NDA 209092
IND 152691

WRITTEN REQUEST – AMENDMENT 1

Novartis Pharmaceuticals Corporation
Attention: Colin Vechery, PharmD
Global Program Regulatory Director
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Vechery:[1]

Please refer to your correspondence dated March 19, 2024, requesting changes to FDA's February 16, 2022, Written Request for pediatric studies for Kisqali (ribociclib).

The changes you proposed are in reference to the regimen under Drug Information incorporating the revisions to specify that the dosage of ribociclib in combination with topotecan and temozolimide will be determined by the outcome of Phase 1-Part A of the study. Additionally, we made a few minor editorial edits.

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 February 16, 2022, as amended by this letter must be submitted to the Agency on or before December 14, 2029, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) / 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:

[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.

- 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- the status of the application (i.e., withdrawn after the supplement has been filed or pending);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, contact Jacqueline Glen, Regulatory Project Manager, at (240) 402-9558 or Jacqueline.Glen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
- Complete Copy of Written Request as Amended, with Changes Marked
- Complete Copy of Written Request as Amended

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

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Dear Dr. Vechery:

Please refer to your correspondence dated March 19, 2024, requesting changes to FDA's February 16, 2022, Written Request for pediatric studies for Kisqali (ribociclib).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on February 16, 2022, remain the same. (Text added is underlined. Text deleted is strikethrough.)

This study investigates the potential use of ribociclib in the treatment of patients with relapsed or refractory neuroblastoma and other solid tumors.

BACKGROUND:

Neuroblastoma (NB) is the third most common childhood malignancy and is the most common extracranial solid tumor in childhood and the principal cause of death due to cancer in infancy. More than 1200 cases/year are diagnosed in the United States (U.S.) and Europe. The tumors often arise in tissues of the sympathetic nervous system, typically in the adrenal medulla or para-spinal ganglia, and spread to other areas including the abdomen, chest, bone or bone marrow. Patients with neuroblastoma exhibit or present with extremely heterogeneous clinical courses. The most frequent signs and symptoms are caused by tumor mass and metastases, including abdominal distention, decreased appetite, weight loss, bone pain, leg weakness or difficulty walking, fever, hypertension, and irritability. Neuroblastoma is classified into three risk groups (low, intermediate and high) depending on age, extent of disease, histology and cytogenetic abnormalities. Around 50% are high-risk neuroblastoma (HR-NB), defined as unresectable or metastatic tumors with amplification of the MYCN oncogene in any age group, or those age over 18 months with metastatic disease.

Key treatment options for patients with relapsed or refractory neuroblastoma comprise surgery and/or radiotherapy, salvage chemotherapy, 131I-MIBG therapy, and immunotherapeutic agents. However, these interventions are associated with long- and

short-term toxicities. Five-year overall survival (OS) for patients with relapsed or refractory high-risk neuroblastoma is less than 20%.

Additionally, relapsed or refractory solid tumors other than NB will be studied in Phase 1 Part A and B, including Medulloblastoma (MB), High Grade Glioma (HGG), Malignant Rhabdoid Tumor (MRT), and Rhabdomyosarcoma (RMS), which will be assessed to determine the activity of ribociclib and guide potential further evaluation.
MB is the most common malignant brain tumor in children, accounting for around a quarter of primary central nervous system (CNS) neoplasms and around half of all posterior fossa tumors. In the U.S., approximately 250 new patients are diagnosed annually. The majority of MB arise in children, with a median age of 9 years, and a peak in incidence between the ages of 3 and 7 years. While the overall cure rate is around 70%, patients with high-risk disease continue to have poor outcome and experience long-term morbidity. With aggressive surgery, craniospinal radiotherapy, and chemotherapy, the 5-year survival rate is about 30-60% with high-risk disease. Treatments for recurrent childhood MB include surgery to remove the tumor as possible, radiation therapy especially in patients who previously received radiation and chemotherapy, and chemotherapy. Chemotherapies with cisplatin- or topotecan-containing regimens given during and after radiation therapy are the available standard treatment for older children, but only 20% to 40% of children younger than 3-4 years have non-disseminated medulloblastoma. However, these multi-agent cytotoxic chemotherapies are associated with significant long-term toxicities (e.g., neurocognitive impairment) in surviving patients. Therefore, participating in a clinical trial for a novel therapy that may offer improved efficacy with a better safety profile is an option for these patients.

HGG accounts for 3-7% of all childhood brain tumors. These tumors (Grades III and IV per WHO classification of brain tumors) arise from cells within the glial lineage. It is a histologically heterogeneous group of tumors, and the most common histologic subtypes are anaplastic oligodendroglioma (AO), anaplastic astrocytoma (AA), and glioblastoma multiforme (GBM). The reported age-adjusted incidence of 0.26 per 100,000 population is likely an underestimate.

