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Pharmacokinetics of a novel human intravenous immunoglobulin 10% in patients with primary immunodeficiency diseases: Analysis of a phase III, multicentre, prospective, open-label study

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ABSTRACT

Intravenous immunoglobulin (IVIG) therapy is commonly used to treat patients with primary antibody deficiency. This prospective, open-label, non-randomised, multicentre, phase III trial investigated the pharmacokinetics of a new 10% liquid IVIG product (panzyga®; Octapharma) in 51 patients aged 2–75 years with common variable immunodeficiency (n = 43) or X-linked agammaglobulinaemia (n = 8). Patients were treated with IVIG 10% every 3 (n = 21) or 4 weeks (n = 30) at a dose of 200–800 mg/kg for 12 months. Total immunoglobulin G (IgG) and subclass concentrations approximately doubled from pre- to 15 min post-infusion. The maximum concentration of total IgG (mean ± SD) was 21.82 ± 5.83 g/L in patients treated 3-weekly and 17.42 ± 3.34 g/L in patients treated 4-weekly. Median trough IgG concentrations were nearly constant over the course of the study, remaining between 11.0 and 12.2 g/L for patients on the 3-week schedule and between 8.10 and 8.65 g/L for patients on the 4-week schedule. The median terminal half-life of total IgG was 36.1 (range 18.5–65.9) days, with generally similar values for the IgG subclasses (26.7–38.0 days). Median half-lives for specific antibodies ranged between 21.3 and 51.2 days for anti-cytomegalovirus, anti-*Haemophilus influenzae*, anti-measles, anti-tetanus toxoid, anti-varicella zoster virus antibodies, and anti-*Streptococcus pneumoniae* subtype antibodies. Overall, IVIG 10% demonstrated pharmacokinetic properties similar to those of other commercial IVIG 10% preparations and 3- or 4-weekly administration achieved sufficient concentrations of IgG, IgG subclasses, and specific antibodies, exceeding the recommended level needed to effectively prevent serious bacterial infections.

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1. Introduction

Primary immunodeficiency diseases (PID) are a heterogeneous group of disorders characterised by an inability of the immune system to mount a sufficient response to invading pathogens (Durandy et al., 2013; Grimbacher et al., 2016; Picard et al., 2018). Antibody deficiencies requiring IgG replacement therapy, such as agammaglobulinaemia and common variable immune deficiency (CVID), are the most common forms of PID (Bonagura, 2013). Immunoglobulin G (IgG), isolated from pooled serum collected from multiple (usually several thousand) donors, is used to treat predominant antibody deficiency. IgG therapy reduces the frequency and severity of infections and duration of hospitalisation (Wood, 2012). IgG may be administered by intravenous or subcutaneous routes. Commercially available intravenous immunoglobulin (IVIG) products include older lyophilised formulations, along with 5% and 10% liquid formulations. Lyophilised formulations take time to reconstitute, and 5% liquid formulations require higher volumes of fluid to be administered, which can be critical in patients with significant cardiac or renal disease, and longer infusion times (Stein, 2010). In contrast, 10% liquid formulations require smaller volumes and have shorter infusion times.

The half-life of IgG is relatively long for a plasma protein and the pharmacokinetics are concentration-dependent (Roopenian and Akilesh, 2007). It is important to establish the pharmacokinetic properties of each individual IVIG formulation as pharmacokinetic differences among various IVIG and subcutaneous immunoglobulin (SCIG) preparations may be important in deciding which is most appropriate for an individual patient (Bonagura, 2013). Pharmacokinetic data are also important to ensure that adequate concentrations of total IgG, IgG subclasses and IgG antibodies specific to common pathogens as well as adequate trough concentrations are achieved with dosing schedules of a particular preparation.

A new high-yield, high-purity, glycine-stabilised human intravenous immunoglobulin at a concentration of 100 mg IgG/mL (10%) solution has been developed by Octapharma AG (panzyga® 10%; Lachen, Switzerland). Its manufacture involves various precipitation and chromatography processes for harvesting and purifying IgG, as well as two dedicated steps for pathogen safeguarding. IVIG 10% is manufactured from a large pool of at least 3500 donations of human fresh-frozen plasma, ensuring that it contains a diverse range of antibodies directed against pathogens and foreign antigens. The objective of this report is to present the pharmacokinetic findings from the NGAM-01 study, which assessed the efficacy, safety, pharmacokinetics and quality of life outcomes with IVIG 10% therapy in patients with predominant antibody deficiency (Borte et al., 2017).

2. Materials and methods

2.1. Study design

All 51 patients with predominant antibody deficiency who participated in the prospective, open-label, non-controlled, non-randomised phase III study (ClinicalTrials.gov record NCT01012323) of human IVIG 10% underwent evaluation of serum IgG pharmacokinetic parameters.

