

Population Pharmacokinetic (PPK) Modelling Analyses of Tovorafenib in Patients with *RAF*-Altered, Relapsed/Refractory (R/R) Paediatric Low-Grade Glioma (pLGG), Advanced Solid Tumours, and Healthy Adults

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Background and Objectives

- Genetic alterations and dysregulation of the MAPK pathway have been found in many different types of adult and paediatric cancers [1].
- One of the most frequently altered genes in this pathway is *BRAF* [2].
- Tovorafenib is an oral, selective, CNS-penetrant, type II *RAF* kinase inhibitor that received US FDA accelerated approval for patients ≥ 6 months of age with R/R *BRAF*-altered pLGG based on results from the Phase 2 FIREFLY-1 trial (NCT04775485) [3].
- Here we describe the development of a PPK model for tovorafenib in adults and paediatrics and the assessment of clinical relevance of covariate effects.

Methods

- Preliminary PPK model was developed using data from the Phase 1 C28001 (NCT01425008) and Phase 1b C28002 (NCT02327169) adult studies (**Figure 1**).
- The preliminary PPK model was then updated with paediatric, adolescent, and young adult data from the Phase 2 FIREFLY-1 and adult data from a Phase 1 rBA study (**Figure 1**).
- The structural and covariate models were reassessed in the updated PPK model.
- Univariate analysis was conducted to assess the relative importance of covariate effects.

