

Clinical trial design evaluation in pediatric oncology: Phase I dose finding trial design optimization exemplified by brigatinib (ITCC-098)

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Introduction

- The primary aim of phase I clinical trials is to define the recommended phase II dose (RP2D). Matching the adult target pharmacokinetic (PK) exposure is often a RP2D selection criterion, besides establishing clinical safety by assessing dose-limiting toxicities (DLT).
- In many phase I trials, non-compartmental analysis (NCA) is used to derive PK parameters.
- However, NCA may not adequately describe the PK depending on the number, timing of samples, and the number of patients^{1,2}.
- Intense sampling design for NCA to accurately capture PK is often unfeasible in pediatric trials³, while the small dataset often precludes developing a population PK (POPPK) model solely on the pediatric data.

Aim

- Instead of NCA, determine pediatric PK based on a POPPK model informed by the limited pediatric samples collected in the trial and available adult PK results using a Bayesian framework (\$PRIOR subroutine of NONMEM)^{4,5}, without the access of granular adult data.
- Evaluate the feasibility of this modeling approach, estimate the expected brigatinib exposure by the POPPK model and compare with the RP2D informed by NCA.

Method

- Trial design:** The phase I part of ITCC-098 trial enrolled pediatric patients with ALK positive malignancies, age ≥ 1 -<18, and WT >10 kg. Two brigatinib (tablet; QD dosing) dose levels (DL) were tested (Table 1). A sparse PK sampling schedule was used, samples were collected on Day 1 and 22 (Fig. 1).
- RP2D:** Determine by the incidence of DLT (rolling-6 design), efficacy and the DL leading to an equivalent target exposure ($AUC_{ss,tau}$ of 20.3 h*mg/L, $\pm 20\%$) from the approved adult dosing.
- Pediatric Brigatinib PK:** Describe by i) NCA, as stated in the protocol; ii) A POPPK model informed by both collected pediatric data and the adult PK using a Bayesian framework (PRIOR subroutine in NONMEM). Proposed workflow shown in Fig. 2. The reference model is a prior published brigatinib POPPK model for adult⁶ (Fig. 3 & Table 2). Expected $AUC_{ss,tau}$ for the two DLs were informed by the POPPK model clearance estimate in a simulated children dataset. POPPK analyses were performed using *NONMEM* (version 7.5). Simulations were performed using the R package *mrgsolve*.

Table 1. Pediatric patients Brigatinib tablet dosing scheme

	Adult (mg; QD)		Children >10 to <18 kg		Children 18 - 40 kg		Children >40 kg	
	Lead-in (7-day)	Cycle 1+ (28-day)	Lead-in	Cycle 1+	Lead-in	Cycle 1+	Lead-in	Cycle 1+
Dose level 1	90	180 [approved dose; target AUC]	30	60	60	120	90	180
Dose level 2	90	240 [highest tolerated dose]	30	90	60	150	90	240

