PIND 144573

WRITTEN REQUEST – AMENDMENT 1

Pfizer Inc.
Attention: Melissa J. McMahon, M.S.
Director, Global Regulatory Affairs
10646 Science Center Drive
San Diego, CA 92121

Dear Ms. McMahon:

Please refer to your correspondence dated February 3, 2022, requesting changes to FDA's August 3, 2020, Written Request for pediatric studies for Inlyta (axitinib).

We refer to our April 5, 2022, electronic mail (email) communication containing a clinical comment and to your April 5, 2022 email response containing an agreement with a revision to the Written Request as proposed by the FDA.

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on August 3, 2020, remain the same. (Text added is underlined. Text deleted is strikethrough.)

These studies investigate the potential use of axitinib in the treatment of pediatric patients with recurrent or refractory solid tumors, including advanced translocation renal cell carcinoma (tRCC).

Axitinib is a tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptor (VEGFR), indicated in adult patients with advanced renal cell carcinoma (aRCC) after failure of 1 prior systemic treatment.

Pediatric renal tumors are rare, representing 4% to 6% of all malignancies in patients under the age of 20 years. The most common type of pediatric renal tumors are Wilms' tumors (~90%), whereas renal cell carcinoma (RCC) is rare with an estimated annual incidence of 0.1-1 per million children and accounting for approximately 2% of all new pediatric renal tumors (Pastore et al, 2006; Syed et al, 2017). Evidence from the Surveillance, Epidemiology, and End Results (SEER) database confirms that the onset of pediatric RCC is typically during the second decade of life and extremely rare in patients <6 years of age.
In contrast to adults, where clear cell renal cell carcinoma (ccRCC) is the most common RCC (70-88%) (Chowdhury et al, 2011; Kroeger et al, 2013), translocation renal cell carcinoma (tRCC), a non-ccRCC subtype that harbors chromosomal translocations involving members of the microphthalmia transcription fact (MiT) family (Xp11

(transcription factor E3 [TFE3] and EB [TFEB]) is the most common RCC in children (Perlman, 2010; Cajaiba et al, 2018). The Xp11 tRCCs have been included as a separate entity in the 2004 World Health Organization (WHO) renal tumor classification (Argani et al, 2004), and account for approximately 20-47% of all pediatric aRCC (et al, 2015; Perlman, 2010; Cajaiba et al, 2018). tRCC also occurs in adults but at a much lower frequency than in children (Argani et al, 2007; Zhong et al, 2012).

Treatment options for pediatric RCC are primarily surgical, given the known resistance to standard chemotherapy and radiotherapy (Syed et al, 2017). Although the histological and molecular characteristics of ccRCC and tRCC are different, studies have shown antitumor activity of VEGFR TKIs in adult patients with ccRCC and non-ccRCC histologies (Armstrong et al, 2016; Tannir et al, 2016). There are several retrospective studies in adult patients treated with VEGFR TKIs or monoclonal antibodies showing clinical activity (Malouf et al, 2010; Choueiri et al, 2010). Objective responses were reported in pediatric patients with tRCC after treatment with sunitinib (Malouf et al, 2010; Chowdhury et al, 2013). Collectively, these data support the potential of VEGFR TKIs, including axitinib, across all histologies in adult aRCC as well as pediatric aRCC.

In 2019, pembrolizumab and avelumab, monoclonal antibodies inhibiting the programmed-death receptor 1 and its ligand (PD-1/PD-L1), were approved for first-line treatment adult patients with aRCC in combination with axitinib.

The majority of pediatric patients with RCC are candidates for systemic treatment, and most are patients with tRCC. Considering the increased tumor prevalence of the tRCC subtype in the pediatric population (Geller et al, 2015; Perlman, 2010; Cajaiba et al, 2018), its aggressive nature and advanced presentation (Choo et al, 2017; Ellis et al, 2014; Meyer et al, 2007), as well as the limited data generated in both adults and children to date, tRCC has been identified as the subtype to evaluate the efficacy and safety of axitinib given in combination with a check point inhibitor.