2.2. Inclusion and exclusion criteria

Full inclusion and exclusion criteria are described in the primary study publication (Borte et al., 2017). Briefly, patients (aged ≥2 years and ≤75 years) were included if they had a confirmed diagnosis of CVID or X-linked agammaglobulinaemia (XLA) and had previously been treated with a commercial IVIG preparation every 3 or 4 weeks for at least 6 infusions at a constant dose between 200 and 800 mg/kg, with documented IgG trough serum levels of ≥5.5 g/L during the two previous infusions prior to study enrolment.

Patients with severe liver impairment (alanine aminotransferase > 3× upper limit of normal), abnormal renal function (creatinine > 120 µmol/L), congestive heart failure (New York Heart Association class III or IV), non-controlled arterial hypertension (systolic BP > 160 mm Hg or diastolic BP > 90 mm Hg) or those positive for human immunodeficiency virus, hepatitis C virus, or hepatitis B virus were excluded from the study, as were pregnant or breastfeeding women.

2.3. Treatment

Full treatment details have been presented in the primary study publication (Borte et al., 2017). IVIG 10% at a dose of 200–800 mg/kg was infused every 3 or 4 weeks (based on patients' previous IVIG dosing schedule) for 12 months, unless medical conditions or other circumstances resulted in a patient's withdrawal from the study. Patients received either 17 or 13 IVIG 10% infusions, depending on whether their regular treatment interval was 3 or 4 weeks, respectively. To insure precise infusion rates, an infusion pump was used, starting at a rate of 0.01 mL/kg/min (60 mg/kg/h) for the first 30 min; if tolerated, rates were increased every 30 min to a maximum infusion rate of 0.08 mL/kg/min (480 mg/kg/h).

2.4. Pharmacokinetic assessments and statistical analysis

Blood samples were drawn immediately before each infusion for the determination of trough serum IgG concentrations. Additional blood samples for analysis of trough antigen-specific IgG antibodies to cytomegalovirus (CMV), *H. influenzae*, measles, tetanus, varicella zoster virus (VZV), and 7 *S. pneumoniae* subtypes (types 4, 6B, 9V, 14, 18C, 19F, 23F) were taken before the first infusion and at 3 to 4 weeks after the last infusion depending on the patient's dosing scheme.

Pharmacokinetic assessments were carried out after the 7th infusion (4-week schedule) or after the 9th infusion (3-week schedule). For analysis of serum concentrations of total IgG and IgG subclasses (IgG1, IgG2, IgG3 and IgG4) over the course of the treatment interval, blood samples were drawn prior to the infusion, and then at 15 ± 5 min, 60 ± 10 min, 24 ± 1 h, 72 ± 6 h, 7 days ± 6 h, 14 ± 3 days and 21 ± 3 days (for patients on the 3-week infusion schedule) or 28 ± 3 days (for patients on the 4-week infusion schedule) after the end of the 9th or 7th infusion, respectively.

The following pharmacokinetic parameters were calculated for total IgG, IgG subclasses and specific antibodies: peak plasma concentration (C_{max}); time from start of administration to peak plasma concentration (T_{max}); trough plasma concentration (C_{min}); terminal half-life ($t_{1/2}$); area under the serum concentration-time curve from time 0 to the end of the dosing period (AUC_{0-tau}); elimination rate constant (k_{el}); volume of distribution (Vd, measured for total IgG and IgG subclasses only).

The specialised software Phoenix® WinNonlin® version 6.3 (Certara L.P. [Pharsight], St. Louis, MO) was used for the calculation of non-compartmental pharmacokinetic parameters.

3. Results

3.1. Patient demographics and treatment regimens

In total, 51 patients comprising 13 children (≥2 to < 12 years), 12 adolescents (≥12 to < 16 years) and 26 adults (≥16 years) from 11 study centres in the USA and Europe participated in the study. Baseline demographics and characteristics of the patients are presented in Table 1. Out of the 51 patients enrolled in the study, 43 patients (84.3%) were diagnosed with CVID and eight patients (15.7%) were diagnosed with XLA. A total of 45 patients (88.2%) took prior medication other than a commercial IVIG before entering the study. Overall, 21 patients received IVIG 10% in a 3-week interval and 30 patients received treatment in a 4-week schedule.

Table 1
Baseline characteristics and demographics.

Characteristic	N = 51
Gender, n (%)	
Male	33 (64.7)
Female	18 (35.3)
Mean ± SD age, years	26.8 ± 19.3
Age class, n (%)	
≥2 to < 12 years	13 (25.5)
≥12 to < 16 years	12 (23.5)
≥16 to ≤75 years	26 (51.0)
Disease type, n (%)	
CVID	43 (84.3)
XLA	8 (15.7)
Ethnic group, n (%)	
Caucasian	43 (84.3)
Hispanic	7 (13.7)
Not reported	1 (2.0)
Mean ± SD BMI, kg/m^2	22.5 ± 6.47
Mean ± SD body weight, kg	
≥2 to < 12 years	24.3 ± 6.6
≥12 to < 16 years	57.3 ± 10.8
≥16 to ≤75 years	76.5 ± 19.7

BMI, body mass index, CVID, common variable immunodeficiency; SD, standard deviation; XLA, X-linked agammaglobulinaemia.

