DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211192/S-001

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT
RELEASE FROM POSTMARKETING REQUIREMENT
NEW POSTMARKETING REQUIREMENTS

Agios Pharmaceuticals, Inc.
Attention: Jamie Cohen, PhD
Director, Regulatory Affairs
88 Sidney Street
Cambridge, MA 02139

Dear Dr. Cohen:

Please refer to your Supplemental New Drug Application (sNDA) dated December 21, 2018, received December 21, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tibsovo® (ivosidenib) tablets; 250 mg.

This Prior Approval supplemental new drug application provides for the use of Tibsovo® (ivosidenib) tablets for the treatment of adult patients with newly-diagnosed acute myeloid leukemia (AML) who are ≥ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "*SPL Standard for Content of Labeling Technical Qs and As"* at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.
The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

We have received your submission dated October 12, 2018, containing the final report for the following postmarketing requirement listed in the July 20, 2018, approval letter.

PMR 3444-2 Complete your ongoing Study AG120-C-012, *A Phase 1, open-label, single-dose study to evaluate the pharmacokinetics, safety, and tolerability of AG-120 in subjects with mild or moderate hepatic impairment or normal hepatic function*.

The timetable you submitted on July 13, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 10/2018

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there is a postmarketing requirement listed in the July 20, 2018, approval letter that is still open.

RELEASE FROM POSTMARKETING REQUIREMENT

We have received your submission dated December 17, 2018, reporting on the following postmarketing requirement listed in our July 20, 2018, approval letter.

PMR 3444-3 Conduct a clinical pharmacokinetic trial to determine an appropriate safe dose of ivosidenib in patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test with hepatic impairment (moderate) dosed with ivosidenib to steady-state vs. patients with normal hepatic function dosed with ivosidenib to steady-state. This may be performed as a sub-study in the ongoing Phase 1 Study AG120-C-001, *A Phase 1, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-120 in Subjects with Advanced Hematologic Malignancies with an IDH1 Mutation*. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*. Depending on the results, a clinical pharmacokinetic trial in patients with severe hepatic impairment may be required.

The original timetable you submitted on July 13, 2018, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	4/2019
Trial Completion:	11/2022
Final Report Submission:	6/2023

We have reviewed your submission and have determined that you are released from the above postmarketing requirement for the following reason: the scope of the postmarketing requirement will not be sufficient to address the related issues identified during review for the new indication. The above postmarketing requirement will be replaced by the new postmarketing requirement as described below.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Tibsovo® (ivosidenib) was approved on July 20, 2018, we have become aware of changes in ivosidenib exposure with severity of hepatic impairment based on the results of the hepatic impairment study (AG120-C-012) and the need for appropriate dose recommendations for this patient population who have co-morbidities (i.e., organ impairment) that preclude the use of intensive induction chemotherapy. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risk of long-term toxicities of ivosidenib or assess a signal of excessive drug toxicity from severe hepatic and renal impairment on the pharmacokinetics of ivosidenib.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 3596-1 Conduct a clinical pharmacokinetic trial to determine an appropriate safe dose of ivosidenib in patients with hematologic malignancies who have a susceptible IDH1 mutation with moderate (total bilirubin >1.5 to 3 × ULN and any AST) and severe (total bilirubin >3 × ULN and any AST) hepatic impairment dosed with ivosidenib to steady-state versus patients with normal hepatic function dosed with ivosidenib to steady-state. This may be performed as a substudy in the ongoing Phase 1 Study AG120-C-001, *A Phase 1, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-120 in Subjects with Advanced Hematologic Malignancies with an IDH1 Mutation*. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*.

The timetable you submitted on April 2, 2019 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/20
Trial Completion:	02/25
Final Report Submission:	09/25

PMR 3596-2 Conduct a clinical pharmacokinetic trial to determine an appropriate safe dose of ivosidenib in patients with hematologic malignancies who have a susceptible IDH1 mutation with severe renal impairment (creatinine clearance 15-29 mL/min) dosed with ivosidenib to steady-state versus patients with normal renal function dosed with ivosidenib to steady-state. This may be performed as a substudy in the ongoing Phase 1 Study AG120-C-001, *A Phase 1, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-120 in Subjects with Advanced Hematologic Malignancies with an IDH1 Mutation*. This trial should be designed and conducted in accordance with the FDA Guidance for Industry

entitled *Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*.

The timetable you submitted on April 2, 2019 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/20
Trial Completion:	02/25
Final Report Submission:	09/25

Submit clinical protocols to your IND 119341, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Laura Wall, Regulatory Project Manager, at 301-796-2237.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Prescribing Information
Medication Guide

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/

ANN T FARRELL
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