Current therapies for children with relapsed or refractory HGGs are limited. Independent of other known prognostic factors, such as age, tumor location and histology, the extent of surgical resection is one of the strongest predictors of survival in children with HGG. Given the infiltrative nature of HGGs, there is high likelihood of local recurrence. Thus for older children (>3 years of age), adjuvant radiotherapy to the tumor bed and surrounding margin has become a standard. Among younger patients (<3 years of age), radiotherapy is generally not used due to its substantial neurocognitive toxicity. These patients are often treated with radiation-sparing approaches such as chemotherapy alone. Multiple trials have also been conducted in pediatric patients with HGGs utilizing biologic agents in combination with focal radiotherapy, but none have demonstrated a benefit in overall survival (OS).

Long-term outcomes are poor despite aggressive multimodality therapy. Temozolomide is most often used in the recurrent disease setting. However, in 5 trials evaluating temozolomide monotherapy or temozolomide-based combinations, the ORR in recurrent or refractory pediatric HGG ranged from 0-12%. Treatment for patients with relapsed, refractory, and resistant HGGs remains a significant unmet need. Therefore, evaluations of new agents/treatment regimens in clinical trial setting are needed.

Malignant Rhabdoid Tumors (MRT) are extremely aggressive malignancies that generally occur in infants and young children. The most common locations are in the kidney and CNS, although they can arise in most soft-tissue sites. The incidence rate of MRT is about 1 per million children per year. These tumors have no standard or effective therapeutic regimens. Most patients receive intensive multimodality treatment, including surgery, radiotherapy, chemotherapy, and sometimes high-dose chemotherapy with stem-cell rescue. Despite this aggressive approach, prognosis for children with MRT is poor. Mean survival with surgical intervention alone is 3 months and with adjuvant chemotherapy and radiotherapy is 8 months. For MRT that was not surgically removed, chemotherapy is indicated. It may include vincristine, actinomycin, and doxorubicin with or without cyclophosphamide. With these agents, the estimated survival rate for patients with MRT was only 23%. Therefore, the development of new strategies with improved effectiveness and less toxicity burden and with more targeted drugs is warranted.

Rhabdomyosarcoma (RMS) is a malignancy arising from soft tissue of mesenchymal origin. It accounts for approximately 3.5% of the cases of cancer among children aged 0 to 14 years, and 2% of the cases among adolescents and young adults aged 15 to 19 years. The incidence is 4.5 cases per 1 million children, about 350 cases per year. The histologic subtypes of rhabdomyosarcoma include embryonal, alveolar, and other mixed types. Most common primary sites of RMS are genitourinary tract (31%), head and neck (25%), and extremities (~13%). The disease is usually curable in children with localized disease who receive combined-modality therapy, with >70% of patients surviving 5 years after diagnosis. However, relapses are common among patients with unresectable disease in an unfavorable site at diagnosis or who have metastatic disease at diagnosis.

All children with RMS require multimodality therapy with systemic chemotherapy, with a consideration of surgery and/or radiation therapy. The intensity and duration of the chemotherapy are dependent on the risk group assignment. For progressive or recurrent childhood RMS, the selection of further treatment depends on many factors, including the site(s) of progression or recurrence, previous treatment, and the individual patient's overall disease condition. Chemotherapy regimens to treat progressive or recurrent rhabdomyosarcoma include carboplatin/etoposide, isosfamide/carboplatin/etoposide, cyclophosphamide/topotecan, gemcitabine/docetaxel, topotecan/vincristine/doxorubicin, vincristine/irinotecan/temozolomide,

vinorelbine/cyclophosphamide ± sirolimus, etc. Additionally, treatment options with new agents are under investigation in clinical trials.

Ribociclib is a small molecule inhibitor of cyclin-dependent kinase 4 (CDK4) and CDK6. Ribociclib is approved in the U.S. for the following indications:

- In combination with an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; and
- In combination with fulvestrant, for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy or following disease progression on endocrine therapy.

Preclinical data suggest that multiple pediatric tumors harbor genetic alterations in cyclin pathway genes. Cyclin D1 and CDK4 are over-expressed in neuroblastoma cell lines and xenograft models suggest CDK inhibitors alone and in combination with other chemotherapeutic agents (including temozolomide and topotecan) have anti-tumor effects.

Data from Study CLEE011X2102 (NCT 01747876) and Study ESMART (NCT 02813135) provide initial information regarding the safety and antitumor activity of ribociclib as a single agent and in combination with topotecan and temozolomide. Study CLEE011X2102 was a multicenter dose escalation study conducted in 32 pediatric patients in with solid tumors including neuroblastoma, malignant rhabdoid tumors, rhabdomyosarcoma and anaplastic meningioma. The maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) for ribociclib were 470 mg/m2 orally once daily and 350 mg/m2 orally once daily, respectively, on Days 1-21 of a 28-day cycle. Of 15 patients with neuroblastoma, 7 had stable disease.
Study ESMART (NCT 02813135) was a multi-center activity-estimating study of ribociclib in combination with topotecan and temozolomide (TOTEM; temozolomide 100 mg/m2 once daily + topotecan at 0.50 mg/m2 once daily on Days 1-5), followed by ribociclib orally once daily on Days 6-21 of a 28-day cycle, in pediatric patients with advanced solid tumors. The pediatric RP2D for the TOTEM combination was temozolomide 150 mg/m2 PO once daily followed by topotecan at 0.75 mg/m2 IV once daily for 5 consecutive days (Days 1-5) of a 28-day cycle. Of 14 evaluable patients, 2 had stable disease.

