To View Online:
https://www.certara.com/case-study/dose-optimization-using-population-pk-for-an-orphan-drug/

CERTARA®
Accerlating Medicines, Together

CASE STUDY

DOSE OPTIMIZATION USING POPULATION PK FOR AN ORPHAN DRUG

Nobelpharma

RAPALIMUS® Tablets (sirolimus) is Nobelpharma's orphan drug developed from an oral medication that is sold as an organ transplant immunosuppressant by Pfizer Inc. in the US. Due to its properties as an mTOR inhibitor, physicians in academia and researchers had been actively studying and collecting data in an effort to find applications of RAPALIMUS for other diseases. Based on the findings of this research, Japan-based Nobelpharma obtained marketing approval from the Pharmaceuticals and Medical Devices Agency (PMDA), Japan's health authority, for RAPALIMUS as the first medication for lymphangioleiomyomatosis, a lung disease caused by abnormal growth of smooth muscle cells, in 2014.

Recently, Nobelpharma gained approval for a new indication for RAPALIMUS to treat a refractory lymphatic disease by using data from investigator-driven clinical trials led by Michio OZEKI M.D. (Department of Pediatrics, Gifu University, Japan). These trials targeted intractable lymphatic anomalies that mainly affect children (Lymphatic malformation, Generalized lymphatic anomaly, Gorham-Stout disease, and Lymphangiectasia). This project was supported by a Certara consulting team that established a population pharmacokinetic model, ran simulations for dose-setting based on body surface area, and prepared relevant document for approval, among other vital tasks.

In 2019, Nobelpharma worked alongside Michio OZEKI M.D. and collaborated with Certara to determine the optimum dose of RAPALIMUS by performing a population pharmacokinetic (PPK) analysis with a non-linear mixed-effects model. This analysis was performed using RAPALIMUS trough levels in whole blood acquired from clinical trials of patients with intractable lymphatic anomalies, clinical research involving patients with intractable vascular tumors and vascular malformations, clinical research involving patients with intractable lymphatic anomalies, clinical studies of healthy adults, and clinical studies of patients with lymphangioleiomyomatosis.

As a result of this analysis, factors affecting the pharmacokinetics of RAPALIMUS were identified and drug exposure levels were described based on a two-compartment model with a first-order absorption process that incorporated adjustments for body weight and age in accordance with the principles of allometry. This information was also included in the drug package insert. Due to large individual differences in pharmacokinetics, post-marketing therapeutic drug monitoring (TDM) of individual patients receiving doses in both body surface area categories was also considered important, and a recommendation to "adjust the dose depending on patient status and trough levels in the blood" was included in the drug label.

Given that the clinical trials targeted rare diseases and were conducted in high-risk patients, dose-optimization was challenging due to the small number of patients.

To View Online:
https://www.certara.com/case-study/dose-optimization-using-population-pk-for-an-orphan-drug/

CERTARA®

CASE STUDY

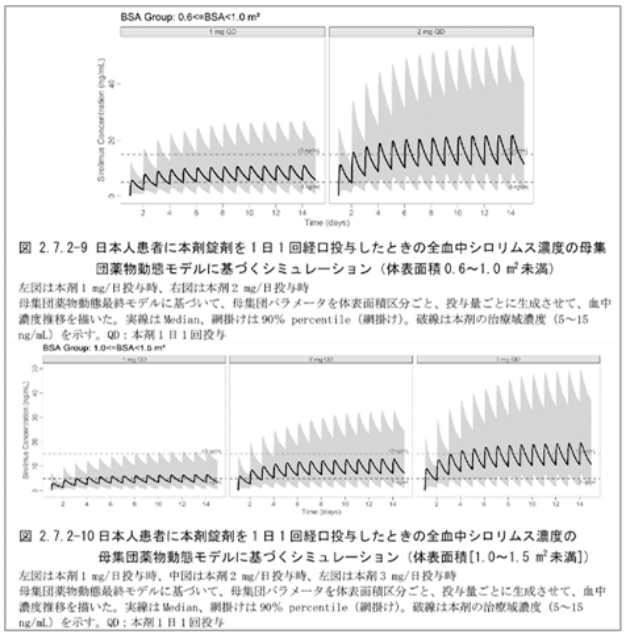

図 2.7.2-9 日本人患者に本剤錠剤を1日1回経口投与したときの全血中シロリムス濃度の母集団薬物動態モデルに基づくシミュレーション（体表面積 0.6～1.0 m² 未満）

