.061)	20 (41.7)	237 (0.101)
Mild	6 (18.2)	21 (0.151)	4 (25.0)	10 (0.055)	20 (41.7)	187 (0.08)
Moderate	2 (6.1)	3 (0.022)	1 (6.3)	1 (0.006)	4 (8.3)	50 (0.021)
Severe	0	0	0	0	0	0
Causally related local non-serious AEs (excluding infections)						
All	0 (0)	0 (0)	1 (6.3)	1 (0.006)	17 (35.4)	162 (0.069)
					16 (33.3) [†]	83 (0.036) [†]
Mild	0 (0)	0 (0)	1 (6.3)	1 (0.006)	17 (35.4)	160 (0.068)
					16 (33.3) [†]	81 (0.035) [†]
Moderate	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.1)	2 (0.001)
Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Causally related systemic non-serious AEs (excluding infections)						
All	7 (21.2)	24 (0.173)	5 (31.3)	10 (0.055)	8 (16.7)	75 (0.032)
Mild	6 (18.2)	21 (0.151)	4 (25.0)	9 (0.050)	7 (14.6)	27 (0.011)
Moderate	2 (6.1)	3 (0.022)	1 (6.3)	1 (0.006)	3 (6.3)	48 (0.020)
Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAEs (including infections)						
All	2 (6.1)	2 (0.014)	2 (12.5)	2 (0.011)	6 (12.5)	8 (0.03)
Mild	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.1)	1 (< 0.001)
Moderate	2 (6.1)	2 (0.014)	2 (12.5)	2 (0.011)	5 (10.4)	5 (0.002)
Severe	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.1)	2 (0.001)
Causally related SAEs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Causally related AEs leading to discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.1)	1 (< 0.001)
AEs leading to death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

*Rate per infusion = total number of AEs divided by the total number of infusions under treatment. [†]Data excluding 13-year-old patient A who reported 48.8% (79 of 162) of the local AEs deemed related causally to IGSC 20% treatment; all 79 AEs were of mild severity. SAE = serious adverse event; n = total number of patients or total number of infusions under treatment. IGIV = intravenous immunoglobulin; IGSC = subcutaneous immunoglobulin.

serious infections during IGSC 20% administration (one bronchitis and one influenza infection). While receiving IGSC 20% treatment, patients missed school/work at an annualized rate of 15.55 days. For the 34 (70.8%) patients who required antibiotics to treat infections during IGSC 20% treatment the annualized rate of days on antibiotics was 18.11. The rate of hospitalization was 0.15 event/year for a duration of 1.66 days/year. The rate of acute (urgent or unscheduled) physician visits due to infection or other illness was 3.77 events/year (Table 2).

Safety

No causally related serious AE (SAE) occurred during IGSC 20% treatment (Table 3). During the entire course of

the study, there were 12 unrelated SAEs: two SAEs were severe in nature (acute myocardial infarction and ventricular fibrillation), nine were moderate [lymphadenopathy, forearm fracture, bacterial pneumonia (two events, as described above), thoracic vertebral fracture, enteritis, chronic sinusitis, brain stem infarction and rhinorrhoea] and one mild (nasal septum deviation). The rate of non-serious AEs was 0.223 event/infusion during IGSC 20% treatment. In period 1, the incidence of non-serious AEs was 0.712 event/infusion during IGIV 10% administration and 0.193 event/infusion for patients receiving IGSC 16%. Of 2349 IGSC 20% infusions administered during the study, 2166 infusions (92.2%) were not associated with a causally related non-serious AE; there was no severe AE deemed causally related to IGSC 20% (Table 3).