Fig. 1 Pediatric patients Brigatinib PK data overview

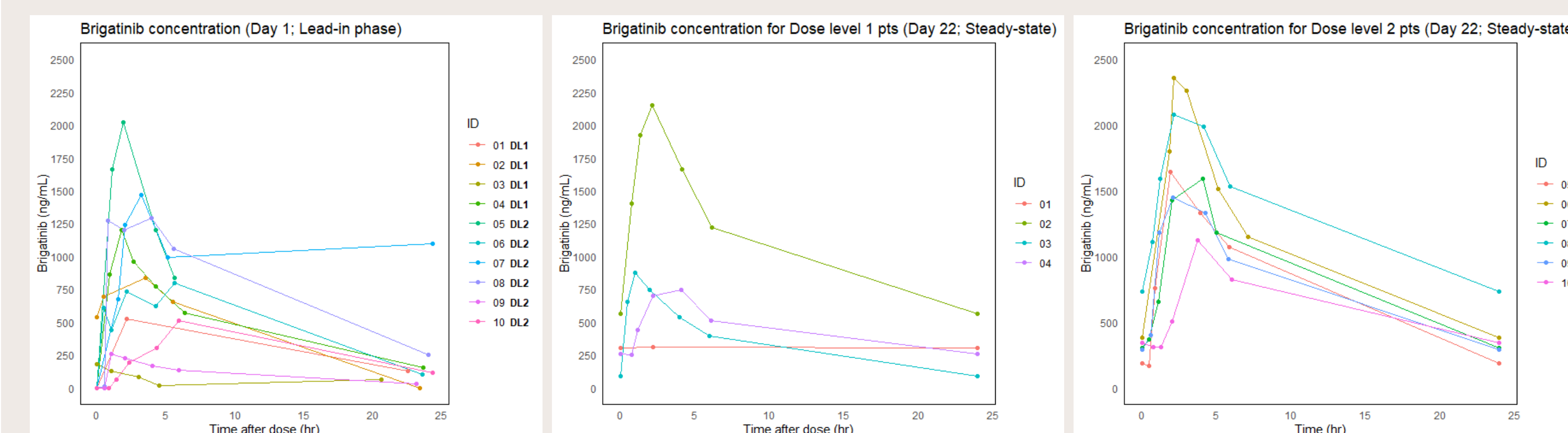


Fig. 2 Schematic workflow of proposed modeling method to evaluate pediatric PK in early phase trial

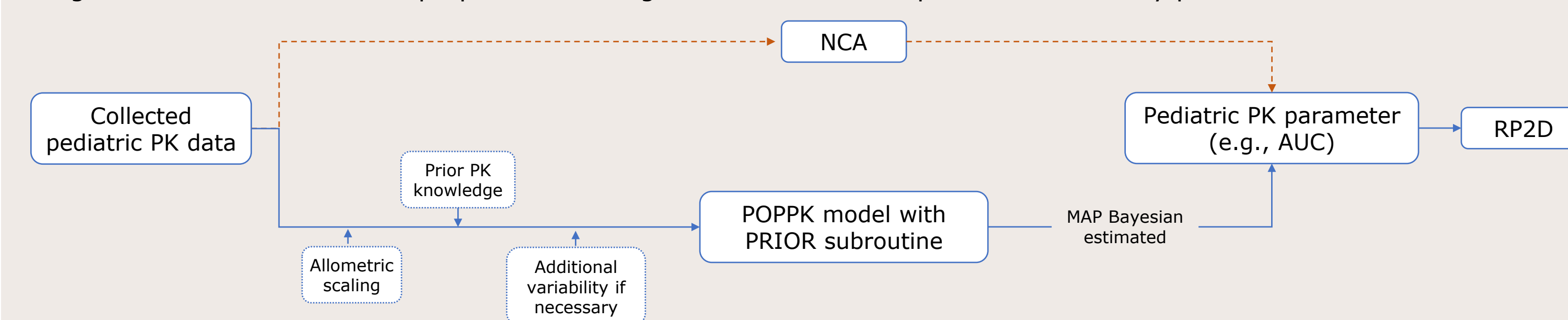
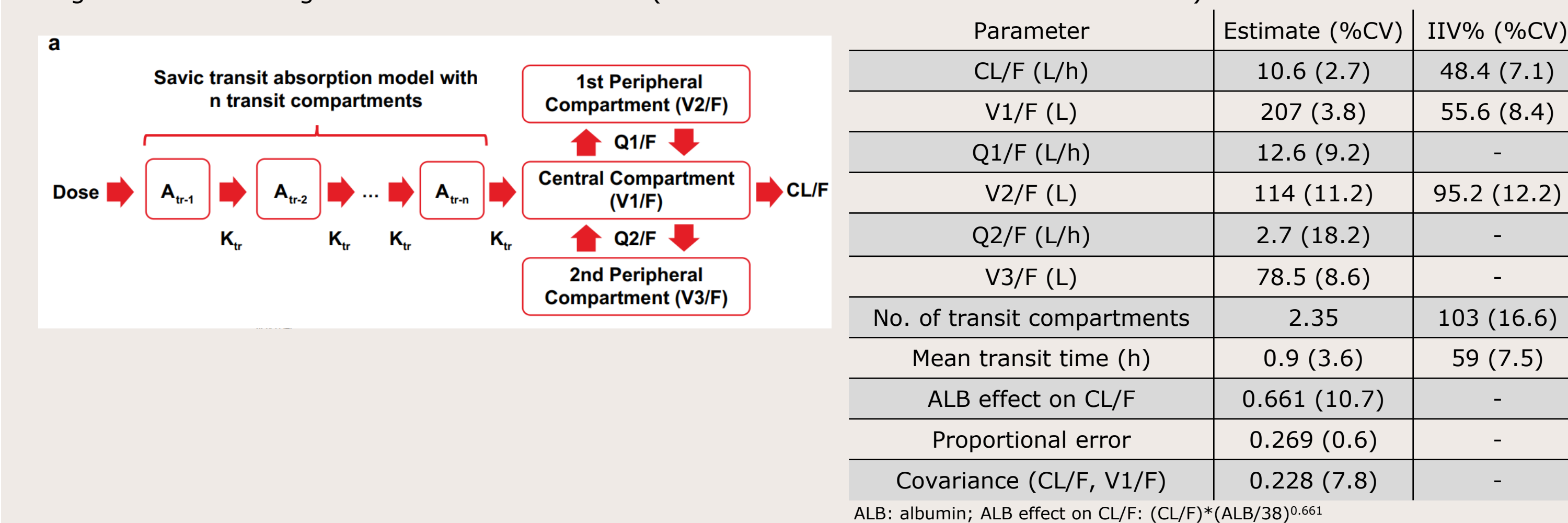


