

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216196Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 119825

MEETING MINUTES

Agios Pharmaceuticals, Inc.
Attention: Christina Baladi
Director, Regulatory Affairs
88 Sidney Street
Cambridge, MA 02139

Dear Ms. Baladi:¹

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for mitapivat (AG-348).

We also refer to the telecon between representatives of your firm and the FDA on April 7, 2020. The purpose of the meeting was to discuss the adequacy of the proposed content and format of this NDA.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, Wanda Nguyen, PharmD, Senior Regulatory Health Project Manager at 301-796-2808.

Sincerely,

{See appended electronic signature page}

Tanya Wroblewski, MD,
Clinical Team Leader
Division of Hematology Products
Office of Oncologic Diseases
Center for Drug Evaluation and Research (CDER)

Enclosure:

- Meeting Minutes

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>.



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: April 7, 2020, 11:00 – 12:00 (EST)
Meeting Location: Teleconference

Application Number: IND 119825
Product Name: mitapivat (AG-348)
Indication: Treatment of adult with pyruvate kinase deficiency
Sponsor Name: Agios Pharmaceuticals, Inc.

Meeting Chair: Tanya Wroblewski, MD
Meeting Recorder: Wanda Nguyen, PharmD

FDA ATTENDEES

Office of Oncologic Diseases/ Division of Nonmalignant Hematology

Ann Farrell, MD, Director
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Tanya Wroblewski, MD, Clinical Team Leader
Carrie Diamond, MD, Clinical Reviewer

Office of Cardiology, Hematology, Endocrinology and Nephrology

Ellis Unger, MD, Director
Mary Thanh Hai, MD, Deputy Director

Office of Biostatistics/Division of Biometrics V

Yeh-Fong Chen, PhD, Statistical Team Leader
Kate Li Dwyer, PhD, Statistical Reviewer

Office of Clinical Pharmacology

Li Wang, PhD, Clinical Pharmacology Reviewer
Yuching Yang, PhD, PBPK Co-Lead

Office of Regulatory Operations for Oncologic Diseases/Division of Hematologic Malignancies II

Wanda Nguyen, PharmD, Regulatory Project Manager

SPONSOR ATTENDEES

Agios Pharmaceuticals

Chris Bowden, MD, Chief Medical Officer

Sarah Gheuens, MD, Vice President, Clinical Development

Robert Charnas, PhD, Vice President, Regulatory Affairs

Margarida Geraldes, Vice President, Biostatistics and Programming

Christina Baladi, Director, Regulatory Affairs

Cynthia Iyekegbe, PharmD, Fellow, Regulatory Affairs,

Feng Tai, PhD, Director, Biostatistics

Peter Hawkins, PhD, Senior Director, Medical Safety and Risk Management

1.0 BACKGROUND

Agios Pharmaceuticals submitted IND 119825 mitapivat on March 28, 2014. Mitapivat was granted orphan designation on March 24, 2015 and fast track designation on April 27, 2017 for the treatment of PK deficiency.

In addition to this meeting, prior to the planned NDA submission, Agios intends to request a Type B pre-NDA meeting upon topline data availability and a CMC pre-NDA meeting.

FDA sent Preliminary Comments to Agios Pharmaceuticals on April 3, 2020.

2.0 QUESTIONS AND RESPONSES

2.1. Clinical

Preamble:

Agios is nearing completion of two trials to test the effect of AG-348 on the anemia of patients with pyruvate kinase deficiency. The Agency is interested in your response to a question about the choice of the primary endpoint in each trial.

Study 006 is a phase 3 randomized double blind placebo controlled study consisting of a dose optimization period followed by a fixed dose period in 76 patients with PK deficiency who have a baseline hemoglobin of ≤ 10 g/dL and who are “non-transfusion dependent” defined as no transfusions within 4 months of starting the protocol. The primary endpoint is defined as a ≥ 1.5 g/dL increase in Hb concentration from baseline that is sustained at 2 or more assessments at weeks 26, 20 and 24.

The patient population is transfusion independent and may therefore have mild chronic anemia and not require treatment. Given the potential for heterogeneity due to genetics and baseline severity of clinical phenotype, what evidence do you

have that the primary endpoint you have chosen is one that can demonstrate a benefit that outweighs the toxicity of AG-348?

Study 007 is a Phase 3 single arm open-label trial consisting of a dose optimization period followed by a fixed dose period in 25 subjects with transfusion dependent PK deficiency who have a minimum of 6 transfusion episodes in the 12 months preceding the date of providing the informed consent for the trial. The primary endpoint is the proportion of patients who achieve a reduction in transfusion burden defined as $\geq 33\%$ reduction in the number of RBC units transfused during the 24 weeks of Part 2 compared with the historical transfusion burden standardized to 24 weeks.

Given the potential for heterogeneity due to genetics and baseline severity of clinical phenotype, what evidence do you have that the primary endpoint you have chosen can demonstrate a benefit that outweighs the toxicity of AG-348. Please provide a justification for the choice of a 33% reduction in the number of RBC units transfused during the 24 weeks of Part 2 in the primary endpoint.

Meeting Discussion: The Agency and Sponsor discussed the Agency's concern that it will be difficult to show that a 1.5g/dL rise in hemoglobin demonstrates benefit in the population chosen for Study 006 (chronic anemia that does not require RBC transfusions). The Agency asked the Sponsor for information to address this concern and for information to support the endpoint chosen for Study 007. The Sponsor stated that once the topline data from Studies 006 and 007 was available, that it would schedule a pre-NDA meeting.

Question 1: Does the Agency agree with the proposed clinical studies from which data will be included in the NDA, as well as the cutoff dates and type of report to be provided for each study?

FDA Response to Question 1:

No. See preamble. We have concerns with the populations and endpoints you have chosen for Studies 006 and 007. You have not clearly demonstrated that your endpoints would support an application. The concerns are as follows:

Study 006:

A non-transfusion dependent study population may not represent the population of PK deficient individuals most likely to gain clinically meaningful benefit from treatment with mitapivat. Patients may be chronically anemic and have mild to no symptoms at baseline. Therefore, the clinical meaning of a change in hemoglobin concentration ($>1.5\text{gm/dL}$) is unclear in this population.

Study 007:

The single-arm nature of this study introduces significant challenges in deciding if the reduction in RBC units which is observed in the 25 patients treated on Study 007 can be

extrapolated to a post approval population of patients with transfusion dependent PK deficiency which is treated with AG-348.

Meeting Discussion: The Agency stated that the formatting appears reasonable. However, the Agency stated the Sponsor needs to provide information that the endpoints and patient populations chosen for Studies 006 and 007 are ones which will demonstrate the benefit of mitapivat therapy in pyruvate kinase deficiency and that topline data will be needed to make an assessment of the endpoints and patient populations at the pre-NDA meeting.

Question 2: *Regarding the Integrated Summary of Efficacy (ISE)*

- a. *Does the Agency agree with the proposed content, datasets, and analyses, and format of the ISE?*
- b. *Does the Agency agree with the proposal to include the narrative portion of the ISE with the Module 2.7.3 and the integrated tables, listings, and figures (TLFs) within Module 5.3.5.3?*

FDA Response to Question 2:

- a. Your approach appears reasonable.
- b. Yes, this is acceptable as long as the narrative portion is concise enough to meet the size limitations of module 2.

Meeting Discussion: There was no discussion.

Question 3: *Regarding the Integrated Summary of Safety (ISS),*

- a. *Does the Agency agree with the proposed content, datasets, analyses, pooling strategy, and format of the ISS?*
- b. *Does the Agency agree with the proposal to include the narrative portion of the ISE within Module 2.7.4 and the integrated TLFs within module 5.3.5.3?*

FDA Response to Question 3:

- a. Your approach appears reasonable.
- b. Yes, this is acceptable as long as the narrative portion is concise enough to meet the size limitations of module 2.

Meeting Discussion: There was no discussion.

Question 4: *Does the Agency agree with the proposed cutoff date, contents, and plan for the safety update report and that the report can be submitted at Day 90 instead of Day 120?*

FDA Response to Question 4:

Your approach appears reasonable.

Meeting Discussion: There was no discussion.

Question 5: *Does the Agency agree with the proposed approach for providing subject narratives and case report forms (CRFs) in the NDA submission?*

FDA Response to Question 5:

In general your approach appears reasonable, however please see preamble.