Studies of axitinib are not requested in patients less than 12 months of age, including neonates, because RCC is extremely rare in this age group.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

To obtain needed pediatric information on axitinib, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study(ies)*:

Based on review of the available nonclinical toxicology and clinical data in children, no additional animal studies are required at this to support the clinical studies described in this Written Request.

- *Clinical studies:*

Study 1:

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- *Study Objectives:*

The primary objectives include:
- To estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of axitinib administered orally twice daily, every 28-days to children with recurrent or refractory solid tumors.
- To define and describe the toxicities of axitinib administered on this schedule.
- To characterize the pharmacokinetics of axitinib in children with cancer.

The secondary objectives include:
- To preliminarily define the antitumor activity of axitinib within the confines of a Phase 1 study.
- To preliminarily assess biomarkers of kidney injury during axitinib treatment in children, and correlate finding with blood pressure, pharmacokinetics and response.

- *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.

- *Study endpoints:*

  - Primary endpoints include:
    - The occurrence of first-cycle dose-limiting toxicities (DLTs).
    - Estimation of MTD, all AEs/SAEs as characterized by type, frequency, severity (as graded by National Cancer Institute. Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.0), timing, seriousness, and relationship to study therapy.
    - PK parameters: AUC and Cmax.

  - Secondary endpoints include:
    - Confirmed objective response rate (ORR) based on RECIST v1.1 and duration of response (DR)

- *Safety Endpoints/Monitoring:*

  - Collection and analysis of all adverse events (AEs) (including secondary acute myeloid leukemia/myelodysplastic syndrome), serious AEs (SAEs), pregnancy, deaths (fetal death and neonatal death), laboratory test evaluations, vital signs, and specific toxicities (growth plate and thyroid).

  - Radiological evaluation of bone development and thyroid function.

  All adverse events must be monitored until symptom resolution or until the condition stabilizes.

- *Statistical information, including power of study(ies) and statistical assessments:*

  - A Rolling 6 design to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D), including descriptive summaries of all toxicities, and safety and laboratory data.

  - The MTD of axitinib defined as the maximum dose for which fewer than one-third of patients experienced a DLT.
  - Response summarized based on the best overall response (BOR) reported for each patient with a point estimate of each category's percentage.

  - ORR defined as the percentage of patients with a best overall confirmed response of CR or PR with a point estimate of the percentage along with the 95% confidence interval (CI) using the Clopper-Pearson method.

  - DR summarized with Kaplan-Meier (KM) methods in order to generate KM curves and produce descriptive statistics (median, 25% and 75% quartiles, minimum, maximum).

- 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.

Study 2:

AREN1721 – A randomized Phase 2 trial of axitinib/nivolumab combination therapy vs. single agent nivolumab for the treatment of TFE/translocation renal cell carcinoma (tRCC) across all age groups.

- *Study Objectives:*

  The primary objective is:
  - To establish the clinical activity, assessed primarily by progression-free survival, of nivolumab therapy with or without axitinib for advanced transcription factor E3/translocation morphology renal cell carcinoma (TFE/tRCC).

  The secondary objectives are:
  - To further define the activity and toxicities of the two study arms in the treatment of TFE/tRCC across all ages.

  The exploratory objective is:
  - To characterize axitinib PK parameters when given in combination with nivolumab in the pediatric population.

- *Patients to be Studied:*

  - Patients ≥ 12 months at enrollment, with unresectable or metastatic tRCC.

A minimum of ~~Approximately 66~~ 28 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. Randomization will incorporate stratification (<18 years vs. ≥18 years) and prior systemic therapy for RCC (none, anti-VEGF therapy, systemic therapy other than anti-VEGF ~~yes or no~~). The study must enroll at least 6 patients aged 12-17 years (inclusive) and 3 patients younger than 12 years in the axitinib/nivolumab combination arm. If the requested minimum number of pediatric patients are not achieved at the time of the primary analysis, an extension phase of up to 1 year can be implemented to enroll the remaining number of pediatric patients in the axitinib/nivolumab combination arm provided that the efficacy threshold is met and enrollment metrics at the time of the primary analysis supports a reasonable likelihood of enrolling additional pediatric patients within the given age groups within this timeframe; data from this

extension cohort will be submitted as part of the complete study report within the timeframe stipulated in the Written Request.

