Office of Clinical Pharmacology Integrated Review

NDA Number	202324/S-016 (SDN 1855)
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Submission Date	1/23/2024
Submission Type	Pediatric Labeling Supplement and Pediatric Exclusivity Determination
Brand Name	INLYTA
Generic Name	Axitinib
Dosage Form and Strength	Tablets: 1 and 5 mg
Route of Administration	Oral
Proposed Indication	No new indication is proposed
Applicant	Pfizer
Associated IND	(b) (4)
OCP Review Team	DCPII: Runyan Jin, Ph.D. (reviewer), Lauren Price, Pharm.D. (TL) DPM: Hauli Wu, Ph.D. (reviewer), Jingyu Yu, Ph.D. (TL)
OCP Final Signatory	Stacy Shord, Pharm.D. Deputy Division Director, DCPII

1. EXECUTIVE SUMMARY

Axitinib is an inhibitor of receptor tyrosine kinases including vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2, and VEGFR-3. It was approved as a single agent, for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy and in combination with avelumab or pembrolizumab, for the first-line treatment of adult patients with advanced RCC. The approved recommended starting dosage in adults is 5 mg twice daily (BID) orally as a single agent or in combination. Axitinib is supplied as tablets in two strengths (1 and 5 mg).

The Written Request (WR) – Amendment 3 for axitinib was issued by the FDA on 1/3/2024 and consists of three studies that investigate the potential use of axitinib for the treatment of pediatric patients with recurrent or refractory solid tumors, including advanced translocation renal cell carcinoma (tRCC). Supplement 016 contains the clinical reports for Study ADVL1315 (Study 1) and AREN1721 (Study 2) and reports of population pharmacokinetic (PopPK) and exposure-response (E-R) analyses (Study 3) to support the labeling updates in Section 8.4. In addition, a pediatric exclusivity determination request was submitted.

Based on pharmacokinetic (PK) data collected in Studies ADVL1315 and AREN1721, exposure of axinitib in pediatric patients who received axitinib at the maximum tolerated dosage (MTD) of

2.4 mg/m^2 BID was lower than exposure previously observed in adults who received the approved recommended starting dosage of 5 mg BID. In general, the review team agrees that the components in current submission met the WR requirements from a clinical pharmacology perspective.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 202324/S-016. This supplement has met the components of the Written Request – Amendment 3 from a clinical pharmacology perspective. The labeling for axitinib was revised to describe the exposure of axitinib in pediatric patients compared to exposure in adult patients in Section 8.4.

2. COMPREHENSIVE CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Overview of the Regulatory Backgroud

The Applicant submitted a Proposed Pediatric Study Request (PPSR) for axitinib on 6/3/2019 and requested the issuance of a WR for the evaluation of axitinib in patients with advanced tRCC to support the use of axitinib in the pediatric population. FDA issued an Inadequate Study Request letter stating that the Sponsor should justify why tRCC is the only indication being evaluated, asking for specification of the minimum number of pediatric patients to be enrolled in studies, and requested PK data and exploration of E-R relationships between axitinib systemic exposure and selected efficacy and toxicity endpoints. After multiple correspondence regarding the PPSR between the Applicant and FDA, a WR for axitinib was finally issued on 8/3/2020. Subsequently, the WR was amended three times between April 2022 and January 2024. Refer to the Clinical Review for additional information on changes in each amendment. The WR consists of three studies as listed in **Table 1** that investigate the potential use of axitinib in the treatment of pediatric patients with recurrent or refractory solid tumors, including advanced tRCC.

Table 1: Description of Each Study in WR

Study	Description
Study 1 ADVL1315	A Phase 1 study of the VEGF receptor tyrosine kinase inhibitor axitinib in children with recurrent or refractory solid tumors
Study 2 AREN1721	A randomized Phase 2 trial of axitinib/nivolumab combination therapy vs. single agent nivolumab for the treatment of transcription factor E3 (TFE) tRCC across all age groups
Study 3 Pooled PK Analysis	The objectives of PopPK analysis in pediatric patients are to explore the effect of age and body size on axitinib CL/F and Vd/F and make predictions on the dosing of axitinib in pediatric patients in different age groups

The Applicant has now completed the studies described in the final pediatric WR – Amendment 3 (dated 1/3/2024). This labeling supplement is intended to support the inclusion of relevant information in the Inlyta® (axitinib) prescribing information (pediatric use section) and to

request pediatric exlusivity. The Applicant is not seeking an indication for axitinib as monotherapy or in combination with nivolumab for the treatment of pediatric patients with tRCC or any other solid tumor, as the available data in pediatric patients do not conclusively support a favorable benefit/risk profile.

2.2 General Pharmacology and Clinical Pharmacokinetics

The clinical pharmacology of axitinib in adult patients has previously been described in detail in the clinical pharmacology review of the original NDA 203324 submission. Refer to the original NDA Clinical Pharmacology Review for a detailed description of the clinical pharmacology data. Briefly, the median T_{max} ranged from 2.5 to 4.1 hours following a single oral 5 mg dose. At steady state, axitinib exhibits approximately linear pharmacokinetics within the 1 mg to 20 mg dose range. In adult patients with advanced RCC (n=20), at the 5 mg BID dose in the fed state, the geometric mean (CV%) C_{max} and $AUC_{0\text{-}24h}$ were 28 (79%) ng/mL and 265 (77%) ng.h/mL, respectively. The geometric mean (CV%) clearance and apparent volume of distribution were 38 (80%) L/h and 160 (105%) L, respectively. The plasma half-life ranged from 2.5 to 6.1 hours.

2.3 Clinical Pharmacology Questions

2.3.1 How do the exposure of axitinib and PK parameters in pediatric patients compared to that of adult patients receiving the approved recommended starting dosage of 5 mg BID?

Post-hoc axitinib exposure and BSA-normalized PK parameters were derived for each pediatric patient from the 2 pediatric studies based on a PopPK model that integrated PK data from both adult and pediatric clinical trials of axitinib. The post-hoc parameters were compared to data from adult patients who received the approved recommended starting dosage (5 mg BID). A total of 22 pediatric patients (<18 years of age) were included in the PopPK analysis: 18 patients from Study ADVL1315 who received axitinib monotherapy and 4 patients from Study AREN1721 who received the combination of axitinib + nivolumab. Among the 22 pediatric patients, 2 were 17 years old and were excluded from PK parameter and exposure summaries. All pediatric patients received a starting dosage of either 2.4 mg/m^2 BID or 3.2 mg/m^2 BID. Refer to **Appendix 1 – Pharmacometrics Review** for detailed assessment.

Descriptive statistics of post-hoc axitinib exposure and BSA-normalized PK parameters in adults administered the approved recommended starting dosage (5 mg BID) and in pediatric patients <17 years of age at each studied dose level are listed in **Table 2**.

