CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216196Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 19, 2022
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216196
Product Name and Strength:	Pyrukynd (mitapivat) tablets, 5 mg, 20 mg, 50 mg
Applicant/Sponsor Name:	Agios Pharmaceuticals, Inc
OSE RCM #:	2021-1227-1
DMEPA 2 Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on December 15, 2021 for Pyrukynd. We reviewed the revised container labels and carton labeling to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

We note one of our recommendations was to replace the day of the week presentation on the blister wallet monthly packs with Day 1, Day 2, etc., however Agios stated they evaluated the preference for daily designation through a steering committee of patients with pyruvate kinase deficiency. In addition to patient preference, Agios stated "the printed days of the week allows patients to better track doses taken and mediates nonadherence". We note the designation on the taper pack blister wallets is Day 1, Day 2, etc. as the taper can begin at various days. As such, we find the proposal from Agios acceptable. The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Karpow, C. Label and Labeling Review for Pyrukynd (NDA 216196). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2021 NOV 17. RCM No.: 2021-1227.

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/s/

CELESTE A KARPOW
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 5, 2022
To:	Courtney Hamilton, PharmD, BCPS Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	PYRUKYND (mitapivat)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 216196
Applicant:	Agios Pharmaceuticals, Inc.

1 INTRODUCTION

On June 17, 2021, Agios Pharmaceuticals, Inc., submitted for the Agency's review an original New Drug Application (NDA) 216196 for PYRUKYND (mitapivat) tablets, for oral use. The proposed indication is for the treatment of adult patients with pyruvate kinase (PK) deficiency.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Non-Malignant Hematology (DNH) on June 23, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for PYRUKYND (mitapivat) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft PYRUKYND (mitapivat) tablets PPI received on June 23, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 27, 2021.
- Draft PYRUKYND (mitapivat) tablets Prescribing Information (PI) received on June 23, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 27, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

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LASHAWN M GRIFFITHS
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 5, 2022

To: Courtney Hamilton, PharmD, BCPS, Regulatory Project Manager, Division of Non-malignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, (DNH)

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for PYRUKYND (mitapivat) tablets, for oral use

NDA: 216196

In response to DNH's consult request dated June 23, 2021, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI), for the original NDA submission for PYRUKYND (mitapivat) tablets, for oral use (Pyrukynd). Per communications by electronic mail with Courtney Hamilton on January 3, 2022, OPDP has reviewed the proposed carton and container labeling as well.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNH (Courtney Hamilton) on December 27, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on December 15, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2021367
NDA#/Referenced IND for NDA:	NDA 216196/ IND 119825
Applicant:	Agios Pharmaceuticals
Established Name/Trade Name:	mitapivat
Indication:	Treatment of adult patients with pyruvate kinase deficiency (PKD) ☒Rare Disease/Orphan Designation
PDUFA Goal Date:	February 17, 2021
Review Division:	Division of Non-malignant Hematology (DNH)
Clinical Reviewer:	Hyon-Zu Lee
Clinical Team Leader (TL)	Tanya Wroblewski
Regulatory Project Manager:	Courtney Hamilton
COA Reviewer:	Mira Patel, Ph.D.
COA TL:	Selena Daniels, Pharm.D., Ph.D.
COA Division Director:	David Reasner, Ph.D.
Instruments reviewed:	1. Pyruvate Kinase Deficiency Diary (PKDD) ☒ Patient-reported outcome (PRO) 2. Pyruvate Kinase Deficiency Impact Assessment (PKDIA) ☒ Patient-reported outcome (PRO)

Table of Contents

1. EXECUTIVE SUMMARY

In this submission, the applicant is seeking approval of mitapivat for the treatment of adult patients with pyruvate kinase deficiency (PKD). (b) (4)

(b) (4)

The data from Study AG348-C-006 demonstrated that mitapivat had statistically significant improvement[1] in the selected secondary efficacy patient-reported outcome (PRO) endpoints compared with placebo. Despite achievement of statistical significance in both instruments, we have concerns regarding the reliability of the scores analyzed as part of the endpoints. Further, there were minimal observed score changes, if any, when looking at the item-level data at the raw score scale (e.g., some item scores reflect less than one category change on the raw score scale).