2.2. Statistics

Question 6: *Does the Agency agree with the analyses as proposed in the statistical analysis plans (SAPs) for the following?*

- a. *Study AG-348-C-006, with specific regard to the primary and secondary efficacy endpoints and testing hierarchy?*
- b. *Patient-reported outcome (PRO) in-trial validation?*
- c. *Study AG348-C-007?*

FDA Response to Question 6:

Please see the preamble. We also have the following recommendations for study Study AG-348-C-006:

- For primary endpoint of hemoglobin response, we recommend use Cochran-Mantel-Haenszel test as your primary analysis and logistic regression as your sensitivity analysis to avoid any invalidity of model assumption. However, we have concerns about the clinical meaningfulness of this endpoint. Please see preamble.
- For key secondary endpoint of average change from baseline in Hb concentration, we recommend using ANCOVA approach as your primary analysis method. Model based imputation approach such as MMRM may be used as sensitivity analysis because missing at random (MAR) assumption will most likely not be met. You should also provide several sensitivity analyses such as tipping point analyses to assess the effect of the missing data.
- We acknowledge your plans to use data from the ongoing Study AG348-C-006 for the assessment of the psychometric properties and performance of the proposed PRO instruments, the Pyruvate Kinase Deficiency Diary (PKDD) and the Pyruvate Kinase Deficiency Impact Assessment (PKDIA). However, we are unable to review your psychometric analysis plan in the absence of the final qualitative research report that provides supporting evidence of content validity of the instruments.

We will review your qualitative and quantitative PRO data at the time of NDA submission. Per the FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, if

PRO information is provided electronically, it should be placed in section 5.3.5.3 of the electronic common technical document. This would also be applicable for other clinical outcome assessment information (e.g., clinician-reported outcome assessments etc.). We refer you to the Appendix of the FDA PRO Guidance for the components that should be included in a PRO evidence dossier.

Meeting Discussion: The Sponsor asked the Agency to confirm that the local lab values can be used in instances when central lab values are not available due to the COVID-19 pandemic. The Agency stated that local lab values would be acceptable.

Question 7: *Does the Agency agree with the structure and format of the statistical datasets and programs to be submitted within the NDA?*

FDA Response to Question 7:

For the pivotal studies 006 and 007, we have the following general recommendations in preparing an application. Please see preamble.

- Provide executable SAS programs with adequate document(s) to allow FDA to derive the analysis datasets from the raw datasets you submitted.
- Provide the SAS programs as well as format library files used for efficacy and safety data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.

Meeting Discussion: The Agency confirms that the Sponsor's response comments are acceptable.

2.3. Clinical Pharmacology

Question 8: *Does the Agency agree with the proposed contents and approach for the population pharmacokinetics and exposure-response analyses and the associated pharmacometric analysis plans, and the proposed contents of the clinical pharmacology package are adequate to support an NDA?*

FDA Response to Question 8:

We agree with the proposed approach for population pharmacokinetics and exposure-response analyses and the associated pharmacometric analysis plans. In general, PBPK analysis can be used for evaluation of the drug-drug interaction (DDI) potential of your investigational drug (mitapivat) as perpetrator towards cytochrome P450 enzymes (such as CYP2Cs) and selected drug transporters. However, the current experience of using PBPK analysis to prospectively predict the inhibition potential of a drug on the transporters such as P-gp, OATP1B1/3 and MATEs is limited.

The predictability of PBPK modeling on the DDI with a gastric acid-reducing agent has not been fully established. In general, a PBPK modeling to evaluate the effect of elevated gastric pH on PK should be developed using in vitro parameters (such as solubility, or dissolution) measured in bio-relevant conditions and verified with all available clinical datasets. In addition, we recommend you collect mitapivat solubility data in a smaller pH interval in pH range 3-7. Alternatively, you may conduct clinical study to assess the effect of concomitant gastric acid-reducing agent on the PK of mitapivat. Please also refer to FDA's recommendation regarding your PBPK analysis on May 24, 2019. Whether the PBPK analyses are adequate for these intended uses will be determined during the NDA review.

Meeting Discussion: There was no discussion.

2.4. Nonclinical

Question 9: *Does the Agency agree with the proposed contents of the nonclinical package are adequate to support an NDA, including the studies for which Standard for Exchange of Nonclinical Data (SEND) datasets are proposed to be submitted in the NDA?*

FDA Response to Question 9:

The nonclinical program described in the meeting package appears sufficient to support an NDA submission for mitapivat. The adequacy of the data to support the NDA submission will be determined during the review of your application. We remind you that SEND datasets are required to be submitted with both GLP and non-GLP nonclinical study reports. See information under DATA STANDARD FOR STUDIES below for further guidance.

However, please see responses above and the preamble.

Meeting Discussion: **There was no discussion.**

2.5. Other

Question 10: *Does the Agency agree with the studies for which financial disclosure information is proposed to be submitted in the NDA?*

FDA Response to Question 10:

Your approach appears reasonable.

Meeting Discussion: **There was no discussion.**

Question 11: *Does the Agency agree with table of contents (TOC) for the NDA is acceptable?*

FDA Response to Question 11:

Your approach appears reasonable.

Meeting Discussion: **There was no discussion.**

Question 12: *Does the Agency agree with the proposed documentation to be submitted as part of the NDA is sufficient for the Office of Scientific Investigations purposes of site inspection selection?*

FDA Response to Question 12:

Your approach appears reasonable.

Meeting Discussion: There was no discussion.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 14, 2020, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at [FDA.gov](https://www.fda.gov).²

PREA REQUIREMENTS

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(s) 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

² <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information³ and Pregnancy and Lactation Labeling Final Rule⁴ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time

³ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁴ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.^[1]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,^[2] as well as email access to the eData Team (cdereadata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page^[3] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards

[1] <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

[2] <https://www.fda.gov/media/88173/download>

[3] <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.^[4] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide^[5] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.^[6] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.^[7]

[4] <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

[5] <https://www.fda.gov/media/88173/download>

[6] <https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

[7] <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER*

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

Submissions (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁵

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items from this meeting.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's responses to the Agency's preliminary meeting comments are appended.

⁵ <https://www.fda.gov/media/85061/download>

Provided below are Agios Pharmaceutical, Inc (Agios)'s responses to the Agency's preliminary comments for the Pre-NDA meeting scheduled for Tuesday, April 7th, 2020 (received via email on 3 April 2020). During the meeting, Agios would like to focus on Preamble, Questions 1, 6, and 7. No further clarification on Questions 2, 3, 4, 5, 8, 9, 10, 11, and 12 are needed during the meeting.

PREAMBLE

FDA Comments:

Agios is nearing completion of two trials to test the effect of AG-348 on the anemia of patients with pyruvate kinase deficiency. The Agency is interested in your response to a question about the choice of the primary endpoint in each trial.

Study 006 is a phase 3 randomized double-blind placebo controlled study consisting of a dose optimization period followed by a fixed dose period in 76 patients with PK deficiency who have a baseline hemoglobin of ≤ 10 g/dL and who are non-transfusion dependent defined as no transfusions within 4 months of starting the protocol. The primary endpoint is defined as a ≥ 1.5 g/dL increase in Hb concentration from baseline that is sustained at 2 or more assessments at weeks 26, 20 and 24.

The patient population is transfusion independent and may therefore have mild chronic anemia and not require treatment. Given the potential for heterogeneity due to genetics and baseline severity of clinical phenotype, what evidence do you have that the primary endpoint you have chosen is one that can demonstrate a benefit that outweighs the toxicity of AG-348?

Study 007 is a Phase 3 single arm open-label trial consisting of a dose optimization period followed by a fixed dose period in 25 subjects with transfusion dependent PK deficiency who have a minimum of 6 transfusion episodes in the 12 months preceding the date of providing the informed consent for the trial. The primary endpoint is the proportion of patients who achieve a reduction in transfusion burden defined as $\geq 33\%$ reduction in the number of RBC units transfused during the 24 weeks of Part 2 compared with the historical transfusion burden standardized to 24 weeks.

Given the potential for heterogeneity due to genetics and baseline severity of clinical phenotype, what evidence do you have that the primary endpoint you have chosen can demonstrate a benefit that outweighs the toxicity of AG-348. Please provide a justification for the choice of a 33% reduction in the number of RBC units transfused during the 24 weeks of Part 2 in the primary endpoint.

Agios Response:

Agios would like to address the Agency's question regarding the choice of the primary endpoints during the meeting, and additionally discuss the patient populations and safety profile of mitapivat.

QUESTION 1

Does the Agency agree with the proposed clinical studies from which data will be included in the NDA, as well as the cutoff dates and type of report to be provided for each study?

