NDA 202806

**WRITTEN REQUEST – AMENDMENT 5**

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 dated November 23, 2021, requesting changes to FDA's March 1, 2016 Written Request for pediatric studies for Tafinlar (dabrafenib).

We also refer to the minutes for the Type C meeting held on November 29, 2021 regarding a proposed amendment to the Written Request related to difficulties with obtaining a sufficient number of patients with centrally confirmed BRAFV600 results in Study 2 and you subsequent correspondence dated December 3, 2021 with this updated information. Your plans to (b) (4) and you therefore performed the confirmatory testing given the emerging results of Study 2. The original plan to obtain central confirmation of BRAFV600 status in 40 patients on Study 2 was not achieved because it was determined retrospectively that specimens from 3 patients were insufficient for analysis. However, during this meeting, you indicated that data from the central assessment of BRAF V600 mutational status from a total of 50 pediatric patients with HGG across Studies 1 and 2 combined is available, and assessment of concordance between local and central testing can be performed in these patients. This will provide a greater number of patients with centrally assessed mutational status across the two studies in the context of emerging data suggesting robust responses to dabrafenib in pediatric patients with HGG.

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 October 23, 2017, March 22 and May 14, 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

[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.

Amendment 5. Amendment 5 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 Studies 1 and 2.

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

**Study 1:** At least 48 patients, with at least 40 patients evaluable for response assessment.

Part I - At least 6 patients; additional recruitment will depend on the occurrence of dose-limiting toxicities.
Part II – At least 40 patients with at least 10 evaluable patients for each disease- specific expansion cohort (HGG, LGG, LCH).

**Study 2:** At least 40 patients.

~~Additional patients may be enrolled in Study 2 to ensure that there at least 40 patients with locally assessed and centrally confirmed BRAF V600 mutation and histologic Grades III & IV glioma by WHO criteria, and baseline measurable disease by Response Assessment in Neuro Oncology (RANO) that is confirmed by 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.

Across Studies 1 and 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).

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 October 23, 2017, March 22 and May 14, 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.

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):

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

- Complete Copy of Written Request as Amended (Clean Copy of the Amended WR Should Be Attached Here)

**ATTACHMENT 1**
**WRITTEN REQUEST (WR) – AMENDMENT 5**

These studies investigate the potential use of dabrafenib in the treatment of pediatric patients with relapsed or refractory solid tumors containing BRAF V600 activating mutations and in the treatment of adolescent patients with unresectable or metastatic melanoma containing BRAF V600 activating mutations.

Despite the improvements in survival observed in the last three decades as a result of the multidisciplinary approach applied overall to pediatric solid tumors, including brain tumors, the prognosis for patients with recurrent or metastatic disease remains poor.

Dabrafenib (Tafinlar®) is an oral kinase inhibitor with activity against some mutated forms of BRAF kinase. It was approved in 2012 as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Dabrafenib, in combination with trametinib, was subsequently approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test.

BRAF is a protein that mediates the RAS-RAF-MEK-ERK signaling pathway and is involved in a variety of cellular functions including cell proliferation, cell cycle arrest, terminal differentiation, and apoptosis. Multiple cancer-associated mutations have been identified in the BRAF gene, including the V600E activating mutation which has been identified at a high frequency in certain cancer types. While BRAF inhibition with dabrafenib has been associated with tumor response in adult patients with BRAF V600 mutant melanoma, it is not clear that a similar rate of response can be generalized across all BRAF V600 mutant tumor types. Children and adolescents with refractory solid tumors harboring the BRAF V600 mutation are a population with limited treatment options in which the safety and efficacy of dabrafenib should be evaluated. Pediatric cancers that express the BRAF V600 mutation in a subpopulation of patients include recurrent or advanced melanoma, Langerhans cell histiocytosis (LCH), low- and high-grade gliomas, and papillary thyroid cancer (PTC).

Melanoma in the pediatric population is rare; however, the incidence across all age groups continues to increase at a rate of approximately 2% per year in individuals less than 20 years of age. Although prepubescent patients appear to have different disease characteristics compared to adult melanoma patients (higher likelihood of predisposition syndromes, nodal metastases at diagnosis, nodular or spitzoid histology, thicker lesions and head/face/neck primaries), adolescents are comparable to adult patients with regard to key primary tumor characteristics (primary site, histology, stage at diagnosis, specific genetic mutations, thickness, and level of invasion). Additionally, survival in both the adult and pediatric populations is predicted by characteristics of the melanoma (e.g., primary site, histology, stage at diagnosis, thickness, and level of invasion) but not by age. This information supports extrapolation of tumor response data from adults with melanoma treated with dabrafenib to adolescent patients, if the systemic exposures achieved in adolescent patients are similar to that in adults.

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).

Other pediatric tumors that harbor BRAF V600 mutations include LCH and PTC. Although there are effective first-line local and systemic therapies for these conditions, patients with multiply recurrent or progressive disease after failing primary therapy have limited treatment options. These usually consist of further cytotoxic chemotherapy which has generally not been shown to impact survival, and in some cases of refractory LCH, allogeneic stem cell transplantation (SCT). Salvage cytotoxic chemotherapy regimens and SCT are associated with significant treatment-related morbidity and mortality. For the subgroup of patients with refractory BRAF V600 mutation positive disease, dabrafenib may offer an improved safety profile and therapeutic benefit.

