

Modeling and simulation approach of everolimus PK/PD towards completing a pediatric development

Francois Pierre Combes,^{1*} Heidi Einolf,¹ Peijuan Zhu,¹ Neva Coello,² Tycho Heimbach,¹ Handan He,¹ Kai Grosch²

¹Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ, USA; ²Novartis Pharma AG, Postfach, Basel, Switzerland

*Presenting author

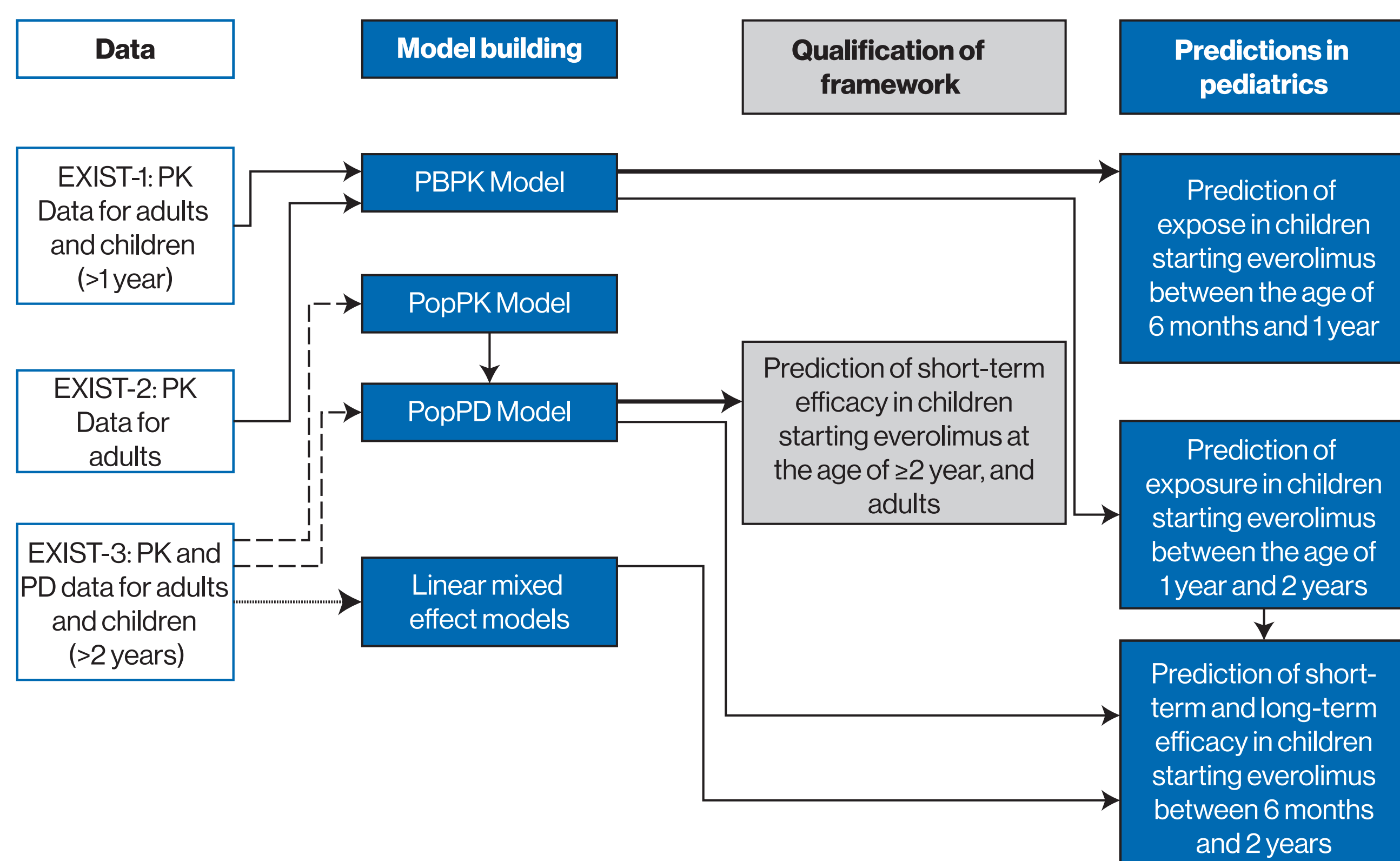
Introduction

- Tuberous sclerosis complex (TSC) is a genetic disorder characterized by multiple benign tumors throughout the body. It is caused by mutations in either *TSC1* or *TSC2* genes, resulting in constitutive overactivation of mammalian target of rapamycin (mTOR) [1].
- Epileptic seizures, reported in up to 90% of patients, are one of the most common presenting symptoms of TSC and may start in children from the age of 6 months onwards. The seizure semiology varies and can change throughout a patient's lifetime [2]. Approximately 60% of the patients remain treatment refractory [3,4].
- Everolimus, an mTOR inhibitor, achieves antitumor activity by inhibiting the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR pathway and also by downregulating angiogenesis [5].
- Based on results from the pivotal EXIST-3 trial (NCT01713946), adjunctive everolimus therapy was approved for the treatment of partial-onset refractory seizures in adults and children aged ≥ 2 years with TSC [6].
 - The dose of everolimus in patients < 6 years of age was 9 mg/m² and 6 mg/m² with and without the concomitant administration of cytochrome P450 (CYP3A4)/phosphoglycoprotein (PgP) inducers, respectively.
- To continue the development of everolimus for patients aged between 6 months and 2 years, we conducted a modeling and simulation approach to estimate the expected pharmacokinetics (PK) and efficacy (short- and long-term) of everolimus as adjunctive treatment.
- Here, we present the results of this approach aimed to understand whether the recommended dose of 6 mg/m² would maintain the everolimus target exposure range of 5–15 ng/mL in patients aged between 6 months and 2 years, resulting in a reduction in seizure frequency (RSF) from baseline.