Additional studies with ribociclib and TOTEM are warranted to further investigate potential antitumor activity in patients with advanced solid tumors. Studies in neonates and patients <1 year old will not be included due to extremely low incidence of patients under 1 year of age that have relapsed or refractory solid tumors.

To obtain needed pediatric information on ribociclib, 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 study described below.

In the setting of identification of dose-limiting toxicities in the first two cohorts of the dose-escalation part of Study 1 (Phase 1 - Part A) evaluating the combination regimen of ribociclib, topotecan, and temozolomide, FDA issued Amendment 1 to incorporate revisions to specify that the dosage of ribociclib in combination with topotecan and temozolomide will be determined by the outcome of Phase 1 - Part A of the study.

- *Nonclinical study(ies)*

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

- *Clinical study:*

  Study 1: Phase I/II multicenter study to assess efficacy and safety of ribociclib (LEE011) in combination with topotecan and temozolomide (TOTEM) in pediatric patients with relapsed or refractory neuroblastoma and other solid tumors

  Phase I - Part A is the dose finding part of the Phase I/II study in patients with relapsed or refractory (R/R) Neuroblastoma (NB) and other solid tumors (including Medulloblastoma [MB], High Grade Glioma [HGG], Malignant Rhabdoid Tumor [MRT], and Rhabdomyosarcoma [RMS]), to determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of ribociclib (LEE011) in combination with topotecan and temozolomide (TOTEM).

  Phase I - Part B is the cohort expansion part of the Phase I/II study with multiple expansion cohorts to assess the antitumor activity and safety of ribociclib (LEE011) in combination with topotecan and temozolomide (TOTEM) in patients with R/R NB (cohort 1), MB (cohort 2), HGG (cohort 3), MRT (cohort 4), and RMS (cohort 5).

  The Phase II part of the Phase I/II study will be a multi-center, two-arm, randomized, double blinded, placebo-controlled parallel group trial in patients 12 months to ≤ 21 years of age in R/R NB. Specific tumor type(s) to be studied outside of neuroblastoma will be selected based on the results and enrollment of Study 1 (Phase 1- Part A and Phase 1- Part B) and will be mutually agreed upon by FDA and Novartis prior to initiation.

- *Study Objectives:*

Phase I, Part A

- Primary objective: to determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of ribociclib in combination with topotecan and temozolomide (TOTEM)

- Secondary objectives:
  - to characterize the safety and tolerability of ribociclib in combination with TOTEM
  - to characterize the PK of ribociclib in combination with topotecan and temozolomide (TOTEM)

Phase I, Part B

- Primary objective: to evaluate antitumor activity in NB and 4 other solid tumors (MB, HGG, MRT, and RMS) as assessed by Overall Response Rate (ORR) of ribociclib in combination with TOTEM

- Secondary objectives:
  - to assess the treatment effect of ribociclib in combination with TOTEM as assessed by Duration of Response (DOR), Progression Free Survival (PFS) and Overall Survival (OS) versus placebo plus TOTEM
  - to characterize the safety and tolerability of ribociclib in combination with TOTEM
  - to characterize the PK of ribociclib in combination with TOTEM

Phase II

- Primary objective: to evaluate the treatment effect as assessed by Overall Response Rate (ORR) of ribociclib in combination with TOTEM versus placebo plus TOTEM

- Key secondary objectives:
  - to assess the treatment effect of ribociclib in combination with TOTEM as assessed by Progression Free Survival (PFS) versus placebo plus TOTEM
  - to assess the treatment effect of ribociclib in combination with TOTEM as assessed by Duration of Response (DOR) versus placebo plus TOTEM

- Other secondary objectives:
  - to assess the treatment effect of ribociclib in

combination with TOTEM as assessed by Overall Survival (OS) versus placebo plus TOTEM
- to characterize the safety and tolerability of ribociclib in combination with TOTEM
- to characterize the PK of ribociclib, topotecan and/or temozolomide

- *Patients to be studied:*
  - *Age group in which study will be performed:*
    12 months – 21 years old
  - Number of patients to be studied:
    Phase I, Part A: At least 18 patients with R/R solid tumors

    Phase I, Part B: Patient numbers per cohort are provided in the table below. Stage 1 is a futility gate to continue to Stage 2.

