Steady-State Serum IgG Trough Levels Are Adequate for Pharmacokinetic Assessment in Patients With Immunodeficiencies Receiving Weekly Immune Globulin Subcutaneous (Human) 20% Solution (Ig20Gly)

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Background

- Primary immunodeficiency diseases (PID) are a heterogeneous group of > 400 genetic disorders characterized by absent or deficient antibody production, which can lead to frequent and severe infections[1]
- In PID, subcutaneous (SC) administration of immunoglobulin (IG) replacement therapy (SCIG; usually daily to every 2 weeks) reduces the risk of infections, may be self-infused at home, and is associated with fewer systemic adverse events than intravenous administration (IVIG; every 3–4 weeks)[2]
- SCIG treatment options include:
  - Cuvitru® (Immune Globulin Subcutaneous [Human] 20% Solution [Ig20Gly]; Baxalta US Inc., a member of the Takeda group of companies), a purified, ready-to-use liquid preparation of concentrated, functionally intact human immunoglobulin G (IgG) developed specifically for SC administration[3]
  - GammaGard® (Immune Globulin Infusion [Human], 10% Solution; Baxalta US Inc., a member of the Takeda group of companies)[4]
  - Gamunex® (Immune Globulin Injection [Human] 10% Solution; Grifols Therapeutics Inc.)[5]
  - Hizentra® (Immune Globulin [Human] 20% Liquid; CSL Behring AG)[6]
  - HyQvia® (Immune Globulin Infusion 10% [Human] with Recombinant Human Hyaluronidase; Baxalta US Inc., a member of the Takeda group of companies)[7]
- The pharmacokinetic (PK) properties of exogenous IG vary by route of administration
  - Although IVIG treatment results in an early, high peak of IG serum concentration (C_{max}), the slower absorption of SCIG from the SC infusion site results in a more gradual and stable increase in IG serum concentration, with a lower C_{max} than the peak achieved with IVIG infusions[2,8]
  - The increased dosing frequency of SCIG, as compared with IVIG, may contribute to the stable, steady-state IG levels observed throughout the dosing cycle and the occurrence of higher IG trough levels[8,9]
- Clinical trials investigating IG therapies in PID commonly characterize serum IgG PK profiles through serial evaluation of serum IgG levels taken during IG treatment[10–12]
  - Although serial sampling generally facilitates the provision of valuable PK data, this practice has drawbacks, including added logistical challenges and costs for the conduct of clinical trials and the burden of multiple blood draws for patients, particularly pediatric ones, in whom venipuncture can be emotionally distressing[13]
  - Fewer blood-collection timepoints for PK profile characterization may benefit patients and investigators in clinical trials

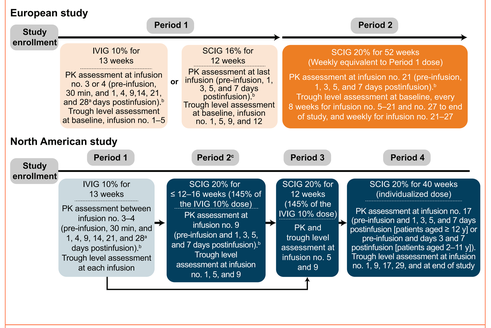
Objective

- To evaluate PK profiles for SCIG and IVIG therapies in patients with PID for whether serum IgG trough level measurement alone can provide a PK assessment that is comparable with serial sampling

Methods

- PK data of weekly Ig20Gly treatment were obtained from 2 prospective, open-label, noncontrolled, multicenter phase 2/3 licensing studies in patients with PID in Europe (NCT01412385; EudraCT #: 2010-019459-23) and North America (NCT01218438)[11,14] (**Figure 1**)
  - Patients aged ≥ 2 years with a documented diagnosis of PID requiring immunoglobulin replacement therapy, a stable monthly dose of IVIG or SCIG of IgG equivalent (0.3–1.0 g/kg body weight / 4 weeks) for ≥ 3 months before the first study treatment, and serum IgG trough levels > 5 g/L at screening were included

Figure 1. Design of Ig20Gly Phase 2/3 Licensing Studies



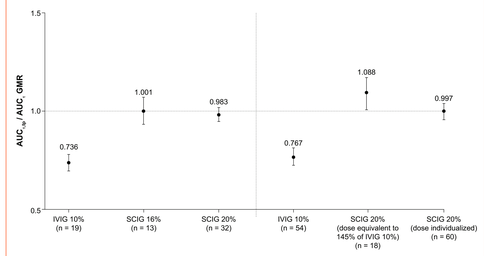
[a]In patients receiving IVIG 10% at 4-week treatment intervals.
[b]Assessment limited to patients who were ≥ 12 years old.
[c]Treatment in Period 3 started as soon as the adjusted dose, which was 145% of IVIG 10%, was identified. Consequently, patients in Period 1 who had enrolled after the adjusted dose information had become available entered directly into Period 3.
Ig20Gly, Immune Globulin Subcutaneous (Human) 20% Solution; IVIG, intravenous immunoglobulin; PK, pharmacokinetic; SCIG, subcutaneous immunoglobulin; y, year.