左図は本剤1 mg/日投与時、右図は本剤2 mg/日投与時
母集団薬物動態最終モデルに基づいて、母集団パラメータを体表面積区分ごと、投与量ごとに生成させて、血中濃度推移を描いた。実線は Median、網掛けは 90% percentile（網掛け）。破線は本剤の治療域濃度（5～15 ng/mL）を示す。QD：本剤1日1回投与

図 2.7.2-10 日本人患者に本剤錠剤を1日1回経口投与したときの全血中シロリムス濃度の母集団薬物動態モデルに基づくシミュレーション（体表面積[1.0～1.5 m² 未満]）

左図は本剤1 mg/日投与時、中図は本剤2 mg/日投与時、左図は本剤3 mg/日投与時
母集団薬物動態最終モデルに基づいて、母集団パラメータを体表面積区分ごと、投与量ごとに生成させて、血中濃度推移を描いた。実線は Median、網掛けは 90% percentile（網掛け）。破線は本剤の治療域濃度（5～15 ng/mL）を示す。QD：本剤1日1回投与

表 2.7.2-13 日本人患者に本剤錠剤を1日1回経口投与したときの全血中シロリムス濃度の母集団薬物動態モデルに基づくシミュレーション結果の要約

体表面積区分（m²）	本剤の投与量	$C_{min,ss}$ (ng/mL) *1 Median	$C_{min,ss}$ (ng/mL) *1 90% Percentile	5～15 ng/mL の患者割合*2 (%)	$C_{max,ss}$ (ng/mL) *1 Median	$C_{max,ss}$ (ng/mL) *1 90% Percentile
≥0.6～<1.0	1 mg/日	5.72	0.930 - 20.0	45.7	11.6	4.35 - 27.7
	2 mg/日	11.4	1.86 - 40.0	41.7	23.1	8.69 - 55.3
≥1.0～<1.5	1 mg/日	3.58	0.566 - 12.1	31.5	6.79	2.39 - 16.9
	2 mg/日	7.16	1.13 - 24.2	50.1	13.6	4.78 - 33.7
	3 mg/日	10.7	1.70 - 36.2	43.2	20.4	7.17 - 50.6
≥1.5	1 mg/日	2.76	0.489 - 9.09	20.6	4.96	1.70 - 12.4
	2 mg/日	5.51	0.977 - 18.2	44.0	9.92	3.40 - 24.8
	3 mg/日	8.27	1.47 - 27.3	48.6	14.9	5.09 - 37.2

$C_{max,ss}$：定常状態時の最高血中濃度、$C_{min,ss}$：定常状態時のトラフ濃度、
*1：母集団薬物動態最終モデルに基づいて、3歳以上の男女各100例、計3400例生成させて、$C_{min,ss}$、$C_{max,ss}$ の Median 及び90% percentile、治療域の患者の割合を求めた。
*2：$C_{min,ss}$ が本剤の治療域濃度（5～15 ng/mL）にある患者の割合

"The patient group was small and contained a limited variety of patient characteristics, hence dosage standardization (for inclusion in the drug package insert) would have been impossible without the PPK model-based simulation technique. We worked with Certara to resolve this problem.

Certara's lead consultant, Dr. Mayumi Hasegawa, quickly understood our requests, performed her assessments, and communicated her recommendations to other analysts clearly and concisely, which was of immense help. We are also grateful to Mayumi for resolving many of our concerns.

Going forward, we want to collect data that allows for more robust simulations and intend to update the PPK model. We would also like to develop this model into a PK/PD model for other diseases."

About Nobelpharma Co., Ltd.

Nobelpharma Co., Ltd. was founded in 2003 with a mission to "Contribute to Society by Providing Critical Pharmaceuticals and Medical Devices for neglected diseases." Nobelpharma endeavors to accelerate drug development by developing pharmaceuticals and medical devices that meet medical needs not addressed by other companies and quickly deliver therapeutic drugs to the patients who await them.

Nobelpharma