Table-1 Phase I – Part B- Sample Size and Decision rules for expansion cohorts

Tumor Indication	ORR (Historical Controls)	Stage 1 (Interim Futility)		Stage 2		Response Criteria
		Minimum sample size	Minimum no. of responders*	Minimum sample size	Minimum no. of responders	
Neuroblastoma	15%	NA	NA	20	6 (30%)	INRC
Medulloblastoma	30%	10	4 (40%)	28	13 (46%)	RECIST v1.1
High Grade Glioma	10%	10	2 (20%)	20	5 (25%)	RANO
Malignant rhabdoid tumors	10%	10	2 (20%)	20	5 (25%)	RECIST v1.1
Rhabdomyosarcoma	30%	10	4 (40%)	28	13 (46%)	RECIST v1.1

*Refers to the minimum number of responsders needed to proceed to Stage 2. If the minimum number of responders for a given cohort is not reached at the time of the interim analysis, no additional patients will be enrolled to that cohort.

The PK parameters of ribociclib (i.e., AUC, Cmax, clearance) will be determined with dense sampling obtained from a minimum number of patients in each of the following age groups across the entire pediatric development program: 6 patients per age group, 12 months to 6 years of age, and between 6 to < 12 years of age. PK evaluation will be included for all enrolled patients 12 years of age and older.

Sparse PK sampling will be obtained for ribociclib throughout the treatment period in all ribociclib-treated patients during Phase 1 and Phase 2 of the proposed study. This PK data can be supportive of exposure response analysis and PopPK analysis with pooled data from completed and ongoing clinical studies. Samples will be obtained from a minimum number of patients in each of the following age groups across the entire pediatric development program: 6 patients per age group, 12 months to 6 years of age, and between 6 to < 12 years of age.

Data will be pooled from all phases of Study 1 to conduct population PK analysis (i.e., assess the effect of body weight and age on Ribociclib PK) and exposure- response analyses for measures of efficacy/activity, safety, and pharmacodynamic biomarkers as the data allow.

Phase II: A minimum of 97 patients will be randomized in the two treatment arms in a 2:1 ratio (approximately 32 patients in placebo + TOTEM arm, and approximately 65 patients in ribociclib + TOTEM arm)

- *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. Provide details of the planned strategy to ensure appropriate distribution of ethnic and racial groups. 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:*
  Phase I part A:
  - Primary Endpoint: Incidence of Dose Limiting Toxicities (DLTs) in Cycle 1
  - Secondary Endpoints: Plasma concentrations of ribociclib and derived PK parameters such as AUC, Cmax, Tmax

- *Efficacy endpoints*
  Phase I part B
  - Primary Endpoint: Confirmed ORR as assessed by Blinded Independent Review Committee (BIRC) using the International Neuroblastoma Response Criteria (INRC) for the neuroblastoma cohort, Response Assessment in Neuro-Oncology (RANO) for the

HGG cohort, and Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) for MB, MRT, and RMS cohorts
- Secondary Endpoints: DOR, and PFS using tumor-specific response criteria, as assessed by BIRC assessment, and OS

Phase II ~~part~~:
- Primary Endpoint: Confirmed ORR as assessed by BIRC using INRC
- Key Secondary Endpoints: DOR as assessed by BICR using INRC, and PFS as assessed by BICR using INRC
- Other Secondary Endpoints: OS

- *Safety endpoints*
  For all study parts:
  - Incidence, type, and severity of adverse events per CTCAE v5.0
  - Tolerability: dose interruptions, reductions, dose intensity, and duration of exposure for all treatment components

- A Study Steering Committee (SCC) that will include some independent members who are not sponsor representatives or trial investigators will oversee conduct of the Phase 1 portion. An independent Data Monitoring Committee (IDMC) will be utilized for the Phase II portion of the trial. Both committees will comply with the recommendations in FDA's Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees https://www.fda.gov/media/75398/download.

- *Known drug safety concerns and monitoring:* Known drug safety concerns for which monitoring will be conducted in this study design include neutropenia, Hepatobiliary Toxicity, QT Interval Prolongation, and Interstitial Lung Disease/Pneumonitis

- *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:* Age-appropriate oral liquid dosage form. (b) (4)

[redacted] (b) (4)

- *Route of administration:* Oral- Ribociclib and Temozolomide; IV- Topotecan

- *Regimen:* ~~Ribociclib in combination with topotecan and temozolimide~~The d~~D~~os~~e~~age of ribociclib in combination with topotecan and temozolomide ~~to~~ will be determined by ~~the outcome of~~ results of Phase 1 - Part A of the study.

  - ~~Topotecan (0.75 mg/m^2/day IV on Days 1-5)~~
  - ~~Temozolomide (150 mg/m^2/day PO on Days 1-5)~~
  - ~~Ribociclib (provisional doses 200 [starting dose], 280, and 350 mg/m^2/day PO on Days 1 – 21 in a 28 day cycle).~~

  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 prepared 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 preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

The relative bioavailability of any formulation used in the studies and the effect of food on bioavailability must be characterized. The relative bioavailability and food effect studies comparing the approved drug to the age-appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:* For the Phase I part A, an adaptive Bayesian Logistic Regression Model (BLRM) guided by the Escalate with overdose control (EWOC) principle will guide the dose escalation of the combination treatment to its MTD/RP2D. For the Phase I part B and the Phase II, the Statistical analysis plan will be agreed upon as part of the protocol review by FDA.