FDA Comments:

No. See preamble. We have concerns with the populations and endpoints you have chosen for Studies 006 and 007. You have not clearly demonstrated that your endpoints would support an application. The concerns are as follows:

Study 006:

A non-transfusion dependent study population may not represent the population of PK deficient individuals most likely to gain clinically meaningful benefit from treatment with mitapivat. Patients may be chronically anemic and have mild to no symptoms at baseline. Therefore, the clinical meaning of a change in hemoglobin concentration (>1.5gm/dL) is unclear in this population.

Study 007:

The single-arm nature of this study introduces significant challenges in deciding if the reduction in RBC units which is observed in the 25 patients treated on Study 007 can be extrapolated to a post approval population of patients with transfusion dependent PK deficiency which is treated with AG-348.

Agios Response:

Agios acknowledges the Agency's points made in the preamble with regards to the primary endpoint and patient populations. Assuming the totality of data from Studies AG348-C-006 and AG348-C-007 are compelling and supportive of a new drug application, Agios would like to clarify that the contents of the submission proposed in the briefing book with regards to the types of reports and cut-off dates for each study, are appropriate to support the initial New Drug Application of mitapivat. Agios would like to discuss this further during the meeting.

QUESTION 2

Regarding the Integrated Summary of Efficacy (ISE)

a. Does the Agency agree with the proposed content, datasets, and analyses, and format of the ISE?

b. Does the Agency agree with the proposal to include the narrative portion of the ISE with the Module 2.7.3 and the integrated tables, listings, and figures (TLFs) within Module 5.3.5.3?

FDA Comments:

a. Your approach appears reasonable.

b. Yes, this is acceptable as long as the narrative portion is concise enough to meet the size limitations of module 2.

Agios Response:

Agios acknowledges the Agency's comments and does not require further discussion.

QUESTION 3

Regarding the Integrated Summary of Safety (ISS),

a. Does the Agency agree with the proposed content, datasets, analyses, pooling strategy, and format of the ISS?

b. Does the Agency agree with the proposal to include the narrative portion of the ISE within Module 2.7.4 and the integrated TLFs within module 5.3.5.3?

FDA Comments:

a. Your approach appears reasonable.

b. Yes, this is acceptable as long as the narrative portion is concise enough to meet the size limitations of module 2.

Agios Response:

Agios acknowledges the Agency's comments and does not require further discussion.

QUESTION 4

Does the Agency agree with the proposed cutoff date, contents, and plan for the safety update report and that the report can be submitted at Day 90 instead of Day 120?

FDA Comments:

Your approach appears reasonable.

Agios Response:

Agios acknowledges the Agency's comment and does not require further discussion.

QUESTION 5

Does the Agency agree with the proposed approach for providing subject narratives and case report forms (CRFs) in the NDA submission?

FDA Comments:

In general your approach appears reasonable, however please see preamble.

Agios Response:

Agios acknowledges the Agency's comment and does not require further discussion.

QUESTION 6

Does the Agency agree with the analyses as proposed in the statistical analysis plans (SAPs) for the following?

- a. Study AG-348-C-006, with specific regard to the primary and secondary efficacy endpoints and testing hierarchy?*
- b. Patient-reported outcome (PRO) in-trial validation?*
- c. Study AG348-C-007?*

FDA Comments:

Please see the preamble. We also have the following recommendations for study Study AG-348-C-006:

- For primary endpoint of hemoglobin response, we recommend use Cochran-Mantel-Haenszel test as your primary analysis and logistic regression as your sensitivity analysis to avoid any invalidity of model assumption. However, we have concerns about the clinical meaningfulness of this endpoint. Please see preamble.
- For key secondary endpoint of average change from baseline in Hb concentration, we recommend using ANCOVA approach as your primary analysis method. Model based imputation approach such as MMRM may be used as sensitivity analysis because missing at random (MAR) assumption will most likely not be met. You should also provide several sensitivity analyses such as tipping point analyses to assess the effect of the missing data.
- We acknowledge your plans to use data from the ongoing Study AG348-C-006 for the assessment of the psychometric properties and performance of the proposed PRO instruments, the Pyruvate Kinase Deficiency Diary (PKDD) and the Pyruvate Kinase Deficiency Impact Assessment (PKDIA). However, we are unable to review your psychometric analysis plan in the absence of the final qualitative research report that provides supporting evidence of content validity of the instruments.

We will review your qualitative and quantitative PRO data at the time of NDA submission. Per the FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, if PRO information is provided electronically, it should be placed in section 5.3.5.3 of the electronic common technical document. This would also be applicable for other clinical outcome assessment information (e.g., clinician-reported outcome assessments etc.). We refer you to the Appendix of the FDA PRO Guidance for the components that should be included in a PRO evidence dossier.

Agios Response:

Agios acknowledges the Agency's comments. Given the ongoing COVID-19 pandemic, Agios would like to discuss the acceptability of using local lab values in instances when central lab values are not available, for the analysis of Hemoglobin Response, the primary endpoint in Study AG348-C-006.

QUESTION 7

Does the Agency agree with the structure and format of the statistical datasets and programs to be submitted within the NDA?

FDA Comments:

For the pivotal studies 006 and 007, we have the following general recommendations in preparing an application. Please see preamble.

- Provide executable SAS programs with adequate document(s) to allow FDA to derive the analysis datasets from the raw datasets you submitted.
- Provide the SAS programs as well as format library files used for efficacy and safety data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.

Agios Response:

Agios acknowledges the Agency's comments and would like to clarify the planned approach. Agios will provide for the pivotal studies 006 and 007:

- SDTM data sets as .xpt files with accompanying define.xml, annotated CRF and Study Data Reviewers Guide
- ADaM data sets as .xpt files with accompanying define.xml, and Analysis Data Reviewers Guide
- Format library files and executable SAS programs used to generate the following:
 - All ADaM data sets
 - All efficacy analyses
 - Key safety analyses including AE summaries and summaries of laboratory data graded per CTCAE
 - SAS macros

QUESTION 8

Does the Agency agree with the proposed contents and approach for the population pharmacokinetics and exposure-response analyses and the associated pharmacometric analysis plans, and the proposed contents of the clinical pharmacology package are adequate to support an NDA?

FDA Comments:

We agree with the proposed approach for population pharmacokinetics and exposure-response analyses and the associated pharmacometric analysis plans. In general, PBPK analysis can be used for evaluation of the drug-drug interaction (DDI) potential of your investigational drug (mitapivat) as perpetrator towards cytochrome P450 enzymes (such as CYP2Cs) and selected drug transporters. However, the current experience of using PBPK analysis to prospectively predict the inhibition potential of a drug on the transporters such as P-gp, OATP1B1/3 and MATEs is limited.

The predictability of PBPK modeling on the DDI with a gastric acid-reducing agent has not been fully established. In general, a PBPK modeling to evaluate the effect of elevated gastric pH on PK should be developed using in vitro parameters (such as solubility, or dissolution) measured in bio-relevant conditions and verified with all available clinical datasets. In addition, we recommend you collect mitapivat solubility data in a smaller pH interval in pH range 3-7. Alternatively, you may conduct clinical study to assess the effect of concomitant gastric acid-reducing agent on the PK of mitapivat. Please also refer to FDA's recommendation regarding your PBPK analysis on May 24, 2019. Whether the PBPK analyses are adequate for these intended uses will be determined during the NDA review.

Agios Response:

Agios acknowledges the Agency's comments and does not require further discussion.

QUESTION 9

Does the Agency agree with the proposed contents of the nonclinical package are adequate to support an NDA, including the studies for which Standard for Exchange of Nonclinical Data (SEND) datasets are proposed to be submitted in the NDA?

FDA Comments:

The nonclinical program described in the meeting package appears sufficient to support an NDA submission for mitapivat. The adequacy of the data to support the NDA submission will be determined during the review of your application. We remind you that SEND datasets are required to be submitted with both GLP and non-GLP nonclinical study reports. See information under DATA STANDARD FOR STUDIES below for further guidance.

However, please see responses above and the preamble.

Agios Response:

Agios acknowledges the Agency's comments and does not require further discussion.

QUESTION 10

Does the Agency agree with the studies for which financial disclosure information is proposed to be submitted in the NDA?

FDA Comments:

Your approach appears reasonable.

Agios Response:

Agios acknowledges the Agency's comment and does not require further discussion.

QUESTION 11

Does the Agency agree with table of contents (TOC) for the NDA is acceptable?

FDA Comments:

Your approach appears reasonable.

Agios Response:

Agios acknowledges the Agency's comment and does not require further discussion.

QUESTION 12

Does the Agency agree with the proposed documentation to be submitted as part of the NDA is sufficient for the Office of Scientific Investigations purposes of site inspection selection?

FDA Comments:

Your approach appears reasonable.