3.2. Total IgG and IgG subclass pharmacokinetics

Mean serum concentrations of IgG and IgG subclasses prior to and 15 min post IVIG 10% infusion are reported in Table 2. In general, median values demonstrated an approximate 2-fold increase from pre- to post-infusion. Median total IgG concentrations increased from a pre-infusion level of 9.3 g/L to 17.6 g/L at 15 min post-infusion.

Mean serum concentrations of total IgG and IgG subclasses followed a similar pattern after an IVIG 10% infusion, with a steeper decline from their peaks just after the end of infusion followed by a slower terminal elimination phase (Fig. 1). This profile was observed both for the 3-weekly and 4-weekly treatment schedules. As expected, IgG1 and IgG2 were present in much higher concentrations than the IgG3 and IgG4 subclasses (Fig. 1).

In most IgG and IgG subclass pharmacokinetic parameters, a wide degree of inter-patient variability was evident. The pharmacokinetic estimates for the IgG subclasses and total IgG are presented in Table 3. For total IgG and all four IgG subclasses the median values in patients on 3-week schedule were about 20% to 30% higher than in patients on 4-week schedule.

Over the course of the study, median trough IgG levels varied between 11.0 and 12.2 g/L for patients on the 3-week IVIG 10% schedule and between 8.1 and 8.7 g/L for patients on the 4-week schedule. The lowest trough plasma concentration of IgG calculated for both treatment schedules was above 6.8 g/L: the median (minimum–maximum) was 13.2 (7.7–20.4) g/L for 3-weekly administration and 9.0 (6.8–20.6) g/L for 4-weekly administration. A greater proportion of patients received a dose of IVIG 10% > 0.5 g/kg on the 3-week schedule (52.38%; mean dose of 520 mg/kg/infusion or 173 mg/kg/week) than on the 4-week schedule (36.67%; mean dose of 453 mg/kg/infusion or 113 mg/kg/week).

The estimated median terminal half-life of total IgG for both 3- and 4-week groups was 36.1 days (range 18.5–65.9[1]), with similar values reported for IgG 1, IgG2 and IgG4 (median 30.7 to 38.0 days), and a lower value for IgG3 (26.7 days). For IgG3 and IgG4, there was a greater degree of variability in half-life among patients than for IgG1 and IgG2 (Table 3).

[1] One profile showed a $t_{1/2}$ of 131.7 days, which was treated as an outlier/artefact and excluded from analyses.

3.3. Specific antibodies

Pharmacokinetic data for antibodies against CMV, *H. influenzae*, measles, tetanus, VZV, and 7 *S. pneumoniae* subtypes are listed in Table 4. The data show high levels of a broad range of specific antibodies directed against these pathogens. There was no trend favourable to the 3-week or 4-week treatment schedule. Median half-lives for specific antibodies ranged between 21.3 and 51.2 days for anti-CMV, anti-*H. influenzae*, anti-measles, anti-tetanus toxoid, and anti-VZV antibodies, and between 31.1 and 35.9 days for anti-*S. pneumoniae* subtype antibodies.

Particularly marked increases in antibody median trough levels from first infusion to treatment end were noticed in both treatment schedules for anti-measles (824.0 to 1300.0 mIU/mL for the 3-week schedule and 680.5 to 1051.0 mIU/mL for the 4-week schedule), anti-*H. influenzae* (1.64 to 2.36 µg/mL for the 3-week schedule and 1.30 to 1.68 µg/mL for the 4-week schedule) and anti-*S. pneumoniae* serotype 6B (1.94 to 2.56 µg/mL for the 3-week schedule and 1.39 to 1.55 µg/mL for the 4-week schedule). All these trough levels are considered as being protective. Other *S. pneumoniae* serotypes showed a slight increase of antibody trough concentrations over time in at least one of the two treatment schedules. Trough antibody concentrations remained stable over the course of the study for anti-CMV, and showed a slight decrease for anti-tetanus toxoid (3-week schedule) and anti-VZV antibodies (4-week schedule).

3.4. Safety

Patients in the 4-weekly group had a higher incidence of serious AEs (SAEs; 13 vs. 5%). In contrast, more patients in the 3-weekly treatment group had severe AEs than patients in the 4-weekly group (24 vs. 7%). Only two patients required premedication (3.9% of patients) for three infusions (0.4% of infusions). Study medication-related (possible or probable) treatment-emergent AEs occurred during 38 infusions (5.1% of infusions: 2.7% in children, 2.2% in adolescent, and 7.8% in adult infusions); headache was the most abundant and noted in 22 infusions (3.0%).