- *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 ribociclib 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.[1] You are encouraged to contact the reviewing Division for further guidance.

For studies started after December 17, 2017, study data must 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 December 2029. 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

[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
[2] https://www.fda.gov/media/154109/download

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.

Reports of the studies that meet the terms of the Written Request dated February 16, 2022, as amended by this letter must be submitted to the Agency on or before December 14, 2029, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) / 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);
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FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[3]

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

If you have any questions, contact Jacqueline Glen, Regulatory Project Manager, at (240) 402-9558 or Jacqueline.Glen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

NDA 209092
IND 152691

WRITTEN REQUEST – AMENDMENT 1

Novartis Pharmaceuticals Corporation
Attention: Colin Vechery, PharmD
Global Program Regulatory Director
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Vechery:

Please refer to your correspondence dated March 19, 2024, requesting changes to FDA's February 16, 2022, Written Request for pediatric studies for Kisqali (ribociclib).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on February 16, 2022, remain the same.

This study investigates the potential use of ribociclib in the treatment of patients with relapsed or refractory neuroblastoma and other solid tumors.

BACKGROUND:

Neuroblastoma (NB) is the third most common childhood malignancy and is the most common extracranial solid tumor in childhood and the principal cause of death due to cancer in infancy. More than 1200 cases/year are diagnosed in the United States (U.S.) and Europe. The tumors often arise in tissues of the sympathetic nervous system, typically in the adrenal medulla or para-spinal ganglia, and spread to other areas including the abdomen, chest, bone or bone marrow. Patients with neuroblastoma exhibit or present with extremely heterogeneous clinical courses. The most frequent signs and symptoms are caused by tumor mass and metastases, including abdominal distention, decreased appetite, weight loss, bone pain, leg weakness or difficulty walking, fever, hypertension, and irritability. Neuroblastoma is classified into three risk groups (low, intermediate and high) depending on age, extent of disease, histology and cytogenetic abnormalities. Around 50% are high-risk neuroblastoma (HR-NB), defined as unresectable or metastatic tumors with amplification of the MYCN oncogene in any age group, or those age over 18 months with metastatic disease.

Key treatment options for patients with relapsed or refractory neuroblastoma comprise surgery and/or radiotherapy, salvage chemotherapy, 131I-MIBG therapy, and immunotherapeutic agents. However, these interventions are associated with long- and

short-term toxicities. Five-year overall survival (OS) for patients with relapsed or refractory high-risk neuroblastoma is less than 20%.

Additionally, relapsed or refractory solid tumors other than NB will be studied in Phase 1 Part A and B, including Medulloblastoma (MB), High Grade Glioma (HGG), Malignant Rhabdoid Tumor (MRT), and Rhabdomyosarcoma (RMS), which will be assessed to determine the activity of ribociclib and guide potential further evaluation.
MB is the most common malignant brain tumor in children, accounting for around a quarter of primary central nervous system (CNS) neoplasms and around half of all posterior fossa tumors. In the U.S., approximately 250 new patients are diagnosed annually. The majority of MB arise in children, with a median age of 9 years, and a peak in incidence between the ages of 3 and 7 years. While the overall cure rate is around 70%, patients with high-risk disease continue to have poor outcome and experience long-term morbidity. With aggressive surgery, craniospinal radiotherapy, and chemotherapy, the 5-year survival rate is about 30-60% with high-risk disease. Treatments for recurrent childhood MB include surgery to remove the tumor as possible, radiation therapy especially in patients who previously received radiation and chemotherapy, and chemotherapy. Chemotherapies with cisplatin- or topotecan-containing regimens given during and after radiation therapy are the available standard treatment for older children, but only 20% to 40% of children younger than 3-4 years have non-disseminated medulloblastoma. However, these multi-agent cytotoxic chemotherapies are associated with significant long-term toxicities (e.g., neurocognitive impairment) in surviving patients. Therefore, participating in a clinical trial for a novel therapy that may offer improved efficacy with a better safety profile is an option for these patients.

HGG accounts for 3-7% of all childhood brain tumors. These tumors (Grades III and IV per WHO classification of brain tumors) arise from cells within the glial lineage. It is a histologically heterogeneous group of tumors, and the most common histologic subtypes are anaplastic oligodendroglioma (AO), anaplastic astrocytoma (AA), and glioblastoma multiforme (GBM). The reported age-adjusted incidence of 0.26 per 100,000 population is likely an underestimate.

Current therapies for children with relapsed or refractory HGGs are limited. Independent of other known prognostic factors, such as age, tumor location and histology, the extent of surgical resection is one of the strongest predictors of survival in children with HGG. Given the infiltrative nature of HGGs, there is high likelihood of local recurrence. Thus for older children (>3 years of age), adjuvant radiotherapy to the tumor bed and surrounding margin has become a standard. Among younger patients (<3 years of age), radiotherapy is generally not used due to its substantial neurocognitive toxicity. These patients are often treated with radiation-sparing approaches such as chemotherapy alone. Multiple trials have also been conducted in pediatric patients with HGGs utilizing biologic agents in combination with focal radiotherapy, but none have demonstrated a benefit in overall survival (OS).

