Population PK analysis of Pegaspargase in Japanese and non-Japanese patients with acute lymphoblastic leukemia

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Objective

Support submission of Pegaspargase in Japan via:

- Characterization of the PK of asparaginase activity (AA)
- Assessment of the impact of Japanese population in the PK of AA.
- Illustration of the PK behavior of AA via simulations.

Background

Asparaginase is an important agent in the treatment of acute lymphoblastic leukemia. PEG-L-asparaginase (Pegaspargase) is Escherichia coli L-asparaginase (L-ASP) coated with covalently linked large polyethylene glycol (PEG) polymers. The pharmacokinetic (PK) of Pegaspargase is characterized by measurement of AA.

Data and Methods

- A legacy PK model [1] based on the data from three studies (AALL07P4, CCG-1962 and DFCI-11-001) was used as the starting point of the PK analysis of AA (Figure 1).
  - The legacy model indicated that clearance (CL), maximum elimination capacity (V_{max}) and central volume of distribution (V_c) increased with body surface area (BSA) and Japanese population had lower CL.
- Data from a Japanese study (SHP674-201) were added to the legacy data to update the population PK model for AA.
- Pegaspargase 2500 U/m^2 or 82.5 U/kg was administered via intravenous (IV) infusion or intramuscular (IM) injection.
- Based on the structural legacy model including the mechanistic covariate (BSA) effects, an updated exploratory covariate search (Japanese effect on Michaelis-Menten constant, concentration at half maximum elimination capacity (K_m), CL and V_c) was performed to obtain the final AA model.
- The final AA model was used to simulate AA in the US and Japanese populations and assess % of patients with AA ≥ 0.1 U/mL at 14 days after the first and seventh every two weeks dose (steady-state). A total of 10000 patients were simulated for each population.
- The simulated patients were assigned to three different dose groups based on their age and BSA.
  - Group 1: Age ≤ 21 years and BSA < 0.6 m^2 received Pegaspargase 82.5 U/kg.
  - Group 2: Age ≤ 21 years and BSA ≥ 0.6 m^2 received Pegaspargase 2500 U/m^2.
  - Group 3: Age > 21 years received Pegaspargase 2000 U/m^2.

Results

- In addition to the covariates in the legacy model, the final AA model also included Japanese effect on K_m (Table S1). Equations for the final covariate model are presented in Equation 1.
- The final population PK model for AA indicated an acceptable predictive performance for AA (Figure S1-S3).
- Forest plots (Figure 2) illustrated that the impact of Japanese covariate on maximum activity (C_{max}) and area under the activity-time curve up to day 25 after single dose ($AUC_{0\text{-}25d}$) after a single dose (SiD) was not clinically meaningful (i.e., between 0.8 and 1.25 relative change).
- Forest plot (Figure 2) also showed that, given a fixed BSA adjusted dose level of 2500 U/m^2, the impact of BSA on C_{max} and $AUC_{0\text{-}25d}$ after a SiD was not clinically meaningful.
- Simulations based on the final AA model and relevant distributions of BSA for Japanese and US populations, where dose levels were based on age and BSA values, showed that more than 97% of the patients in US and Japanese populations had AA ≥ 0.1 U/mL at 14 days after first and seventh dose (Table 1).

$$
\begin{aligned}
CL\ (L/h) &= 0.00238\ (L/h) \cdot \left(\frac{BSA\ (m^2)}{0.835\ (m^2)}\right)^{1.07} \cdot \begin{cases} 1 & \text{if Non Japanese} \\ (1-0.406) & \text{if Japanese} \end{cases} \\
V_c\ (L) &= 1.34\ (L) \cdot \left(\frac{BSA\ (m^2)}{0.835\ (m^2)}\right)^{1.30} \\
V_{max}\ (L) &= 1.91\ (L) \cdot \left(\frac{BSA\ (m^2)}{0.835\ (m^2)}\right)^{1.14} \\
K_m\ (U/L) &= 80.5\ (U/L) \cdot \begin{cases} 1 & \text{if Non Japanese} \\ (1-0.825) & \text{if Japanese} \end{cases}
\end{aligned}
\qquad (1)
$$

Conclusions

- The legacy AA model was successfully updated in application to the current analysis data set.
- The final AA model predicted that the Japanese patients would have 41% lower CL and 83% lower K_m than that of the non-Japanese patients.
- The effects of Japanese population and lyophilized formulation of Pegaspargase were confounded in the current analysis data. Hence, the impact of Japanese covariate should be interpreted carefully.
- There is no clinically meaningful difference in C_{max} and $AUC_{0\text{-}25d}$ after a SiD between the non-Japanese and Japanese patients.
- Simulations indicated that all subgroups in both US and Japanese populations had more than 97% of the patients with AA ≥ 0.1 U/mL at 14 days after first (primary efficacy endpoint in the Part 2 of study SHP674-201) and seventh dose of Pegaspargase.
- Using the reproducible report and processes prepared with the legacy analysis, the report was delivered in less than 5 Weeks.

