Pharmacokinetic properties of Privigen® in Japanese patients with primary immunodeficiency

Tomohiro Morioa, Gautam Bahetib, Michael A. Tortoricib, Jutta Hofmanncc and Mikhail A. Rojavinb

aDepartment of Pediatrics and Developmental Biology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan; bCSL Behring LLC, King of Prussia, PA, USA; cCSL Behring AG, Bern, Switzerland

ABSTRACT
This prospective, Phase 3, open-label, study (EudraCT: 2016-001631-12) evaluated pharmacokinetic (PK) characteristics of 3-/4-weekly Privigen® (IgPro10, CSL Behring, King of Prussia, PA, USA) in Japanese patients with PID. PK parameters including serum trough immunoglobulin (IgG) level before next infusion during the wash-in/wash-out phase (Ctrough), area under the concentration-time curve from time point zero to the last time point with quantifiable concentration (AUC0-last), dose-adjusted AUC0-last (dAUC), lowest and highest observed IgG levels (Cmin, Cmax), time to reach Cmax (Tmax), and total clearance (CL) were analyzed for both regimens of Privigen® (dose: 138–554 mg/kg body weight). Ten patients were included in this analysis (3-/4-weekly: n = 2/n = 8). Ctrough, levels achieved ranged 7.96–10.05 g/L. Cmax was observed approximately 1 h after the start of the infusion in both regimens. Mean (SD [not applicable for 3-weekly data]) PK parameters: Cmax 16.60 and 14.20 (5.53) g/L; Cmin 10.60 and 8.53 (3.89) g/L; AUC0-last 5971 and 6591 (2633) g•h/L; dAUC 0.41 and 0.46 (0.19) g•h/L/ mg; CL 2.53 and 2.53 (1.00) mL/h and median Tmax 1.19 and 1.14 h, for 3-/4-weekly dosing regimens, respectively. Privigen® PK characteristics in Japanese patients were similar between dosing regimens and to previously-reported results in non-Japanese patients with PID.

1. Introduction
Primary immunodeficiency (PID) is a heterogenous group of diseases characterized by intrinsic or genetic defects in one or more components of the immune system [1–3]. More than 350 genetic disorders are categorized as a PID to date, with many new disorders frequently being recognized [4–6]. Prevalence of the specific PIDs varies substantially across different geographical regions [7]. PID results in increased susceptibility to various infections and many other organ-specific (e.g., respiratory and gastrointestinal) complications [3,8]. Antibody deficiencies represent the most common type of PID and are characterized by an inability to produce an effective antibody response to a number of pathogens [3,4,8].

Immunoglobulin G (IgG) replacement therapy remains the mainstay of treatment for patients with PID, specifically for antibody deficiencies [9–11]. Adequate IgG replacement therapy results in reduced infection rates and improved quality of life in patients with PID [12,13]. Intravenous IgG (IVIG) is one of the most common methods of IgG administration, usually delivered at an interval of 3–4 weeks with an infusion duration of 1–4 h, depending on individual dose and flow rate [10,11,14]. IVIG infusions are usually conducted in either a hospital or an infusion center under the observation of qualified medical personnel, which makes IVIG suitable for patients who prefer not to self-infuse [9–11]. IVIG results in a rapid and high increase in serum IgG concentration followed by a biphasic decline, starting with a relatively rapid decline over 2 days and a subsequent slow decline over the next few days, with an overall half-life of approximately 30–40 days [9,11].

Different IVIG formulations are available for the treatment of PID [4]. These products differ in their concentration, osmolality, sugar, sodium, amino acid, and IgA content [14]. Privigen® (IgPro10, CSL Behring, King of Prussia, PA, USA) is a ready-to-use, sterile, 10% liquid IVIG therapy, indicated for the treatment of PID, chronic immune thrombocytopenia (ITP) and chronic inflammatory demyelinating polyneuropathy (CIDP) in the United States [15]. Privigen® is approved for the treatment of Guillain-Barré syndrome, Kawasaki disease and CIDP in the European Union [16]. In Japan,
Privigen® is approved for the treatment of CIDP in 2019 [17]. Privigen® is the first and only IVIG designed with proline stabilization [18], which limits the formation of idiotype/anti-idiotype dimers and protein aggregates and thereby improves stability and clinical tolerability [19].

The pharmacokinetic (PK) properties of Privigen® are well-established in non-Japanese patients with PID [20–22]. However, to date, studies reporting PK characteristics of Privigen® in Japanese patients with PID have not been performed. This is, therefore, the first study that evaluated the PK characteristics of Privigen® specifically in Japanese patients with PID. Here, the disposition of Privigen® was evaluated and PK calculated following 3- or 4-weekly infusions of Privigen® and compared between dosing intervals.