The low rate of other infections (3.7 per patient/year) confirms that the dosing and corresponding trough levels observed in this study were adequate. The average dose administered was 485 mg/kg body weight per infusion or 138 mg/kg/week, being in line with doses recommended in the core summary of product characteristics. For further details on the safety profile please refer to the main panzyga® publication of Borte et al., 2017.

4. Discussion

This study characterises the pharmacokinetics of total IgG, IgG subclasses and specific antibodies after administration of IVIG 10% in patients with predominant antibody deficiency. Pharmacokinetic assessments were conducted after patients had received IVIG 10% for 24 weeks (seven infusions in the 4-week schedule or nine infusions in the 3-week schedule), at which time any carryover from previous IgG therapy would have been eliminated.

As expected, administration of IVIG typically produces an immediate rise in serum IgG concentration followed by a rapid fall as IgG exits the vasculature into the extracellular space and the lymphatics, finally entering a slower period of decline associated with catabolism as IgG in these fluid spaces equilibrates and constantly enters and exits the circulation (Bonilla, 2008). In the context of IVIG replacement therapy, key parameters are IgG trough levels (immediate pre-infusion) and the elimination half-life to describe the expected rate of disappearance of replacement IgG (Bonilla, 2008).

Patients in this study received IVIG 10% at doses between 200 and 800 mg/kg of body weight, in either a 3- or 4-week schedule, to remain consistent with their IVIG therapy before entering the study. Serum

Table 2
Serum levels of total IgG and IgG subclasses before and after infusion with IVIG 10%.

	Sampling time					
	Pre-infusion			15 min post infusion		
	3-week group (n = 21)	4-week group (n = 30)	All patients (n = 51)	3-week group (n = 21)	4-week group (n = 30)	All patients (n = 51)
Total IgG, g/L	11.8 (7.4, 20.2)	8.2 (6.0, 18.8)	9.3 (6.0, 20.2)	19.8 (9.3, 30.2)	16.1 (12.4, 26.0)	17.6 (9.3, 30.2)
IgG1, g/L	7.0 (4.1, 12.2)	5.3 (3.7, 14.1)	5.7 (3.7, 14.1)	12.6 (5.1, 19.8)	10.2 (7.8, 18.9)	10.8 (5.1, 19.8)
IgG2, g/L	3.9 (2.2, 6.6)	2.9 (2.2, 4.2)	3.3 (2.2, 6.6)	6.8 (3.3, 11.5)	5.7 (4.3, 7.6)	6.1 (3.3, 11.5)
IgG3, g/L	0.3 (0.1, 0.5)	0.2 (0.1, 0.9)	0.2 (0.1, 0.9)	0.6 (0.1, 0.9)	0.5 (0.3, 1.2)	0.5 (0.1, 1.2)
IgG4, g/L	0.4 (0.2, 1.1)	0.2 (0.1, 1.5)	0.3 (0.1, 1.5)	0.8 (0.3, 1.6)	0.6 (0.4, 1.9)	0.6 (0.3, 1.9)

All values are presented as median (minimum, maximum).

