NDA 204114

WRITTEN REQUEST – AMENDMENT 3

Novartis Pharmaceuticals Corporation
Attention: Carolyn Zhu, PharmD
Global Program Regulatory Manager, Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Zhu:[1]

Please refer to your correspondence submitted to NDA 202806, dated November 23, 2021, requesting changes to FDA's March 1, 2016, Written Request for pediatric studies for Mekinist (trametinib).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on March 1, 2016, and as amended on March 22, 2018, and October 19, 2020, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Based on discussions with the sponsor, and in the setting of emerging data suggesting robust radiographic responses in patients with HGG, FDA issued Amendment 3. Amendment 3 provided revisions to the minimum number of patients with high grade glioma (HGG) with centrally confirmed BRAF V600 mutations; rather than a minimum of 40 patients in Study 2, the revised WR stated that a minimum of 50 patients with centrally confirmed BRAF V600 mutations would be enrolled across Study 1 Part II and Study 2.

- *Patients to be Studied*
  - *Number of patients to be studied:*

    Study 2: At least 40 patients ~~will be studied.~~

    ~~Additional patients may be enrolled in~~ Across Study 1 Part II of the Tafinlar WR and Study 2, additional patients may be enrolled to ensure that there are at least ~~40~~ 50 patients with ~~locally assessed and centrally confirmed~~ BRAF V600 mutation as determined by central testing, ~~and~~ histologic Grades III & IV glioma by WHO criteria, and baseline measurable disease

[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.

by Response Assessment in Neuro-Oncology (RANO) that is confirmed by Blinded Independent Review Committee (BIRC).

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 March 1, 2016, as amended by this letter and by previous amendments dated March 22, 2018, and October 19, 2020, must be submitted to the Agency on or before October 31, 2022, 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.[2]

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.

If you have any questions, call Jana Highsmith, Regulatory Project Manager, at (301) 348-1823.

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

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 (Clean Copy of the Amended WR Should Be Attached Here)

ATTACHMENT 1
WRITTEN REQUEST (WR) – AMENDMENT 3

These studies investigate the potential use of trametinib in the treatment of pediatric patients with advanced relapsed/refractory malignant solid tumors with activation of the RAS/RAF/MEK signaling pathway, including low- and high-grade gliomas, as well as adolescent patients with BRAF V600 mutant-positive malignant melanoma.

Despite advances made over the past 30 years in the treatment of pediatric solid tumors, treatment remains suboptimal for many types of pediatric cancers and the prognosis for the majority of pediatric patients with recurrent, refractory, or metastatic tumors remains poor. Improvement in the outcomes of pediatric patients with refractory solid malignancies through utilization of targeted therapies aimed at blocking pathways necessary for tumor survival are an area of interest. Trametinib is a reversible inhibitor of mitogen-activated, extracellular signal-regulated kinase 1 (MEK1) and MEK2 activation and of MEK1 and MEK2 kinase activity. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. Trametinib is currently indicated as a single agent or in combination with dabrafenib, for the treatment of adult patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. Trametinib is not indicated for treatment of patients who have received prior BRAF-inhibitor therapy.

Preliminary data from ongoing trials of trametinib in adult patients with other advanced solid tumors and from other MEK inhibitor clinical programs suggest that trametinib may have beneficial effects in tumor types other than melanoma. Based on its mechanism of action, trametinib has the potential to provide therapeutic benefit to pediatric patients with advanced or relapsed recurrent solid tumors that may involve activation of the RAS/RAF/MEK signaling pathway, which includes recurrent or advanced BRAF V600 mutant melanoma, other BRAF mutant-positive solid tumors (such as Langerhans cell histiocytosis (LCH) and low- and high-grade gliomas), neuroblastoma, and neurofibromatosis- related malignancies (such as optic pathway gliomas and plexiform neurofibromas).

The incidence of pediatric high grade glioma (HGG) in the United States is approximately 0.85 per 100,000 (CBTRUS, 2012). The most common HGGs are anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM). Other less common pediatric HGGs include anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic ganglioglioma, anaplastic pilocytic astrocytoma and giant cell glioblastoma and gliosarcoma. After primary treatment with surgery and adjuvant chemotherapy and/or radiotherapy, the majority of patients with HGG develop recurrent disease. There is no accepted second-line therapy in clinical practice, and the literature reports approximately 10% response rates for patients who have failed frontline therapy and are treated with temozolomide. The median survival after initial diagnosis of a HGG is eighteen to twenty-four months. BRAF V600E mutations have been detected in approximately 10% of pediatric HGGs, and there are case reports of durable responses observed in pediatric patients with HGG treated with vemurafenib. This information supports the evaluation of dabrafenib in pediatric patients with HGGs with BRAF V600 activating mutations. Additionally, given the improved treatment effect observed in adult patients with BRAF mutant melanoma when

dabrafenib is combined with trametinib as compared to dabrafenib alone, evaluation of the combination regimen may be worth exploring in this molecular subset of pediatric HGGs.