- Using IgG trough and PK data (ie, area under the curve [AUC], C_{max} and trough concentration [C_{trough}]) from published literature, a comparison of 4 other IG products in patients who had PID (SCIG products: Hizentra, GammaGard, Gamunex, and HyQvia; IVIG products: GammaGard and Gamunex) was performed
  - Data for Hizentra were obtained from 2 studies conducted in Europe and the US[15]
  - For IVIG and SCIG administration of GammaGard, PK data were obtained from a multicenter, prospective, open-label North American study[4,16]
  - For IVIG and SCIG administration of Gamunex, PK data were obtained from an open-label, crossover North American trial in patients who had previously received or were receiving IgG replacement therapy at the time of the study[5,17]
  - For HyQvia, PK data were obtained from a prospective, open-label, noncontrolled, multicenter US trial[7,18]
- Trough-predicted area under the curve ($AUC_{τ,tp}$) was estimated based on IgG trough concentrations using the following formula: $AUC_{τ,tp}$ = steady-state trough concentration during a dosage interval ($C_{trough,ss}$) × dosage interval (τ)
  - $AUC_{τ,tp}$ was compared with the reported $AUC_τ$ that was derived from PK profiles calculated from serial sampling of IgG levels
    - Point estimates of the geometric mean ratio (GMR) of the 2 parameters ($AUC_{τ,tp}$ / $AUC_τ$) and 90% confidence intervals (CIs) were calculated for the Ig20Gly licensing studies
    - Products were compared by determining the differences between $AUC_{τ,tp}$ and $AUC_τ$ and between C_{max} and C_{trough}

Results

- The 2 licensing studies of weekly Ig20Gly in PID reported mean values of $AUC_{τ,tp}$ for SCIG 16% and SCIG 20%, which were only slightly lower than the reported $AUC_τ$, with point estimates of GMR of $AUC_{τ,tp}$ versus $AUC_τ$ between 0.983–1.088. All 90% CIs were within the commonly used equivalence limit of 0.80–1.25 (**Figure 2** and **Table 1**)
  - In comparison, mean values of $AUC_{τ,tp}$ for IVIG were consistently approximately 23–26% lower than the reported $AUC_τ$ (**Table 2**)
  - The point estimates of GMR (90% CI) of $AUC_{τ,tp}$ versus $AUC_τ$ were 0.736 (0.696–0.779) and 0.767 (0.726–0.811) for the European study and North American study, respectively (**Figure 2** and **Table 1**)
- A comparison of other IgG products revealed differences between IVIG and SCIG therapies (**Table 2**)
  - Both IVIG products had a mean C_{max} of more than double the C_{trough}; however, differences between the means of C_{max} and C_{trough} for all SCIG products were < 20.0%, except for HyQvia, for which the difference was 33.0%
  - Comparison between 2 products with SCIG and IVIG formulations showed that the IVIG formulations had higher mean values for C_{max} but lower mean values for C_{trough} than the SCIG formulations did. Also compared with their SCIG formulations, mean values of $AUC_{τ,tp}$ were lower and the differences between $AUC_{τ,tp}$ and $AUC_τ$ were greater for IVIG formulations
  - Differences between $AUC_{τ,tp}$ and $AUC_τ$ were > 20.0% for all IVIG products, and were < 10.0% for all SCIG products, except for HyQvia, for which the difference was 17.5%

Figure 2. Trough-Predicted $AUC_{τ,tp}$ Versus Reported $AUC_τ$ for IVIG and SCIG in 2 Phase 2/3 Studies of Ig20Gly



Error bars represent 90% CIs. Horizontal reference line = GMR of 1.0.
AUC, area under the curve; $AUC_τ$, area under the curve calculated from serum IgG concentration-time profiles; $AUC_{τ,tp}$, trough level-predicted area under the curve; CI, confidence interval; GMR, geometric mean ratio; Ig20Gly, Immune Globulin Subcutaneous (Human) 20% Solution; IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin; τ, dosing interval (3–4 weeks for IVIG, 1 week for SCIG).

Table 1. Geometric Mean Ratio of Point Estimates and 90% CIs for Trough-Predicted $AUC_{τ,tp}$ Versus Reported $AUC_τ$ in 2 Phase 2/3 Studies of Ig20Gly