Methods

- The modeling and simulation approach study consisted of a framework of three different models that were used together to enable the prediction of precise and reliable patient exposure metrics (trough concentrations C_{min}) and efficacy (RSF) in children aged between 6 months and 2 years (Figure 1).

Figure 1. Workflow for modeling and simulation



PBPK, physiology-based pharmacokinetics; PD, pharmacodynamics; PK, pharmacokinetics; PopPK, population pharmacokinetics; PopPD, population pharmacodynamics.

- Physiology-based PK (PBPK) model** – model built and validated using Simcyp® simulation software (Certara, L.P., Princeton, NJ) to predict the everolimus exposure (C_{min}) in patients aged between 6 months and 1 year using the following approach:
 - An adult PBPK model was built to predict everolimus PK after single and multiple doses and interaction with CYP3A4 perpetrators
 - This model was then qualified to predict PK in adult TSC patients (age, 18–62 years) from EXIST-1, EXIST-2, and EXIST-3. The qualified adult model compound file was then used to predict PK in pediatric patients
 - The compound file was refined “top-down” using a recently published ontogeny for CYP3A4⁷ and adjustments in absorption and distribution parameters for pediatric subjects < 12 years of age. The model was qualified to predict everolimus PK in pediatric TSC patients (aged 1 to < 18 years) from EXIST-1 and EXIST-3
- Population pharmacodynamics (PD) model** – count data model built based on the short-term PD data from EXIST-3 to predict daily seizures count and short-term efficacy (RSF) in patients of different age groups using the patient level C_{min} data predicted from the PBPK model. Seizures probability was described by a Poisson distribution:

$$P(Y_{i,d} = n) = \frac{\lambda_{i,d}^n}{n!} e^{-\lambda_{i,d}}$$
 where the individual mean number of seizures $\lambda_{i,d}$ is influenced by the age of the patient, and over time by the placebo and the everolimus C_{min} effect with