- *Study endpoints:*
  - The primary endpoint will be PFS.
  - Secondary endpoints:
    - Overall Survival (OS) and Objective Response Rate (ORR)
    - All adverse events (AEs) and serious adverse events (SAEs) as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0), timing, seriousness, and relationship to study therapy.
  - Exploratory endpoints:
    - PK blood samples will be collected from pediatric patients in the axitinib/nivolumab combination arm. PK parameters will include CL/F and Vd/F based on Population PK analysis.

- *Safety Endpoints/Monitoring:*
  - Collection and analysis of AEs, SAEs, secondary malignancy, pregnancy, pregnancy loss and deaths neonatal, laboratory test evaluations, and vital signs.
  - Additionally, all Grade 3 non-hematologic toxicities and all Grade 4-5 or higher adverse events occurring during protocol therapy or within 30 days of treatment discontinuation will be actively monitored.

  All adverse events must be monitored until symptom resolution or until the condition stabilizes.

- *A Data Monitoring Committee (DMC)* must be included to protect the interests of patients and the scientific integrity for all clinical trial research. The DMC will review reports of interim analyses of study toxicity and outcomes prepared by the study statistician, in conjunction with the study chair's report. The DMC may recommend the study be modified or terminated based on these analyses and determines whether and to whom outcome results may be released prior to the release of study results.

- *Statistical information, including power of study(ies) and statistical assessments:*

PFS, is defined as the time from randomization to the earliest occurrence of disease progression (as defined by modified RECIST criteria for immunotherapy) or death due to any cause among patients who initiated protocol treatment.

Using a one-sided alpha = 0.1~~0~~5, the study will provide 80% power to detect a hazard ratio (HR) of 0.4~~5~~0 based on ~~approximately 56~~ 22 PFS events.

A futility interim analysis is planned at ~~approximately~~ 50% information fraction (~~approximately 28~~ 11 PFS events). The study would be stopped for futility if the observed HR is greater than 1.00. Under the current simulation assumptions in the revised protocol, the chance of stopping for early futility would be 50% if the true HR=1.0, 15% if the true HR=0.5, and 8% if the true HR=0.4 ~~conditional power under HR = 0.50 were less than 30%.~~

The final PFS analysis would occur at the earlier of two years of follow-up obtained for each patient still at risk for a PFS event ~~after the last patient enrolls~~, or when 22 ~~56~~ PFS events a~~w~~were observed. A stratified log-rank test and a Cox proportional hazards model will be used to analyze the treatment differences. The estimated HR will be presented with a 70~~90~~% confidence interval (CI) to align with the overall alpha level of the primary log-rank test. Stratification factors include age and prior therapy. At the analysis stage, however, stratification factors may be collapsed and/or omitted depending on the final counts. An unstratified analysis may also be done.

Secondary analyses include overall response rate (ORR), overall survival (OS), and adverse events (AEs). The ORR will be analyzed with a logistic regression model for overall response, stratified by age and prior therapy for RCC. The odds ratio and 70~~90~~% CI will be reported in addition to each treatment arm's ORR. Stratification factors again may be collapsed and/or omitted depending on the final counts.

OS will be analyzed in a similar manner to PFS.

AEs will be descriptively summarized. ~~Additionally, AE event rates and 95% exact CI will be provided.~~ The Fisher exact test may be used to test for differences between the treatment arms. Such tests will be considered descriptive in nature and are not powered.

Study 3:

Pooled PK Analysis

The objectives of population PK 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.

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.

The population PK modeling approach is planned to analyze pediatric PK data from the Phase 1 Study ADVL1315 and Study AREN1721.

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 below limit of quantitation (BLQ) 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.

Exposure-response relationships will also be explored. Sequential PK-PD modeling/analysis will be conducted with respect to key safety and efficacy endpoints, using population PK model post hoc predictions of steady state exposure metrics. Covariates that may account for the inter-individual variability in the PK-PD parameters will be explored as part of the PK-PD modeling/analysis where feasible.

The following information pertains to all clinical studies in the Written Request.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

- *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. The excipients are precedented in marketed products for pharmaceutical use. Lactose monohydrate is an excipient used in the drug product formulation. The tablets are appropriate and suitable for an accurate and safe administration of axitinib to pediatric patients.