Agios Response:

Agios acknowledges the Agency's comment and does not require further discussion.

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/

TANYA M WROBLEWSKI
04/14/2020 09:30:08 PM



IND 119825

MEETING MINUTES

Agios Pharmaceuticals, Inc.
Attention: Gregory Smith
Sr. Manager, Regulatory Affairs CMC
88 Sidney Street
Cambridge, MA 02139

Dear Mr. Smith:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AG-348 Sulfate Hydrate.

We also refer to your July 9, 2018, correspondence requesting a meeting to

We also refer to the teleconference between representatives of your firm and the FDA on September 17, 2018. The purpose of the meeting was to obtain FDA feedback on the following CMC topics:

- Acceptability of the proposed starting materials and starting material control strategy
- Proposed registration stability specifications for AG-348 drug substance and drug product
- Proposed registration stability study design for AG-348 drug substance and drug product
- Suitability of the proposed dissolution method development strategy

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Rabiya Haider, Pharm.D., at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Anamitro Banerjee, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

IND 119825
Page 2

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2
Meeting Date and Time: September 17, 2018; 2:00PM-3:00PM EST
Meeting Location: Teleconference
Application Number: 119825
Product Name: AG-348
Indication: For use in patients with pyruvate kinase deficiency
Sponsor Name: Agios Pharmaceuticals Inc.

FDA ATTENDEES

Office of Pharmaceutical Quality Office of New Drug Products (ONDP)

Anamitro Banerjee, Ph.D., Branch Chief
William Adams, Ph.D., Drug Product Reviewer
Raymond Frankewich, Ph.D., Drug Substance Reviewer
Joan Zhao, Ph.D., Biopharmaceutics Reviewer
Banu Zolnik, Ph.D. Acting Quality Assessment Lead (Biopharmaceutics)

Office of Program and Regulatory Operations

Rabiya Haider, PharmD., Regulatory Business Process Manager

SPONSOR ATTENDEES

ChongHui Gu, Ph. D-Vice President, CMC
Ben Lane, Ph. D.-Director, Process Chemistry
Tyson Chasse, Ph. D.-Director, Analytical Chemistry
Kyle Bui, Ph. D.-Associate Director, Analytical Chemistry
Jeff Grassi-Senior Scientist, Analytical Chemistry
Eric Simone, Ph. D.-Associate Director, Formulations
Gregory Smith, M.S.-Senior Manager, Regulatory Affairs CMC
Kathleen Church-Senior Director, Regulatory Affairs CMC

1.0 BACKGROUND

The purpose of the requested meeting is to obtain FDA feedback on the following CMC topics:

- Acceptability of the proposed starting materials and starting material control strategy
- Proposed registration stability specifications for AG-348 drug substance and drug product

- Proposed registration stability study design for AG-348 drug substance and drug product
- Suitability of the proposed dissolution method development strategy

FDA sent Preliminary Comments to Agios Pharmaceuticals Inc. on September 6, 2018.

1.0 DISCUSSION

Question 1:

Agios proposes that the following materials are appropriate as the registered starting materials for the manufacture of AG-348 drug substance. Does the Agency agree?

(b) (4)

FDA Response to Question 1:

Yes, we agree with the proposed starting materials (SM).

(b) (4)

However, the following concerns were generated upon review of the briefing package, which we ask you to address.

(b) (4)

Meeting Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 2:

Agios considers that the starting material specifications are suitable to control the quality of the starting materials. Does the Agency agree?

FDA Response to Question 2:

Be advised that the specifications for SM will be evaluated when the NDA is reviewed. Currently we have no concerns with the SM specifications but consider the comments in our response to Question 1 above and make any revisions to the SM specifications that are warranted by the data generated.

Meeting Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 3:

Agios considers that the tests proposed are suitable to control the quality of the AG-348 registration stability drug substance. Does the Agency agree?

FDA Response to Question 3:

Be advised that the specification for AG-348 drug substance will be evaluated when the NDA is reviewed. At this time we have no concerns with the drug substance specification other than the following:

[REDACTED] (b) (4)

Meeting Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 4:

Agios intends to submit the NDA with [REDACTED] (b) (4) as the drug substance manufacturer. For registration stability, Agios plans to submit at least 12 months of long-term and 6 months of accelerated stability data for three production scale primary stability batches manufactured at [REDACTED] (b) (4) (clinical supply manufacturer) [REDACTED] (b) (4). In addition, Agios plans to submit at least 6 months of long-term and accelerated stability data for one production scale primary stability batch (site-specific stability) manufactured at [REDACTED] (b) (4). Agios also commits to put the first three commercial production batches (commitment batches) on stability. Does the Agency agree with the proposed drug substance stability plan to support NDA submission?

FDA Response to Question 4:

We agree with the proposed plan for stability data collection, except that we request that you submit at least 12 months long-term and 6 months accelerated data for the one drug substance batch produced at proposed commercial manufacturer [REDACTED] (b) (4). In addition, we

request that you submit data demonstrating equivalence of impurity profiles and other aspects of the drug substance manufactured at (b) (4) and (b) (4)

Meeting Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 5:

Agios proposes to test the four production scale primary stability batches of AG-348 drug substance according to the stability protocols provided. If the data are acceptable and statistical analysis (per ICH Q1E) supports extrapolation of the long-term data to (b) (4) months, does the Agency agree that the proposed tests, time-points, and storage conditions are suitable to support a proposed retest period of (b) (4) months for drug substance stored long-term at or below (b) (4) °C?

FDA Response to Question 5:

The evaluation of the stability data and the determination of a retest date for AG-348 drug substance will be part of the NDA review. We have no concerns with the proposed tests, storage conditions, and testing schedule proposed to collect the stability data. Be advised that storage at (b) (4) and changes in (b) (4) (which could potentially affect the quality of the drug product) could be an issue during the NDA review.

Meeting Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 6:

Agios considers that the proposed tests and acceptance criteria are suitable to control the quality of the AG-348 Tablets, 5 mg, 20 mg, and 50 mg as registration stability batches of drug product. Does the Agency agree with the proposed tests and acceptance criteria for the drug product?

FDA Response to Question 6:

The tests in the proposed specification appear to be sufficient in that they address identity, purity, assay, dissolution and content uniformity. We note that the proposed criterion for (b) (4) is much higher than in the submitted batch analysis data. The proposed criteria for Related Substances should be supported by CMC information regarding potential and observed impurities, related substances and degradation products. Final determination of the adequacy of the drug product specifications will be made at the time of the NDA review.

It is noted that the proposed dissolution acceptance criterion ($Q = (b) (4) \%$ at $(b) (4)$ min) appears permissive and not supported by data. However, the adequacy of the proposed dissolution acceptance criterion will be determined during NDA review based on the totality of the dissolution data (see response to Q10 for further data/information needed in the dissolution method development report). We recommend that you collect and report dissolution data

(individual, mean, SD, profiles) from the clinical trial and the primary (registration) batches (throughout the stability program) and include a detailed discussion of the justification of the proposed dissolution acceptance criterion.

Meeting Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 7:

The proposed commercial drug product will be blue film-coated AG-348 Tablets, 5 mg, 20 mg, and 50 mg imprinted with M5, M20, or M50 on one side in black ink, respectively. Agios proposes to submit the NDA with at least 12 months of long-term and six months of accelerated stability data for three production scale primary stability batches of blue filmcoated AG-348 Tablets, 5 mg, 20 mg, and 50 mg. These batches were manufactured at the proposed commercial site using the proposed commercial formulation and manufacturing process, except that only one batch will be imprinted with the proposed commercial ink for each dosage strength (the additional two batches will be plain-faced).

Does the Agency agree that the proposed stability plan, utilizing three production scale primary stability batches of drug product for each dose strength (1 imprinted batch and 2 plain-faced), is suitable to support a proposed expiration dating period for the proposed imprinted commercial product?

FDA Response to Question 7:

Your proposal could be acceptable. In the NDA, FDA expects at least three batches of each tablet strength made using different NDA registration API lots, preferably the NDA registration lots. We note that the commercial formulation, tablet manufacturing process and manufacturing site are to be used. To support the proposal, you will need to establish chemical and physical equivalence for the drug substance lots. The tablet batches should have equivalent batch release test results including drug release profiles. The size of each drug substance lot and tablet (b) (4) batch should be addressed along with any holding times and conditions for these materials.

We recommend that you provide comparative dissolution profiles using the proposed dissolution method as well as in three additional pH 1.2, 4.5 and 6.8 media. If possible, provide similarity data using similarity f_2 test or other appropriate statistical test to support imprinting or difference API source not impacting the performance of the drug product.