Long-term outcomes are poor despite aggressive multimodality therapy. Temozolomide is most often used in the recurrent disease setting. However, in 5 trials evaluating temozolomide monotherapy or temozolomide-based combinations, the ORR in recurrent or refractory pediatric HGG ranged from 0-12%. Treatment for patients with relapsed, refractory, and resistant HGGs remains a significant unmet need. Therefore, evaluations of new agents/treatment regimens in clinical trial setting are needed.

Malignant Rhabdoid Tumors (MRT) are extremely aggressive malignancies that generally occur in infants and young children. The most common locations are in the kidney and CNS, although they can arise in most soft-tissue sites. The incidence rate of MRT is about 1 per million children per year. These tumors have no standard or effective therapeutic regimens. Most patients receive intensive multimodality treatment, including surgery, radiotherapy, chemotherapy, and sometimes high-dose chemotherapy with stem-cell rescue. Despite this aggressive approach, prognosis for children with MRT is poor. Mean survival with surgical intervention alone is 3 months and with adjuvant chemotherapy and radiotherapy is 8 months. For MRT that was not surgically removed, chemotherapy is indicated. It may include vincristine, actinomycin, and doxorubicin with or without cyclophosphamide. With these agents, the estimated survival rate for patients with MRT was only 23%. Therefore, the development of new strategies with improved effectiveness and less toxicity burden and with more targeted drugs is warranted.

Rhabdomyosarcoma (RMS) is a malignancy arising from soft tissue of mesenchymal origin. It accounts for approximately 3.5% of the cases of cancer among children aged 0 to 14 years, and 2% of the cases among adolescents and young adults aged 15 to 19 years. The incidence is 4.5 cases per 1 million children, about 350 cases per year. The histologic subtypes of rhabdomyosarcoma include embryonal, alveolar, and other mixed types. Most common primary sites of RMS are genitourinary tract (31%), head and neck (25%), and extremities (~13%). The disease is usually curable in children with localized disease who receive combined-modality therapy, with >70% of patients surviving 5 years after diagnosis. However, relapses are common among patients with unresectable disease in an unfavorable site at diagnosis or who have metastatic disease at diagnosis.

All children with RMS require multimodality therapy with systemic chemotherapy, with a consideration of surgery and/or radiation therapy. The intensity and duration of the chemotherapy are dependent on the risk group assignment. For progressive or recurrent childhood RMS, the selection of further treatment depends on many factors, including the site(s) of progression or recurrence, previous treatment, and the individual patient's overall disease condition. Chemotherapy regimens to treat progressive or recurrent rhabdomyosarcoma include carboplatin/etoposide, isosfamide/carboplatin/etoposide, cyclophosphamide/topotecan, gemcitabine/docetaxel, topotecan/vincristine/doxorubicin, vincristine/irinotecan/temozolomide,

vinorelbine/cyclophosphamide ± sirolimus, etc. Additionally, treatment options with new agents are under investigation in clinical trials.

Ribociclib is a small molecule inhibitor of cyclin-dependent kinase 4 (CDK4) and CDK6. Ribociclib is approved in the U.S. for the following indications:

- In combination with an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; and
- In combination with fulvestrant, for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy or following disease progression on endocrine therapy.

Preclinical data suggest that multiple pediatric tumors harbor genetic alterations in cyclin pathway genes. Cyclin D1 and CDK4 are over-expressed in neuroblastoma cell lines and xenograft models suggest CDK inhibitors alone and in combination with other chemotherapeutic agents (including temozolomide and topotecan) have anti-tumor effects.

Data from Study CLEE011X2102 (NCT 01747876) and Study ESMART (NCT 02813135) provide initial information regarding the safety and antitumor activity of ribociclib as a single agent and in combination with topotecan and temozolomide. Study CLEE011X2102 was a multicenter dose escalation study conducted in 32 pediatric patients in with solid tumors including neuroblastoma, malignant rhabdoid tumors, rhabdomyosarcoma and anaplastic meningioma. The maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) for ribociclib were 470 mg/m2 orally once daily and 350 mg/m2 orally once daily, respectively, on Days 1-21 of a 28-day cycle. Of 15 patients with neuroblastoma, 7 had stable disease.
Study ESMART (NCT 02813135) was a multi-center activity-estimating study of ribociclib in combination with topotecan and temozolomide (TOTEM; temozolomide 100 mg/m2 once daily + topotecan at 0.50 mg/m2 once daily on Days 1-5), followed by ribociclib orally once daily on Days 6-21 of a 28-day cycle, in pediatric patients with advanced solid tumors. The pediatric RP2D for the TOTEM combination was temozolomide 150 mg/m2 PO once daily followed by topotecan at 0.75 mg/m2 IV once daily for 5 consecutive days (Days 1-5) of a 28-day cycle. Of 14 evaluable patients, 2 had stable disease.