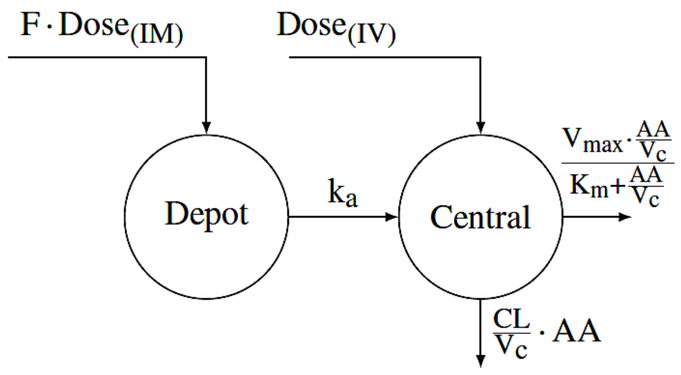

Figure 1. Illustration of the PK model for AA: a 1-compartment model with a first-order absorption, two bioavailability (F) estimates for the first and later doses for the IM route of administration, and a combined linear and saturable elimination.

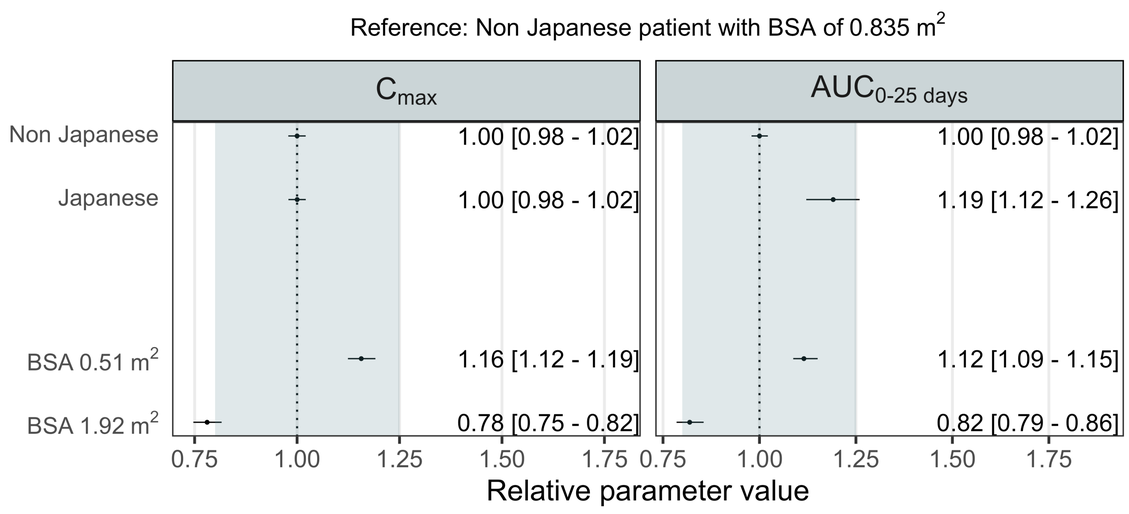

Figure 2. Forest plots illustrating the covariate effects on C_{max} and $AUC_{0\text{-}25d}$ after a single dose, conditioned on a typical reference subject, based on the final AA model. Closed dots and error bars, together with their specific values, represent the median of the predicted relative change from the reference subject and its associated 90% CIs; these values are calculated based on 250 sampled parameter vectors from the variance-covariance matrix obtained from NONMEM. The parameter values for a reference subject are shown by the solid vertical lines; the dashed vertical lines indicate the 80%-125% margins relative to the reference subject.

	n[a]	14 days since first dose[b]	14 days after seventh dose
US			
Age ≤ 21 years & BSA < 0.6 m^2	674	98.66	100.0
Age ≤ 21 years & BSA ≥ 0.6 m^2	5207	99.83	99.92
Age > 21 years	4119	97.48	99.98
Japan			
Age ≤ 21 years & BSA < 0.6 m^2	841	98.22	100.0
Age ≤ 21 years & BSA ≥ 0.6 m^2	6659	99.82	99.95
Age > 21 years	2500	97.36	99.92

[a] Number of patients
[b] A dose begins at infusion start.