Sponsor Response:

Agios acknowledges the agency's feedback around changing drug substance suppliers, including the requirements for showing equivalency of drug substance and drug product batches when a change to the drug substance manufacturing site is made.

Agios seeks additional clarification around the requirements for showing comparability for printed vs. plain-faced tablets. If a single drug substance manufacturer is filed (b) (4) Agios plans to provide stability data for three batches of drug product for each dosage strength (5 mg,

20 mg, and 50 mg). One batch for each strength will be printed/coated and two batches will be plain-faced/coated.

Can the agency confirm that the proposed stability plan, utilizing three production scale primary stability batches of drug that product for each dose strength (1 printed/coated and 2 plain-faced/coated), is suitable to support a proposed expiration dating period for the proposed printed commercial product?

Agios would also like clarification around the requirement for comparative dissolution of printed/coated vs. plain-faced/coated tablets. The printing on AG-348 Tablets, 5 mg, 20 mg, and 50 mg is (b) (4) and does not change the surface area of the tablets. Therefore, Agios does not intend to provide comparative dissolution between (b) (4) supplier. Does the agency agree with this approach?

Meeting Discussion:

FDA communicated that if (b) (4) is not used as a commercial drug substance supplier, then the proposed scheme for the drug product stability batches is acceptable. FDA reiterated their recommendation that the sponsor provide comparative dissolution data for plain-face/printed tablets for AG-348 as part of a complete NDA submission package and FDA agrees that imprinting is not expected to affect tablet quality.

Question 8:

Agios proposes to submit the NDA with at least 12 months of long-term and six months of accelerated stability data for three production scale primary stability batches of blue filmcoated AG-348 Tablets, 5 mg, 20 mg, and 50 mg. These batches were manufactured as outlined in Question 7 using three batches of AG-348 drug substance manufactured at (b) (4) (clinical supply manufacturer). In addition, Agios proposes to submit at least 6 months of long-term and accelerated stability data for a fourth batch of blue film-coated AG-348 Tablets, 5 mg, 20 mg, and 50 mg imprinted with M5, M20, or M50 on one side in black ink, respectively, which will be manufactured using AG-348 drug substance from (b) (4) (the commercial drug substance manufacturer).

Does the Agency agree that the proposed stability plan, utilizing three production scale primary stability batches of AG-348 Tablets, 5 mg, 20 mg, and 50 mg manufactured using AG-348 drug substance from (b) (4) and one batch of AG-348 Tablets, 5 mg, 20 mg, and 50 mg manufactured using AG-348 drug substance from (b) (4) is suitable to support a proposed expiration dating period?

FDA Response to Question 8:

Your proposal is acceptable if the four batches of each tablet strength are shown to be equivalent at release; manufactured by the proposed commercial process; and manufactured at the proposed commercial manufacturing site.

Meeting Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 9:

Agios proposes to test the four production scale primary stability batches of AG-348 Tablets, 5 mg, 20 mg, and 50 mg according to the stability protocols provided. If the data are acceptable and statistical analysis (per ICH Q1E) supports extrapolation of the long-term data to (b) (4) months, does the Agency agree that the proposed tests, time-points, and storage conditions are suitable to support a proposed expiry period of (b) (4) months for AG-348 Tablets, 5 mg, 20 mg, and 50 mg stored long-term at 20°C-25°C (68-77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]?

FDA Response to Question 9:

Based on the CMC information in the meeting package and the variables that are described, we recommend that at least 12 months of stability data be provided on each of the four NDA registration batches of each tablet strength. Extrapolation of the data for shelf life determination will be made as part of the NDA review based on the CMC information presented in the application. The proposed study storage conditions are acceptable to support the proposed label storage condition statement.

Meeting Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 10:

AG-348 Tablets, 5 mg, 20 mg, and 50 mg were formulated as immediate-release solid oral dosage forms (b) (4)

(b) (4)

(b) (4)

(b) (4)

Agios intends to employ standard USP dissolution test conditions and specification aligned with the guidance for industry for a (b) (4) immediate-release solid oral dosage form. Does the Agency agree that this approach is suitable for commercial testing of AG-348 Tablets?

FDA Response to Question 10:

The proposed dissolution parameters and overall testing conditions appear reasonable provided that you submit data to support the selection of the proposed dissolution method as the optimal test for your drug product.

A final determination regarding the adequacy of the proposed QC dissolution method and acceptance criterion will be made during NDA review. However, you have the option of submitting dissolution method development and analytical method validation reports for review and feedback under an amendment to your IND. If you decide to submit it to the IND, please include in the cover letter of the IND amendment that you are seeking a feedback from the Division of Biopharmaceutics regarding the adequacy of the proposed QC dissolution method.

FDA has the following recommendations regarding the dissolution information that should be collected for your proposed drug product and submitted under your NDA or IND (*as appropriate*).

Dissolution Method: Provide in your submission the dissolution method development and validation report supporting the selection of the proposed dissolution test evaluating the proposed drug product. The report should include the following:

- a. Solubility data of the drug substance over the physiologic pH range.
- b. Detailed description of the dissolution method being proposed for the evaluation of the product, along with the developmental parameters supporting the selection of the proposed dissolution method as the optimal test for the proposed drug product (e.g., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, media pH, sink conditions, use of sinker and enzyme, if applicable, etc.). If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. Clearly specify the testing conditions associated with each method development study. The dissolution profile should be complete or whenever a plateau is reached (i.e., no increase over 3 consecutive time-points). It is recommended the use of at least twelve dosage units per testing variable and sampling time points (e.g., 10, 15, 20, 30, 45, 60 min etc.).
- c. Data supporting the discriminating ability of the selected dissolution method. In general, ensure that the testing conducted to demonstrate the discriminating ability of the selected dissolution method compares the dissolution profiles of the reference (target) drug product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes, critical formulation variables, and critical process parameters (e.g., $\pm$ 10-20% change to the specified values or ranges for these variables). Submit the dissolution profile data and similarity testing results obtained with appropriate statistical test (e.g., f_2 values) comparing the test and reference drug products. In addition, if available, submit data showing that the selected dissolution method can reject product that is not bioequivalent to the reference-target drug product.
- d. A list of the critical material attributes (CMAs) and critical process parameters (CPPs) affecting dissolution.
- e. Supportive validation data for the dissolution methodology (bench testing) and analytical method used for assaying the dissolution samples (specificity, precision, accuracy, linearity/range, stability, robustness, etc. For general recommendations on method validation, refer to the USP Chapters “The Dissolution Procedure: Development and Validation” <1092> and “Validation of Compendial Methods” USP Chapter <1225>.

- f. Complete dissolution multi-point profile data for each variable tested during method development, assessment of discriminating ability, and validation [individual (n=12), mean, SD, % CV at each time point and mean profiles). Report the dissolution data as the cumulative percentage of drug dissolved (the percentage is based on the drug product's label claim). For the submission of the dissolution data, refer to data presentation below.

Dissolution Acceptance Criterion: For the selection of the dissolution acceptance criterion of the proposed drug product, consider the following:

- a. Use the multi-point dissolution data (n=12) from the pivotal clinical/PK drug product-batches and primary registration batches for the setting of the dissolution acceptance criterion of the proposed drug product.
- b. Ensure that the in vitro dissolution profile is complete or if incomplete dissolution occurs, where the plateau of drug dissolved is reached (i.e., no increase over 3 consecutive time-points).
- c. Base your selection for the dissolution acceptance criterion on the average in vitro dissolution data of each batch/lot under study, equivalent to USP Stage 2 testing (n = 12). Select the sampling time point where Q = 80 % dissolution occurs.
- d. Include a detailed discussion of the justification of the proposed dissolution acceptance criterion in the appropriate section of the eCTD.

Dissolution Data Presentation: In the dissolution method development report (INDs/NDAs), and/or batch analysis section (NDAs), present detailed experimental dissolution data as follows:

For **IND/NDA** Submissions:

- In the narrative portion of the dissolution report, include individual vessel data as much as possible, particularly regarding investigation of selection of equipment, media, agitation speed, etc.
- In addition to the mean dissolution data presented in graphical and tabular formats, submit in the "Batch Analysis" section 3.2.P.5.4 of your NDA the individual vessel dissolution data for the batches of the proposed product used in the pivotal clinical/PK and registration/stability studies in Microsoft Excel ".xls or .xlsx" format. If available, include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions.
- Provide in your IND/NDA the dissolution data as described in the example below.