2. Materials and methods

2.1. Study design

This PK analysis was part of a prospective Phase 3, open-label, single-arm study (EudraCT number: 2016-001631-12) designed to evaluate the PK parameters of 3- or 4-weekly Privigen® infusions in Japanese patients with PID. The study (Protocol No: 2016-0018 IgPro10_3004) was approved by the Institutional Review Boards of Tokyo Medical and Dental University, Kyushu University Hospital, Doko Medical University Hospital, Kanagawa Children’s Medical Center, Haradoi Hospital, Hiroshima Citizen Hospital, Fukuoka University Hospital, and Gifu University Hospital. All patients provided informed consent.

2.2. Patient population

The study included male or female Japanese patients with a diagnosis of PID, aged ≥6 years with a body-weight of ≥19 kg at the time of recruitment, who were on stable doses (within ±10% of an average dose in mg/kg in the last 6 months) of any IVIG product currently approved in Japan administered at regular 3- or 4-weekly intervals for ≥6 months prior to study entry, and who reported ≥1 historic IgG trough level of ≥5 g/L during the 6 months prior to study entry.

Key exclusion criteria included patients with a newly-diagnosed PID, who were not receiving IgG replacement therapy, with ongoing active serious infection at the time of screening, with ongoing or history of concomitant malignancies of lymphoid cells, who had allergic reactions to IgG in the past 3 months prior to study entry or who were receiving concomitant treatment with steroids at the time of screening.

Patients received either 3-weekly or 4-weekly infusions of IgPro10 based on their pre-study treatment schedule as prescribed by their physician and this treatment schedule was not modified during the duration of the study.

2.3. Dosing and sampling

The Privigen® dose was selected as per the patient’s last steady-state dose recorded for the previous IVIG product. The dose range for Privigen® was anticipated to be approximately 200–600 mg/kg per dosing cycle. Individual stable doses outside this range were not considered as a protocol deviation. Based on the IVIG dosing cycle of patients, the duration of the wash-in/wash-out for each of the enrolled patients was estimated to be up to 4 months. Serum samples for PK analysis were collected during the last dosing cycle of Privigen®, starting at Week 13. PK sampling for 3-weekly and 4-weekly intravenous infusions is presented in Figure 1.

2.4. PK parameters

PK parameters were calculated by non-compartmental analysis (NCA) using Model 202 for constant infusion in Phoenix™ WinNonlin® Version 6.3 (Pharsight Corp., St. Louis, MO, USA). Actual sampling times calculated relative to the start of dose infusion, as well as the actual doses, were used for the analysis. PK parameters calculated in the present analysis included: area under the concentration-time curve (AUC) from time point zero to the last time point with quantifiable concentration (AUC\(_{0\text{–}\text{last}}\)), calculated using log-linear trapezoidal method; dose-adjusted AUC\(_{0\text{–}\text{last}}\) (dAUC\(_{\text{c}}\)) calculated as AUC\(_{0\text{–}\text{last}}\)/total dose administered (actual dose*body weight); trough IgG level prior to the next infusion during the wash-in/wash-out phase (C\(_{\text{trough}}\)); the lowest (C\(_{\text{min}}\)) and highest (C\(_{\text{max}}\)) observed IgG level within a dosing interval; the time to reach C\(_{\text{max}}\) (T\(_{\text{max}}\)) and total clearance (CL), calculated as dose/AUC\(_{0\text{–}\text{last}}\), where actual doses were used for the calculation of CL. Calculated PK parameters were compared between 3-weekly and 4-weekly intravenous infusions of Privigen®.

2.5. PK statistical analysis

The PK analysis was based on the "Pharmacokinetic Analysis Set" (PKAS). The PKAS included all patients who received ≥1 dose or a partial dose of Privigen® and for whom ≥1 measurable IgG concentration was available following Privigen® infusion without any major deviations related to Privigen®.
administration. Individual concentration-time profiles and mean (standard deviation [SD]) values by treatment and patient were plotted. For all PK parameters, except $T_{\text{max}}$, summary statistics were calculated. Mean, SD, median, minimum, and maximum were calculated in addition to the coefficient of variation (CV), geometric mean, geometric percent CV (CV%), and 95% confidence interval (CI) around the geometric mean. The geometric parameters were derived by log-transforming the concentrations and calculating mean, SD and 95% CI of the log-transformed data. The parameters were back-transformed to the original scale by exponentiation. For $T_{\text{max}}$, $n$, median, minimum and maximum were calculated.