Table 1. Percentage of patients with simulated AA 0.1 U/mL at 14 days after first and seventh doses, stratified by country and groups of patients, using the final AA model.

References

[1] Population PK report. REP-1-SER-ONC-PMX-1. Population PK analysis of Oncaspar in Japanese and non-Japanese patients with acute lymphoblastic leukemia. Pharmetheus; 2022.

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Supplementary material

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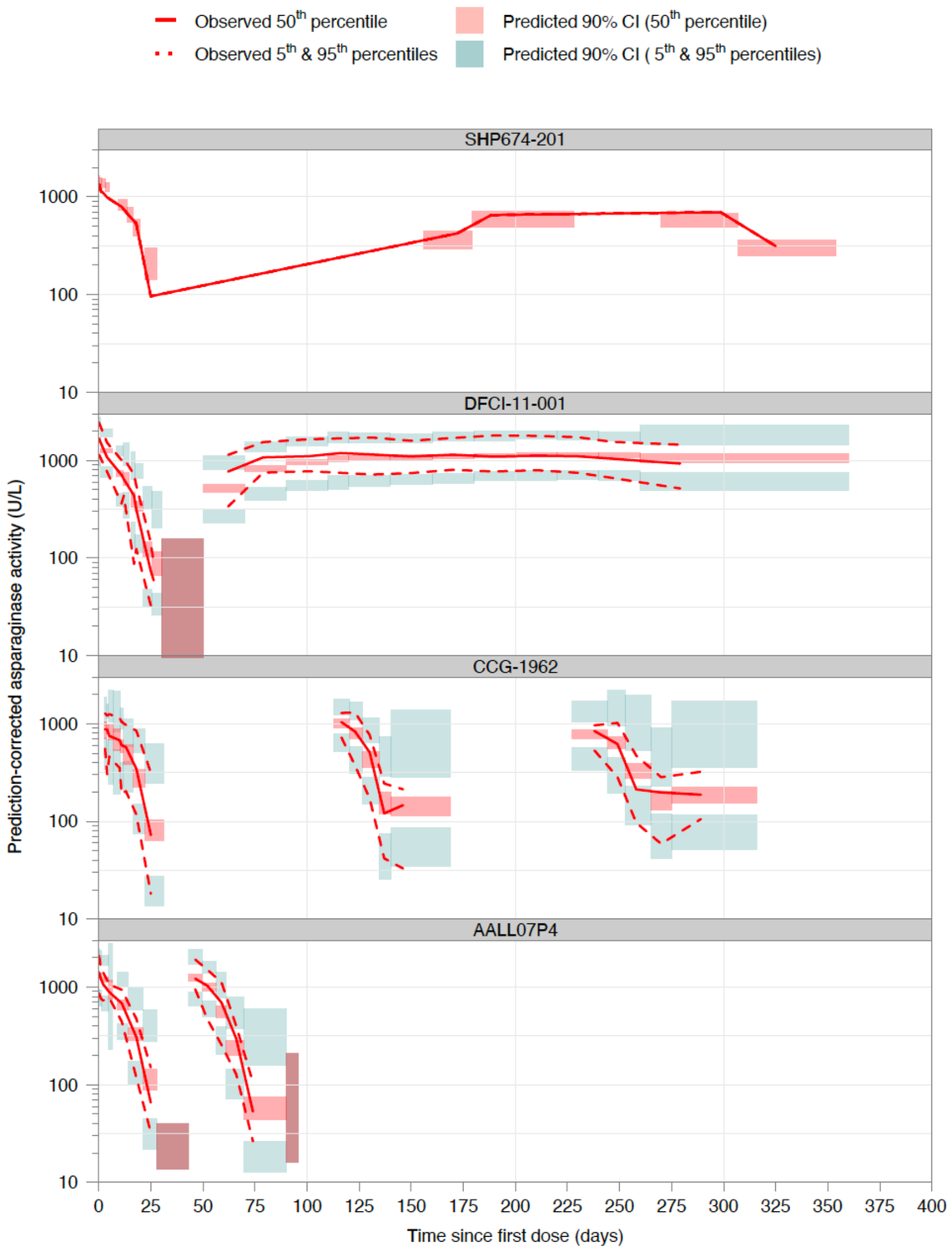

Figure S1. Prediction-corrected VPC (pcVPC) of AA versus time since first dose, stratified by study, for the AA analysis data set, using the final AA model. Since study SHP674-201 included relatively small number of patients (< 50), outer percentiles are not included in the pcVPC for this study. Data are presented on a semi-logarithmic scale. Time points associated with BLQ observations were included in the pcVPC.