$$\lambda_{i,d} = \lambda_i \times E_{placebo,i,d} \times E_{everolimus,i,d}$$
 With $E_{placebo,i,d} = 1 + (Max_{PCB} - 1) * (1 - e^{-slope_{PCB} * (t-Tlag)})$ and $E_{everolimus,i,d} = 1 - Emax_{RAD,i,d} \times Cmin_{i,d} / (Cmin_{i,d} + C50_i)$.
 - $Emax_{RAD,i,d}$ being also time-varying, increasing to 100% over time, and influenced by the age of the patients at the start of everolimus
 - Developed in Monolix Suite 2016R1
- Linear mixed effect model** – model built based on the long-term PD data from EXIST-3 to predict long-term efficacy (RSF) in patients aged < 2 years using the time-normalized predicted exposure (TN C_{min})
 - Simulated concentrations (C_{min}) from the PBPK model for 200 subjects
 - This model was a multiplicative linear regression model. TN C_{min} was computed from the start of everolimus up to 96 weeks of treatment for every 12-week interval. The model equation is expressed as follows:

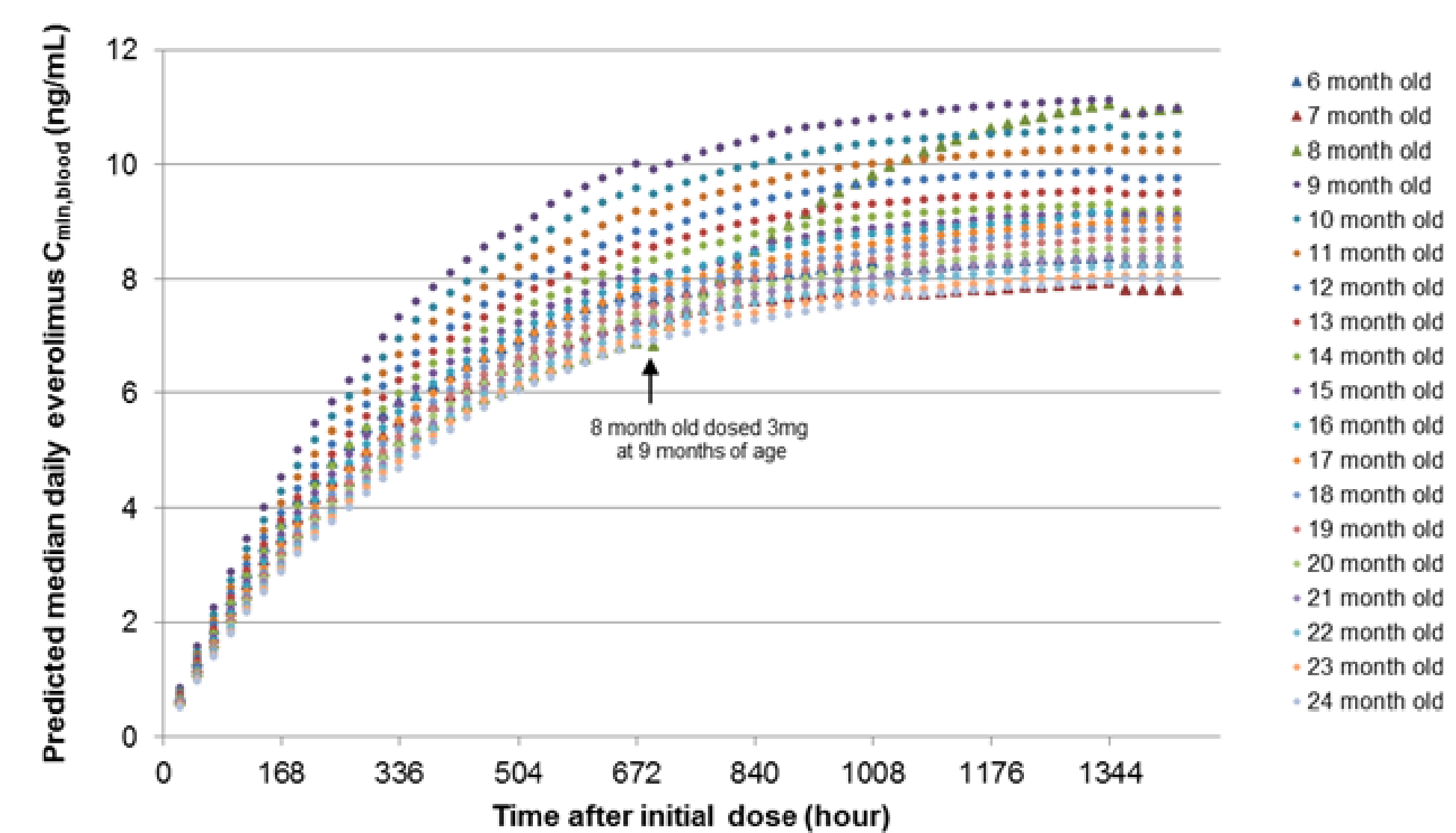
$$\log(SF_{ij}) = \mu + s_i + \beta_1 \log(SFBL_{ij}) + \beta_2 \log(P_{TNCmin_{ij}}) + (\beta_3 + s'_i) time + \epsilon_{ij}$$
 where ($p_{TNCmin_{ij}}$) is the TN simulated C_{min} predicted by the PBPK model