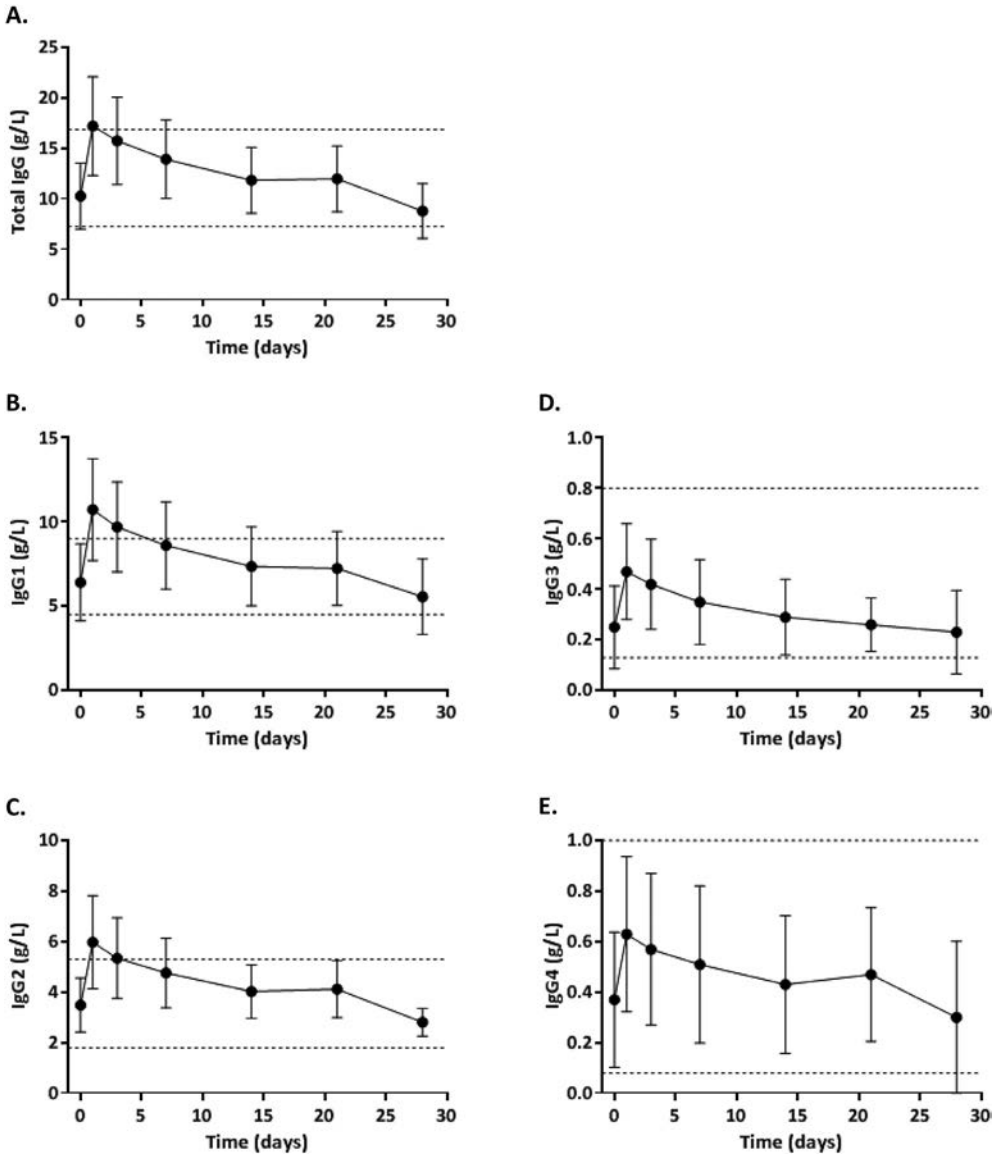

Fig. 1. Serum concentrations (mean ± standard deviation) of (A) total IgG and (B–E) IgG subclasses following infusion with IVIG 10% in 30 patients on a 4-week schedule. The dotted lines indicate the normal physiological serum range of immunoglobulin (normal ranges as described here: http://www.globalrph.com/labs_i.htm).

total IgG trough (pre-infusion) levels were nearly constant for both treatment groups over the course of the study (median values prior to the first infusion was 11.9 g/L, at follow-up 12.2 g/L [3-week group] and median values prior to infusion one: 8.1 g/L, at follow-up: 8.7 g/L [4-week group]) and remained above the recommended trough level of 5–6 g/L. It is worth noting that there is evidence to suggest that the incidence of infection decreases as IgG trough levels increase, up to a maximum of 10 g/L (Gardulf et al., 2006; Orange et al., 2010), indicating that the higher trough concentrations with the 3-weekly dosing schedule may provide better protection against infection than the 4-weekly schedule. However, in this study more patients experienced infections other than serious bacterial infections (SBIs) in the 3-weekly

Table 3
Pharmacokinetic parameter estimates for total IgG and its subclasses after infusion of IVIG 10% at 3-weekly or 4-weekly intervals.
Note, data from one patient in the 3-week group was excluded because of a very high T_{max} value (170 h) so were considered an outlier/artefact.