	Final model
Run	25
OFV	–4192
Condition number	3.10142e+12

		Final model		
	Unit	Value	RSE (%)	SHR (%)
V_{max}	U/h	1.91	5.20	
V_c	L	1.34	1.38	
k_a	1/h	0.0211	10.5	
K_m	U/L	80.5	15.6	
CL	L/h	0.00238	2.49	
F first dose		0.799	4.15	
F after first dose		0.940	2.99	
BSA on V_{max}		1.14	4.44	
BSA on V_c		1.30	2.18	
BSA on CL		1.07	4.27	
Japanese[a] on CL		-0.406	19.0	
Japanese[a] on K_m		-0.825	3.76	
RUV_1	CV	0.0592	7.07	
RUV_2	CV	1.14	5.68	
$RUVC_{50}$	U/L	226	7.73	
IIV V_{max}	CV	0.284	11.2	22.5
IIV V_c	CV	0.176	7.71	17.6
Corr. IIV V_{max}-V_c	Corr.	0.741	9.91	
IIV k_a	CV	0.306	38.4	16.4
Corr. IIV V_{max}-k_a	Corr.	0.848	19.1	
Corr. IIV V_c-k_a	Corr.	0.984	20.4	
IIV K_m	CV	0.736	10.3	33.6
Corr. IIV V_{max}-K_m	Corr.	0.918	11.9	
Corr. IIV V_c-K_m	Corr.	0.414	21.9	
Corr. IIV k_a-K_m	Corr.	0.569	24.8	
IIV CL	CV	0.0533	28.8	63.1
IIV RUV_1	CV	1.13	11.5	44.3

The RSE for IIV and RUV parameters are reported on the approximate SD scale. [a] Japanese patient. Reference patient: non Japanese patient with BSA of 0.835 m^2

Table S1. Parameter estimates of the final AA model.