Results

PBPK-predicted PK of everolimus in pediatric patients with TSC

- Actual doses for patients aged between 6 months and 2 years following a target dose of 6 mg/kg dose were 2 and 3 mg, respectively. In Figure 2, which shows the daily C_{min} values for patients based on the age they started everolimus, simulations showed a slightly higher concentration for younger patients (median steady state C_{min} –8.29 ng/mL for a 6-month-old).
- The PBPK-predicted C_{min} at the end of 24 weeks of everolimus treatment for simulated patients aged between 6 months and 2 years was in the range of 7.7–10.5 ng/mL, well within the targeted range of 5–15 ng/mL.

Figure 2. PBPK model-predicted median daily everolimus C_{min} blood values over a 2-month period in TSC pediatric patients aged between 6 and 24 months at the initial dose in the absence of CYP3A4/PgP inducers



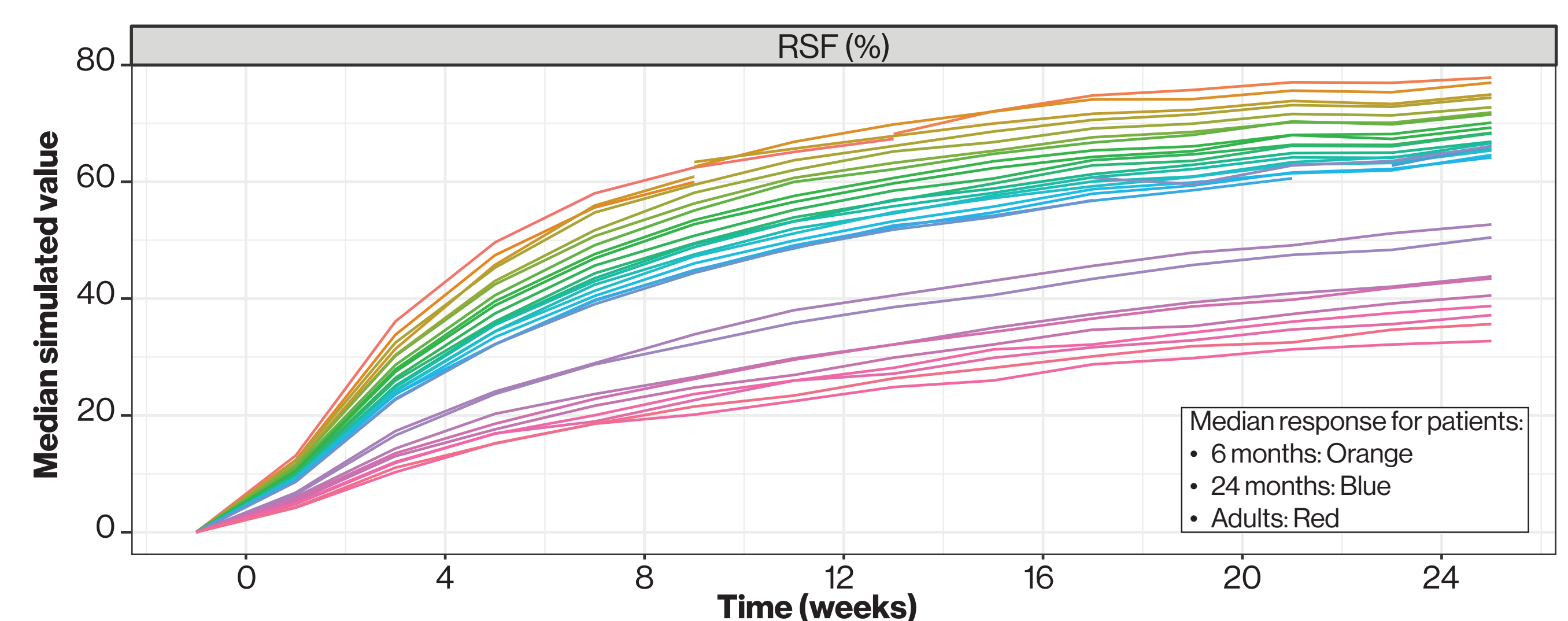
The triangle and circle symbols indicate patients dosed with a 2 and 3 mg dose, respectively, with the exception of the 8 month old who had a dose increase to 3 mg at 9 months of age. The doses were based upon the simulated population median BSA value to achieve a 6 mg/m² dose.