- *Route of administration*
  Oral

- *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 and nivolumab will be administered as follows:

  - 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/m^2 PO BID)
    - Patients aged ≥18 years will receive the starting adult dose (5 mg PO 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

- *Labeling that may result from the study(ies):* You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section505A(j) of the Act, regardless of whether the study(ies) demonstrate that axitinib is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. For Study 1, all pediatric patients enrolled should be categorized using one of the following designations for race: White, Black, Asian or Other. For Study 2, all pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to

you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the guidance addendum.[1] You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on FDA.gov[2] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before January 29, 2024. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies) but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated August 3, 2020, as amended by this letter must be submitted to the Agency on or beforeJanuary 29, 2024 , in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[1]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

[1] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

If you have any questions, call Idara Ojofeitimi, Regulatory Project Manager, at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, MD
Acting Associate Director, Pediatric Oncology
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Complete Copy of Written Request as Amended

PIND 144573

WRITTEN REQUEST

PF Prism C.V.
c/o Pfizer Manufacturing Holding LLC
Attention: Melissa J. McMahon, MS
Director, Global Regulatory Affairs
10646 Science Center Drive
San Diego, CA 92121

Dear Ms. McMahon:

Reference is made to your 06 June 2019, Proposed Pediatric Study Request (PPSR) for axitinib. Reference is also made to your revised PPSRs submitted on October 30, 2019, March 11 and May 4, 2020, in response to our August 6, 2019, February 3 and April 10, 2020 Inadequate PPSR correspondence, respectively.

These studies investigate the potential use of axitinib in the treatment of pediatric patients with recurrent or refractory solid tumors, including advanced translocation renal cell carcinoma (tRCC).

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  - 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.

Study 2:

AREN1721 – A randomized Phase 2 trial of axitinib/nivolumab combination therapy vs. single agent nivolumab for the treatment of TFE/translocation renal cell carcinoma (tRCC) across all age groups.

- *Study Objectives:*

  The primary objective is:
  - To establish the clinical activity, assessed primarily by progression-free survival, of nivolumab therapy with or without axitinib for advanced transcription factor E3/translocation morphology renal cell carcinoma (TFE/tRCC).

  The secondary objectives are:
  - To further define the activity and toxicities of the two study arms in the treatment of TFE/tRCC across all ages.

  The exploratory objective is:
  - To characterize axitinib PK parameters when given in combination with nivolumab in the pediatric population.

- *Patients to be Studied:*

  - Patients ≥ 12 months at enrollment, with unresectable or metastatic tRCC.

A minimum of 28 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. Randomization will incorporate stratification (<18 years vs. ≥18 years) and prior systemic therapy for RCC (none, anti-VEGF therapy, systemic therapy other than anti-VEGF). The study must enroll at least 6 patients aged 12-17 years (inclusive) and 3 patients younger than 12 years in the axitinib/nivolumab combination arm. If the requested minimum number of pediatric patients are not achieved at the time of the primary analysis, an extension phase of up to 1 year can be implemented to enroll the remaining number of pediatric patients in the axitinib/nivolumab combination arm provided that the efficacy threshold is met and enrollment metrics at the time of the primary analysis supports a reasonable likelihood of enrolling additional pediatric patients within the given age groups within this timeframe; data from this extension cohort will be submitted as part of the complete study report within the timeframe stipulated in the Written Request.

- *Study endpoints:*

  - The primary endpoint will be PFS.

  - Secondary endpoints:

- Overall Survival (OS) and Objective Response Rate (ORR)
- All adverse events (AEs) and serious adverse events (SAEs) as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0), timing, seriousness, and relationship to study therapy.

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

- *Safety Endpoints/Monitoring:*

  ▪ Collection and analysis of AEs, SAEs, secondary malignancy, pregnancy, pregnancy loss and deaths neonatal, laboratory test evaluations, and vital signs.

  ▪ Additionally, all Grade 3 non-hematologic toxicities and all Grade 4-5 or higher adverse events occurring during protocol therapy or within 30 days of treatment discontinuation will be actively monitored.

  All adverse events must be monitored until symptom resolution or until the condition stabilizes.