Parameter, median (min, max)	Group	Total IgG	IgG1	IgG2	IgG3	IgG4
C_{min}, g/L	3-week	13.2 (7.7, 20.4)	7.8 (4.4, 12.7)	4.5 (2.2, 6.7)	0.3 (0.1, 0.5)	0.4 (0.2, 1.1)
	4-week	9.0 (6.8, 20.6)	5.4 (4.1, 15.2)	3.0 (2.3, 4.4)	0.2 (0.1, 0.8)	0.3 (0.2, 1.6)
C_{max}, g/L	3-week	20.5 (14.6, 33.3)	12.7 (8.6, 19.8)	7.3 (3.3, 11.5)	0.6 (0.3, 0.9)	0.8 (0.3, 1.6)
	4-week	16.5 (12.7, 26.0)	10.3 (7.9, 18.9)	5.7 (4.4, 7.9)	0.5 (0.3, 1.2)	0.6 (0.4, 1.9)
T_{max}, hours	3-week	2.9 (2.1, 25.9)	2.7 (2.1, 25.0)	2.6 (2.1, 74.1)	2.6 (2.1, 26.0)	2.5 (1.6, 25.0)
	4-week	2.5 (1.8, 26.3)	2.4 (1.8, 26.3)	2.4 (1.8, 26.3)	2.5 (1.8, 69.0)	2.4 (1.8, 3.3)
$t_{1/2}$, days	3-week	32.9 (18.5, 76.6)	38.6 (15.5, 72.8)	38.0 (16.2, 65.4)	26.2 (11.5, 59.6)	30.7 (12.5, 68.6)
	4-week	37.4 (18.7, 131.7)	35.6 (18.5, 134.7)	38.3 (17.7, 127.7)	27.3 (13.4, 397.9)	30.7 (16.4, 250.3)
AUC_{0-tau}, h·g/L	3-week	7364 (5300, 11,919)	4483 (3117, 7171)	2507 (1290, 4025)	179 (87, 259)	244 (99, 645)
	4-week	6980 (5567, 13,778)	4368 (3197, 10,302)	2458 (1879, 3060)	156 (93, 565)	213 (153, 1134)
k_{el}, 1/1000·h	3-week	0.88 (0.4, 1.6)	0.76 (0.4, 1.9)	0.76 (0.4, 1.8)	1.10 (0.5, 2.5)	0.94 (0.4, 2.3)
	4-week	0.77 (0.2, 1.6)	0.81 (0.2, 1.6)	0.75 (0.2, 1.6)	1.06 (0.1, 2.2)	0.94 (0.1, 1.8)
Vd, L/kg	3-week	0.09 (0.0, 0.1)	0.08 (0.0, 0.2)	0.09 (0.0, 0.1)	0.09 (0.0, 0.2)	0.09 (0.0, 0.2)
	4-week	0.09 (0.0, 0.2)	0.07 (0.0, 0.2)	0.08 (0.0, 0.2)	0.09 (0.0, 0.2)	0.10 (0.0, 0.1)

AUC_{0-tau}, area under the IgG serum concentration-time curve from time 0 to the end of the dosing period; C_{max}, peak IgG plasma concentration; C_{min}, trough IgG plasma concentration; k_{el}, elimination rate constant; SD, standard deviation; $t_{1/2}$, terminal half-life; T_{max}, time from start of administration to peak IgG plasma concentration; Vd, volume of distribution.

Table 4
Derived pharmacokinetic parameters for antigen-specific antibodies after infusion of IVIG 10% (all patients N = 51).

Parameter, median (min, max)	Baseline (pre-infusion 1) value	C_{max}, μg/mL	T_{max}, h	AUC_{0-tau}, h × μg/mL	C_{min}, μg/mL	$t_{1/2}$, days
CMV IgG	30.0	44.0[a]	2.4	19,811.2[b]	30.5[a]	51.2
	(17.0, 49.0)	(31.0, 57.0)	(1.8, 26.3)	(13,353.1, 28,314.5)	(20.0, 49.0)	(19.0, 239.8)
H. influenzae IgG	1.6	3.8	2.5	1417.9	2.0	34.7
	(0.7, 9.0)	(1.9, 9.0)	(1.6, 69.1)	(720.0, 6048.0)	(1.2, 9.0)	(14.6, 425.8)
Measles IgG	0.7	2.3[c]	2.8	773.5[d]	1.0[c]	26.8
	(0.3, 2.3)	(1.3, 5.0)	(1.8, 169.9)	(493.2, 1200.1)	(0.3, 1.9)	(13.7, 317.7)
Tetanus IgG	2.1	5.0[c]	2.4	1779.6[d]	2.1[c]	21.3
	(0.6, 5.0)	(2.3, 5.0)	(1.8, 73.8)	(612.7, 3110.1)	(0.6, 5.0)	(7.9, 2205.8)
Varicella zoster IgG	150.0	150.0[e]	2.3	75,600.0[f]	150.0[e]	24.9
	(89.4, 150.0)	(150.0, 150.0)	(0.3, 3.8)	(39,977.7, 100,800.0)	(29.6, 150.0)	(9.3, 3386.4)
Serotype 4	0.9	2.0	2.6	687.0	0.9	33.4
	(0.2, 4.6)	(0.8, 7.0)	(1.8, 27.4)	(360.3, 2565.3)	(0.5, 4.8)	(16.8, 185.1)
Serotype 6B	1.6	3.7	2.5	1386.5	1.9	33.4
	(0.7, 8.3)	(2.0, 10.7)	(1.8, 69.1)	(721.0, 5408.7)	(1.0, 8.0)	(17.7, 213.4)
Serotype 9V	1.6	3.7	2.6	1394.9	1.9	34.2
	(0.5, 4.3)	(1.9, 8.7)	(1.6, 27.0)	(704.8, 2925.5)	(1.0, 5.1)	(14.5, 103.3)
Serotype 14	5.9	14.4	2.6	5619.7	8.6	35.9
	(2.1, 26.3)	(6.4, 40.1)	(1.6, 74.1)	(2247.2, 17,017.5)	(3.2, 31.6)	(20.2, 161.8)
Serotype 18C	1.7	4.3	2.5	1625.1	2.2	34.0
	(0.7, 15.3)	(1.8, 23.0)	(1.6, 74.1)	(644.2, 5825.2)	(0.9, 11.0)	(15.2, 92.3)
Serotype 19F	4.6	11.9	2.5	4319.1	5.6	32.7
	(2.4, 18.4)	(5.7, 32.5)	(1.8, 27.0)	(2183.9, 11,719.1)	(2.9, 16.0)	(13.4, 195.0)
Serotype 23F	1.6	4.1	2.6	1503.8	2.1	31.1
	(0.5, 8.1)	(1.8, 8.3)	(1.6, 27.4)	(652.5, 3993.4)	(0.8, 5.5)	(16.7, 90.8)