C_{min} , trough concentration; CYP, cytochrome P450; PBPK, physiology-based pharmacokinetics; PgP, phosphoglycoprotein; PK, pharmacokinetics; TSC, tuberous sclerosis complex.

Predicted short-term efficacy of everolimus

- Using the PBPK-predicted C_{min} , the population PD model predicted that the RSF (5th–95th percentiles) was at least 66.1% (50.3%–75.8%) for a patient starting everolimus at the age 2 years and 77.8% (60.6%–87.6%) for a patient starting everolimus at the age of 6 months (Figure 3).
- The predicted responder rate (5th quantile; 95th quantile) at the 24-week C_{min} was $\geq 57.5\%$ (52.5%; 63%) at 21 and 22 months and 67.5% (61.5%; 72.5%) at 6 months.

Figure 3. Predicted short-term efficacy of everolimus in pediatric patients

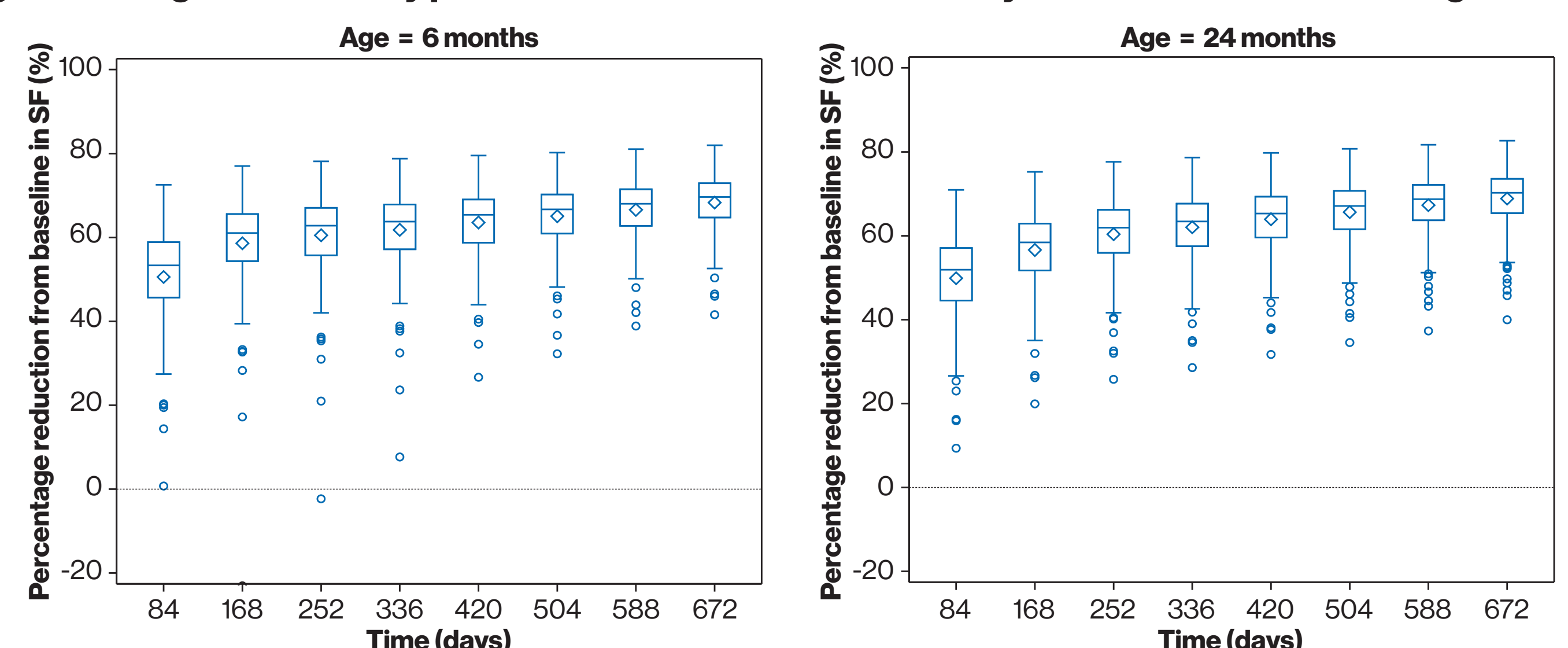


RSF, reduction in seizure frequency.

Predicted long-term efficacy of everolimus

- A 0.5-fold lower baseline seizure frequency (SF) was predicted to reduce RSF by 49.41% (95% confidence interval [CI], 45.68–52.89).
- For a 2-fold increase in TN C_{min} , the predicted RSF was 21.39% (95% CI, 13.30–28.74). Every additional 12 weeks of exposure to everolimus was predicted to have a modest but significant effect on SF, resulting in a further decrease of SF by 5.64% (95% CI, 3.54–7.70) per period (Figure 4).
- On an average, a 50% RSF was achieved by the first 12 weeks and a reduction of around 70% at the end of 2 years.

Figure 4. Long-term efficacy prediction over 12-week intervals by baseline median SF and age



SF, seizure frequency.

Conclusions