3. Results

3.1. Patient demographics and disposition

Overall, the study enrolled 11 patients; 2 patients on 3-weekly infusions, and 9 patients on 4-weekly infusions. One patient in the 4-weekly infusion group left the study before PK sampling and was thus excluded from the PKAS. This patient had a history of psoriasis at the time of screening and was withdrawn from the study to receive a prohibited immunosuppressive concomitant medication. Worsening of psoriasis was not considered to be related to Privigen $^\text{\textregistered}$ based on the patient’s medical history. The remaining 10 patients (3-weekly infusions, $n = 2$ and 4-weekly infusions, $n = 8$) had no major protocol deviations and were included in the PK analysis.

The study included Japanese patients with a female to male ratio of 1:4. The median (range) age of patients was 30 (9–67) years, and the majority (8 patients, 80%) were 18–64 years of age; the remaining patients were aged 2–11 years ($n = 1$) and 65–84 years ($n = 1$) (Table 1). Overall, the median (range) body weight was 62.1 (27.5–78.9) kg with a median (range) body mass index of 21.4 (16.3–28.3) and a high proportion of patients (6 patients, 60%) were diagnosed with X-linked agammaglobulinemia, resulting in the inclusion of a large proportion of male patients. (Table 1). Serum IgG concentration at the first diagnosis of PID and serum IgG trough levels at baseline are shown in Table 1.

3.2. Privigen $^\text{\textregistered}$ infusion parameters

Privigen $^\text{\textregistered}$ doses were determined based on the individual pre-study treatment schedule of each patient and ranged from 138 to 556 mg/kg per dosing cycle. The mean (SD) doses were similar between 3- and 4-weekly groups, at 272.7 (30.82) mg/kg and 283.4 (132.15) mg/kg, respectively. Administration and doses of Privigen $^\text{\textregistered}$ were well adhered to, with 90% of the patients able to tolerate infusions at a flow
rate of 8 mg/kg/min (5.6 mL/kg/h), and about 50% for flow rates of up to 12 mg/kg/min (7.2 mL/kg/h).

### 3.3. Serum IgG concentrations and PK parameters

All PK parameters analyzed in this study were similar between the two dosing regimens with no significant differences (Table 2). However, results should be interpreted with caution due to the small sample size in the 3-weekly infusion group ($n = 2$). Because of this, SD, CV%, and 95% CI data were not available for the PK parameters of the 3-weekly infusion group parameters, and thus are reported only for the 4-weekly infusion group.

Mean (SD) $C_{\text{trough}}$ levels were similar between 3- and 4-weekly infusion groups, and ranged from 7.96 to 10.05 g/L. Geometric mean (95% CI) of $C_{\text{trough}}$ levels was also similar between 3-weekly and 4-weekly infusion groups (Table 2). The change in $C_{\text{trough}}$ levels from ‘prior to initial infusion’ to ‘prior to last infusion’ was negligible in both infusion groups with a difference (mean [SD]) of $0.86 (0.50)$ g/L in the 3-weekly and $0.30 (0.44)$ g/L in the 4-weekly infusion group.

The individual patient serum IgG concentration-time profile curves showed variability between

### Table 1. Baseline demographic characteristics of patients (PKAS).

| Parameter                          | Privigen$^\circledast$ ($N = 10$) |
|------------------------------------|------------------------------------|
| Age, years                         |                                    |
| Mean (SD)                          | 31.1 (16.9)                        |
| Median (range)                     | 30.0 (9.0, 67.0)                   |
| Age categories, n (%)              |                                    |
| 2 to 11 years                      | 1.0 (10.0)                         |
| 12 to 17 years                     | 0.0                                |
| 18 to 64 years                     | 8.0 (80.0)                         |
| 65 to 84 years                     | 1.0 (10.0)                         |
| Gender, n (%)                      |                                    |
| Female                             | 2.0 (20.0)                         |
| Male                               | 8.0 (80.0)                         |
| Race, n (%)                        |                                    |
| Japanese                           | 10.0 (100.0)                       |
| Weight at Day 1, $^a$ kg           |                                    |
| Mean (SD)                          | 60.3 (13.8)                        |
| Median (range)                     | 62.1 (27.5, 78.9)                  |
| BMI, kg/m$^2$                      |                                    |
| Mean (SD)                          | 22.1 (3.2)                         |
| Median (range)                     | 21.4 (16.3, 28.3)                  |
| PID, n (%)                         |                                    |
| CVID                               | 3.0 (30.0)                         |
| XLA                                | 6.0 (60.0)                         |
| Other immunodeficiency             | 1.0 (10.0)                         |
| IgG level at time of first PID diagnosis,$^b$ g/L | |
| Mean (SD)                          | 0.9 (1.1)                          |
| Median (range)                     | 0.6 (0.1, 3.4)                     |
| Pre-study IgG trough level, g/L    | 8.9 (4.1)                          |
| Median (range)                     | 7.5 (5.2, 18.4)                    |