AUC_{0-tau}, area under the IgG serum concentration-time curve from time 0 to the end of the dosing period; C_{max}, peak IgG plasma concentration; C_{min}, trough IgG plasma concentration; CMV, cytomegalovirus; IgG, Immunoglobulin G; $t_{1/2}$, terminal half-life; T_{max}, time from administration to peak IgG plasma concentration. Serotype (4-23F) refers to anti-*S. pneumoniae* antibodies.

[a] U.
[b] h × U.
[c] IU/mL.
[d] h × IU/mL.
[e] U/mL.
[f] h × U/mL.

group with higher IgG trough levels than in the 4-weekly group with lower IgG trough levels. This could have been by chance as the patients continued with their treatment schedule and dosage they had received before study participation. It is also possible that patients with a more compromised immune system and, therefore, at greater risk of developing such infections, were placed on a 3-weekly schedule (Borte et al., 2017). On the other hand, both patients with SBIs were in the 4-weekly group with lower IgG trough levels. All 4 SBIs had onset dates between 24 and 32 days after last infusion when their IgG concentrations were lower than the average IgG trough levels (mean of 6.7 g/L; range: 6.0–7.9 g/L).

The higher IgG trough levels observed in patients on the 3-week schedule (range between 11.34 g/L and 12.27 g/L; SD between 2.69 and 3.42) may result in part from the fact that a larger proportion of patients within this group received IVIG 10% doses > 0.5 g/kg compared with patients on the 4-week schedule who had significantly lower IgG trough levels (range between 8.48 g/L and 8.98 g/L; SD between 2.16 and 3.02). It has been recommended that for the treatment of antibody deficiency, IgG concentrations remain above a minimum trough level of 5 g/L based on data from patients with chronic lung disease (Roifman et al., 1987), although an optimal trough level to minimise risk of serious infections has not been definitively established.

A more realistic determination of an acceptable trough level may be the patient's baseline IgG level (before being started on IVIG) and ultimately should be determined by clinical outcomes for individual patients (Bonagura, 2013; Matucci et al., 2015). The mean trough plasma concentration values after 24 weeks of therapy with IVIG 10% were well above this threshold for both the 3-week and 4-week infusion intervals and were comparable to those reported for other IVIG products (Schroeder Jr and Dougherty, 2012; Wasserman, 2014).

The terminal half-lives of IgG and IgG subclasses in the present study were comparable to those reported in a number of clinical trial of 10% liquid IVIG products in antibody deficient patients (Bjorkander et al., 2006; Church et al., 2006; European Medicines Agency, 2010; Wasserman et al., 2009; Ballow et al., 2003; Berger et al., 2010; Bleasel et al., 2012; Wasserman, 2014; Wasserman et al., 2012). Similar to what has previously been reported in the literature for IVIG preparations, there was a wide range in the terminal half-life for IgG (18.5 to 65.9 days) in the present study. This may in part relate to inherent difficulties in studying IVIG in immunodeficient patients, including a potential confounding effect of endogenous immunoglobulin production and the concentration-dependent nature of IgG catabolism, as well as the ethical prohibition of withholding IVIG to permit more accurate estimation of IgG half-life through serial measurements of IgG concentrations over several half-life intervals (Bonilla, 2008; Wasserman et al., 2009). The wide variability in rates of decay of replacement IgG makes comparisons between different regimens and different IVIG preparations difficult (Bonilla, 2008).

In the present study, the pharmacokinetic profiles and half-lives of the antigen-specific IgG antibodies mirrored those of total IgG and IgG subclasses. The median half-lives of anti-*H. influenzae*, anti-tetanus toxoid, anti-*S. pneumoniae*, anti-measles and anti-CMV antibodies were in the range of 21.3 to 51.2 days and similar to published values (Berger et al., 2010; Wasserman et al., 2009; Wasserman et al., 2012). Trough levels of specific antibodies were stable or increased across the course of the study, a trend similar to that reported by Nobre et al. (2014). At present, specific antibody concentrations required for protection from infection have not been fully defined and the lack of any standardised tests to estimate specific antibody concentrations makes comparisons of parameters such as antibody trough levels difficult, and limits the opportunity for meaningful information regarding appropriate IVIG doses to prevent infections (Schroeder Jr and Dougherty, 2012).