Fig. 3 & Table 2. Brigatinib adult POPPK model⁶ (reference model used in PRIOR subroutine)



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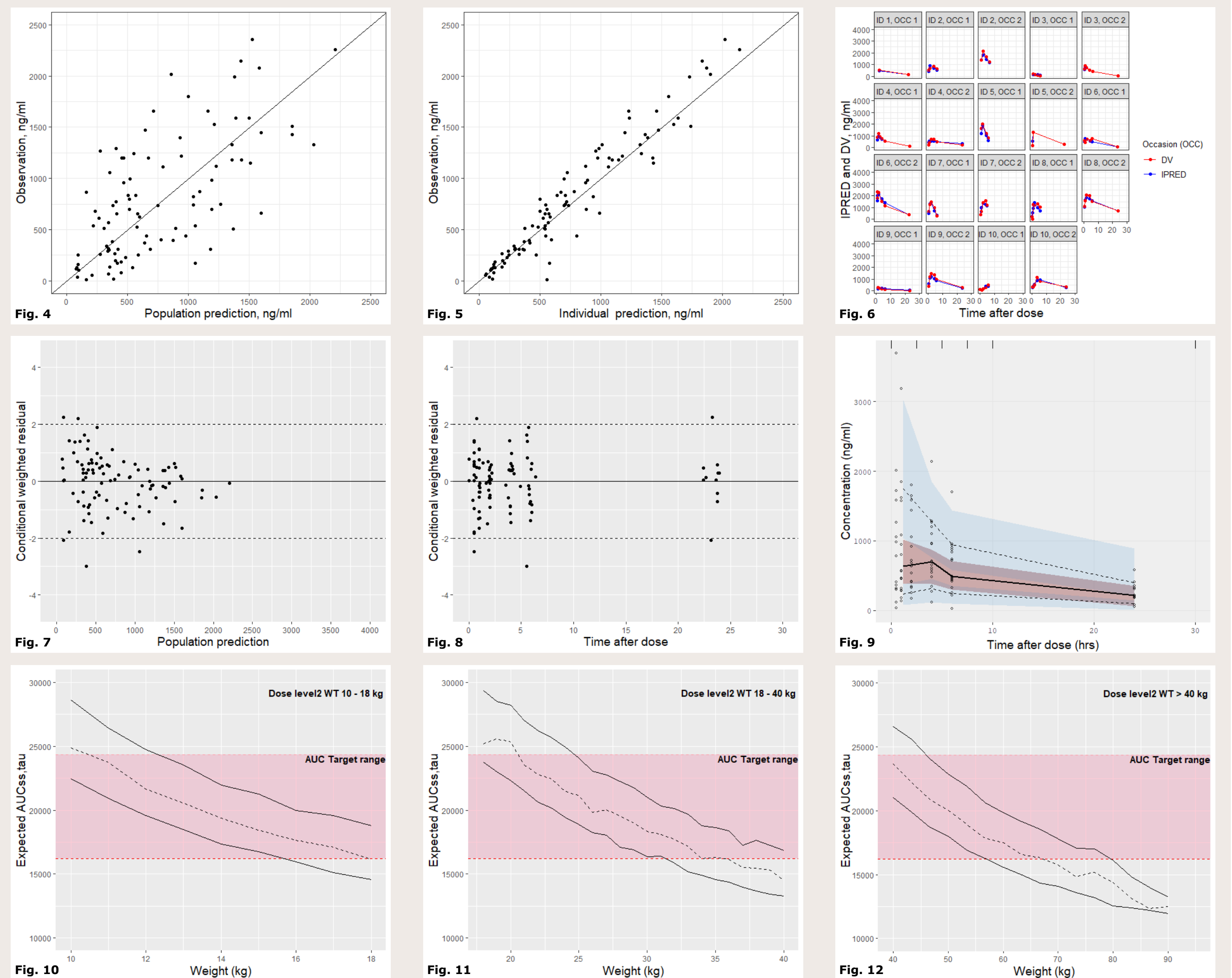
Results