Pediatric low-grade glioma (LGG) is a tumor that is also characterized by the presence of the BRAF V600 activating mutation in approximately 19% of patients. While the median progression free survival (PFS) for all patients with LGG treated with various cytotoxic chemotherapy regimens for progressive disease following surgery is about five years, recent literature reports that the subgroups of patients with tumors harboring a BRAF V600 mutation have a decreased radiographic response rate to cytotoxic drugs as compared to unselected groups and a PFS of about two years. Based on preliminary data from ongoing Study 1 in this WR demonstrating 12 responses among 32 patients with LGG treated with single agent dabrafenib, it is reasonable to further evaluate dabrafenib in combination with trametinib in patients with progressive LGG (Study 3).

To obtain needed pediatric information on trametinib, the Food and Drug Administration (FDA) is hereby making a formal WR, 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. Similar to other oncology drug development programs, overall response rate (ORR) and duration of response will be evaluated in early studies to detect potential antitumor activity signals, and PFS is considered an acceptable surrogate endpoint that is reasonably likely to predict clinical benefit and can be used to assess efficacy in later studies; however, final concurrence with efficacy endpoints for later studies will depend on the tumor type(s) selected for further study.

Based on tumor biology and clinical experience adolescent patients with unresectable and metastatic BRAF-V600 mutant melanoma in have a similar disease course and response to therapeutic intervention compared to adult patients; hence, the efficacy of trametinib in adolescent patients with unresectable and metastatic BRAF-V600 mutant melanoma can be extrapolated from the adequate and well-controlled studies supporting approval of trametinib in adult patients. Pharmacokinetic and safety data in the studies included in this WR, supported by data from studies in adults, will be used to establish the dosing and safety of trametinib in this patient population.

FDA is not requesting studies in neonates because solid tumors are diagnosed infrequently in the neonatal period. Additionally, when tumors are diagnosed in neonates, they generally do not require chemotherapeutic intervention and are not relapsed or refractory to standard treatments during the neonatal period.

Based on discussions with the sponsor, and in the setting of emerging data suggesting robust radiographic responses in patients with HGG, FDA issued Amendment 3. Amendment 3 provided revisions to the minimum number of patients with high grade glioma (HGG) with centrally confirmed BRAF V600 mutations; rather than a minimum of 40 patients in Study 2, the revised WR stated that a minimum of 50 patients with centrally confirmed BRAF V600 mutations would be enrolled across Study 1 Part II and Study 2.

- *Nonclinical study(ies)*:

  Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this WR.

- *Clinical studies:*

  Study 1: An open label trial of trametinib alone and in combination with dabrafenib. The trial consists of the following three components.

- Part A: A single arm dose escalation component studying trametinib monotherapy in pediatric patients with relapsed/refractory solid tumors to determine a recommended phase 2 dose (RP2D) of trametinib in specific age groups.
- Part B: Tumor-specific expansion cohorts studying trametinib monotherapy administered at the RP2D identified in Part A of Study 1 in pediatric patients with relapsed/refractory neuroblastoma, unresectable neurofibromatosis type 1 (NF1)-associated plexiform neurofibromas, recurrent/unresectable low grade gliomas associated with BRAF tandem duplication with fusion, or NF-1-associated gliomas.
- Part C: A single arm dose escalation component studying trametinib in combination with dabrafenib in pediatric patients with refractory BRAF V600-mutant solid tumors to determine a RP2D of trametinib in combination with dabrafenib. Any pediatric patients with BRAF V600 mutant unresectable or metastatic melanoma are to enroll into this arm of the study.
- Part D: Tumor-specific expansion cohorts studying trametinib in combination with dabrafenib administered at the RP2D of the combination identified in Part C in pediatric patients with refractory BRAF V600-mutant LGG or LCH.