Example - Reporting of individual vessel dissolution data

Cell A1 – Identifying Batch/Lot Label, and dissolution method/media used

	A	B	C	D	E	F	G	H	I	J
1	Test lot 12345 (QC method/QC media)									
2		1	2	4	6	8	10	12		
3	1	3	15	62	98	99	99	98		
4	2	3	15	64	94	92	95	95		
5	3	3	9	37	80	96	97	97		
6	4	4	13	44	79	97	98	99		
7	5	3	12	39	71	96	98	98		
8	6	3	14	60	98	97	99	99		
9	7	4	13	44	82	93	98	98		
10	8	5	22	89	97	98	97	97		
11	9	4	16	64	96	98	96	96		
12	10	4	14	57	98	96	99	99		
13	11	4	16	63	96	96	97	97		
14	12	6	22	87	96	93	96	96		
15										
16										
17										
18										
19										
20										
21										
22										

Cell A2 – blank

Individual Unit Number (starting from cell A3 numerical values signifying the test unit)

Use one sheet for each unique batch/lot. Label accordingly in Cell A1

Sampling Times (starting from cell B2 numerical values indicating collection times (minutes or hours))

Dissolution Data (starting from cell B3 numerical values indicating percent drug release)

Sheet1 Sheet2 Sheet3

Follow the instructions provided in “**Specifications for File Format Types Using eCTD Specifications**” – updated March 2, 2017 (link below).
<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM347471.pdf>

Sponsor Response:

The detailed feedback on dissolution development and expectations of demonstrating potential discriminating capability of the dissolution method was received and appreciated. As noted in Question 10:

[Redacted content] (b) (4)

Does the Agency agree that Agios can apply the FDA guidance [Redacted content] (b) (4)

[Redacted content]

Meeting Discussion:

FDA advised Agios [Redacted content] (b) (4)
 therefore the guidance does not apply. Please provide the information/data in the dissolution method development report as we requested in our preliminary response to Question 10. FDA reiterated that selection of rotation speed and apparatus should be supported by additional data. Agios informed FDA

 ^{(b) (4)} **FDA recommended that the Sponsor should submit this data to the application.**

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/

ANAMITRO BANERJEE
09/19/2018



IND 119825

MEETING MINUTES

Agios Pharmaceuticals, Inc.
Attention: Christina Baladi
Associate Director, Regulatory Affairs
88 Sidney Street
Cambridge, MA 02139

Dear Ms. Baladi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AG-348.

We also refer to the meeting between representatives of your firm and the FDA on July 18, 2017. The purpose of the meeting was to discuss the results from the Phase 2 study AG348-C-002, the recommended pivotal dose, the proposed pivotal trial designs, and the overall nonclinical and clinical development plans for AG-348 for the treatment of patients with pyruvate kinase (PK) deficiency.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jennifer Lee, Regulatory Project Manager at (240) 402-4622.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: July 18, 2017; 10:00 – 11:00 AM (ET)
Meeting Location: 10903 New Hampshire Avenue; Building 22, Room 1315
Silver Spring, MD 20993

Application Number: IND 119825
Product Name: AG-348
Indication: Treatment of patients with PK deficiency
Sponsor/Applicant Name: Agios Pharmaceuticals, Inc.

Meeting Chair: R. Angelo de Claro, MD
Meeting Recorder: Jennifer J. Lee, PharmD

FDA ATTENDEES

Office of Hematology and Oncology Products/Division of Hematology Products

Al Deisseroth, MD, PhD – Supervisory Associate Division Director
R. Angelo de Claro, MD – Clinical Team Leader
Nicholas Richardson, DO, MPH – Clinical Reviewer
Jennifer Lee, PharmD – Regulatory Project Manager

Office of Hematology and Oncology Products/Division of Hematology Oncology Toxicology

Chris Sheth, PhD – Supervisory Pharmacologist
Luan Lee, PhD – Pharmacologist

Office of Biostatistics/Division of Biometrics V

Yuan Li Shen, DrPh – Biometrics Team Leader
Lola Luo, PhD – Biometrics Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V

Bahru Habtemariam, PharmD – Clinical Pharmacology Team Leader
George (Guoxiang) Shen, PhD – Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Chris Bowden, MD – Chief Medical Officer

Ann Barbier, MD, PhD – Vice President, Clinical Development
Susan Bodie, PharmD – Director, Clinical Science
Marie-Helene Jouvin, MD – Medical Director, Clinical Development
Lei Hua, PhD – Associate Director, Biostatistics
Yanqiong Zhang, PhD – Senior Director, Biostatistics
Charles Kung, PhD – Director, Biology
Jacqueline Cinicola, MS – Senior Director, Regulatory Affairs
Christina Baladi, Associate Director, Regulatory Affairs
Varsha Iyer, PhD – Associate Director, Clinical Pharmacology
Peter Hawkins, PhD – Director, Medical Safety and Risk Management
Josh Powe, PhD DACVP – Associate Director, Pathology/Toxicology (via phone)
Afsaneh Mohebbi, PhD – Program Lead (via phone)
Megan Pace – Program Executive

1.0 BACKGROUND

AG-348 is a proposed pan-activator of alleles of the red blood cell (RBC)-specific form of pyruvate kinase (PKR) associated with PK deficiency. It restores the glycolytic pathway activity that is disrupted in PK deficiency and normalizes RBC metabolism. AG-348 is currently under development by Agios for the treatment of patients with PK deficiency. The Phase 1 testing of AG-348 as a single ascending dose (SAD; Study AG348-C-001) and multiple ascending doses (MAD; Study AG348-C-002) in healthy adult subjects is complete. The Phase 2 open-label trial in adult patients with PK deficiency, AG348-C-003 (DRIVE-PK), has completed enrollment in the Core Period and the Extension Period is currently ongoing.

On April 3, 2017 Agios submitted an End-of-Phase 2 meeting request to discuss the results from AG348-C-002, the recommended pivotal dose, the proposed pivotal trial designs, and the overall nonclinical and clinical development plans for AG-348 for the treatment of patients with PK deficiency. AG-348 was also granted Fast Track designation on April 27, 2017 for its proposed indication.

FDA sent Preliminary Comments to Agios on July 13, 2017.

2. DISCUSSION

Preamble: The Agency acknowledges and appreciates the continued drug development effort in a rare disease such as pyruvate kinase (PK) deficiency. However, the Agency has concerns regarding certain aspects of the AG-348 development program. The main concerns are the proposed patient population in the non-transfusion dependent PK deficiency study and the proposed (b) (4) study design.

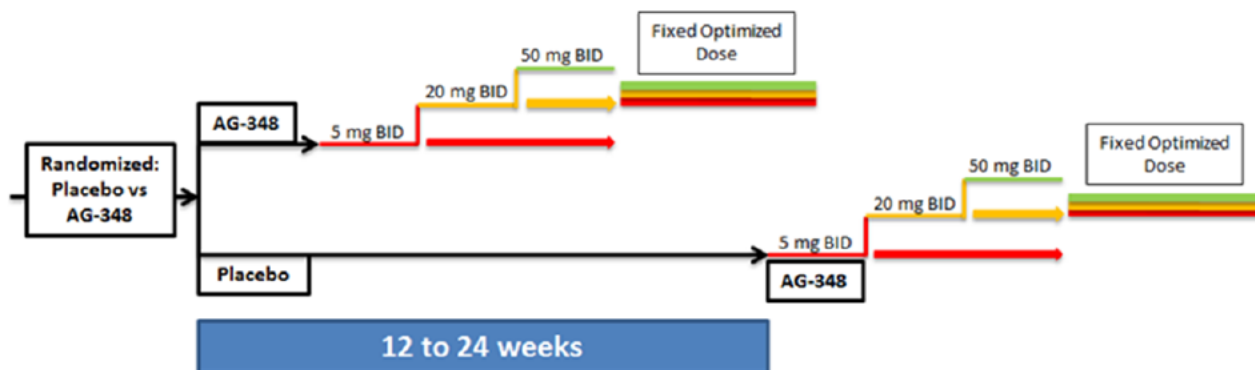
The proposed non-transfusion dependent study population is not representative of the PK deficiency patient population most likely to gain clinically meaningful benefit from treatment with AG-348. The proposed population includes patients with PK deficiency that have mild chronic anemia and may be asymptomatic. These patients may not require supportive treatment and thus the potential clinical benefit of AG-348 is uncertain. The Agency acknowledges the genetic heterogeneity of the patient population, the variability of response to AG-348 by

genotype, and the strategy to include a broad patient population. However, the inclusion of patients that may not require treatment complicates the balance of benefit and risk with AG-348 treatment. Further, known risks of AG-348 are aromatase inhibition, hepatotoxicity, hypertriglyceridemia, withdrawal hemolysis, insomnia, and drug-drug interactions. Additionally, AG-348 contains a sulfonamide moiety that confers a predicted risk of hepatotoxicity, usually idiosyncratic hepatotoxicity that includes hepatocellular and cholestatic injury, based on quantitative structure-activity relationship (QSAR) models. The potential risk with AG-348 treatment outweighs any potential benefit in patients with mild chronic anemia that are asymptomatic. The patient population most likely to gain clinically meaningful benefit from treatment with AG-348 is patients with non-transfusion dependent PK deficiency that have chronic symptomatic anemia and patients with transfusion-dependent PK deficiency. Investigation of a patient population with a moderate to severe PK deficiency phenotype is critical to adequately conduct a benefit-risk evaluation for treatment with AG-348.