Table 2: Summary of Simulated Axitinib Exposure at Steady-State and BSA-Normalized Post-hoc PK Parameters by Axitinib Dose Level

Parameter; GeoMean (CV%)	Axitinib Dose Level		
	Pediatric Patients		Adults
	2.4 mg/m^2 (n=16)	3.2 mg/m^2 (n=4)	5 mg (n=590)
$AUC_{0\text{-}24h,ss}$ (ng*hr/mL)	217 (103)	234 (77)	366 (62)
$C_{max,ss}$ (ng/mL)	24 (61)	24 (81)	32 (60)

CL/F/BSA (L/hr/m^2)	22 (97)	28 (78)	15 (61)
Vc/F/BSA (L/m^2)	78 (43)	86 (48)	50 (36)
Note: AUC_{0-24}=axitinib area under the concentration-time curve for 24 hours; CL/F/BSA=BSA-normalized apparent axitinib clearance; Vc/F/BSA= BSA-normalized apparent axitinib central volume of distribution			

(Data Source: Table 1 and Table 2 in Response to FDA IR 19-Apr-2024)

Overall, the available concentration data was sufficient to make a comparison of axitinib exposure and PK parameters between pediatric patients administered the MTD and adult patients administered the approved recommended starting dosage (5 mg BID). Results showed that axitinib exposure in pediatric patients who received the MTD of axitinib at 2.4 mg/m^2 BID were lower than those previously observed in adult patients who received the approved recommended starting dosage of 5 mg BID. This observation occurred despite the MTD in pediatric patients (2.4 mg/m^2 BID) being lower than the BSA-normalized dose used in adults after applying an average BSA of 1.7 m^2 (2.9 mg/m^2 BID). The next higher dose level (3.2 mg/m^2 BID) was not tolerated in pediatric patients.

2.3.2 Do the components in the current submission fulfill the Written Request – Amendment 3 from a clinical pharmacology perspective?

In general, the review team agrees that the components in current submission meet the WR requirements from a clinical pharmacology perspective.

Study 1 – ADVL1315

Written Request Amendment 3 Clinical Pharmacology Components

- Age and number of patients to be studied
  - Patients aged >12 months and <18 years of age at the time of study enrollment.
  - A minimum of 2 evaluable patients with recurrent or refractory solid tumors at each dose level for determination of MTD.
  - Once the MTD or recommended Phase 2 dose is defined, up to 6 additional patients with recurrent or refractory solid tumors to acquire PK data.

- Clinical pharmacology related study endpoints
  - Secondary endpoints: PK parameters: AUC and C_{max}

- PK parameters calculated for each patient and treatment using noncompartmental analysis of concentration-time data. Samples below the lower limit of quantitation set to zero for analysis. Actual sample collection times where available used for the PK analysis.

Information Submitted by the Applicant

Study ADVL1315 was a dose escalation study of axitinib in 19 pediatric patients (5 to 17 years old) with recurrent or refractory solid tumors sponsored and conducted by the COG. The mean (range) age was 11.8 (5-17) years. Patients received axitinib tablets orally BID in 28-day

cycles with or without food. Of the 19 patients enrolled, 13 were assigned to Dose Level 1 (DL 1; 2.4 mg/m^2 BID) and 6 to Dose Level 2 (DL 2; 3.2 mg/m^2 BID). Overall, 9 patients were 1 to <12 years in DL 1 (n=8) and DL 2 (n=1) and 10 patients were 12 to <18 years in DL 1 (n=5) and DL 2 (n=5).

There were no reported DLTs during Cycle 1 in the 11 patients evaluable for DLT at DL 1. At DL 2, 2 of the 5 DLT-evaluable patients reported 1 DLT each (tumor hemorrhage, palmar-plantar erythrodysesthesia syndrome) during Cycle 1. Therefore, DL 1 of 2.4 mg/m^2 BID was determined as MTD and RP2D of axitinib in pediatric patients with recurrent/refractory solid tumors.

A total of 12 patients in Dose Level 1 (2.4 mg/m^2 BID) and 6 patients in Dose Level 2 (3.2 mg/m^2 BID) provided blood samples for the evaluation of axitinib PK. The exposure of axitinib following a single dose on Day 1 and multiple doses on Day 8 are listed in **Table 3** for each dose level. In general, axitinib PK increased with an increase in dose. There was minimal accumulation based on geometric mean exposures comparing Day 1 to Day 8. Inter-participant variability for axitinib exposure was high, ranging from 55% to 139% for $AUC_{0\text{-}8h}$ and 49% to 97% for C_{max} across both dose levels and days.

Table 3: Summary of Axitinib Exposure for DL 1 and DL 2

Geometric Mean (% CV)	**Axitinib DL 1 (n=12)**	**Axitnib DL 2 (n=6)**
Day 1		
T_{max} (hr)[a]	2 (1, 4)	2 (1, 4)
C_{max} (ng/mL)	20 (97)	35 (49)
$AUC_{0\text{-}8h}$ (ng*hr/mL)	77 (118)	131 (55)
Day 8		
T_{max} (hr)[a]	1.5 (0, 4)	2 (1, 4)
C_{max} (ng/mL)	39 (93)	42 (72)
$AUC_{0\text{-}8}$(ng*hr/mL)	120 (139)	142 (80)
Note: [a]Tmax: median (range)		

(Data source: Table 12 in the CSR of Study ADVL1315)

Review Team Comments

- The number of patients in each age subgroup and the number of patients for PK analyses met the minimum requirement in the WR.
- 6 DLT-evaluable patients were enrolled to the lower dose level followed by 5 DLT-evaluable patients at the higher dose level (+1 patient who was not DLT-evaluable) to determine the MTD. After the MTD was determined, an additional 7 patients were enrolled at the lower dose level to obtain additional PK data. Among the 7 additional patients enrolled at the lower dose, 6 had PK samples collected for a total of 12 patients with PK at the lower dose level and 5 were evaluable for DLT.
- The Applicant provided the exposure data for AUC and C_{max} in the CSR. The Applicant's summary tables included patients aged 17 years of age.

Study 2 – AREN1721

Written Request Amendment 3 Clinical Pharmacology Components

- Age and number of patients to be studied
  - Patients ≥ 12 months at enrollment, with unresectable or metastatic tRCC
  - A minimum of 12 patients (children and adults) will be randomly assigned to one of the 2 treatment arms (axitinib + nivolumab or nivolumab alone) in a 1:1 ratio.
  - The study must enroll at least 2 patients aged 12-17 years (inclusive) and 3 patients younger than 12 years in the axitinib/nivolumab combination arm.

- Clinical pharmacology related study endpoints
  - Exploratory endpoints: PK blood samples will be collected from pediatric patients in the axitinib/nivolumab combination arm. PK parameters will include CL/F and V_d/F based on Population PK analysis.