Table 4. Causally related adverse events (AEs) during IGSC 20% treatment

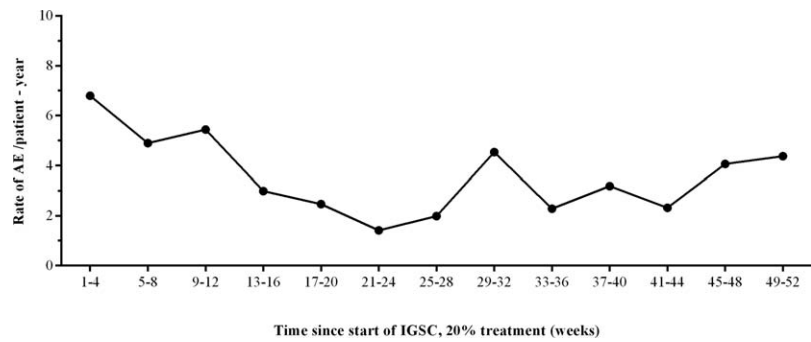
System organ class	Preferred MedDRA term (version 17.1)	AEs	Number (%) of patients (<i>n</i> =48)	Rate of AEs per infusions (<i>n</i> =2349)
		<i>n</i>	<i>n</i> (%)	<i>R</i> *
Nervous system disorders	Headache	22	3 (6.3)	0.0094
Vascular disorders	Hypotension	1	1 (2.1)	0.0004
Gastrointestinal disorders	Diarrhoea	47	2 (4.2)	0.0200
	Abdominal pain	1	1 (2.1)	0.0004
General disorders and administration site conditions	Local reactions	163	17 (35.4)	0.0694
	●Infusion site erythema (including injection site erythema)	54	10 (20.8)	0.0230
	●Infusion site swelling	46	4 (8.3)	0.0196
	●Injection site pruritus (including infusion site pruritus)	30	7 (14.6)	0.0128
	●Injection site pain (including infusion site discomfort and infusion site pain)	24	6 (12.5)	0.0102
	●Infusion site urticaria	5	1 (2.1)	0.0021
	●Infusion site bruising	1	1 (2.1)	0.0004
	Fatigue	3	2 (4.2)	0.0013
	Investigations	Positive direct Coomb's test	1	1 (2.1)

*Rate per infusion = total number of AEs divided by the total number of infusions under treatment. IGSC = subcutaneous immunoglobulin.

Systemic AEs assessed as causally related to IGSC 20% treatment were reported in 16.7% of patients with an incidence of 0.032 event/infusion. The most frequent systemic AEs related to IGSC 20% infusion were diarrhoea (0.02 event/infusion) followed by headache (0.0094 event/infusion) and fatigue (0.0013 event/infusion). While on IGSC 20% treatment, 6.3% of patients experienced headache, 4.2% had diarrhoea and 4.2% reported fatigue (Table 4). Most (46 of 47) of the diarrhoea events were observed in one patient with CVID who had a medical history of ongoing recurrent diarrhoea prior to the study. Excluding this patient, only one patient (2.1%) experienced one event of diarrhoea that was deemed related to IGSC 20% (0.0004 event/infusion). Other systemic AEs deemed causally related to IGSC 20% (hypotension, abdominal pain and positive direct Coomb's test) were rarely reported, each at a rate of 0.0004 events/infusion in 2.1% of patients. There was no event of laboratory-confirmed haemolysis during periods 1 or 2 with IGSC 20% administration. In six patients a temporary decline in haemoglobin of 2.0 g/dl or more was reported [during IGIV 10% treatment (*n* = 1), during IGSC 16% treatment (*n* = 2) and during IGSC 20% administration (*n* = 5)]. However, at no time was there a concordance of other laboratory test (e.g. Coomb's test, haptoglobin, free haemoglobin, LDH, urine, haemosiderin) results, indicating a diagnosis of haemolysis in those patients.