Study 2: An open label, single arm study of dabrafenib in combination with trametinib in pediatric patients with refractory, relapsed or progressive BRAF V600 mutation positive HGG who have progressed after at least one line of therapy (Study 2 of the dabrafenib WR).

Study 3: A randomized, controlled study of dabrafenib and in combination with trametinib in pediatric patients with BRAF V600 mutation positive LGG requiring systemic therapy after optimal surgical management (Study 3 of the dabrafenib WR).

The efficacy of trametinib in adolescent patients (12 to less than 18 years of age) with unresectable or metastatic melanoma with BRAF V600E or V600K mutations will be supported by extrapolation utilizing trametinib pharmacokinetic (PK) data from adolescent patients with melanoma or BRAF V600 mutation positive solid tumors other than melanoma and exposure-response relationships observed in adult patients with unresectable or metastatic melanoma with BRAF V600E or BRAF V600K mutations.

- *Objectives of each study:*

Study 1

- Primary Objectives.
  - To identify the optimal safe and tolerable dose of trametinib and dabrafenib that achieves similar exposures to those achieved in adults, for chronic dosing in pediatric patients.
  - To characterize the PK of trametinib in adolescent patients to support extrapolation of efficacy for the BRAF V600E and V600K mutation-positive

unresectable or metastatic melanoma indication. To characterize the adverse reaction profile of trametinib monotherapy in patients aged 1 month to < 18 years of age and trametinib and dabrafenib in patients aged 12 months to <18 years of age.

- Secondary and Exploratory Objectives.
  - To assess the safety and activity of trametinib when administered alone at the RP2D to pediatric patients with relapsed refractory neuroblastoma, unresectable NF1-associated plexiform neurofibromas, recurrent/unresectable LGG associated with BRAF tandem duplication with fusion, or NF1-associated gliomas.
  - To identify the RP2D of trametinib in combination with dabrafenib in pediatric patients.
  - To assess the safety and antitumor activity of the combination of trametinib and dabrafenib administered at the RP2D to pediatric patients with BRAF V600- mutant LGG, LCH, and advanced melanoma.
  - To characterize the PK of trametinib and to contribute to a population PK model in pediatric patients.
  - To characterize the PK of trametinib and dabrafenib when administered in combination to pediatric patients.
  - To explore the pharmacodynamic effects of trametinib on relevant biomarkers (including at least phosphorylated ERK (p-ERK) and explore correlations with antitumor activity.
  - To assess the acceptability and palatability of the age-appropriate powder for oral solution formulation and the acceptability of the film-coated tablets.

Study 2

- To estimate the ORR and the response duration in pediatric patients with locally confirmed BRAF V600 mutation positive HGG.
- To characterize the PK, safety and tolerability of dabrafenib in combination with trametinib in pediatric patients with BRAF V600 mutation positive HGG.

Study 3

- To compare the centrally confirmed ORR (complete response [CR] + partial response [PR]) of patients with BRAF V600E mutated LGG treated with dabrafenib in combination with trametinib versus standard of care
- To compare duration of response and PFS across treatment arms
- To assess overall survival (OS)
- To further characterize the population PK, safety and tolerability in pediatric patients with BRAF V600 mutation positive LGG treated with dabrafenib in combination with trametinib.

FDA concurrence with the final protocol and statistical analysis plan for Studies 2 and 3, if warranted based upon the results of Study 1, will be obtained prior to enrolling the first patient in the study (ies)

- *Patients to be Studied:*
  - *Age group in which studies will be performed*:

    Study 1

    - Parts A and B (trametinib monotherapy): Pediatric patients 1 month to less than 18 years of age.
    - Part C and D (trametinib and dabrafenib combination therapy): Pediatric patients 12 months to less than 18 years of age. Patients < 1 year of age will not be enrolled due to rarity of the specific cancer types to be studied in infants < 1 year of age, particularly in the relapsed/refractory setting.

    Studies 2 and 3

    - Pediatric patients 12 months to less than 18 years of age. Patients < 1 year of age will not be enrolled due to rarity of the specific cancer types to be studied in infants < 1 year of age, particularly in the relapsed/refractory setting.