Figure 1 Schematic of Model Development

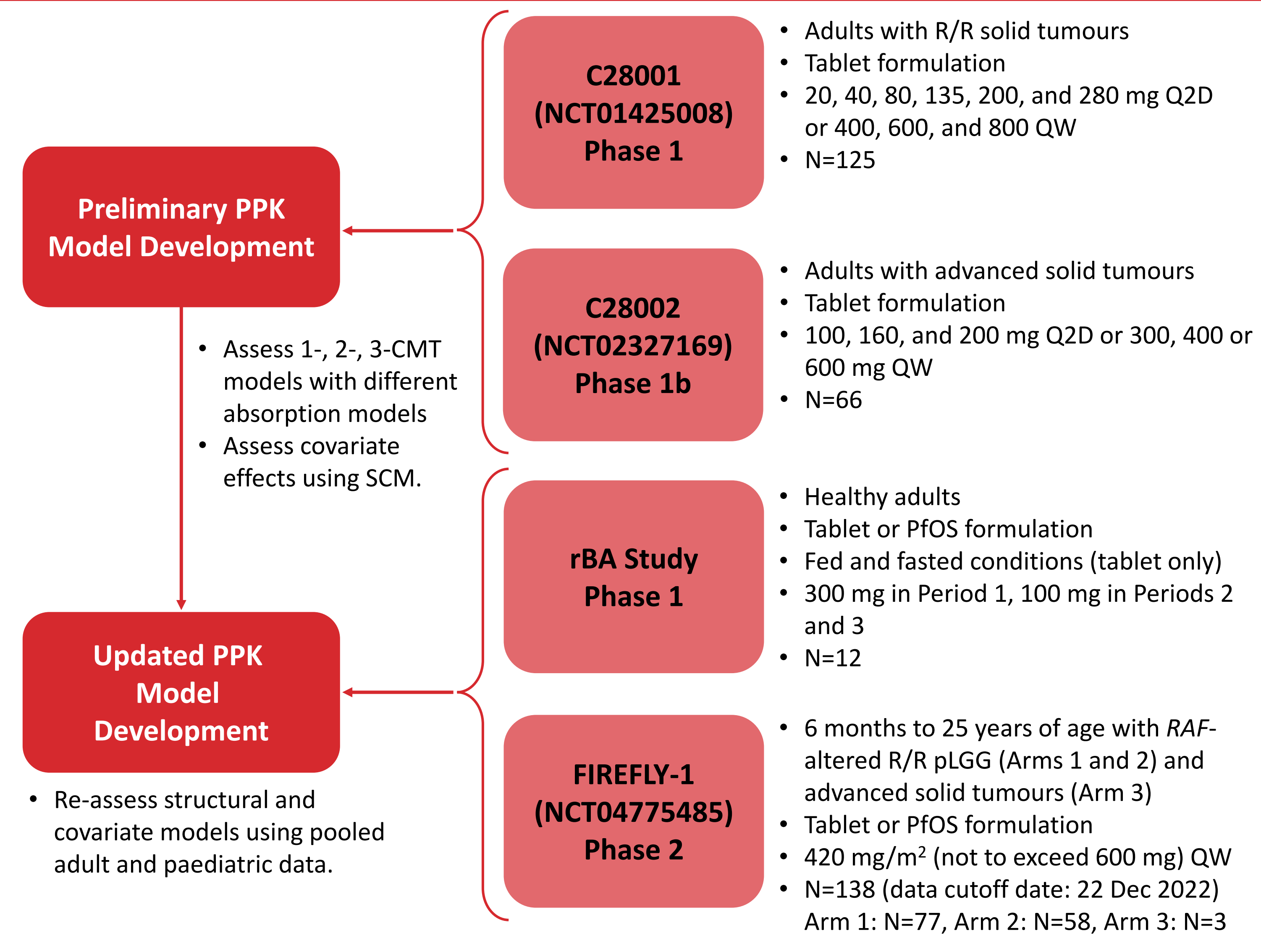


Table 1 Summary of Baseline Covariates

Covariate		Statistic	C28001 (N=125)	C28002 (N=66)	rBA Study (N=12)	FIREFLY-1 (N=138)	Overall (N=341)
Age (years)	Median [Range]		65.0 [33.0, 94.0]	62.0 [24.0, 78.0]	41.0 [35.0, 54.0]	9.00 [1.00, 24.0]	48.0 [1.00, 94.0]
Age (category)	Infant (1 month to <2 yrs)		0 (0%)	0 (0%)	0 (0%)	3 (2.2%)	3 (0.9%)
	Child (2 to <6 yrs)		0 (0%)	0 (0%)	0 (0%)	27 (19.6%)	27 (7.9%)
	Child (6 to <12 yrs)		0 (0%)	0 (0%)	0 (0%)	66 (47.8%)	66 (19.4%)
	Adolescent (12 to <18 yrs)		0 (0%)	0 (0%)	0 (0%)	36 (26.1%)	36 (10.6%)
	Adult (≥18 yrs)		125 (100%)	66 (100%)	12 (100%)	6 (4.3%)	209 (61.3%)
Sex	Female		57 (45.6%)	39 (59.1%)	6 (50.0%)	65 (47.1%)	167 (49.0%)
	Male		68 (54.4%)	27 (40.9%)	6 (50.0%)	73 (52.9%)	174 (51.0%)
BSA (m²)	Median [Range]		1.89 [1.38, 2.92]	1.81 [1.39, 2.44]	1.83 [1.54, 2.22]	1.12 [0.440, 2.19]	1.70 [0.440, 2.92]
	Missing (%)		1 (0.8%)	2 (3.0%)	-	-	3 (0.9%)

Note: Missing BSA was set to the population median during covariate analysis.

Table 2 Parameter Estimates for the Updated PPK Model

Parameters	Updated PPK Model				
	Estimates	RSE (%)	Random Effects		Shrinkage (%)
			IIV	RSE (%)	
CL/F (L/hr)	1.20	3.93	0.0896	11.0	12.0
Vc/F (L)	118	1.92	0.0575	18.5	25.0
Ka (Tablet) (1/hr)	3.31	3.39	0.285	11.7	16.8
Ka (PfOS) (1/hr)	0.81	27.2	0.917	26.5	14.6
BSA on CL/F	1.04	7.45	-	-	-
BSA on Vc/F	1.30	5.50	-	-	-
Sex (male) on CL/F	0.215	32.4	-	-	-
Food (high-fat meal) effect on Ka (Tablet)	-0.543	10.9	-	-	-
Covariance of CL/F and Vc/F	0.0337	25.5	-	-	-
Residual Error					
Additive error on log scale	0.321	3.49	-	-	9.36

- The PK of tovorafenib was well characterized by a 1-CMT model with a 3-CMT transit absorption model for the tablet formulation and a first-order absorption model with no transit CMT for the PfOS formulation.
- Formulation types did not impact model-predicted tovorafenib exposure, supporting the comparable rBA between the tablet and PfOS formulations.
- Inclusion of paediatric data confirmed that a BSA-based dosing strategy was appropriate to account for the influence of body size on tovorafenib PK in paediatric patients with *RAF*-altered R/R pLGG or advanced solid tumours.