Information Submitted by the Applicant

Study AREN1721 was a randomized trial of axitinib/nivolumab combination therapy vs. single agent nivolumab for the treatment of TFE/tRCC across all age groups (7 to 41 years old). Axitinib was administered at a starting dose of 5 mg orally BID for patients ≥ 18 years of age, and at 2.4 mg/m^2 (maximum of 5 mg/dose) orally BID for patients < 18 years of age. Nivolumab was given at either 240 mg IV Q2W or 480 mg IV Q4W for patients ≥ 18 years of age, and at 3 mg/kg (maximum of 240 mg/dose) IV Q2W for patients < 18 years of age. Overall, 7 patients enrolled in Arm A (axitinib + nivolumab), 2 patients enrolled in Arm B (axitinib monotherapy), and 5 patients enrolled in Arm C (nivolumab monotherapy). Arm B was closed due to enrollment challenges. For pediatric patients, 5 patients were 1 to <12 years in Arm A (n=3) and Arm C (n=2) and 4 patients were 12 to <18 years in Arm A (n=2) and Arm C (n=2). One patient in the <12 years age group crossed over from Arm C to Arm A.

Of the 10 patients who received at least one dose of axitinib in Study AREN1721, 4 pediatric patients provided sparse blood samples for evaluation of axitinib PK including 3 of the 4 patitents enrolled to Arm A and 1 patient crossed over from Arm C to Arm A. All 4 patients provided PK samples on Cycle 1 Day 1 and 3 of the 4 patients provided PK samples on Day 1 of Cycle 2 and Cycle 3. Following a single oral dose of axitinib on Day 1, mean C_{max} was 20 ng/mL with high inter-participant PK variability (CV%=114%). Axitinib was rapidly absorbed with a median (range) T_{max} value of 2 (2, 2.7) hours. In general, there was minimal accumulation with continuous BID dosing. In addition, axitinib C_{max} and T_{max} were consistent in patients who received axitinib monotherapy and those who received the combination of axitinib and nivolumab. Refer to Study 3 for PK parameters including CL/F and V_d/F based on PopPK analysis.

Review Team Comments

- The number of patients in each age subgroup met the minimum requirement in the WR.
- The applicant provided the exposure data for AUC and C_{max} in the CSR and PK parameter data of CL/F and V_d/F in the PopPK report.
- PopPK analysis was conducted as requested.

Study 3: Pooled PK Analysis

Written Request Amendment 3 Clinical Pharmacology Components

- Study objectives
  - Explore the effect of age and body size on axitinib CL/F and Vd/F and make predictions on the dosing of axitinib in pediatric patients in different age groups

- Age and number of patients to be studied
  - The pooled analysis will include at least 8 patients each in the 12 months to <12 years, and 12 to <18 years categories. The PK concentration analysis set will include all treated patients who have at least 1 axitinib concentration above the lower limit of quantitation in patients treated with axitinib. The PK parameter analysis set will include all treated patients who have at least 1 of the PK parameters for axitinib.

- PK sampling schedule
  - For Study ADVL1315, blood samples for axitinib were to be collected at pre- dose, and at 1, 2, 4, 6, and 8 hours after the AM dose on Cycle 1 Day 1 and Cycle 8 Day 1. A cycle of therapy was considered to be 28 days.
  - For Study AREN1721, blood samples for axitinib will be collected at 2, 4 and 6 hours post-dose on Cycle 1 Day 1. In addition, one PK sample at pre-dose will be collected on Cycle 2 Day 1 and on Cycle 3 Day 1. A cycle of therapy is considered to be 28 days. A total of 5 PK samples per patient is planned for pediatric patients in the combination (axitinib + nivolumab) arm.
  - Furthermore, for patients who cross over from the nivolumab arm to the axitinib/nivolumab combination arm blood samples for axitinib PK will be collected at pre-dose and 2, 4, and 6 hours post-dose at a scheduled visit following the crossover.

- Exposure-response (E-R) relationships will also be explored with respect to key safety endpoints. Exposure metrics will be generated using population PK model post hoc predictions. Covariates that may account for the interindividual variability in the PK-PD parameters will be explored as part of the PK-PD modeling/analysis where feasible.

Information Submitted by the Applicant

Plasma concentration-time data were pooled from 19 studies in both healthy participants and patients (2 studies, ADVL1315 and AREN1721, include pediatric participants) with solid tumors including RCC. There were a total of 612 participants in the dataset with at least one non-BLQ PK observation constructed by pooling data from axitinib studies in adult participants (N=590) and pediatric participants (N=22).

Study ADVL1315 (N=18, axitinib monotherapy), and Study AREN1721 (N=4, axitinib + nivolumab). Stratified by age category for pediatrics, 11 patients were aged < 12 years old and 11 patients were 12 to <18 years old.

Serial PK samples were collected following single-dose administration in the healthy volunteer studies and in solid tumor studies A4060010, and A4061022. Sparse PK samples were collected at predose and a 1-2 hour post-dose following multiple-dose administration in the RCC Phase 2 studies (A4061012, A4061023, and A4061035). In study ADVL1315, PK

samples were collected on pre-dose, and at 1, 2, 4, 6, and 8 hours after the AM dose on Day 1 and Day 8, Cycle 1. In study AREN1721, axitinib PK samples were collected on Cycle 1, Day 1 at 2, 4, and 6 hours after AM dose of axitinib and Cycles 2 and 3, Day 1 at pre-dose of axitinib.

Refer to **Appendix 1 - Pharmacometrics Review** for the detailed assessment of the PopPK and E-R analyses. Briefly, PK of axitinib in adult and pediatric participants was described by a linear two-compartment model, which is similar to the PopPK model developed for adult participants in the original axitinib NDA submission. BSA was a significant covariate on central volume of distribution (V_c) for participants less than 18 years old; however, the effect of BSA on V_c for pediatric patients was not considered clinically meaningful given the overall variability in exposure observed in pediatric patients (CV% of 71% for AUC_{0-24h}). Although the effects of BSA and age (age <12 years vs. 12 to < 18 years) were both significant on CL during the first round of forward inclusion, neither BSA nor age were significant covariates on axitinib CL in pediatric participants after the inclusion of the effect of BSA on V_c in pediatric patients. As noted above, 2 patients who were 17 years old were excluded from PK parameter and axitinib exposure summaries for consistency with the regulatory definition of pediatric patients (i.e., <17 years).

Review Team Comments

- There was one discrepancy in PK sampling times for Study ADVL1315 between the exact terms of the WR and the actual PK sampling times as shown below. Of note, the protocol for Study ADVL1315, including the actual PK sampling schedule, was submitted to the IND prior to issuance of the WR and therefore the language of "Cycle 8 Day 1" appears to be an administrative error in the WR. The PK of axitinib in Study ADVL1315 was adequately characterized based on the actual PK sampling times.
  - Exact language from WR (highlight added): For Study ADVL1315, blood samples for axitinib were to be collected at predose, and at 1, 2, 4, 6, and 8 hours after the AM dose on Cycle 1 Day 1 and Cycle 8 Day 1. A cycle of therapy was considered to be 28 days.
  - Actual PK sampling times: Day 1, Cycle 1: pre-dose and at 1, 2, 4, 6, and 8 hrs after the AM dose and Day 8, Cycle 1: pre-dose and at 1, 2, 4, 6, and 8 hrs after the AM dose
- One patient crossed over from the nivolumab arm to the axitinib/nivolumab combination arm. Blood samples for PK analysis were planned to be collected on the day of the first axitinib dose at 2, 4, and 6 hrs post-dose followed by pre-dose samples on Day 1 of Cycles 2 and 3 of the combination therapy. Blood samples for PK were collected per protocol at 2, 4, and 6 hrs after the first dose of axitinib. The patient who crossed over discontinued treatment prior to Cycle 2 Day 1 of combination therapy and therefore did not have a pre-dose sample collected. Given that the WR does not specify on which day the pre-dose sample would be collected, the data provided meet the terms of the WR.
- The sampling times were implemented in the corresponding studies. Some individual patients had missing samples. For ADVL1315, 7 samples are missing from 2 patients. For AREN1721, 3 samples are missing from 1 patient. The impact of missing these samples in the PopPK analysis is limited.
- The PopPK analysis approach by pooling pediatric and adult data is acceptable from a clinical pharmacology perspective. The geometric mean CL/F and Vd/F in pediatric patients who received 2.4 mg/m^2 BID (N=16) were 22 $L/h/m^2$ and 78 L/m^2, respectively;