- This modeling and simulation approach study confirmed that everolimus at the dose of 6 mg/m² is efficacious in reducing daily seizure frequency in children aged between 6 months and 2 years with TSC-associated refractory seizures, with exposure concentrations maintained within the recommended target range of 5–15 ng/mL.
- Long-term treatment with everolimus can provide further benefit in reducing seizure frequency in pediatric patients with TSC-associated treatment-refractory seizures.

References

- Crino, et al. *N Engl J Med*, 355:1345–1356, 2006.
- Chu-shore CJ, et al. *Epilepsia*, 51(7):1236–1241, 2010.
- Upreti VV, et al. *J Clin Pharmacol*, 56(3):266–83, 2016.
- Overwater IE, et al. *Epilepsia*, 56(8):1239–1245, 2015.
- Chen X, et al. *Mol Cancer Res*, 11(10):1269–1278, 2013.
- Curatolo P, et al. *Eur J Paed Neurol*, 16:582–586, 2012.
- French JA, et al. *Lancet*, 388:2153–63, 2016.

Acknowledgments

We thank the patients and their families, investigators, and the steering committee members of the EXIST studies. We thank Rama Mylapuram for her medical editorial assistance with this poster and Janne Harjunpaa for his support on the long-term modeling.

Poster presented at Population Approach Group in Europe (PAGE) 2018, Montreux, Switzerland

Text: Q653da

To: 8NOVA (86682) US Only
+18324604729 North, Central and South Americas, Caribbean, China
+447860024038 UK, Europe & Russia
+46737494608 Sweden, Europe

Visit the web at:

<http://novartis.medicalcongressposters.com/Default.aspx?doc=653da>

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from the author of this poster.

Scan this QR code