Local reactions were the most common related AEs during IGSC 20% treatment (0.0694 event/infusion; Table 4). Overall, 35.4% of patients reported local AEs related to IGSC 20% treatment during the study. In total 2228, of 2349 (94.8%) of IGSC 20% infusions were administered without the occurrence of a causally related local AE. In addition, the proportion of patients affected by a related local AE decreased in the course of the study: at the beginning of the study, 12.5% of patients experienced a local AE related to IGSC 20% treatment; after infusion 4, related local AEs occurred in 0–9% of patients. The rate of AEs/patient-year over time is shown in Fig. 2. Of note, 79 of a total of 162 causally related local AEs were reported in a single patient (patient A) by the parent; all of them were mild, and this patient/parent desired to continue and completed the study. In addition, the patient/parent expressed preference for IGSC 20% over the other immunoglobulin treatment options at the end of study. In a subanalysis excluding related local AEs reported by this patient, the frequency of local AEs related to IGSC 20% treatment was low, with 0.036 event/infusion. Another patient, aged 16 years (patient B), experienced three local AEs of mild pain assessed by the investigator as possibly (two) or probably (one) related to IGSC 20% infusion and chose to discontinue from the study due reportedly to pain during and after administration. Both adolescent patients had been receiving IGIV 10% during period 1.

Fig. 2. Related local adverse events (AEs) reported over time during immunoglobulin (Ig) treatment administered subcutaneously (IGSC) 20% treatment. Annualized rate of related local AEs over time for the planned treatment period (52 weeks). Annualized rate of causally related local AEs = number of causally related local AEs divided by the total number of patient-years under IGSC 20% treatment.



IGSC 20% administration characteristics

Patients received IGSC 20% at a mean [\pm standard deviation (s.d.)] weekly dose of 0.125 ± 0.042 g/kg/week for a median duration of 358 days (range = 127.0–399). Dose increase due to insufficient (5 g/l or below) trough levels was required for two patients with CIVD. One of them was a 65-year-old patient who was previously on a subcutaneous immunoglobulin dose at the lower end of the recommended dose range, resulting in borderline IgG trough levels. The other patient was a 17-year-old who showed a persistent decrease in IgG trough levels despite increasing the IGSC 20% dose several times. Concomitantly, this patient developed an enlarged lymph node which was examined histologically as a benign lymphoproliferation. A total of 2346 infusions of IGSC 20% were administered during the study, 74.1% (1740 of 2349) of which were at home. Even patients who had transitioned to home care were required per protocol to attend scheduled site visits, and thereby received some infusions at the study site. For 95.8% of patients, at least one IGSC 20% infusion was performed at home with or without professional assistance.

A maximum rate of ≥ 40 ml/h/site was achieved by 41.6% of patients at least once and 22.3% of IGSC 20% infusions were infused at this rate. Close to half the patients (47.9%) received at least one infusion with a volume of ≥ 20 ml/site and this volume was infused per site in 31.8% of infusions. The overall median number of sites/infusion for administration of IGSC 20% was 2.0 (range = 1–5); among patients aged 2–5 years ($n = 5$), a median of one site/infusion (range = 1–2) was used (Table 5). Most (87%) of IGSC 20% infusions were administered in two or fewer sites (two sites: 75.6% of infusions; one site: 11.4%).

Tolerability

The short-term tolerability of IGSC 20% treatment was evaluated by recording infusions for which the infusion rate had to be reduced, or the administration was interrupted/stopped due to tolerability concerns or AEs. No infusion rate reduction, administration interruption/stoppage was required for 99.8% of IGSC 20% infusions. The infusion rate had to be reduced in five (0.2%) IGSC 20% infusions administered to two adolescent patients (patient

C, 12 years old and patient D, 13 years old). A comparison of infusion characteristics for infusions that were and were not associated with causally related AEs showed no correlation between the infusion rates or higher infusion volume per site and the incidence of related local AEs (Fig. 3a,b). Therefore, the selection of relatively lower infusion rates and volumes per site compared with the allowed maximums per protocol was due to patient and/or physician preference rather than tolerability limitations.