  - *Number of patients to be studied:*

    Study 1: A total of at least 70 evaluable patients with at least 60 patients evaluable for the secondary activity endpoint

    - Part A: Up to 36 patients for the dose escalation portion; 4 to 6 patients per age cohort (1 month to less than 2 years, 2 years to 12 years, greater than 12 years to less than 18 years) within the age-group expansion.
    - Part B: At least 30 patients into 3 tumor-specific cohorts (at least 10 patients per cohort, at least 4 patients less than 6 years of age per cohort).
    - Part C and D: A minimum of 30 patients, including at least 4 patients less than 12 years. A minimum of 20 pediatric patients with LGG and a minimum of 10 patients with LCH will be enrolled. There is no minimum enrollment requirement for adolescent melanoma, given the rarity of the disease

    Study 2: At least 40 patients-

    Across Study 1 Part II of the Tafinlar WR and Study 2, additional patients may be enrolled to ensure that there are at least 50 patients with BRAF V600 mutation as determined by central testing, -histologic Grades III & IV glioma by WHO criteria, and baseline measurable disease by Response Assessment in Neuro-Oncology (RANO) that is confirmed by a Blinded Independent

Review Committee (BIRC).

Study 3: At least 102 patients will be randomized in a 2:1 ratio to dabrafenib and trametinib or standard of care, respectively.

Data from a sufficient number of adolescent patients with tumors harboring BRAF V600E or V600K mutations who are evaluable for trametinib PK across all studies must be submitted to support extrapolation of the efficacy of trametinib alone or in combination with dabrafenib in adolescent patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. Data from a minimum of 6 patients who are evaluable for trametinib PK across all studies must be submitted for each of the following age groups: 1 month to < 2 years and 2 to < 12 years of age.

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.

- *Study endpoints:*
  - *Efficacy Endpoints*

Study 1

- ORR and duration of response. Tumor assessments must be performed every 8-12 or up to 24 weeks according to RECIST 1.1 criteria or other imaging-based response criteria appropriate for each studied tumor type studied (e.g., RANO).

Study 2

- Primary endpoint - ORR and duration of response as determined by central review according to RANO criteria. Investigator-assessed ORR is acceptable for treatment decisions.
- Secondary endpoints - OS and PFS.

Study 3

- Primary endpoint - ORR (CR and PR) as determined by central review according to the RANO criteria.
- Secondary endpoints - investigator-confirmed ORR, duration of response, PFS as assessed separately by investigator and independent central reviewer per RANO criteria and OS.

- *Safety Endpoints*

    - The primary safety endpoint for Study 1 is determination of the RP2D of trametinib in pediatric patients based on achievement of similar trametinib systemic exposures to those in adults or the maximum tolerated dose (MTD), whichever occurs first.
    - Safety outcomes for Study 1 must include assessment of adverse events (AEs), electrocardiograms (ECGs), echocardiograms (ECHOs), ophthalmological exams, and changes in height, weight, laboratory values and vital signs. Changes in skeletal maturity will be assessed using height measurements and serial radiographs of growth plates and changes in sexual maturity will be assessed by serial assessment of Tanner stage.
    - Secondary safety outcomes for Studies 2 and 3 are changes in sexual maturity assessed by serial assessments of Tanner stage and changes in skeletal maturity serial assessed using height measurements and serial radiographs of growth plates.
    - The following adverse events must be actively monitored in Study 1, 2, and 3: skin, eye, cardiac, and ophthalmologic toxicities. For patients receiving dabrafenib in addition to trametinib, serious febrile reactions and hyperglycemia must also be actively monitored.

- *Pharmacokinetic/Pharmacodynamic Endpoints*

  Estimated trametinib clearance (CL) and volume of distribution (Vd) from PK samples obtained across all studies from a sufficient number of patients 12 to ≤ 18 years of age and a minimum of 6 patients in each of the following age groups: 1 month to < 2 years and 2 to < 12 years of age. Combine data from all completed studies to develop PK and pharmacodynamic models to explore exposure-response relationships for measures of safety and activity.

- *Known Drug Safety concerns and monitoring:*

  Because of the known risk of BRAF inhibition on the development or acceleration of, actinic keratoses, keratoacanthomas and squamous cell carcinoma (SCC) a risk management plan for the potential occurrence of skin findings, including squamous cell carcinoma, will be utilized for pediatric patients. Routine dermatologic evaluations will be included in all pediatric clinical trials. Dermatological examinations will include examination of skin and assessment of any skin changes. Biopsy in or around skin lesions that change during the study will be obtained if clinically indicated. Documentation of new non-melanoma skin lesions or non-melanoma lesions that change during the study will be obtained. Details regarding the lesion documentation by photography will be included in protocol procedure manuals.