the geometric mean CL/F and Vd/F in pediatric patients who received 3.2 mg/m^2 BID (N=4) were 28 L/h/m^2 and 86 L/m^2, respectively.

- The safety endpoints (diarrhea, fatigue, hypertension, and proteinuria) evaluated in the E-R analysis for safety are the key safety endpoints.

Drug information and Administration (Pertains to All Studies)

Written Request Amendment 3 Clinical Pharmacology Components

- Dosage form
  - Axitinib tablets in 1 mg and 5 mg strengths will be used. These tablet strengths can be used in various combinations to provide dosing flexibility and to accommodate potential dose adjustments, including those necessary for the proposed pediatric use, which will be calculated according to the body surface area (BSA).
  - These tablets are film-coated, which aids swallowability for clinical dosing of pediatric patients, particularly older children and adolescents, given the onset and prevalence of tRCC.

- Dosage Regimen
  - Study 1

    Axitinib administered based on BSA dosing at a starting dose of 2.4 mg/m^2 BID.

Dose Level	Dose of Axitinib Given BID (mg/m^2)
-1	1.8
1	2.4
2	3.2
3	4.2

  - Study 2
    - Axitinib
      - Patients aged <18 years will receive the dose as defined in the Phase 1 study (2.4 mg/m^2 BID; maximum of 5 mg BID)
      - Patients aged ≥18 years will receive the starting adult dose (5 mg BID)
      - The axitinib dose can be escalated from the starting dose at the discretion of the treating physician and based on patient tolerability. For patients ≥18 years, the axitinib dose may be increased by 1 mg BID up to a maximum of 10 mg BID. For patients <18 years, axitinib titration is based on patient BSA, and dose can be increased to a maximum of 7 mg BID. For all patients, no more than 1 dose titration can occur in each 2-cycle period, and provided protocol defined criteria are met (i.e., 2 consecutive cycles are completed with no AE Grade >2, patient is normotensive, and not receiving anti-hypertension medication). The axitinib dose can be reduced to a minimum of 2 mg BID in adult patients, and to 1.8 mg/m^2 BID in children.
    - Nivolumab
      - Patients aged <18 years: 3 mg/kg IV Q2W (with an upper limit of 240 mg IV Q2W).
      - Patients aged ≥18 years: 240 mg IV Q2W or 480 mg IV Q4W

Information Submitted by the Applicant

Axitinib film-coated tablets in 1 mg and 5 mg strength were used in Study 1 and Study 2. Drug doses were calculated according to BSA.

- Study 1

Axitinib was administered based on BSA dosing at a starting dose of 2.4 mg/m^2 BID. 13 patients and 6 patients were assigned to Dose Level 1 and Dose Level 2, respectively.

Dose Escalation Scheme

Dose Level	Dose of Axitinib Given BID (mg/m^2)
-1	1.8
1[a]	2.4
2	3.2
3	4.2

Abbreviations: BID = twice daily.

a. Starting dose level.

- Study 2

Axitinib was administered at a starting dose of 5 mg BID for participants ≥18 years of age, and at 2.4 mg/m^2/dose (maximum of 5 mg/dose) BID for participants <18 years of age. Individual patient dose titration was permitted per protocol at the discretion of the investigator, if the following criteria were met for an individual patient: 2 consecutive cycles are completed with no AE Grade >2 (according to CTCAE), and patient is normotensive and not receiving anti-hypertension medication.

Nivolumab was given at either 240 mg IV every 2 weeks or 480 mg IV Q4W participants ≥18 years of age, and at 3 mg/kg (maximum of 240 mg/dose) IV Q2W for participants <18 years of age.

Review Team Comments

The exclusion criterion for "patients unable to swallow whole tablets" was listed in both pediatric studies.

2.4 Outstanding Issues

None

2.5 Summary of Labeling Recommendations

Applicant's Proposed Language	(b) (4)
FDA Revision	Exposure in pediatric patients who received INLYTA at the maximum tolerated dosage were lower than those previously observed in adults who received the approved recommended starting dosage.
Rationale for Revision	Revised to briefly summarize that exposure differences were observed in pediatric patients compared to adults per the Guidance for Industry entitled "Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling March 2019".

3. Appendix 1 – Pharmacometrics Review

3.1 Population PK Analysis

3.1.1 Executive Summary

In general, the final PPK model adequately characterizes axitinib PK in the pediatric and adult populations, and the model predicted exposure metrics of total daily AUC are adequate for use in the exploratory E-R analysis. Based on the limited data from pediatric patients (N=22, 5 to ≤ 17 years; N=20, 5 to <17 years), age and BSA are not likely to have clinically meaningful impact on axitinib exposure in pediatric patients. Simulations based on the final population PK model suggested that exposure in pediatric patients <17 years of age who received axitinib at the maximum tolerated dosage (2.4 mg/m^2 BID, N=16) were lower than those previously observed in adults who received the approved recommended starting dosage (5 mg BID).

3.1.2 PPK Assessment Summary

General Information	
Objectives of PPK Analysis	• *To develop an integrated, predictive population PK model for axitinib in adult and pediatric participants.* • *To investigate the effects of age and body size on the clearance and the volume of distribution of axitinib in adult and pediatric participants.* • *To provide post-hoc predictions from the final population PK model to be used to generate individual exposure metrics for safety E-R analyses.*
Study Included	***Adult**: A4060010 (Cohorts 3, 5, and 6), A4061004 (TRT 1), A4061006 (TRTs 1 and 2), A4061007, A4061012, A4061018 (TRT 1), A4061021, A4061022, A4061023, A4061026 (TRT 1),*