Pharmacokinetic parameters and serum IgG trough levels

The PK profile of serum IgG in the course of IGSC 20% treatment is depicted in Fig. 4. Following IGSC 20% infusion there was no peak in serum IgG levels when compared to the pre-infusion levels (day 0), and IgG levels remained constant throughout the treatment interval (range = 9.0–9.4 g/l). PK parameters of IGSC 20% administration are summarized in Table 6. The bioavailability of IGSC 20% relative to IGIV 10% was 82.07% (90% CI = 77–88%), as determined from the ratio of the geometric means for the respective AUCs. Serum IgG trough values measured for 6 consecutive weeks of weekly IGSC 20% treatment (weeks 21–27) attained a median of 8.48 g/l (range = 5.17; 13.25). At the end of the IGSC 20% treatment period the median serum IgG trough level was 8.26 (range = 4.27–15.87; Table 7). At the end of period 1, the median serum IgG trough levels attained 7.45 g/l (range = 4.27–12.75) in patients who received IGIV 10% every 4 weeks and 9.53 g/l (range = 5.41–12.28) in patients treated with IGSC 16% once every week (Table 7).

Patient experience

For the LQI that evaluated treatment burden related to Ig therapy and for the patient quality-of-life questionnaires (PEDS_QL, SF-36, and EQ-5D Health), no statistically significant score change was observed between start of period 2 and the 'end-of-study' visit; however, results of the EQ-5D health indicated a trend towards improvement for all age groups (2–11 years, observer: parent; 12 years and older, observer: patient). With the PEDS_QL

Table 5. Administration characteristics for IGSC 20% per age group

Parameters*	Age group (years)					All patients (n = 48)
	2 to < 6 (n = 5)	6 to < 12 (n = 8)	12 to < 18 (n = 12)	18 to < 65 (n = 20)	65 and older (n = 3)	
Duration of infusions (h)						
Infusions (n)	253	408	550	1009	115	2335
Median	0.75	1.0	1.0	1.0	0.5	0.95
Min; max	(0.4; 3.0)	(0.4; 2.5)	(0.3; 3.3)	(0.3; 4.1)	(0.4; 2.3)	(0.3; 4.1)
Number of sites per infusion						
Infusions (n)	253	408	550	1012	115	2338
Median	1.0	2.0	2.0	2.0	2.0	2.0
Min; max	(1; 2)	(1; 2)	(1; 4)	(1; 5)	(1; 3)	(1; 5)
Maximum infusion rate (ml/h/site)						
Infusions (n)	253	408	550	1012	115	2338
Median	20.0	15.0	23.5	20.0	40.0	20.0
Min; max	(2.5; 40.0)	(5.0; 40.0)	(5.0; 40.0)	(5.0; 60.0)	(10.0; 40.0)	(2.5; 60.0)
Infusion volume (ml/site)						
Infusions (n)	253	408	550	1012	115	2338
Median	14.0	11.2	17.5	18.8	16.5	16.6
Min; max	(6.5; 26.0)	(9.5; 27.0)	(10.0; 42.5)	(10.4; 48.0)	(11.1; 20.0)	(6.5; 48.0)

*Only infusions with complete infusion parameters have been considered for each analyses. IGSC = subcutaneous immunoglobulin.

and the LQI, moderate score improvements were observed for patients aged 2–7 years (PEDS_QL observer: parent) and patients aged 2–13 years (LQI; observer: parent), respectively. At the last site visit, 42 of 48 (87.5%) of patients stated that they would choose to continue receiving IGSC 20% treatment over other treatments (Fig. 5). Patient A (who reported almost half of the total adverse reactions in the study) and patients C and D (in whom the infusion rate had to be reduced) also preferred IGSC 20% treatment. Both younger and older age groups were consistent in their desire to continue treatment with IGSC 20%: 21 of 25 (84.0%) of patients ≤ 13 years and 21 of 23 (91.3%) of patients > 13 years preferred IGSC 20% to alternative treatment methods. The majority of patients 'liked' or 'liked very much' the ease of administration (87.5%), the less complex administration process (75%), the total time spent for treatment per month (79.2%) and the overall convenience (89.6%) of IGSC 20% treatment.