Study 4 from the original WR was deleted as part of the second amendment to the WR. Deletion of Study 4 is justified because all tumor types characterized by the BRAF V600 mutation are currently being evaluated in the remaining studies in the present WR and in the trametinib WR.

In summary, dabrafenib has the potential to provide therapeutic benefit to pediatric patients with solid tumors with BRAF V600 activating mutations, which include unresectable or recurrent melanoma, LCH, low- and high-grade gliomas, and PTC. Efficacy in the subgroup of adolescent

patients (12 through 18 years) with unresectable or metastatic BRAF V600 mutation positive melanoma could be determined by extrapolation from results observed in adult patients treated with dabrafenib alone or in combination with trametinib for the same indication. Efficacy in pediatric patients less than 12 years of age with melanoma and in patients 12 months to $\leq$ 18 years of age with BRAF V600 mutation positive solid tumors other than melanoma cannot be extrapolated from adult data and will be determined by the studies outlined in the WR.

If there is encouraging antitumor activity observed with dabrafenib in initial studies, this WR additionally calls for evaluation of dabrafenib in combination with trametinib in patients with BRAF V600 mutation positive HGGs and LGGs. Based on adult studies of patients with BRAF V600-mutant melanoma and non-small cell lung cancer (NSCLC) showing that combination therapy with dabrafenib and trametinib results in increased tumor response rates and durability of responses in comparison with either single agent alone, it is reasonable to hypothesize that there may be increased clinical benefit with the combination regimen in pediatric patients with BRAF V600 mutation positive tumors. Additionally, preliminary and limited safety data for the combination of dabrafenib and trametinib in 12 pediatric patients suggests that the adverse event profile does not differ from that of pediatric patients receiving either agent alone. Specifically, there were no grade 4 or 5 events and no CNS bleeding events in these 12 patients.

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 to reasonably predict clinical benefit and can be used to assess efficacy in later studies.

FDA is not requesting studies in neonates because the occurrence of a refractory solid tumor with a BRAF V600E mutation in this population is rare. Additionally, based on nonclinical studies showing evidence of greater renal toxicity in rats less than 22 days old suggesting a higher risk for renal tubular injury for humans less than 12 months old, infants from birth up to 1 year of age will not be studied.

To obtain needed pediatric information on dabrafenib, 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.

Based on discussions with the sponsor, and in the setting of emerging data suggesting robust radiographic responses in patients with HGG, FDA issued Amendment 5. Amendment 5 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 Studies 1 and 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, single arm, two-part study of dabrafenib in pediatric patients with refractory BRAF V600 mutation positive solid tumors.

  - Part 1 will consist of a dose-escalation phase with a rolling six design to determine the recommended phase 2 dose (RP2D) of dabrafenib in specific age groups.
  - Part 2 will consist of an expansion phase in four disease-specific cohorts (BRAF V600 mutation positive HGG, LGG, LCH, and other refractory BRAF V600 mutated tumors) treated at the RP2D to further characterize pharmacokinetics (PK) and evaluate safety and preliminary efficacy of dabrafenib.

  **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 high grade glioma who have progressed after at least one line of therapy (Study 2 of the trametinib WR).

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

  - RP2D for combination therapy must be determined before initiating enrollment in Study 2.
  - A protocol, including a statistical analysis plan, for studies 2 and 3 must be submitted for FDA review and approval prior to initiating enrollment.

  Efficacy of dabrafenib alone or in combination with trametinib in adolescent patients (12 to less than 18 years of age) with unresectable or metastatic BRAF V600 mutation positive melanoma will be supported by extrapolation utilizing dabrafenib 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 BRAF V600 mutation positive melanoma treated with dabrafenib alone or in combination with trametinib.

- *Objectives of each study:*

  **Study 1**

  - To determine the optimal safe and tolerable dose(s) of dabrafenib that achieves similar exposures to those achieved in adults, for chronic dosing in pediatric patients with relapsed or refractory BRAF V600-mutation positive solid tumors.
  - To characterize the PK of dabrafenib in adolescent patients to support extrapolation of efficacy for the BRAF V600 mutation-positive unresectable or metastatic melanoma indication.
  - To assess preliminary single-agent anti-tumor activity of dabrafenib.
  - To assess the acceptability and palatability of the age-appropriate powder for oral

suspension formulation and the acceptability of the capsules.

**Study 2**

- To estimate the ORR and the response duration in pediatric patients with locally confirmed BRAF V600 mutation positive HGGs.
- 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.

- *Patients to be Studied:*

  - *Age group in which studies will be performed*:

    Studies 1, 2, and 3: Patients 1 to $\leq$ 18 years of age

  - *Number of patients to be studied:*

    **Study 1**: At least 48 patients, with at least 40 patients evaluable for response assessment.

    Part I - At least 6 patients; additional recruitment will depend on the occurrence of dose-limiting toxicities.