			$AUC_τ$, hr*mg/mL			$AUC_{τ,tp}$, hr*mg/mL			$AUC_{τ,tp}$ / $AUC_τ$ GMR	
Study	Treatment	N	Mean	SD	% CV	Mean	SD	% CV	Point Estimate	90% CI
European phase 2/3 study	IVIG 10%	19	276.21	59.28	21.46	203.21	44.49	21.90	0.736	0.696–0.779
	SCIG 16%	13	77.42	28.38	36.65	76.70	24.55	32.01	1.001	0.935–1.071
	SCIG 20%	32	63.51	18.65	29.37	61.75	15.97	25.87	0.983	0.946–1.021
North American phase 2/3 study	IVIG 10%	54	401.68	88.64	22.07	316.63	106.60	33.67	0.767	0.726–0.811
	SCIG 20% (dose equivalent to 145% of IVIG 10%)	18	110.61	23.28	21.05	122.48	36.30	29.64	1.088	1.011–1.170
	SCIG 20% (dose individualized)	60	117.64	24.26	20.63	118.42	30.62	25.86	0.997	0.958–1.037

AUC, area under the curve calculated from serum IgG concentration-time profile; $AUC_{τ,tp}$, trough level-predicted area under the curve; CI, confidence interval; CV, coefficient of variation; GMR, geometric mean ratio; Ig20Gly, Immune Globulin Subcutaneous (Human) 20% Solution; IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin; τ, dosing interval (3–4 weeks for IVIG, 1 week for SCIG); SD, standard deviation.

Table 2. Summary of Pharmacokinetic Parameters for Other SCIG and IVIG Products

	SCIG Products					IVIG Products	
Study	GammaGard[4]	HyQvia[7]	Gamunex[5]	Hizentra (EU)[19]	Hizentra (US)[15]	GammaGard[4]	Gamunex[17]
N	32–57[a]	60	26–36[a]	23	18	32–57[a]	26–36[a]
Product information	Immune Globulin Infusion (Human), 10%	Immune Globulin Infusion (Human), 10% Liquid, With Recombinant Human Hyaluronidase	Immune Globulin Infusion (Human), 10%	Immune Globulin Subcutaneous (Human), 20%	Immune Globulin Subcutaneous (Human), 20%	Immune Globulin Injection (Human), 10%	Immune Globulin Injection (Human), 10%
C_{max}, mean (SD), mg/mL	13.93 (2.89)	16.07 (3.82)	12.2 (2.4)	8.26 (1.26)	16.16 (4.93)	22.40 (5.36)	21.1 (3.9)
C_{trough}, mean (SD), mg/mL	12.02 (2.82)	10.77 (2.75)	11.4 (2.3)	8.10 (1.34)	13.70 (4.39)	10.50 (2.60)	9.6 (2.1)
C_{max}/C_{trough}	1.159	1.492	1.070	1.020	1.180	2.133	2.198
Difference between C_{max} and C_{trough}, %[b]	13.7	33.0	6.6	1.9	15.2	53.1	54.5
$AUC_τ$, mean (SD), hr*mg/mL	2202 (463)	2194 (504)	1900 (380)	1289 (220)	2534 (757)	2390 (546)	2095 (419)
$AUC_{τ,tp}$, mean, hr*mg/mL	2019	1809	1915	1361	2302	1764	1613
Difference between $AUC_{τ,tp}$ and $AUC_τ$, %[c]	–8.3	–17.5	0.8	5.6	–9.2	–26.2	–23.0

[a]Pharmacokinetic parameters were obtained from > 1 study.
[b]Calculated as $(C_{max} - C_{trough})/C_{max}$*100.
[c]Calculated as $(AUC_{τ,tp} - AUC)/AUC_{τ,tp}$*100.
$AUC_τ$, area under the curve calculated from serum IgG concentration-time profiles; $AUC_{τ,tp}$, trough level-predicted area under the curve; C_{max}, maximum concentration; C_{trough}, trough concentration; EU, European Union; GMR, geometric mean ratio; IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin; τ, dosing interval (3–4 weeks for IVIG, 1 week for SCIG); SD, standard deviation; US, United States.

Limitations

- Individual patient data were not available for all products; thus, this retrospective analysis utilized mean/median values reported in the published literature for an indirect comparison of products
- Conclusions about the value of measuring serum IgG trough levels alone for PK assessment of SCIG products at steady-state are limited to SCIG treatment received on a weekly basis

Conclusions

- **Throughout weekly SC administration of Ig20Gly in patients who have PID, steady-state serum IgG trough levels remain stable, allowing for reliable prediction of total exposure ($AUC_τ$) using serum IgG trough levels alone**
- **These results indicate that measuring steady-state serum IgG trough levels alone for PK assessment of weekly SCIG treatment is a reasonable and beneficial alternative to serial PK sampling during clinical development and beyond**
- **Steady-state serum IgG levels were similarly stable in clinical trials for 4 other SCIG products, suggesting that the findings can be generalizable to clinical trials of future IgG products**
- **For patients and investigators, the use of steady-state IgG trough levels for PK assessment may offer multiple benefits, including reduced patient burden and more efficient clinical trial conduct through decreases in study costs and logistical complexity**

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Disclosures

ZL is an employee of Shire US Inc., a Takeda company, and a Takeda stock holder. **LY** is an employee of Baxalta US Inc., a Takeda company, and a Takeda stock holder. **BM** is an employee of Baxalta Innovations GmbH, a Takeda company, and a Takeda stock owner.

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