Discussion

While immunoglobulin replacement therapy administered by the s.c. or the i.v. route is similarly safe and efficient, IGSC may be of particular interest to patients prone to systemic adverse reactions during IGIV therapy or patients preferring self-infusion at home [4,5]. The primary disadvantage of IGSC compared to IGIV preparations is the limited volume that can be infused at a slow rate to each s.c. site. A highly concentrated IgG formulation such as the

IGSC 20% product investigated in this study would offer patients with PIDD a new replacement therapy option with fewer infusion sites and shorter infusion durations compared with other conventional IGSC products.

In this trial, weekly IGSC 20% treatment at monthly doses equivalent to those administered with IGIV 10% or IGSC 16%, was efficacious in preventing infections. The annualized rate of VASBIs per patient during IGSC 20% was low and significantly below the level defined by the FDA [17] and the European Medicines Agency (EMA) Guidelines [23,24] to demonstrate efficacy. Consistent with the protective effect of IGSC 20% in patients with PIDD, the annualized incidence of any infections (4.38 events/patient) in this trial was comparable to the annualized frequency of any infection reported with a licensed IGSC 20% preparation (5.18 events/patient-year) [25] and with other less concentrated IGSC preparations: 3.946 events/patient in a 6-month study with IGSC 16% [26] or 4.1 events/patient with an IGSC 10% product [27], although the validity of direct comparison may be impaired by differences in study designs and product concentrations. Moreover, the annualized rates of days on antibiotics (18.1 days/patient) was approximately four times lower than with another IGSC 20% product in an EU study (72.75 days/patient) [25]. These results, and the outcomes of additional assessments (e.g. days out of school/work; number and duration of hospitalization) establish the efficacy of IGSC 20% in PIDD patients.

To confer protection against infections in PIDD, serum IgG trough levels of > 5 g/l are generally accepted as the required minimum threshold; for some patients, trough

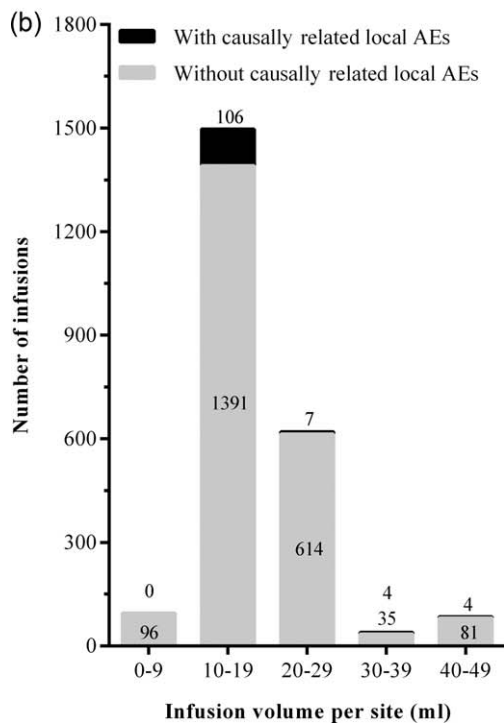
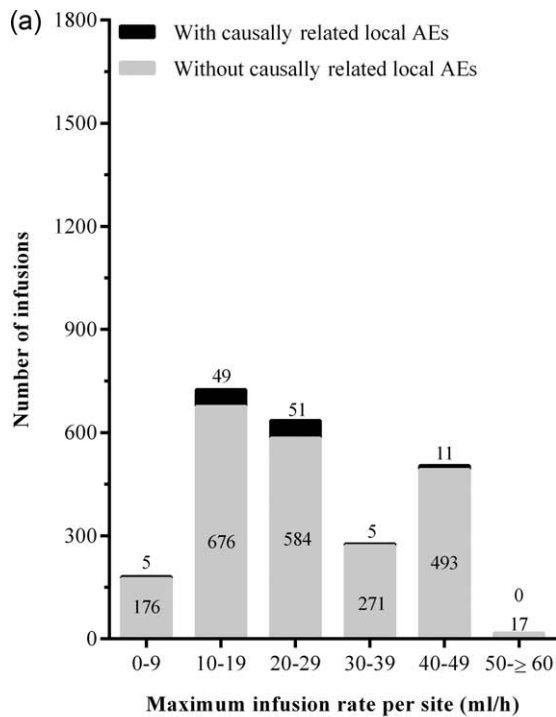


Fig. 3. Tolerability of immunoglobulin (Ig) treatment administered subcutaneously (IGSC) 20% infusions. (a) Infusion volumes; (b) Infusion rates. Numbers above the bars indicate the number of infusions associated with a causally related local AE and numbers inside the bars indicate the number of infusions not associated with any causally related local adverse event (AE). Only infusions with complete infusion histories ($n = 2338$) have been considered for these analyses.