*Table 1. Baseline demographic characteristics of patients (PKAS).*

*Table 2. Serum IgG PK parameters by dosing regimen (PKAS).*

| PK parameter               | 3-weekly infusions ($N = 2$) | 4-weekly infusions ($N = 8$) |
|----------------------------|-------------------------------|-------------------------------|
| $\text{AUC}_{0-\text{last}}$ (g*h/L) |                               |                               |
| Mean (SD)                  | 5971 (NR)                     | 6591 (2633)                   |
| Geometric mean (CV%)       | 5891 (NR)                     | 6239 (34.50)                  |
| 95% CI for the geometric mean | NR                           | 4713–8258                     |
| $C_{\text{max}}$ (g/L)     | 16.60 (NR)                    | 14.20 (5.53)                  |
| Geometric mean (CV%)       | 16.40 (NR)                    | 13.40 (36.40)                 |
| 95% CI for the geometric mean | NR                           | 9.98–18.0                     |
| $C_{\text{min}}$ (g/L)     | 10.60 (NR)                    | 8.53 (3.89)                   |
| Geometric mean (CV%)       | 10.30 (NR)                    | 7.98 (37.40)                  |
| 95% CI for the geometric mean | NR                           | 5.90–10.80                    |
| $C_{\text{trough}}$ (g/L)  | 10.05 (NR)                    | 7.96 (3.78)                   |
| Geometric mean (CV%)       | 9.89 (NR)                     | 7.40 (38.92)                  |
| 95% CI for the geometric mean | NR                           | 5.41–10.14                    |
| $\text{CL}$ (mL/h)         | 2.53 (NR)                     | 2.53 (1.00)                   |
| Geometric mean (CV%)       | 2.49 (NR)                     | 2.36 (42.20)                  |
| 95% CI for the geometric mean | NR                           | 1.68–3.31                     |
| dAUC (g*h/L/mg)$^a$        | 0.41 (NR)                     | 0.46 (0.19)                   |
| Geometric mean (CV%)       | 0.40 (NR)                     | 0.42 (0.20)                   |
| 95% CI for the geometric mean | NR                           | 0.30–0.59                     |
| $T_{\text{max}}$ (h)       | 1.19                          | 1.14                          |
| Min, Max                   | 0.92, 1.47                    | 0.62, 23.37                   |

*Table 2. Serum IgG PK parameters by dosing regimen (PKAS).*

$^a$AUC values are dose-normalized on a per mg dose basis.

**BMI**: body mass index; **CVID**: common variable immunodeficiency; **IgG**: immunoglobulin G; **PID**: primary immunodeficiency; **PKAS**: pharmacokinetic analysis set; **SD**: standard deviation; **XLA**: X-linked agammaglobulinemia.

$^a$If weight on Day 1 was missing, the assessment at Screening is used.

$^b$n = 8.
patients, and one patient, who received 4-weekly infusions, had particularly high levels of IgG. Mean (SD) serum IgG concentrations are presented in Figure 2, where $C_{\text{max}}$ was observed approximately 1 h after the start of the infusion in both groups, with a gradual decline in serum IgG concentration from 24 h post-infusion to 21 days (3-weekly) or 28 days (4-weekly) post-infusion. Mean (SD) $C_{\text{max}}$ was similar between the infusion groups at 16.6 and 14.2 (5.53) g/L for 3- and 4-weekly infusions, respectively. Geometric mean (95% CI) of $C_{\text{max}}$ was also similar between 3- and 4-weekly infusion groups (Table 2). $T_{\text{max}}$ was slightly higher in the 3-weekly infusion group (median [range]: 1.19 [0.92–1.47] h) than the 4-weekly infusion group (1.14 [0.62–23.37] h).

Although there were generally no notable differences, mean (SD) and geometric mean (95% CI) $C_{\text{trough}}$ were found to be slightly higher for the 4-weekly infusion group than the 3-weekly infusion group (mean [SD] 5971 and 6591 [2633] g/h/L; geometric mean [95% CI] 5891 and 6239 [4713–8258] g/h/L for 3- and 4-weekly infusion groups, respectively).

The mean (SD) and geometric mean (95% CI) of dAUC were similar between 3-weekly and 4-weekly infusion groups, as was the mean (SD) and geometric mean (95% CI) of CL (Table 2).