- *A Data Monitoring Committee (DMC)* must be included to protect the interests of patients and the scientific integrity for all clinical trial research. The DMC will review reports of interim analyses of study toxicity and outcomes prepared by the study statistician, in conjunction with the study chair's report. The DMC may recommend the study be modified or terminated based on these analyses and determines whether and to whom outcome results may be released prior to the release of study results.

- *Statistical information, including power of study(ies) and statistical assessments:*

  PFS, is defined as the time from randomization to the earliest occurrence of disease progression (as defined by modified RECIST criteria for immunotherapy) or death due to any cause among patients who initiated protocol treatment.

  Using a one-sided alpha =0.15, the study will provide 80% power to detect a hazard ratio (HR) of 0.40 based on 22 PFS events.

A futility interim analysis is planned at 50% information fraction (11 PFS events). The study would be stopped for futility if the observed HR is greater than 1.00. Under the current simulation assumptions in the revised protocol, the chance of stopping for early futility would be 50% if the true HR=1.0, 15% if the true HR=0.5, and 8% if the true HR=0.4

The final PFS analysis would occur at the earlier of two years of follow-up obtained for each patient still at risk for a PFS event, or when 22 PFS events are observed. A stratified log-rank test and a Cox proportional hazards model will be used to analyze the treatment differences. The estimated HR will be presented with a 70% confidence interval (CI) to align with the overall alpha level of the primary log-rank test. Stratification factors include age and prior therapy. At the analysis stage, however, stratification factors may be collapsed and/or omitted depending on the final counts. An unstratified analysis may also be done.

Secondary analyses include overall response rate (ORR), overall survival (OS), and adverse events (AEs). The ORR will be analyzed with a logistic regression model for overall response, stratified by age and prior therapy for RCC. The odds ratio and 70% CI will be reported in addition to each treatment arm's ORR. Stratification factors again may be collapsed and/or omitted depending on the final counts.

OS will be analyzed in a similar manner to PFS.

AEs will be descriptively summarized. The Fisher exact test may be used to test for differences between the treatment arms. Such tests will be considered descriptive in nature and are not powered.

Study 3:

Pooled PK Analysis

The objectives of population PK 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.

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.

The population PK modeling approach is planned to analyze pediatric PK data from the Phase 1 Study ADVL1315 and Study AREN1721.

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 below limit of quantitation (BLQ) 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.

Exposure-response relationships will also be explored. Sequential PK-PD modeling/analysis will be conducted with respect to key safety and efficacy endpoints, using population PK model post hoc predictions of steady state exposure metrics. Covariates that may account for the inter-individual variability in the PK-PD parameters will be explored as part of the PK-PD modeling/analysis where feasible.

The following information pertains to all clinical studies in the Written Request.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

- *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. The excipients are precedented in marketed products for pharmaceutical use. Lactose monohydrate is an excipient used

in the drug product formulation. The tablets are appropriate and suitable for an accurate and safe administration of axitinib to pediatric patients.

- *Route of administration*
  Oral

- *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 and nivolumab will be administered as follows:

  - 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/m^2 PO BID)
    - Patients aged ≥18 years will receive the starting adult dose (5 mg PO 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

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that axitinib is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. For Study 1, all pediatric patients enrolled should be categorized using one of the following designations for race: White, Black, Asian or Other. For Study 2, all pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the guidance addendum.[1] You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

document "Study Data Specifications," which is posted on FDA.gov[2] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before January 29, 2024. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

    - *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

[2] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

In accordance with section 505A(k)(1) of the FD&C Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

(1) the type of response to the Written Request (i.e., complete or partial response);
(2) the status of the application (i.e., withdrawn after the supplement has been filed or pending);
(3) the action taken (i.e., approval, complete response); or
(4) the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[3]

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the PHS Act, you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found on the Clinical Trials website.[4]

If you have any questions, call Maryam Khazraee, Regulatory Project Manager, at 301-796-7119.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, MD
Acting Associate Director
Pediatric Oncology
Office of Oncologic Diseases
Center for Drug Evaluation and Research

[3] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm
[4] www.ClinicalTrials.gov

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/

GREGORY H REAMAN
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