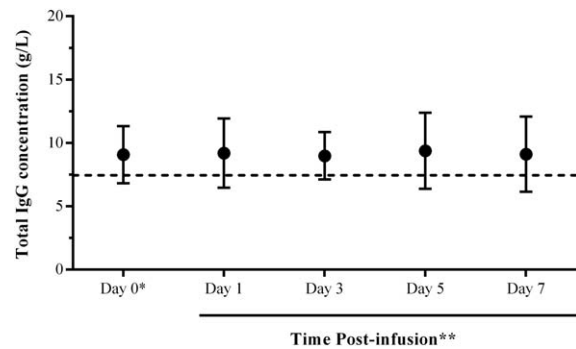


Fig. 4. Pharmacokinetic of immunoglobulin (Ig)G levels during the course of a treatment interval. Samples were collected on day 0 within 60 min prior to the first immunoglobulin (Ig) treatment administered subcutaneously (IGSC) 20% infusion and on days 1, 3, 5 and 7 post-infusion (± 6 h from infusion start). Plotted are the mean serum IgG concentrations in patients aged 12 years and older treated with IGSC 20%; minimum, 28 patients per time-point. Vertical bars represent standard deviations.

levels of at least 7 g/l may be necessary [25–27]. Consistent with the positive efficacy outcome in this trial, median serum IgG trough levels remained above 8 g/l throughout IGSC 20% treatment. The median weekly dose per BW necessary to achieve protective IgG trough levels (0.125 g/kg BW/week) was comparable to doses reported in EU studies conducted with another IGSC 20% product (0.119 g/kg BW/week and 0.156 g/kg BW/week, respectively) [25,28].

The bioavailability of the investigated IGSC 20% product relative to IGIV 10% was assessed as 82% (90% CI = 77–88%). In general, available conventional subcutaneous immunoglobulin preparations have a bioavailability that has been estimated to vary from 65 to 69% [29]. The bioavailability of the new IGSC 20%, calculated as the ratio of the geometric mean of AUC with IGSC 20% over that with IGIV 10%, appears to be higher. This may be due partly to differences in drug composition; however, the mechanisms modulating the bioavailability of SC administered immunoglobulin preparations are not yet well understood and require further research [30–33].

In comparison to IGIV, s.c. administration of Ig is generally associated with a lower incidence of systemic side-effects but a higher rate of causally related local AEs [34]. In the present trial, the rate of any AEs assessed as related to IGSC 20% was low (systemic: 0.032 event/infusion; local: 0.036 event/infusion -excluding one patient who was reported to experience almost half of the total causally related local adverse events- or 0.069 event/infusion, including all patients). The incidence of local AEs related to IGSC 20% was similar to rates observed with a licensed IGSC 20% preparation in an EU study (0.058 event/infusion) [25], and was much lower than rates observed in studies conducted in the United States (0.592 event/infusion) [35] and Japan (0.274 event/infusion) [36]. While a unique 13-year-old patient reported 48.8% of all the related local AEs associated with