Additional studies with ribociclib and TOTEM are warranted to further investigate potential antitumor activity in patients with advanced solid tumors. Studies in neonates and patients <1 year old will not be included due to extremely low incidence of patients under 1 year of age that have relapsed or refractory solid tumors.

To obtain needed pediatric information on ribociclib, 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 study described below.

In the setting of identification of dose-limiting toxicities in the first two cohorts of the dose-escalation part of Study 1 (Phase 1 - Part A) evaluating the combination regimen of ribociclib, topotecan, and temozolomide, FDA issued Amendment 1 to incorporate revisions to specify that the dosage of ribociclib in combination with topotecan and temozolomide will be determined by the outcome of Phase 1 - Part A of the study.

- *Nonclinical study(ies)*

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

- *Clinical study:*

  Study 1: Phase I/II multicenter study to assess efficacy and safety of ribociclib (LEE011) in combination with topotecan and temozolomide (TOTEM) in pediatric patients with relapsed or refractory neuroblastoma and other solid tumors

  Phase I - Part A is the dose finding part of the Phase I/II study in patients with relapsed or refractory (R/R) Neuroblastoma (NB) and other solid tumors (including Medulloblastoma [MB], High Grade Glioma [HGG], Malignant Rhabdoid Tumor [MRT], and Rhabdomyosarcoma [RMS]), to determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of ribociclib (LEE011) in combination with topotecan and temozolomide (TOTEM).

  Phase I - Part B is the cohort expansion part of the Phase I/II study with multiple expansion cohorts to assess the antitumor activity and safety of ribociclib (LEE011) in combination with topotecan and temozolomide (TOTEM) in patients with R/R NB (cohort 1), MB (cohort 2), HGG (cohort 3), MRT (cohort 4), and RMS (cohort 5).

  The Phase II part of the Phase I/II study will be a multi-center, two-arm, randomized, double blinded, placebo-controlled parallel group trial in patients 12 months to ≤ 21 years of age in R/R NB. Specific tumor type(s) to be studied outside of neuroblastoma will be selected based on the results and enrollment of Study 1 (Phase 1- Part A and Phase 1- Part B) and will be mutually agreed upon by FDA and Novartis prior to initiation.

- *Study Objectives:*

Phase I, Part A

- Primary objective: to determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of ribociclib in combination with topotecan and temozolomide (TOTEM)

- Secondary objectives:
  - to characterize the safety and tolerability of ribociclib in combination with TOTEM
  - to characterize the PK of ribociclib in combination with topotecan and temozolomide (TOTEM)

Phase I, Part B

- Primary objective: to evaluate antitumor activity in NB and 4 other solid tumors (MB, HGG, MRT, and RMS) as assessed by Overall Response Rate (ORR) of ribociclib in combination with TOTEM

- Secondary objectives:
  - to assess the treatment effect of ribociclib in combination with TOTEM as assessed by Duration of Response (DOR), Progression Free Survival (PFS) and Overall Survival (OS) versus placebo plus TOTEM
  - to characterize the safety and tolerability of ribociclib in combination with TOTEM
  - to characterize the PK of ribociclib in combination with TOTEM

Phase II

- Primary objective: to evaluate the treatment effect as assessed by Overall Response Rate (ORR) of ribociclib in combination with TOTEM versus placebo plus TOTEM

- Key secondary objectives:
  - to assess the treatment effect of ribociclib in combination with TOTEM as assessed by Progression Free Survival (PFS) versus placebo plus TOTEM
  - to assess the treatment effect of ribociclib in combination with TOTEM as assessed by Duration of Response (DOR) versus placebo plus TOTEM

- Other secondary objectives:
  - to assess the treatment effect of ribociclib in

combination with TOTEM as assessed by Overall Survival (OS) versus placebo plus TOTEM
- to characterize the safety and tolerability of ribociclib in combination with TOTEM
- to characterize the PK of ribociclib, topotecan and/or temozolomide

- *Patients to be studied:*
  - *Age group in which study will be performed:*
    12 months – 21 years old
  - Number of patients to be studied:
    Phase I, Part A: At least 18 patients with R/R solid tumors

    Phase I, Part B: Patient numbers per cohort are provided in the table below. Stage 1 is a futility gate to continue to Stage 2.

Table-1 Phase I – Part B- Sample Size and Decision rules for expansion cohorts

Tumor Indication	ORR (Historical Controls)	Stage 1 (Interim Futility)		Stage 2		Response Criteria
		Minimum sample size	Minimum no. of responders*	Minimum sample size	Minimum no. of responders	
Neuroblastoma	15%	NA	NA	20	6 (30%)	INRC
Medulloblastoma	30%	10	4 (40%)	28	13 (46%)	RECIST v1.1
High Grade Glioma	10%	10	2 (20%)	20	5 (25%)	RANO
Malignant rhabdoid tumors	10%	10	2 (20%)	20	5 (25%)	RECIST v1.1
Rhabdomyosarcoma	30%	10	4 (40%)	28	13 (46%)	RECIST v1.1

*Refers to the minimum number of responsders needed to proceed to Stage 2. If the minimum number of responders for a given cohort is not reached at the time of the interim analysis, no additional patients will be enrolled to that cohort.