- Pediatric PK data from 10 patients (95 PK samples) were analyzed.
- Estimated $AUC_{ss,tau}$ (geometric mean [%CV]) on DL1 (n=4) were 12.3 h*mg/L [67.3] (NCA) and 11.5 [52.6] (MAP Bayesian estimation from the POPPK model); on DL2 (n=6) were 19.0 [29.4] (NCA) and 19.8 [31.1] (MAP Bayesian) both were within the target range (16.2-24.3).
- Results of model development:
 - Brigatinib pediatric PK was described by a three-compartment model with a two-transit compartment input (fixed allometric scaling and \$PRIOR informed by the adult model⁶).
 - Inter-occasion variability was included on the apparent central volume of distribution.
 - Parameter estimates and PRIOR setting of the final model is shown in Table 4.
- The model diagnostic plots are shown below (Fig. 4-9)
- For simulated pediatric pts treated on DL1 (n=6000), 11.4% (>10-<18kg), 48.4% (18–40kg), 22.0% (>40kg) and 30.1% (overall) of the expected $AUC_{ss,tau}$ (informed by the dose and CL/F estimate) fell within the target range; on DL2 (n=6000) were 78.6%, 66.5%, 76.7% and 73.1%, respectively (Fig. 10-12). Majority (>70%) of the expected $AUC_{ss,tau}$ of children treated on DL2 fell within the target range.

Table 4. Brigatinib pediatric POPPK model (reference model used in PRIOR subroutine)

Parameter	Estimate (RSE%)	95% CI	IIV% (RSE%)	IOV (RSE%)	Adult ref. estimates
CL/F (L/h)	14.0 (15.0)	9.88 - 18.1	47.6 (7.1)		10.6 (2.7% CV)
V4/F (L)	191 (21.0)	112 - 270	54.8 (8.4)	OCC1: 82.3 (31.5) OCC2: 71.3 (32.9)	207 (3.8% CV)
Q4/F (L/h)	12.6 (8.3)	10.6 - 14.6	-	-	12.6 (9.2% CV)
V5/F (L)	7.63 (16.3)	5.20 - 10.1	-	-	114 (11.2% CV)
Q5/F (L/h)	2.55 (19.3)	1.59 - 3.51	-	-	2.7 (18.2% CV)
V6/F (L)	77.7 (8.70)	64.4 - 91.0	-	-	78.5 (8.6% CV)
Mean transit time (h)	0.78 (21.4)	0.453 - 1.11	59.2 (16.6)	-	0.9 (3.6% CV)
ALB effect on CL/F	0.666 (10.5)	0.530 - 0.802	-	-	0.661 (10.7% CV)
Proportional error	0.101 (20.4)	0.0606 - 0.141	-	-	0.269 (0.6% CV)
\$PRIOR setting [PRIOR weight]	Non-informative PRIOR [10000] on central PK parameters (CL/F, V4/F, V5/F, MTT Informative PRIOR on Q4 [1.34], Q5 [0.241], V6/F [45.6], ALB effect [0.005]; Informative PRIOR on OMEGA block [87.6]; No prior was used on the residual error				

CL/F: apparent clearance from central compartment; Q4/F: apparent intercompartmental distributional clearance between the central and 1st peripheral compartment; Q5/F: apparent intercompartmental distributional clearance between the central and 2nd peripheral compartment; V4/F: apparent central compartment volume of distribution; V5/F: apparent volume of the 1st peripheral compartment; V6/F: apparent volume of the 2nd peripheral compartment; IIV: inter-individual variability; IOV: inter-occasion variability; OCC: occasion



Conclusion

- This study demonstrated the feasibility to build a POPPK model informed by the limited data collected and prior adult PK knowledge to determine pediatric PK.
- MAP Bayesian estimated $AUC_{ss,tau}$ and majority of the expected $AUC_{ss,tau}$ of children treated on DL2 fell within the target range, which aligns with the RP2D based on NCA. Yet, unlike NCA which relied on few steady-state samples, the POPPK approach accounted for all collected data.
- This approach (the lower workflow of Fig. 2) can be further valuable in simulating exposure to help deciding to include more patients in a certain dose level or to open others. We propose the modeling approach as an efficient and accurate way to evaluate PK of a drug in a trial setting where intense PK sampling design is often not feasible.