Table 6. Pharmacokinetic parameters for IGSC 20% and IGIV 10% treatments

Parameter [unit]	IGSC 20% once a week (n = 31)*		IGIV 10% every 4 weeks (n = 16)*	
	Geometric Mean (95% CI)	Min;max	Geometric Mean (95% CI)	Min;max
AUC [g*days/L]	62.74 (57.38 to 68.59)	37.51;137.32	274.49 (245.07 to 307.45)	168.63;393.35
Clearance [†] [mL/kg/days]	1.83 (1.65 to 2.02)	1.12;3.24	1.51 (1.32 to 1.73)	1.04;2.39
Cmax [g/L]	9.82 (8.97 to 10.74)	5.90;20.69	15.82 (14.65 to 17.09)	11.70;21.24
Tmax [h]	72.42 (55.32 to 94.82)	19.78;192.33	8.46 (3.94 to 18.16)	1.97;101.83
Cmin [g/L]	8.06 (7.36 to 8.83)	4.42;16.33	6.72 (5.91 to 7.65)	4.27;11.66

*Patients aged 12 years and older; [†]Apparent clearance for SC administration. 95% CI = 95% confidence interval; IGSC = s.c.immunoglobulin; IGIV = intravenous immunoglobulin; AUC = area under the curve

IGSC 20% administration, this patient still completed the study and expressed a preference to remain on IGSC 20% treatment post-study. One other patient withdrew from the study because of mild local reactions of pain related to IGSC 20% treatment. None of the causally related local AEs was severe; the vast majority (98.8%) was of mild severity. More than half (64.6%) the patients did not experience any related local AEs and 94.8% of IGSC 20% infusions were not associated with any causally related local AE. IGSC 20% treatment was well tolerated overall: none of the infusions had to be interrupted or stopped due to AEs or tolerability concerns, and only 0.2% of IGSC 20% infusions required a reduction of infusion rate. Of note, the investigated IGSC 20% is stabilized with glycine and has an osmolality within the physiological plasma range; these factors may contribute to its high degree of tolerability compared to immunoglobulin products for subcutaneous administration using other stabilizers and/or with an osmolality outside of the physiological range [37,38]

The high concentration of IGSC 20% resulted in smaller infusion volumes and the favourable tolerability profile enabled the infusion of comparatively large volumes per site at high rates. More than a third of patients achieved a

maximum infusion rate of 40 ml/h/site to 60 ml/l/site, yet all IGSC 20% infusions were administered without interruption or stopping, indicating good overall tolerability of IGSC 20% at least equivalent to the tolerability observed with a similar licensed IGSC 20% product [25]. The possibility that the favourable tolerability of increased infusion rates was related to the amount of subcutaneous adipose tissue is unlikely, as 69% of patients had a body mass index below 25 kg/m².

As a result of the well-tolerated high infusion rates, infusion duration was reduced and fewer infusion sites were required compared to other conventional s.c. products. The median duration of IGSC 20% infusion was 0.95 h, which is shorter than the infusion duration reported for a licensed IGSC 20% product in two studies, median range = 1.14–1.27 h in one study and mean = 1.18 h in the other [25,28]. A median of two infusion sites were used to administer IGSC 20% in this study, which is lower than the 3.3 (mean) infusion sites reported for a licensed IGSC 16% product [28] and substantially lower than the five (median) infusion sites reported for IGSC 10% [27].

Overall, subcutaneous administration of immunoglobulin treatment was well accepted across all age groups,

Table 7. Trough levels of total immunoglobulin (Ig)G at the end of treatment periods

Treatment (interval)	n	Geometric mean (95% CI)	Median (95% CI)	Min; max	
IGIV 10% (4 weeks)	End of period 1	27	7.20 (6.54–7.93)	7.45 (6.29–8.05)	4.27; 12.75
IGSC 16% (1 week)	End of period 1	14	8.97 (7.77–10.35)	9.53 (7.78–11.31)	5.41; 12.28
IGSC 20% (1 week)	Week 21–27	46	8.73 (8.13–9.38)	8.48 (7.94–9.90)	5.17; 13.25
	End of period 2	40	8.27 (7.48–9.13)	8.26 (7.30–8.96)	4.27; 15.87

95% CI = 95% confidence interval. IGIV = intravenous immunoglobulin; IGSC = subcutaneous immunoglobulin.