		A4061033 (TRTs 1 and 3), A4061035, A4061036 (TRT 1), A4061037 (TRT 1), A4061047, A4061050, A4061053 ***Pediatric**: ADVL1315, AREN1721*
Dose(s) Included		***Adult**: 5, 7, or 10 mg single dose (oral), 5 mg BID (oral), 1 mg single dose (IV)* ***Pediatric**: 2.4 or 3.2 mg/m^2 (maximum of 5 mg/dose) BID (oral)*
Population Included		***Adult**: Healthy adults and patients with solid tumors including renal cell cancer* ***Pediatric**: Patients with refractory solid tumors including advanced tRCC*
Population Characteristics (**Table** 4)	General	***Adult**: Age: median 42 years (range: 18-85, 11.2% subj >=65 yr, 2.9% subj >=75 yr); Weight: median 74 kg (range: 36.6-136);501 (85%) male; Race: White: 361 (61%); Black, of African heritage or African American: 29 (5%); Asian (excluding Japanese): 79 (13%); Japanese: 96 (16%); Hispanic: 13 (2.2%); Other: 12 (2%)*
	Organ Impairment	***Adult:** Renal (CRCL, based): n (%) in each category - Normal: 381 (65%), Mild: 139 (24%), Moderate: 64 (11%), Severe: 5 (0.8%), End-stage: 1 (0.2%). Hepatic: participants with mild and moderate impairment from hepatic impairment study were excluded.* ***Pediatric**: Adequate hepatic and renal function (based on protocol)*
	Pediatrics	*Age: median 12 years (range: 5-17, 0% subj <=2 yr, 4.5% subj <=6 yr, 50% subj <=12 yr); Weight: median 41 kg (range: 18, 91); 10 (45%) male; Race: White: 17 (77%); Black, of African heritage or African American: 3 (14%); Asian (excluding Japanese): 1 (4.5%); Other: 1 (4.5%)*
No. of Patients, PK Samples, and BLQ		***Adult**: 13,441 PK samples from 590 subjects; 2,199 of 1,3441 (16%) pre-/post-dose PK samples were BLQ.* ***Pediatric**: 226 PK samples from 22 subjects; 30 of 226 (13%) pre-/post-dose PK samples were BLQ.*
Sampling Schedule	Rich Sampling	*Rich sampling in healthy adults. Sparse and rich sampling in patients from Study A4060010 and A4061022. Sparse sampling only in patients from the rest studies.*
	In ITT Population	*Study ADVL1315: predose, and at 1, 2, 4, 6, and 8 hours after the AM dose on Cycle 1 Day 1 and Cycle 1 Day 8.* *Study AREN1721: 2, 4 and 6 hours post-dose on Cycle 1 Day 1. In addition, one PK sample at pre-dose will be collected on Cycle 2 Day 1 and on Cycle 3 Day 1 (28 days per cycle).*
Covariates Evaluated	Static	*Age (pediatric only), age>60, smoking, Japanese, weight, fasting, Form XLI*
	Time-varying	*BSA (pediatric only)*

Final Model	**Summary**	**Acceptability**
Software and Version	*NONMEM (Version 7.4.3)*	Acceptable
Estimation Algorithm	*FOCEI*	Acceptable
Model Structure	• *Two-compartment model with first-order absorption and a lag time*	Acceptable

	(tlag) as well as first-order elimination • *Besides covariates included in the population PK model for adults in PMAR-00079, the effect of BSA on Vc was included for participants less than 18 years old.*	
Model Parameter Estimates	***Table* 5**	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	*The RSE for all parameters except except smoking on CL were <30%. The RSE for smoking on CL was 43.99%. Shrinkage (%) on IIV for CL, Vc, Q, and ka are 7.41, 17.09, 33.16, and 18.46, respectively.*	Acceptable
BLQ for Parameter Accuracy	*BLQ PK data were disregarded.*	Acceptable
GOF, VPC	***Figure 1***, ***Figure* 2**	Acceptable
Significant Covariates and Clinical Relevance	***Table 6***, **Figure 3**	Acceptable
Labeling Language	**Description**	**Acceptability**
12.3 PK	*Applicant's Proposed Language:* (b) (4)	FDA revised the labeling to describe differences in exposure observed in pediatric patients compared to adults. Refer to **Section 2.5** for details.

Table 4. Summary of Baseline Characteristics and Laboratory Values in the Dataset, Stratified by Study Population.

Covariate	Adult Participants (N=590)	Pediatric Participants (N=22)	Total (N=612)
Age (year)			
Mean (SD)	43.0 (16.4)	12.0 (3.63)	41.9 (17.1)
Median [Min, Max]	42.0 [18.0, 85.0]	12.0 [5.00, 17.0]	41.0 [5.00, 85.0]
Body weight (kg)			
Mean (SD)	75.3 (14.3)	44.3 (19.5)	74.2 (15.6)
Median [Min, Max]	74.0 [36.6, 136]	41.4 [18.3, 91.3]	74.0 [18.3, 136]
BSA (m^2)			
Mean (SD)	1.88 (0.206)	1.31 (0.353)	1.86 (0.238)
Median [Min, Max]	1.89 [1.24, 2.57]	1.28 [0.750, 2.07]	1.88 [0.750, 2.57]
Sex			
Female	89 (15.1%)	8 (36.4%)	97 (15.8%)
Male	501 (84.9%)	10 (45.5%)	511 (83.5%)
Missing	0 (0%)	4 (18.2%)	4 (0.7%)
Race			
Asian (excluding Japanese)	79 (13.4%)	1 (4.5%)	80 (13.1%)
Black	29 (4.9%)	3 (13.6%)	32 (5.2%)
Hispanic	13 (2.2%)	0 (0%)	13 (2.1%)
Japanese	96 (16.3%)	0 (0%)	96 (15.7%)
Other	12 (2.0%)	1 (4.5%)	13 (2.1%)
White	361 (61.2%)	17 (77.3%)	378 (61.8%)

Source: Applicant's Population PK report, Table 4.

Table 5. Parameter Estimates and SE from Final Population PK Model.