The (b) (4) study design is not adequate to demonstrate clinical benefit in patients with PK deficiency. (b) (4)

The study design needs to be able to demonstrate clinically meaningful benefit on objective measures in PK deficiency (e.g., hemoglobin response, duration of hemoglobin response, decreased hemolysis, iron overload, improvement of symptomatic anemia, and decrease in transfusion burden). With an appropriate study population of patients with PK deficiency that are non-transfusion dependent and have chronic symptomatic anemia or are transfusion-dependent, a randomized, placebo-controlled single cross-over study design is recommended to evaluate efficacy (Figure 1).

Figure 1. Single Cross-Over Study Design



Discussion: The Agency provided clarification that the single cross over design would have a randomized treatment duration of 12 to 24 weeks and the primary efficacy endpoint would be assessed at the end of the randomized treatment portion. The Agency considers this design to be more appropriate for the assessment of safety because this design allows for comparison to a control arm.

The Agency recommends analysis of safety and efficacy in the intent to treat population (b) (4)

The Sponsor explained potential issues with a randomized cross over design, which include allocation of patients with a diverse genetic composition, which may be predictive of hemoglobin response. The Sponsor noted that this issue would be better handled with the EERW design. Whether the Agency would consider the results of an EERW design to support an indication would be a review issue. The Sponsor will need to address the limitations identified by the Agency with an EERW design to support an application submission.

2.1. Clinical development

Question 1: Based on the efficacy and safety profile of AG-348 observed to date, Agios is proposing to conduct a Phase 3 trial in non-transfusion-dependent (NTD) adults subjects with PK deficiency, defined as subjects who have had no more than (b) (4) transfusion episodes (days on which a transfusion occurred) in the 12-month period up to the first day of study dosing and no transfusion within (b) (4) months of the first day of study dosing.

Agios has the following questions for the Agency regarding this trial:

- a) The proposed Phase 3 trial includes an open-label lead-in phase with dose optimization, followed by a double-blind, (b) (4) period and an open-label extension period. Does the Agency agree that the design of this trial is acceptable to demonstrate the safety and efficacy of AG-348? Specifically, does the Agency agree with:
 - i. The proposed subject population for this trial?

FDA Response: No, see preamble.

Discussion: *The Sponsor proposes to modify the patient population to hemoglobin less than or equal to 10 g/dL at baseline for the inclusion criteria. The Agency considers this proposal as an acceptable starting point to continue the discussion in regards to the pivotal trial design.*

- ii. The proposed 3-part plan and treatment duration in this trial?

FDA Response: The proposal of Part 1 appears acceptable as a dose-escalation study to determine dose optimization and demonstrate AG-348 activity in patients with PK deficiency. Refer to the preamble for a discussion relevant to Part 2 and 3 of the proposed study design.

The treatment duration appears acceptable. We recommend that all patients should have at least 6 months of treatment to allow for collection of efficacy and safety data and at least 12 months of follow-up data to support evaluation for approval.

Discussion: *No discussion occurred.*

- iii. The use of placebo as the comparator in Part 2 of the trial and the corresponding step-wise scheme to reduce the active dose of the placebo-assigned subjects?

FDA Response: The use of placebo as a comparator and the step-wise approach to reduce the active dose in placebo-assigned subjects is acceptable. The Agency notes the risk of withdrawal hemolysis with abrupt interruption of AG-348. The proposed step-wise dose reduction mitigates the risk of withdrawal hemolysis, but the risk exists. The Agency recommends consideration of other study designs other than

(b) (4)

Discussion: No discussion occurred.

- iv. The proposed AG-348 dose levels and the open-label dose optimization (Part 1) strategy to optimize dosing on a per-subject basis prior to the Part 2 randomization phase?

FDA Response: The Agency has the following concerns regarding your dose selection:

- In your Phase 2 trial, AG-348 doses of 25 to 300 mg BID were evaluated in patients with PK deficiency. However, your proposed starting dose is 5 mg BID based on PK and PD simulation. We are concerned that your simulation extrapolated outside of studied dose range and such extrapolation may not be reliable.
- Given the EC₅₀ of AG-348 is 62 nM and the inverse dose-response relationship observed in your phase 2 trial, your dose escalation proposal in the planned phase 3 trial is not consistent with the PD and clinical response data. Please address this apparent discrepancy.
- AG-348 appears to increase liver alanine aminotransferase (ALT) or aspartate aminotransferase (AST), which are indicators of potential liver toxicity. You should identify the concentration/dose threshold for drug induced liver ALT and AST levels.
- Evaluate the exposure-response relationship between hormonal changes (e.g., testosterone, estradiol) and drug concentration.
- Evaluate if there is any relationship between drug-induced hormonal changes and incidence of insomnia.
- You have indicated that histamine H3 receptor modulation by AG-348 may be leading to the observed insomnia, which occurred at a rate of 32% in the phase 2 trial. Evaluate the dose and concentration thresholds for drug induced insomnia and propose a mitigation plan.

Discussion: *The Agency recommended the Sponsor include justification of the proposed dose in the protocol.*

- b) Does the Agency agree that the proportion of subjects with a [REDACTED] (b) (4) [REDACTED] is appropriate and represents a clinically meaningful primary endpoint in NTD adult patients with PK deficiency?

FDA Response: **The primary endpoint of [REDACTED] (b) (4) is not acceptable because the clinical benefit is unclear in patients with non-transfusion dependent PK deficiency. See preamble for information regarding study endpoints.**

Discussion: *No discussion occurred.*

- c) Regarding the primary endpoint of [REDACTED] (b) (4) rate, does the Agency agree that:
- i. The proposed sample size is acceptable?
 - ii. The proposed analysis methods are appropriate and adequate?

FDA Response: **The Agency cannot comment on the sample size or analytical methods since we do not agree with [REDACTED] (b) (4) as a primary endpoint.**

Discussion: *No discussion occurred.*

- d) Does the Agency agree that the secondary endpoints in the proposed trial are appropriate and reflect relevant measures of clinical improvement for NTD adult patients with PK deficiency?

FDA Response: **The Agency does not agree with the proposed trial population and primary endpoint and is not able to comment on the secondary endpoints. Although, the secondary endpoints should be clinically relevant endpoints to strengthen the overall clinical meaningfulness of the results. Refer also to the preamble.**

Discussion: *No discussion occurred.*

Question 2: Based on the efficacy and safety profile of AG-348 observed to date, Agios is proposing to conduct an additional pivotal trial in transfusion-dependent (TD) adult subjects with PK deficiency, defined as subjects who have had a minimum of 6 transfusion episodes in the 12-month period prior to the date of providing written informed consent.

- a) In addition to the above-referenced Phase 3 trial in the NTD adult population with PK deficiency, and in view of the extreme rarity of TD adult patients with this disease, does the Agency agree that an open-label pivotal trial with a primary endpoint of

(b) (4) and secondary endpoints of (b) (4) is acceptable to demonstrate the tolerability and benefit of AG-348 in adult patients with PK deficiency?

FDA Response: The primary endpoint (b) (4) in patients with transfusion-dependent PK deficiency is not acceptable. (b) (4)

(b) (4)

See
preamble for further information.

Discussion: *The Agency would accept descriptive efficacy to assess the population of patients with transfusion-dependence PK deficiency in order to support a potential indication in this population. The Agency requested that the Sponsor consider whether this population could be integrated in the proposed trial in non-transfusion dependent population as a separate non-randomized cohort.*

- b) Does the Agency agree that the design of the proposed pivotal trial in TD adult subjects with PK deficiency is acceptable? Specifically, does the Agency agree with:
- i. The proposed subject population for this trial?

FDA Response: The proposed transfusion-dependent PK deficiency population is acceptable.

Discussion: *No discussion occurred.*

- ii. The trial size?

FDA Response: See response to Question 2a. The sample size will need to be adjusted as appropriate based on the primary objective.