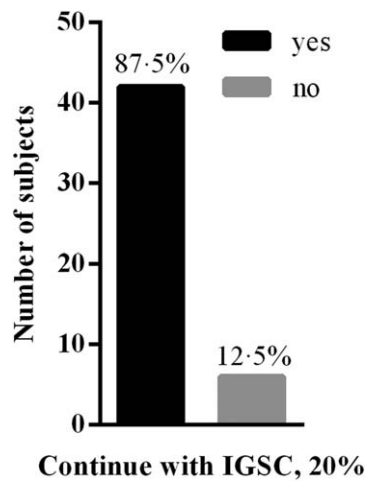


Fig. 5. Patients who chose to continue with immunoglobulin (Ig) treatment administered subcutaneously (IGSC) 20% at the end of the study. Treatment preference was analysed separately for the age groups 2–13 years (observer: parent) and 14 years and older (observer: patient) at the 'end-of-study' visit ($n = 48$). Plotted are the number of patients who declared that they would continue with immunoglobulin (Ig) treatment administered subcutaneously (IGSC) 20% treatment (black bar) and the number of patients who would choose an alternative IgG replacement therapy (grey bar); the proportion of subjects in each category (%) is indicated above the bars.

as evidenced by the few discontinuations during IGSC 20% treatment: 93.8% patients (82% of the 2–<18-year-old patients) treated with IGSC 20% completed the study, suggesting that IGSC 20% treatment interfered minimally with daily activities of adults as well as paediatric patients. Home-based therapy, chosen by a large proportion (95.8%) of patients at least once and performed for 74.0% of infusions overall, may have facilitated adherence to treatment. Patients had a positive experience using IGSC 20% treatment: 87.5% of patients affirmed their preference for IGSC 20% over other antibody replacement treatments. Overall, patient-centred outcomes indicated that PIDD patients preferred receiving s.c. replacement therapy, in line with reports from other studies (reviewed in [5]).

In conclusion, IGSC 20% administered s.c. was safe and well tolerated in patients with PIDD. The efficacy of IGSC 20% treatment after a dose equivalent switch from previous Ig treatment was demonstrated by the low frequency of infections and the maintenance of protective serum IgG trough levels. The positive tolerability profile made infusion of IGSC 20% treatment at high rates possible, and its highly concentrated formulation allowed smaller volumes for equivalent doses to be given per administration. As a result, infusion duration was shortened and the number of infusion sites was decreased compared with available conventional s.c. preparations. The flexibility and convenience of IGSC

20% therapy were appreciated by patients, suggesting that IGSC 20% would be a valuable alternative treatment option for patients with PIDD.

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Author contributions

D. G., W. E., B. M. and H. L. contributed to study conception and design; C. B. wrote the manuscript; M. B., G. K., B. D., L. M., T. H., S. J., B. M., H. L., D. G. and L. Y. contributed to study conduction, as well as acquisition and interpretation of data; C. B., W. E., B. M., H. L., D. G. and L. Y. interpreted the data; W. E. performed the statistical analysis; all authors reviewed the manuscript and approved the final version.

Disclosures

M. B., G. K., B. D., L. M., T. H. and S. J. worked as investigators on this Baxalta (now part of Shire)-funded clinical study. S. J. has received support from CSL Behring, Shire, Baxalta (now part of Shire), Biotest, BPL, Grifols and Octapharma for projects, advisory boards, speaking, meetings and clinical trials. M. B. has participated in advisory boards for Baxalta (now part of Shire), CSL Behring and Octapharma; M. B. has worked as speaker for Baxalta (now part of Shire) and CSL Behring. B. D. has received honoraria from Baxalta (now part of Shire) for participating in a symposium and has received support from CSL Behring, Biotest, Octapharma, HUMAN BioPlazma LLC and LFB for research, speaking, meetings and clinical trial. C. B., W. E., B. M., H. L., D. G. and L. Y. are full-time employees at Baxalta (now part of Shire). W. E., B. M., H. L. and L. Y. are shareholders of Baxalta (now part of Shire).

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Supporting information

Additional Supporting information may be found in the online version of this article at the publisher's web-site:

List of Eligibility Criteria

Fig. S1. Patient disposition.