Parameter	Estimate	SE	RSE (%)	CV (%)	Shrinkage (%)	Bootstrap median [95% CI]	Estimate (PMAR-00079)	RSE (%) (PMAR-00079)
θ_{CL} (L/hr)	14.488	1.177	8.13	-	-	14.598 [12.247 to 17.026]	14.6	8.5
θ_{Vc} (L)	47.186	3.650	7.73	-	-	47.336 [39.687 to 54.315]	47.3	6.2
θ_{Q} (L/hr)	3.905	0.494	12.65	-	-	3.897 [2.991 to 4.952]	4	4.7
θ_{Vp} (L)	373.658	103.441	27.68	-	-	370.684 [195.726 to 612.618]	393	16
θ_{ka} (hr^{-1})	0.484	0.027	5.62	-	-	0.477 [0.426 to 0.538]	0.482	4.8
θ_{Tlag} (hr)	0.455	0.002	0.41	-	-	0.454 [0.447 to 0.458]	0.454	0.41
θ_{F}	0.457	0.036	7.85	-	-	0.462 [0.388 to 0.534]	0.457	6.6
Thetarized σ (PO)	0.583	0.012	2.00	-	-	0.582 [0.558 to 0.605]	0.582	2
Effect of fasting on θ_{ka}	1.987	0.286	14.40	-	-	1.981 [1.431 to 2.573]	1.97	13
Effect of fasting on θ_{F} Form IV	0.331	0.045	13.74	-	-	0.331 [0.246 to 0.421]	0.33	13
Effect of XLI formulation on θ_{F}	-0.116	0.030	25.71	-	-	-0.115 [-0.174 to -0.055]	-0.121	24
Thetarized σ (IV)	0.335	0.050	14.91	-	-	0.332 [0.237 to 0.431]	0.335	9.4
Ratio of ω_{Vc} to ω_{Q}	1.375	0.176	12.79	-	-	1.312 [0.926 to 1.649]	1.37	11
Effect of body weight on θ_{Vc} for age $\geq$ 18	0.772	0.108	13.99	-	-	0.775 [0.591 to 0.991]	0.778	14
Effect of age>60 on θ_{CL}	-0.213	0.055	25.80	-	-	-0.216 [-0.316 to -0.087]	-0.213	26
Effect of smoking on θ_{CL}	1.020	0.449	43.99	-	-	0.994 [0.299 to 2.137]	1.02	44
Effect of Japanese race on θ_{CL}	-0.243	0.059	24.25	-	-	-0.228 [-0.357 to -0.088]	-0.249	25
Effect of BSA on θ_{Vc} for age<18	1.099	0.285	25.98	-	-	1.096 [0.407 to 1.969]	-	-
ω^2_{CL}	0.367	0.034	9.17	60.59	7.41	0.37 [0.3 to 0.451]	0.359	14
$\omega_{Vc}\omega_{CL}$	0.207	0.027	12.93	45.46	-	0.206 [0.147 to 0.264]	0.2	17
ω^2_{Vc}	0.162	0.026	16.13	40.31	17.09	0.155 [0.097 to 0.221]	0.158	15
ω^2_{Q}	0.764	0.127	16.57	87.40	33.16	0.691 [0.427 to 1.003]	0.754	11
ω^2_{ka}	0.592	0.068	11.49	76.97	18.46	0.585 [0.448 to 0.742]	0.593	12
OFV	2511.564	-	-	-	-	-	2392.011	-

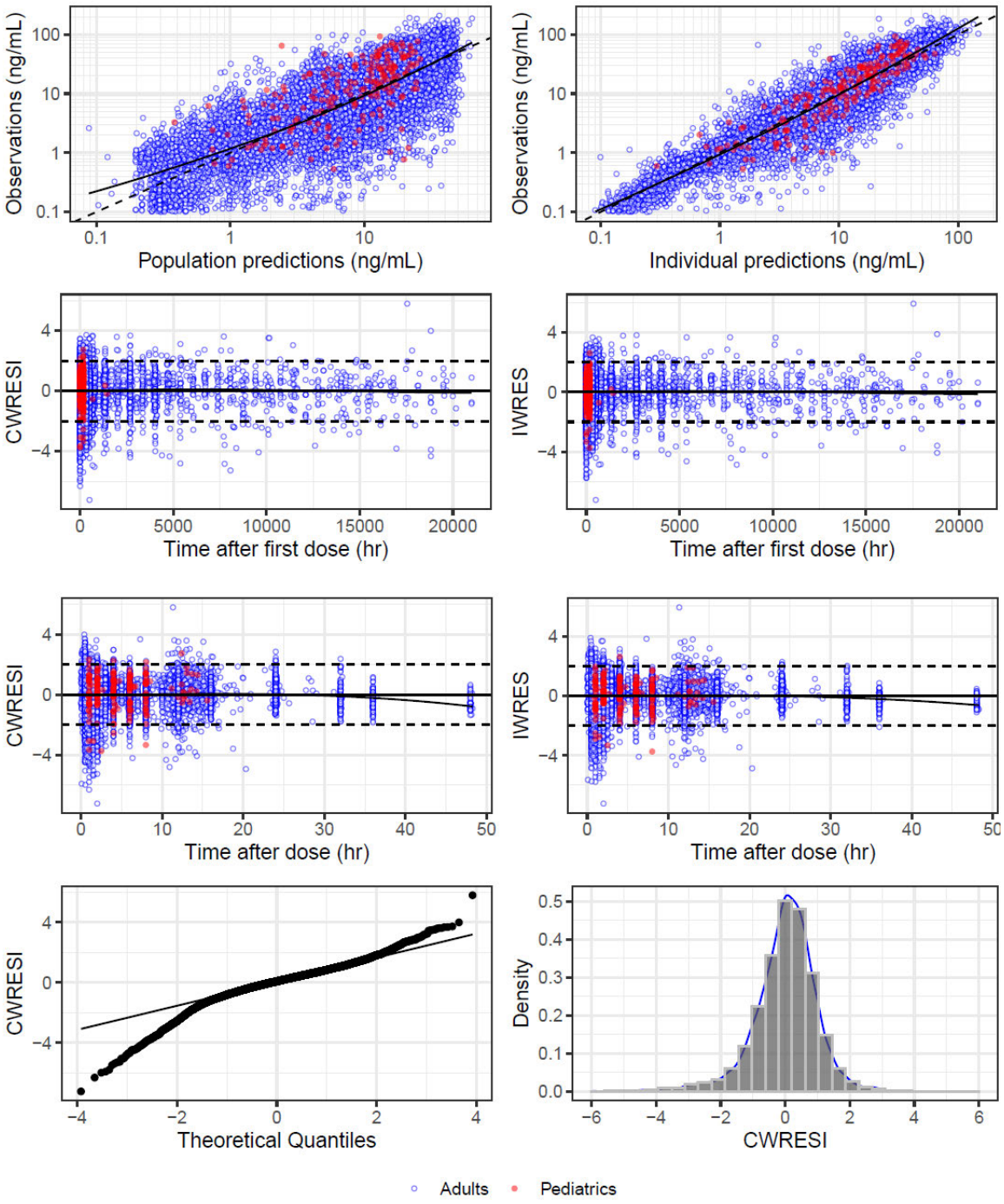
CI=confidence interval; CV=approximate percent coefficient of variation calculated as square root of ω^2 multiplied by 100%; CL=clearance; F=bioavailability; ka=first order absorption rate constant; Q=inter-compartmental clearance; Vc=central volume of distribution; Vp=peripheral volume of distribution; hr=hour; L=liter; OFV=objective function value; (R)SE=(relative) standard error; ω^2=variance of the IIV.
Source: Applicant's Population PK report, Table 9.

Table 6. Summary of Simulated Axitinib Exposure Metrics at Steady-State Stratified by Axitinib Dose Level for Pediatric Population (5 to <17 years)

Axitinib Dose (BID)	N	SS AUC0-24 (ng*hr/mL) GeoMean (Geo CV%)	SS AUC0-24 (ng*hr/mL) Median [Range]	SS Cmax (ng/mL) GeoMean (Geo CV%)	SS Cmax (ng/mL) Median [Range]
2.4 mg/m²	16	216.83 (103.07)	276.6 [40.33 – 1085.11]	23.51 (61.05)	25 [7.86 – 70.31]
3.2 mg/m²	4	233.94 (77)	218.81 [110.33 – 572.68]	24.15 (81.19)	30.24 [9.43 – 43.92]
5 mg	590	365.93 (61.95)	376.69 [31.38 – 1865.76]	31.55 (59.91)	33.27 [4.5 – 150.16]

AUC0-24=axitinib area under the concentration-time curve for 24 hours; GeoMean=geometric mean; Geo CV=geometric coefficient of variation; Cmax=axitinib maximum concentration; Range=minimum-maximum; N=number of patients; SS=steady state.
Source: Applicant's Response to IR (2024 04 25), Table 3.