    Part II – At least 40 patients with at least 10 evaluable patients for each disease-specific expansion cohort (HGG, LGG, LCH).

    **Study 2**: At least 40 patients.

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

Across Studies 1 and 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).

Data from a sufficient number of adolescent patients evaluable for dabrafenib PK across all studies must be submitted to support extrapolation of efficacy of dabrafenib alone or in combination with trametinib in the treatment of adolescent patients with unresectable or metastatic BRAF V600 mutation positive melanoma.

*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 according to Response Criteria in Solid Tumors version 1.1 (RECIST 1.1) for solid tumors, RANO criteria for gliomas and response criteria for LCH as defined in the 2009 Histiocyte Society Evaluations and Treatment Guidelines**.**
    - Acceptability, including palatability, of the oral suspension as assessed by a palatability questionnaire.

    **Study 2**

    - Primary endpoint - ORR and duration of responses 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 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 endpoint for Study 1 is determination of the RP2D of dabrafenib in pediatric patients based on achievement of similar dabrafenib systemic exposures to those in adults or maximum tolerated dose (MTD) defined as the dose level below that which produces a dose limiting toxicity (DLT) in at least one third of evaluable patients during Cycle 1 of treatment, whichever occurs first.

- Safety outcomes for all studies must include a description of adverse events, including the incidence, severity, and clinical outcomes of all adverse events, and the incidence, severity, and clinical outcomes of severe, serious and fatal adverse events, vital signs, routine laboratory parameters, and growth parameters. In addition, effect on growth plates, and assessment of Tanner stages will be included in studies 2 and 3.

- The following known adverse events must be actively monitored: skin toxicity, ocular disorders, serious febrile reactions, hyperglycemia. For patients receiving dabrafenib in combination with trametinib, cardiac toxicity must also be monitored with routine electrocardiogram (ECG) and echocardiogram (ECHO) assessments.

- While there have been no CNS bleeding events in a limited number of pediatric patients treated with the combination of dabrafenib and trametinib, based on safety data from adult trials of this combination, bleeding events, including CNS bleeding, must be monitored and should be considered an adverse event of special interest.

- *Pharmacokinetic/Pharmacodynamic Endpoints*

  Estimated dabrafenib 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 8 patients in each of the following age groups: 1 to < 6 and 6 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:*

  BRAF inhibition can result in the development of, or acceleration of, actinic keratosis, keratoacanthomas and squamous cell carcinoma (SCC); therefore, a risk management plan for the potential occurrence of skin findings, including squamous cell carcinoma, will be utilized for pediatric patients, and will be based on what has been put into place for the adult clinical studies of dabrafenib. Specifically, 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. Skin photography of new non-melanoma skin lesions or non-melanoma lesions that change during the study will be obtained and requested to be forwarded to the Sponsor. Details regarding the lesion documentation by photography will be included in protocol procedure manuals.

  Dabrafenib can result in the development of uveitis, including iritis. Pediatric patients enrolled in dabrafenib studies will be monitored for visual signs and symptoms of uveitis including change in vision, photophobia, and eye pain. The study protocols will provide dose modification guidelines for ocular toxicity and instruct investigators to obtain ophthalmologic

specialty consultation for new ocular symptoms.

Dabrafenib treatment can result in serious febrile reactions and hyperglycemia. Standard vital sign and laboratory parameter monitoring will be included in all pediatric studies.

Additional safety concerns identified from clinical experience with dabrafenib in combination with trametinib include new primary malignancies, bleeding, venous thromboembolism, cardiomyopathy, ocular toxicities, skin toxicities, and interstitial pneumonitis. All patients enrolled in 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 mechanisms of action, both dabrafenib and trametinib can cause fetal harm when administered to a pregnant woman. Since dabrafenib can render hormonal contraceptives ineffective, female patients of reproductive potential will use effective non-hormonal methods of contraception during treatment and for four weeks after the last dose of single agent dabrafenib (Study 1), and during treatment and for four months after the last dose of trametinib (Study 2).

- *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:*

    capsule formulation for children able to swallow capsules, dispersible tablet, or powder for oral suspension formulations.

  - *route of administration:*

    oral

  - *regimen:*

    **Study 1***:* The starting total daily dose for dabrafenib is 3.0 mg/kg. Dose escalation will proceed based on toxicities observed during the first cycle of treatment and PK data.

**Studies 2 and 3:** Dabrafenib will be administered at the RP2D established in Study 1. Dabrafenib in combination with trametinib will be administered at the RP2D for the combination regimen established in Part C of Study MEK116540.

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**

  The primary endpoint will be defining the RP2D of dabrafenib in pediatric patients. This trial will use a Rolling Six dose-escalation design to evaluate the toxicity profile of dabrafenib.
  All statistics will be descriptive.

  **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 dabrafenib in the adolescent (12 to ≤ 18 years) age group with at least 80% power. Population PK analysis should be performed using dabrafenib concentration data obtained from all studies. Effect of age and body size on dabrafenib 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 dabrafenib 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/FormsSubmissionRequire ments/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 trametinib 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.

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**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.**

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/s/

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GREGORY H REAMAN
02/16/2022 12:45:56 PM