While intravenous infusion is the most common method of administering replacement IgG therapy, subcutaneous immunoglobulin (SCIG) formulations have also been investigated in the treatment of PID to address some of the limitations of intravenous therapy, such as systemic side effects, a “wear-off” effect towards the end infusion periods (Rojavin et al., 2016), and the need for a healthcare professional to perform the infusions. Currently, 11 IVIG products (two of which are also approved for subcutaneous injection) and three SCIG products are approved for use in the US by the Food and Drug Administration (FDA, 2008). Differences in the pharmacokinetics of IVIG and SCIG may be important in deciding which mode is appropriate for an individual patient (Bonagura, 2013). IVIG achieves higher peak levels of IgG, while SCIG achieves higher trough levels, probably due to the increased frequency of infusion, usually weekly (Bonagura, 2013; Ochs et al., 2006; Wasserman et al., 2010). A number of studies have implied, in line with the controversial dose adjustment required by the FDA, that the amount of subcutaneously administered human immunoglobulin has to be 1.4 to 1.5 times that of intravenously administered preparations to maintain pharmacokinetic equivalence (based on AUC) (Berger et al., 2011; Ochs et al., 2006; Wasserman et al., 2010; Wasserman et al., 2011a; Wasserman et al., 2011b). However, there are also published studies demonstrating that the same dose, or even a lower dose of SCIG, may be equally effective (Gardulf et al., 2006; Jolles et al., 2011). A principal limitation of subcutaneous administration of human immunoglobulin is the relatively small volume of fluid that can be administered by this route (100 mL per infusion of 20% SCIG or 20 g vs. 1000 mL or 100 g IVIG in an adult), which necessitates more frequent infusions than IVIG (about once per week vs. every 3 or 4 weeks), higher concentrations of the Ig preparation (16% to 20% vs. 5% to 12%) and potentially necessitates multiple infusion sites (Garcia-Lloret et al., 2008). The development of an SCIG product for use in conjunction with recombinant human hyaluronidase has attempted to address some of these issues (Wasserman et al., 2016).

A distinguishing feature of the NGAM-01 study design was that all patients enrolled in the efficacy trial were included in the pharmacokinetic analysis, which is in contrast to many other published studies of IVIG in which only a subset of the efficacy study population was included (Berger et al., 2010; European Medicines Agency, 2010; Wasserman, 2014; Wasserman et al., 2009; Wasserman et al., 2012). In addition to the relatively large number of patients included in this analysis, the strengths of the current study is reflected by the recruitment of patients from both the USA and Europe and the wide age range (≥ 2 to ≤ 75 years) of patients, half of which were children or adolescents. This design ensures the results are applicable to a broad patient population.

5. Conclusion

Pharmacokinetic data from this prospective, open-label, non-controlled, non-randomised, phase III study demonstrate that IVIG 10% (panzyga®), when administered at a dose of 200–800 mg/kg as an infusion every 3 or 4 weeks to patients with predominant antibody deficiency, achieves adequate concentrations of total IgG, IgG subclasses, and IgG antibodies to specific common pathogens. Trough levels of total IgG remained well above the widely accepted threshold of 5–6 g/L. The terminal half-life of total IgG and IgG subclasses were similar to those reported for other commercially available IVIG products. The data also support the more frequent 3-weekly over the 4-weekly administration as patients given infusions every 3 weeks, while receiving on average a 53% higher weekly dose, showed trough plasma concentrations of IgG that were 34–37% higher when compared to those receiving 4-weekly infusions.

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Ethical approval

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP). The study protocol was reviewed and approved by each study site's Independent Ethics Committee or Institutional Review Board before the start of the trial. Written informed consent was obtained from all patients or their parent or legal guardian (in the case of minor patients) prior to study entry.

Conflict of interest

I. R. Melamed's institution received research grant support from CSL Behring, Octapharma, Baxalta and Bio Products Laboratories, and I. R. Melamed has participated on advisory boards for Octapharma and Baxalta. M. Borte's institution has received research grant support from CSL Behring, Octapharma and Baxalta, and M. Borte has participated in advisory boards for CSL Behring and Octapharma. L. Trawnicek is an employee of Octapharma, Vienna, Austria. James N. Moy has received fees as a consultant for Grifols, Prometic, Octapharma, MacroCure and Baxalta. A.-L. Kobayashi has received grant support from Baxalta and Octapharma. R.H. Kobayashi has acted as a consultant for Baxalta, CSL Behring, ADMA, and Octapharma. A. Knutsen has acted as a consultant for Baxalta, CSL Behring, and Octapharma. Hans D. Ochs has acted as consultant for Baxalta, CSL Behring and Octapharma. Drs S. Gupta, W. Smits, A. Pituch-Noworolska, M. Strach, and G. Pulka have no conflicts of interest to declare.

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