Results

- Summary of baseline covariates are shown in **Table 1**.
- The preliminary PPK model structure was a 1-CMT model with a 3-CMT transit absorption model and linear elimination. Sex was identified as a covariate on CL/F and BSA as a covariate on CL/F and Vc/F.
- The updated PPK model structure (**Figure 2, Table 2**) included a first-order absorption model with no transit CMT for the PfOS formulation and a food effect on Ka (tablet) during base model development. Sex and BSA effects were retained in the updated PPK model.
- BSA exponents on CL/F and Vc/F increased in the updated PPK model compared to the preliminary PPK model, suggesting a stronger influence of body size on the PK in paediatric patients.
- Males were estimated to have a 21.5% higher CL/F than females.
- For those who received the tablet formulation, consumption of a high-fat meal was estimated to have a 54.3% lower Ka (tablet) compared to those under the fasted state.
- The effects of formulation and food on model-predicted tovorafenib steady-state exposure were within the 0.8 to 1.25 exposure ratio interval and were not considered to be clinically meaningful (**Figure 3**).

Figure 2 Schematic of Tovorafenib PPK Model Structure

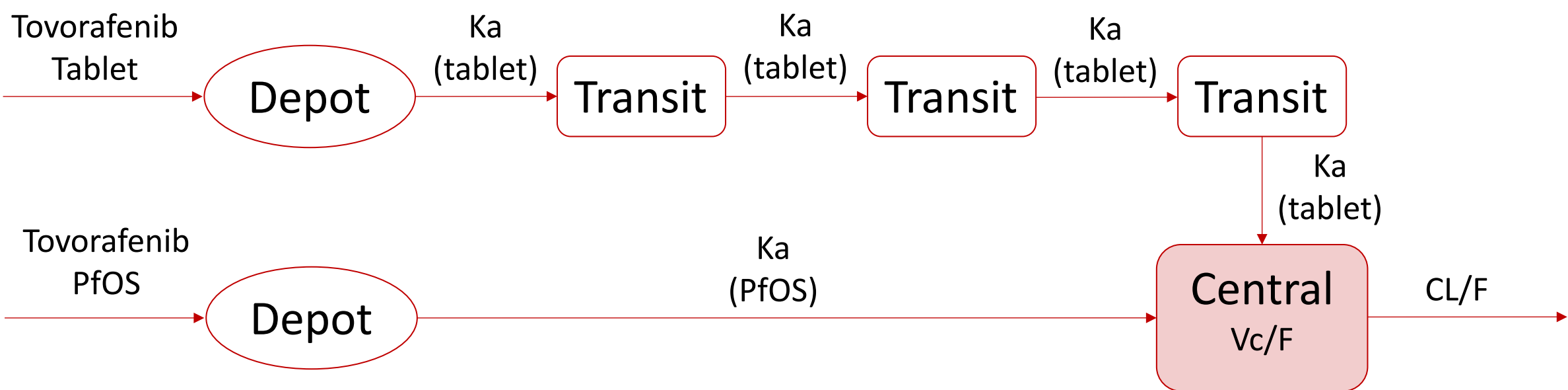
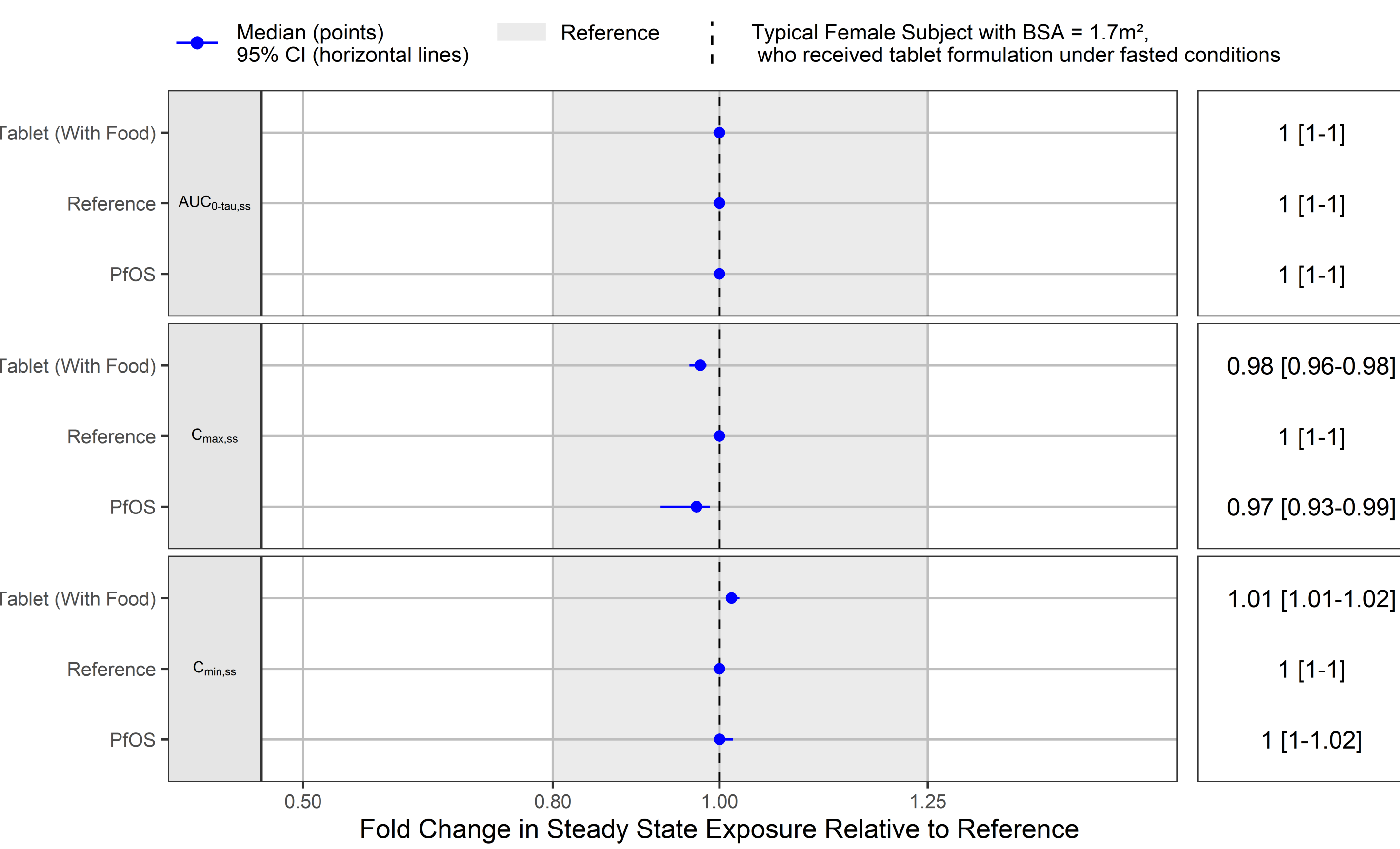


Figure 3 Relative Impact of Formulation and Food on Model-Predicted Tovorafenib Steady-State Exposure



Notes: The grey-shaded region represents the clinically insignificant region. A flat dose of 600 mg was used in the simulations.

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Abbreviations:
AUC_{0-24h,ss}=steady-state area under the concentration-time curve from 0 to the end of the dosing interval; *BRAF*=v-Raf murine sarcoma viral oncogene homolog B; BSA=body surface area; CI=confidence interval; CL/F=apparent clearance; C_{max,ss}=steady-state maximum concentration; C_{min,ss}=steady-state minimum concentration; CMT=compartment; CNS=central nervous system; FDA=Food and Drug Administration; IIV=inter-individual variability; MAPK=mitogen-activated protein kinase; N=number; PfOS=powder for oral suspension; PK=pharmacokinetic; Q2D=every other day; QW=once weekly; rBA=relative bioavailability; RSE=relative standard error; SCM=stepwise covariate modelling; US=United States; Vc/F=apparent central volume of distribution

References:
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