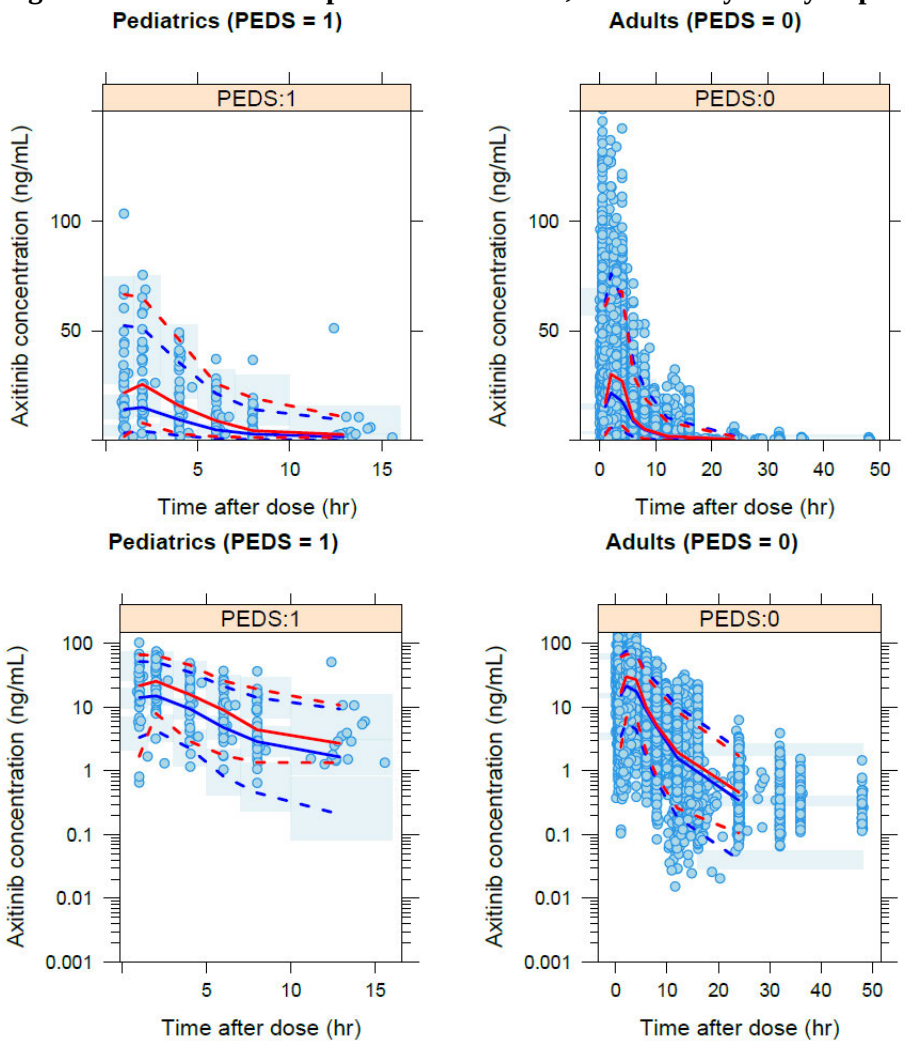
Figure 1. Goodness-of-fit Plots for the Final Population PK Model.



Note: solid line represents LOESS trend. CWRES=conditional weighted residuals; IWRES=individual weighted residuals; hr=hour; LOESS=locally weighted smoothing.

Source: Applicant's Population PK report, Figure 7.

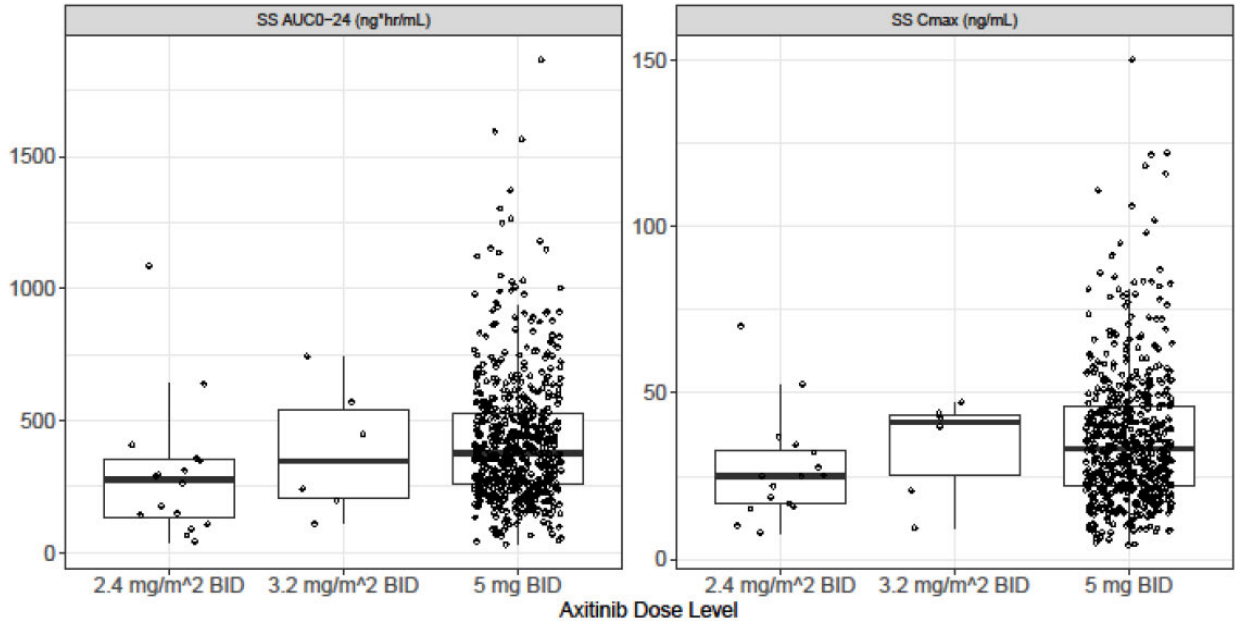
Figure 2. VPC of Final Population PK Model, Stratified by Study Population.



Observed concentration data points, represented by blue scatter points. The red lines represent the median (solid line), 5th percentile (lower dash line) and 95th percentile (upper dash line) of the observed data. The median, 5th percentile and 95th percentile of simulated concentration values are presented by blue lines. 95% confidence intervals for simulated median and each percentile are shown by light blue shaded areas.

Source: Applicant's Population PK report, Figure 12.

Figure 3. Boxplots of Simulated Axitinib Exposure Metrics at Steady-State Stratified by Axitinib Dose Level for Pediatric Population (5-17 years)



AUC0-24=axitinib area under the concentration-time curve for 24 hours; BID=twice daily; Cmax=axitinib maximum concentration; SS=steady state
Source: Applicant's Response to IR (2024 04 25), Figure 3.