4. Discussion

This was the first clinical study to evaluate the PK properties of Privigen® in Japanese patients with PID. In this study, PK assessments were performed after a standard 12 weeks wash-in/wash-out period to eliminate any significant carryover of the pre-study IgG therapies and allow for the evaluation of steady-state dosing of Privigen®. The PK properties of Privigen® were found to be similar following 3-weekly and 4-weekly intravenous administration, with no notable differences in any of the evaluated PK parameters. Serum IgG concentrations ($C_{\text{max}}, C_{\text{min}}$) and $AUC_{0-\text{last}}$ were similar between dosing regimens, considering the limited number of patients in the 3-weekly infusion group. This indicates the possibility that equivalent therapeutic IgG levels can be achieved with a 4-weekly regimen as with a 3-weekly regimen, which offers flexibility in switching from 4-weekly to 3-weekly dosing, for example, in cases where a 4-weekly regimen does not ensure the desired efficacy, in terms of low $C_{\text{trough}}$ levels, high IgG clearance or recurrent infections.

Negligible changes in $C_{\text{trough}}$ levels from ‘prior to initial infusion’ to ‘prior to last infusion’ indicate that stable serum IgG trough levels were maintained both during the study and following a switch from the pre-study IVIG products. $C_{\text{trough}}$ levels at ≥5 g/L are associated with therapeutic protection against infections for many patients with PID, and levels ≥9 g/L offer further enhanced protection in patients with PID [20,23]. However, there is no absolute protective serum IgG level applicable to all patients with PID, and experts in the field agree that IgG dosing often has to be adjusted individually to achieve optimal therapeutic effect [10–12]. $C_{\text{trough}}$ levels observed with 3-weekly and 4-weekly infusions in the present study (7.95–10.90 g/L) were within a range generally accepted to be sufficient to confer protection from infection in the majority of patients with PID.
The PK parameters calculated in Japanese patients in this study were similar to those previously reported in non-Japanese patients. C\text{trough}, levels achieved with Privigen\textsuperscript{®} infusions in the present study are similar to those observed in a previous Privigen\textsuperscript{®} PK study conducted in non-Japanese patients with PID, which reported a relatively constant C\text{trough} levels (approximately 9–10 g/L) throughout the 12-month study period [20]. Similar to pre-study levels. There was no statistically significant difference in C\text{trough} levels between 3-weekly and 4-weekly regimens in this previous study [20], which validates the similar C\text{trough} levels observed between the regimens in the current study.

In another study of non-Japanese patients with PID conducted at multiple sites in the United States and Germany, 3- or 4-weekly Privigen\textsuperscript{®} was administered from 4 to 26 months (data unpublished) [22]. In this previous study, median (range) C\text{min} was 10.2 (5.8–14.7) g/L, C\text{max} was 23.4 (10.4–34.6) g/L, AUC\text{0–last} was 366 (197–443) day\textsuperscript{*}g/L, T\text{max} was 2.3 (1.3–26.3) h and CL was 1.33 (0.87–2.09) mL/day/kg [22]. The higher C\text{max} and AUC\text{0–last} reported in this previous study of non-Japanese patients may be due to the higher median dose of 444.4 mg/kg of Privigen\textsuperscript{®} administered, compared with the present study, where the median dose was 280.9 mg/kg [22]. Despite this difference, the serum IgG concentration-time profile observed in the study of Privigen\textsuperscript{®} PK study in non-Japanese patients [22] is similar to the profile observed in the present study.

In the present PK analysis, the wash-in/wash-out period and sampling points for PK assessments were similar to previous Privigen\textsuperscript{®} studies conducted in non-Japanese patients, enabling the comparison of PK profile between Japanese and non-Japanese patients with PID. However, limitations include the small number of patients, particularly in the 3-weekly infusion group, which restricts the interpretation of results. It can also not be excluded that variability in the dose range, sample size, and duration of treatment in the present study compared with previous studies may affect the comparison of PK parameters between Japanese and non-Japanese patients. In addition, there was no comparator product used in this study.

In conclusion, there were no substantial differences in PK parameters between groups receiving 3-weekly or 4-weekly infusions of Privigen\textsuperscript{®}, which can improve the flexibility of IVIG therapy with Privigen\textsuperscript{®} in patients with PID. Given the small number of patients in the 3-weekly regimen group in this study, further investigation with larger patient samples is warranted to evaluate any differences in PK parameters between the two regimens. In addition, this study suggests for the first time that the PK characteristics of Privigen\textsuperscript{®} are similar between Japanese and non-Japanese patients with PID.

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Disclosure statement

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