Discussion: *No discussion occurred.*

- iii. The use of, and specific methods for obtaining, historical control data (transfusion records) as the comparator in this trial?

FDA Response: The proposed approach and use of historical control data appears reasonable.

Discussion: *No discussion occurred.*

- iv. The strategy to optimize dosing on a per-subject basis prior to the fixed-dose period of the trial?

FDA Response: The dose optimization strategy appears acceptable.

Discussion: No discussion occurred.

- c) Does the Agency agree that the proposed secondary endpoints, [REDACTED] (b) (4) in the proposed pivotal trial in TD adult subjects with PK deficiency are appropriate and reflect relevant measures of the efficacy of AG-348 and clinical improvement for TD adult patients with PK deficiency?

FDA Response: See response to Question 2a and preamble.

Discussion: No discussion occurred.

Question 3: Does the Agency agree that the existing data from DRIVE-PK demonstrate that AG-348 provides clinical benefit in subjects with PK deficiency, a serious disease for which only supportive therapies exist, and that therefore – along with data from 2 completed safety studies of AG-348 in healthy adult subjects (AG-348-C-001 and AG348-C-002) – these data would support the submission and review of a New Drug Application (NDA) under the accelerating approval pathway for AG-348 for the treatment of adult patients with PK deficiency?

FDA Response: No, based on the information provided in the meeting package regarding data from DRIVE-PK, AG-348-C-001, and AG-348-C-002 it appears that the efficacy and safety data are inadequate to support an evaluation for an indication under the accelerated approval pathway. Splenectomy and red blood cell transfusion therapy are considered effective treatment in patients with PK deficiency. Accelerated approval of new drugs for serious and life-threatening illnesses must provide meaningful therapeutic benefit to patients over existing treatments per 21CFR314 Subpart H. Further, the inclusion and exclusion criteria in DRIVE-PK do not identify a patient population with PK deficiency that exhibits chronic symptomatic anemia or requires supportive treatment. Thus, a determination of meaningful therapeutic benefit in patients with PK deficiency treated with AG-348 is not feasible based on the available data. Refer also to preamble.

Discussion: No discussion occurred.

Question 4: Does the Agency agree that a submission package consisting of positive results from the 2 proposed pivotal trials in NTD and TD adult subjects, along with data from DRIVE-PK and the 2 completed safety studies of AG-348 in healthy volunteers (AG348-C-002), would support submission and review of a future NDA for full approval of AG-348 for the treatment of adult patients with PK deficiency? If yes:

- a) Does the Agency agree that the safety database of AG-348 will be acceptable to support the submission and review of a future NDA for full approval of AG-348 for the treatment of adult patients with PK deficiency?

FDA Response: Given the concerns of the proposed patient population, the proposed study design, and the available AG-348 safety and efficacy data, it is premature to comment on the necessary information to support a marketing application for regular approval of AG-348 in the treatment of adult patients with pyruvate kinase deficiency.

Discussion: *No discussion occurred.*

Additional Comments:

Clinical

You will need to document the effects of AG-348 on sleep pattern, sleep duration, and effects of insomnia on patient's quality of life. Revise your monitoring plan to include patient-reported assessments of their sleep-wake cycles and effects on patient's quality of life.

Clinical Pharmacology

FDA has the following recommendations regarding the overall clinical pharmacology development program for AG-348:

1. Identify the pathways by which AG-348 (and its metabolites) are eliminated and excreted to determine the need for organ impairment trial(s). Please refer to the Guidances for Industry [Pharmacokinetics in Patients with Impaired Renal Function](#) and [Pharmacokinetics in Patients with Impaired Hepatic Function](#) for more information.
2. Assess the following items to facilitate rational dose selection for efficacy and safety trials and dose adjustment for specific populations:
 - Effect of intrinsic factors (e.g. renal or hepatic impairment, disease, age, sex, body weight) and extrinsic factors (e.g., concomitant drugs that are strong CYP3A4 inhibitors) on systemic exposure of parent drug and any major metabolites
 - Effect of parent drug and major metabolites on the systemic exposure of concomitant drugs
 - Effect of concomitant gastric acid-reducing agents on the pharmacokinetics of the drug, if the drug is less soluble at pH 6.0–6.5 (with a solubility < clinical dose/250 mL) than at pH 1-2

Statistical

- 1. For regulatory submission purposes, the overall type I error rate should be controlled at a 2-sided 5% level. Please propose multiplicity adjustment for the primary and secondary endpoint analyses to control the overall type I error. The secondary endpoints at a specific time point (which you intend to include in the labeling) and the statistical analysis methods should be pre-specified. However, whether or not one or more secondary endpoints can be included in the labeling will be a review issue.**
- 2. Please submit Protocol/SAP that includes the detailed analysis methods and explanation of how to handle missing data for all the efficacy endpoints and PRO data collected.**
- 3. Please note that the number of patients not being evaluated for the primary and key secondary efficacy endpoints as well as the patient reported outcome endpoints should be kept to a minimum. Too much missing data will undermine the reliability and confidence of the results. Sensitivity analyses should be performed to examine the potential impact of the missing data. A prospectively planned procedure should be included in the protocol for minimizing missing data, for example, including obtaining data from patients at time of early withdrawal. Reasons for missing efficacy or PRO data at the overall score- and item-level should be documented and included in the analysis dataset. For further advice on missing data, see the National Academies of Sciences report on *The Prevention and Treatment of Missing Data in Clinical Trials*. An electronic version of the document can be found from The National Academies Press at http://www.nap.edu/catalog.php?record_id=12955 A special report of the document can be found at <http://www.nejm.org/doi/full/10.1056/NEJMSr1203730>**
- 4. Support the PRO instrument(s) you intend to utilize by available data and/or published peer-reviewed literature guided by the principles laid out in the 2009 FDA Guidance for Industry entitled “Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims” found at www.fda.gov/downloads/Drugs/Guidances/UCM19328.**

Discussion: *No discussion occurred.*

2.0 OTHER IMPORANT MEETING INFORMATION

PREA REQUIREMENTS

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(s) 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 these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of

IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is

intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

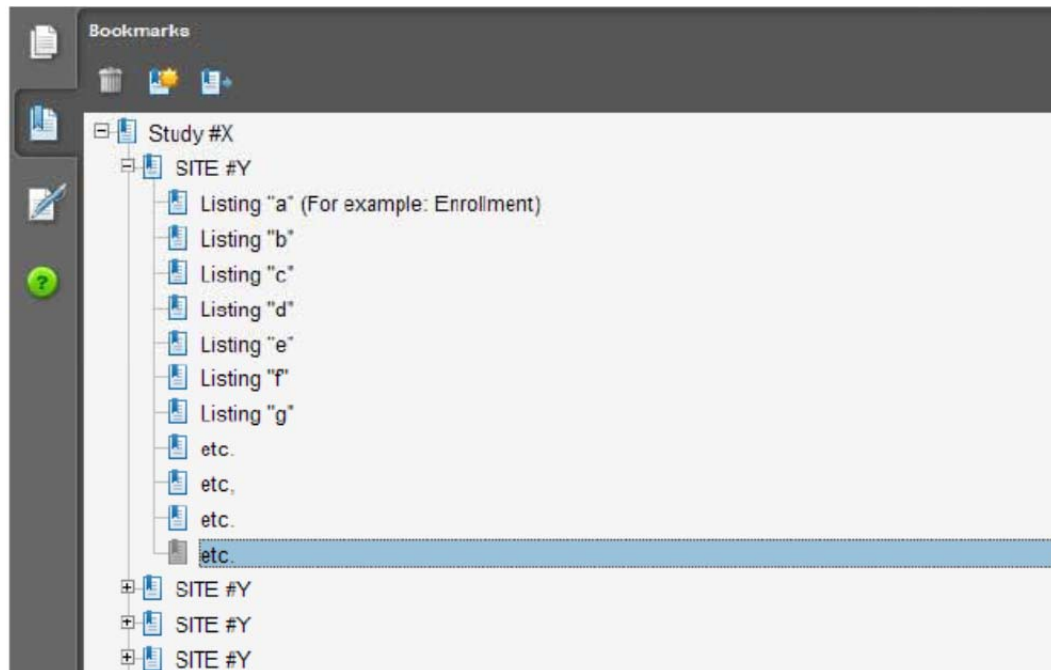
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified.

6.0 ATTACHMENTS AND HANDOUTS

Agios Pharmaceutical's background slides and response to the Agency's meeting preliminary comments and submitted via email on July 16, 2017 are appended.

21 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROMEO A DE CLARO
07/19/2017