The Applicant's population PK analysis is acceptable. Overall, the final population PK model is adequate to characterize the PK profile of axitinib in pediatric and adult population as indicated in the Applicant's goodness-of-fit plots and VPC plots. The FDA reviewer was able to repeat and verify the Applicant's analysis with no significant discordance identified.

3.1.3 PPK Review Issues

No substantive issue.

3.2 Exposure-Response (E-R) Analysis

3.2.1 E-R (safety) Executive Summary

The E-R analysis for safety is considered exploratory due to the limited sample size of data (N=22). Among pediatric patients with refractory solid tumors including advanced tRCC, higher axitinib exposure was associated with increased incidence of Grade ≥1 hypertension. There was no significant E-R relationship for other safety endpoints (Grade ≥1 diarrhea, Grade ≥1 fatigue, and Grade ≥1 proteinuria) though positive trend was observed.

3.2.2 E-R (safety) Assessment Summary

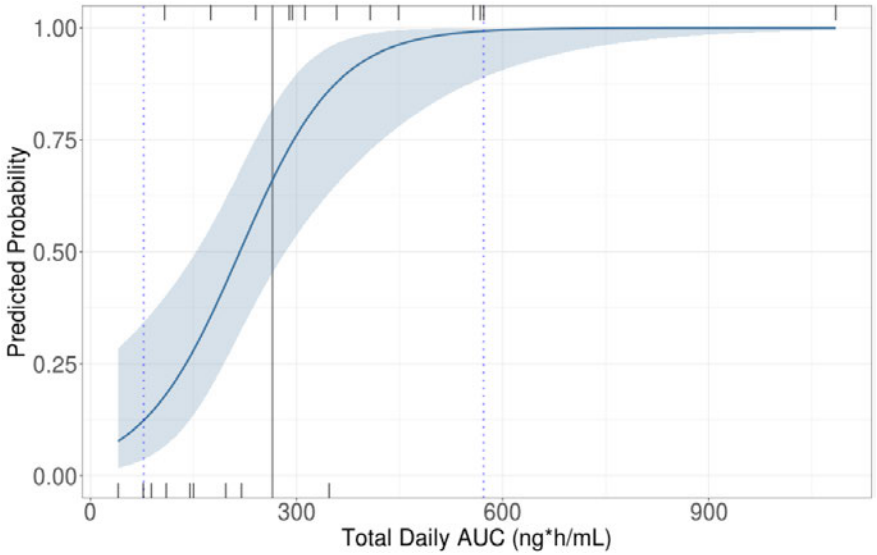
General Information			
Goal of ER analysis		• *To evaluate potential relationships between axitinib dose or axitinib plasma exposure and safety endpoints of interest in pediatric participants.* • *To evaluate potential covariates or confounders in axitinib E-R relationships for safety in pediatric participants.*	
Study Included		*ADVL1315, AREN1721*	
Population Included		*Pediatric patients with refractory solid tumors including advanced tRCC*	
Endpoint		*Diarrhea, fatigue, hypertension, and proteinuria*	
No. of Patients (total, and with individual PK)		*22*	
Population Characteristics (**Table** 4)	General	*None*	
	Organ impairment	*None*	
	Pediatrics (if any)	*Age: median 12 years (range: 5-17, 0% subj <=2 yr, 4.5% subj <=6 yr, 50% subj <=12 yr) ; Weight: median 41 kg (range: 18.3-91.3); 10 (45%) male; Race: White: 17 (77%); Black, of African heritage or African American: 3 (14%); Asian (excluding Japanese): 1 (4.5%); Other: 1 (4.5%)*	
Dose(s) Included		*2.4 or 3.2 mg/m^2 (maximum of 5 mg/dose) BID (oral)*	
Exposure Metrics Explored (range)		*Total daily dose (4 to 12 mg), total daily AUC (40 to 949 ng*h/mL)*	
Covariates Evaluated		*Race, sex, baseline age, baseline body weight, and baseline body surface area*	
Final Model Parameters		**Summary**	**Acceptability**
Model Structure		*Logistic regression*	Acceptable
Model Parameter Estimates		*Hypertension (**Table 7**); E-R relationship for diarrhea, fatigue, and proteinuria was not significant.*	Acceptable
Covariates and Clinical Relevance		*Participants with smaller body surface area are more likely to experience Grade ≥1 fatigue.*	Acceptable
Visualization of significant E-R relationships		*Hypertension (**Figure 4**); a non-significant trend of positive E-R relationship was observed for diarrhea, fatigue, and proteinuria*	Acceptable
Overall Clinical Relevance for E-R		*Participants with higher total daily exposures of axitinib are more likely to experience Grade ≥1 hypertension.*	Acceptable
Labeling Language		**Description**	**Acceptability**
12.2 Pharmacodynamics		*Not applicable*	N/A

Table 7. Parameter Estimates from Final ER Model of Hypertension.

Variables	Estimate	95% CI	z-value	Probability >|z|
Intercept	-3.04	(-6.55; -0.684)	-2.13	0.0334
Total Daily AUC	0.014	(0.0046; 0.0293)	2.3	0.0213
Odds ratio				
Total Daily AUC	1.014	(1.005; 1.03)		
ΔD	**AIC**	**df**	**1-p-Value**	**Log-Lik**
-12.07	21.7	1	<0.0001	-8.85

Abbreviations: CI=confidence interval, z-value=level of marginal significance within a statistical hypothesis test, Probability>|z|=tail area in a 2-tail test, ΔD=change in deviance, AIC=Akaike information criterion, df=degrees of freedom, 1-p-value=one-tailed p-value, Log-Lik=log-likelihood
Source: Applicant's Population PK report, Table 12.

Figure 4. Predicted Probability of Grade ≥1 Hypertension Across Range of Observed Axitinib Total Daily Exposures.



Blue line and shaded region represent median and 80% CI predicted probability of the event. Blue dotted vertical lines represent the observed 5th and 95th percentiles of axitinib last AUC. Grey vertical solid line represents the observed median axitinib last AUC. Rug lines on the top and bottom of the plot indicate the axitinib last AUC for participants who did (top) and did not (bottom) experience this safety event.
Abbreviations: AUC=area under the curve; ng=nanogram; h=hour; mL=milliliter.
Source: Applicant's Population PK report, Figure 6.

The Applicant's E-R analyses for axitinib and safety endpoints (diarrhea, fatigue, hypertension, and proteinuria) are considered acceptable for the purpose of exploring the relationship between axitinib exposure and safety in pediatric patients with refractory solid tumors including advanced tRCC.

3.2.3 E-R Review Issues

No substantive issue.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAUREN S PRICE
06/17/2024 02:17:34 PM

HUALI WU
06/17/2024 02:20:48 PM

JIANG LIU on behalf of JINGYU YU
06/18/2024 02:01:36 PM
signed on behalf on Jerry Yu

STACY S SHORD
06/18/2024 04:24:28 PM