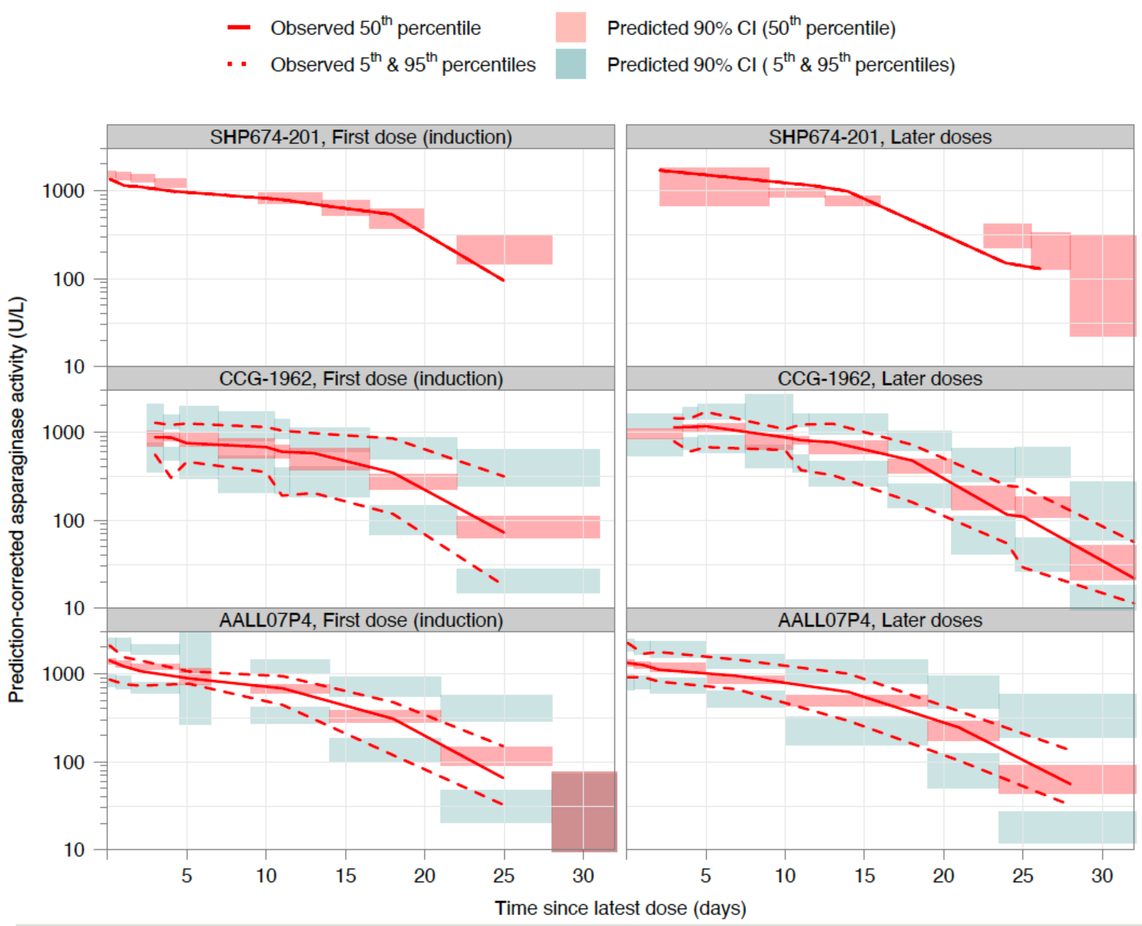

Figure S2. pcVPC of AA versus time since latest dose, stratified by study and dosing occasion, for the AA analysis data set from studies AALL07P4, CCG-1962 and SHP674-201, using the final AA model. Since study SHP674-201 included relatively small number of patients (< 50), outer percentiles are not included in the pcVPC for this study. Data are presented on a semilogarithmic scale. Time points associated with BLQ observations were included in the pcVPC.

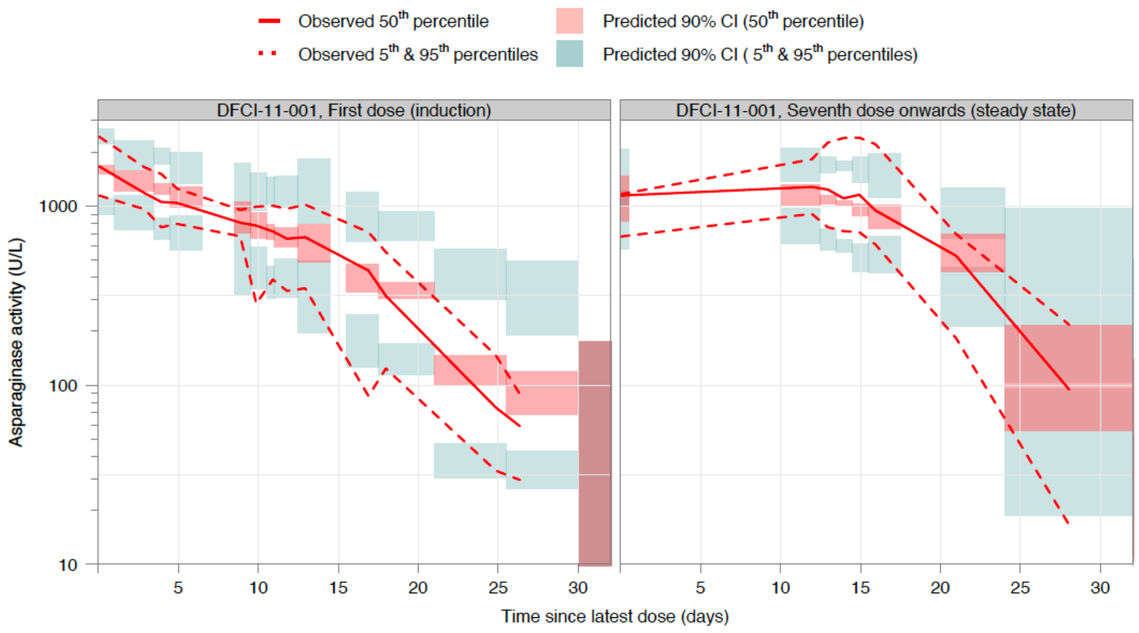

Figure S3. pcVPC of AA versus time since latest dose, stratified by dosing occasion, for the AA analysis data set from study DFCI-11-001 excluding observations from the second to sixth dosing occasions, using the final AA model. Data are presented on a semilogarithmic scale. Time points associated with BLQ observations were included in the pcVPC.

References

[1] Population PK report. REP-1-SER-ONC-PMX-1. Population PK analysis of Oncaspar in Japanese and non-Japanese patients with acute lymphoblastic leukemia. Pharmetheus; 2022.

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