The PK parameters of ribociclib (i.e., AUC, Cmax, clearance) will be determined with dense sampling obtained from a minimum number of patients in each of the following age groups across the entire pediatric development program: 6 patients per age group, 12 months to 6 years of age, and between 6 to < 12 years of age. PK evaluation will be included for all enrolled patients 12 years of age and older.

Sparse PK sampling will be obtained for ribociclib throughout the treatment period in all ribociclib-treated patients during Phase 1 and Phase 2 of the proposed study. This PK data can be supportive of exposure response analysis and PopPK analysis with pooled data from completed and ongoing clinical studies. Samples will be obtained from a minimum number of patients in each of the following age groups across the entire pediatric development program: 6 patients per age group, 12 months to 6 years of age, and between 6 to < 12 years of age.

Data will be pooled from all phases of Study 1 to conduct population PK analysis (i.e., assess the effect of body weight and age on Ribociclib PK) and exposure- response analyses for measures of efficacy/activity, safety, and pharmacodynamic biomarkers as the data allow.

Phase II: A minimum of 97 patients will be randomized in the two treatment arms in a 2:1 ratio (approximately 32 patients in placebo + TOTEM arm, and approximately 65 patients in ribociclib + TOTEM arm)

- *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. Provide details of the planned strategy to ensure appropriate distribution of ethnic and racial groups. 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:*
  Phase I part A:
  - Primary Endpoint: Incidence of Dose Limiting Toxicities (DLTs) in Cycle 1
  - Secondary Endpoints: Plasma concentrations of ribociclib and derived PK parameters such as AUC, Cmax, Tmax

- *Efficacy endpoints*
  Phase I part B
  - Primary Endpoint: Confirmed ORR as assessed by Blinded Independent Review Committee (BIRC) using the International Neuroblastoma Response Criteria (INRC) for the neuroblastoma cohort, Response Assessment in Neuro-Oncology (RANO) for the

HGG cohort, and Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) for MB, MRT, and RMS cohorts
- Secondary Endpoints: DOR, and PFS using tumor-specific response criteria, as assessed by BIRC assessment, and OS

Phase II:
- Primary Endpoint: Confirmed ORR as assessed by BIRC using INRC
- Key Secondary Endpoints: DOR as assessed by BICR using INRC, and PFS as assessed by BICR using INRC
- Other Secondary Endpoints: OS

- *Safety endpoints*
  For all study parts:
  - Incidence, type, and severity of adverse events per CTCAE v5.0
  - Tolerability: dose interruptions, reductions, dose intensity, and duration of exposure for all treatment components

- A Study Steering Committee (SCC) that will include some independent members who are not sponsor representatives or trial investigators will oversee conduct of the Phase 1 portion. An independent Data Monitoring Committee (IDMC) will be utilized for the Phase II portion of the trial. Both committees will comply with the recommendations in FDA's Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees https://www.fda.gov/media/75398/download.

- *Known drug safety concerns and monitoring:* Known drug safety concerns for which monitoring will be conducted in this study design include neutropenia, Hepatobiliary Toxicity, QT Interval Prolongation, and Interstitial Lung Disease/Pneumonitis

- *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:* Age-appropriate oral liquid dosage form. (b) (4) [redacted]

[redacted] (b) (4)

- *Route of administration:* Oral- Ribociclib and Temozolomide; IV- Topotecan

- *Regimen:* The dosage of ribociclib in combination with topotecan and temozolomide will be determined by results of Phase 1 - Part A of the study.

  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 prepared 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 preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step

preparation instructions; packaging and storage requirements; and formulation stability information.

The relative bioavailability of any formulation used in the studies and the effect of food on bioavailability must be characterized. The relative bioavailability and food effect studies comparing the approved drug to the age-appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:* For the Phase I part A, an adaptive Bayesian Logistic Regression Model (BLRM) guided by the Escalate with overdose control (EWOC) principle will guide the dose escalation of the combination treatment to its MTD/RP2D. For the Phase I part B and the Phase II, the Statistical analysis plan will be agreed upon as part of the protocol review by FDA.

- *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 ribociclib 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.[1] You are encouraged to contact the reviewing Division for further guidance.

For studies started after December 17, 2017, study data must 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 December 2029. 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.

[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
[2] https://www.fda.gov/media/154109/download

Reports of the studies that meet the terms of the Written Request dated February 16, 2022, as amended by this letter must be submitted to the Agency on or before December 14, 2029, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) / 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.[3]

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.

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

If you have any questions, contact Jacqueline Glen, Regulatory Project Manager, at (240) 402-9558 or Jacqueline.Glen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

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/

MARTHA B DONOGHUE
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