  Additional safety concerns identified from use of trametinib with dabrafenib in adult patients with melanoma include new primary malignancies, serious febrile reactions and

hyperglycemia. Safety concerns identified from use of trametinib alone or in combination with dabrafenib include hemorrhage, venous thromboembolism, cardiomyopathy, ocular toxicities, skin toxicities, and interstitial pneumonitis. All patients enrolled in Study 1 and Study 2 must be evaluated at baseline and periodically during study therapy for development of these adverse events. Serial ECGs, ECHOs, and ophthalmological exams will be performed to mitigate the risk of severe cardiac and ocular toxicities.

Based on findings from animal studies and their mechanism of action, trametinib can cause fetal harm when administered to a pregnant woman. Female patients of reproductive potential will use effective contraception during treatment with trametinib and for four months after treatment. When used in combination with dabrafenib, non-hormonal methods of contraception will be used because dabrafenib can render hormonal contraceptives ineffective.

In a repeat-dose juvenile toxicity study in juvenile rates, decreased bone length and delay in sexual maturation was noted at trametinib doses resulting in exposures as low as 0.3 times and 1.6 times the human exposure at the recommended adult dose based on AUC, respectively. To mitigate and characterize these risks, changes in skeletal maturity will be serially assessed using height measurements and serial radiographs of growth plates, and sexual maturity will be assessed by serial assessments of Tanner stage.

- *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 WR. 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:*

    - For Study 1,2 and 3: trametinib tablets or powder for oral solution.
    - For Parts C and D of Study 1, 2 and 3: dabrafenib capsules or powder for oral suspension.

  - *route of administration:*

    oral

- *regimen:*

  Study 1:

  - Part A: The starting trametinib dose is 0.0125 mg/kg/day. Dose escalation will proceed based on toxicities observed during the first cycle of treatment and PK data. Approximately 4 to 6 patients will be enrolled in each of the following age groups.
    - Infants and toddlers (1 month to < 2 years of age)
    - Children (2 to ≤ 12 years of age)
    - Adolescents (12 years to < 18 years of age)
  - Part B: Trametinib will be administered at the RP2D identified in Part A of the study.
  - Part C: Trametinib will be administered at the RP2D identified in Part A of the study. The starting dose of dabrafenib will be 50% of the RP2D identified in the pediatric monotherapy trial; dabrafenib will be dose escalated to 100% of the monotherapy RP2D if 50% of the monotherapy RP2D is tolerated.
  - Part D: Trametinib and dabrafenib will be administered at the RP2D identified in Part C of the study.

  Studies 2 and 3:

  - Trametinib and dabrafenib will be administered at the RP2D identified in Part C of Study 1.

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  In accordance with section 505A(e)(2), if

  1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  3) you have not marketed the formulation within one year after the Agency publishes such notice,

  the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can

be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of studies and statistical assessments:*

Study 1

Descriptive statistical analyses will be used to describe the study results for each of the four parts. Efficacy analyses for cohorts in Parts A, B, C and D will be performed separately.

Study 2

The primary endpoint will be ORR. Approximately 40 patients will be enrolled to receive dabrafenib and trametinib. All statistics will be descriptive. The 95% confidence interval (CI) of ORR will be used to describe the effect size. An interim analysis for futility is planned. The statistical analysis plan (SAP) for Study 2 will be agreed upon with FDA prior to enrollment of the first patient in this study.

Study 3

The primary endpoint will be ORR. Approximately 102 patients will be randomized to receive dabrafenib and trametinib or standard of care. The SAP for Study 3 will be submitted to FDA prior to enrollment of the first patient in this study.

Pharmacokinetic analysis:

Studies must be prospectively powered to target a 95% CI within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for trametinib in the adolescent (12 to ≤ 18 years) age group with at least 80% power. Population PK analysis should be performed using trametinib concentration data obtained from all studies. Effect of age and body size on trametinib PK should be assessed. The relationship between systemic drug exposure and selected efficacy and toxicity endpoints may be explored.

- *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 trametinib 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. 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. 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 the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):*

  Reports of Studies 1, 2 and 3 must be submitted to the Agency on or before October 31, 2022. 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 studies. 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 studies, 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 studies 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 studies 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. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the 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 at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

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. Any amendment to this WR will necessitate a corresponding amendment to the dabrafenib WR. 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 Public Health Service Act (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 at 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
02/16/2022 12:48:26 PM