From a COA perspective, the PKDD and PKDIA measure some important aspects of pyruvate kinase deficiency symptoms and associated functional impacts. (b) (4) . If PRO data are labeled from the PKDD, we recommend a description of the items that are overly influencing the change in the total score to avoid misleading claims as well as including any important limitations to the interpretability of the data. For the PKDIA, the regulatory utility of this data is questionable. The PKDIA includes concepts that might be influenced by factors beyond the treatment (e.g., interference with leisure activities, negative impact on relationships) and may not accurately describe clinical benefit.

2 REVIEW CONCLUSIONS

The PKDD and PKDIA were reviewed for content validity and other measurement properties. The following issues were identified (b) (4) .

Issue 1: Content Validity

Both instruments measure some important aspects of pyruvate kinase deficiency symptoms and associated functional impacts. However, the relevancy of some of the items is questionable in participants with mild pyruvate kinase deficiency (i.e., not transfusion-dependent) based on the qualitative and quantitative data. For example,

- Based on item-level distributional data from Study AG348-C-006, the PKDD had skewed responses towards the lower ends of the response options, where 3.17% — 53.06% of participants endorsed the least severe category at baseline across the items in the PKDD (i.e., participants reporting "not at all" to the experience of the symptom). This observed

[1] Based on the pre-specified statistical methods

skewness was most extreme in Items 3 (jaundice) and 4 (bone pain). Qualitative data also showed that bone pain was less relevant and experienced by less participants than other signs and symptoms.

- Similarly, PKDIA had skewed responses towards the lower ends of the response options, where 10.26% ─ 34.62% of participants endorsed the least severe category responses at baseline across the items in PKDIA (i.e., participants reporting "none of the time/not at all" regarding the experience or difficulty with functioning).
- The PKDIA includes concepts that might be influenced by factors beyond the treatment (i.e., interference with leisure activities, negative impact on relationships, additional rest or sleep) and may not provide meaningful information regarding clinical benefit. As such, the regulatory utility of these concepts is unclear.

Issue 2: Other Measurement Properties

- It is difficult to fully evaluate the psychometric properties of the PKDD and PKDIA due to the scoring approach used. Based on the skewness observed in the PKDD and PKDIA item response distributions, the applicant collapsed response options for select items rated 0-10 to result in five response options and then summed the items into a daily sum score. The daily sum score was subsequently converted to a T-score. The applicant has not provided adequate justification regarding their scoring approach. The psychometric analyses were subsequently performed using this scoring approach. As such, the reliability and validity of the T-scores created from PKDD and PKDIA are unable to be verified due to limitations of the scoring approach.

Issue 3: Data Interpretability

- The scoring algorithms adopt multiple score transformations, which result in difficulties in the final score interpretation. Further, the small sample size (n=80) can result in large measurement error in item response theory (IRT) item calibration, which contributes to pervasive uncertainties in IRT scoring. Refer to Section 5.5.3 of this review for more details.
- Based on the response distributions, minimal change is observed at the item-level when looking at the raw score scale of the PKDD and PKDIA. Because there is minimal change demonstrated, it is difficult to assess whether the change constitutes a clinically meaningful change. Further, the external anchor used for anchor-based analyses has limitations (i.e., the measurement concept of the external anchor is the global impact of pyruvate kinase deficiency ["PK deficiency affected me"] and not individually related to pyruvate kinase deficiency symptoms or functional impacts, specifically).

If PRO data are labeled from the PKDD, we recommend a description of the items that are driving the total score may be useful to avoid inclusion of misleading claims as well as any important limitations regarding the interpretability of the data.

3 RECOMMENDATIONS FOR FUTURE STUDIES

For future clinical trials in this indication, it will be important for the Agency to review and concur on the scoring algorithm for the target clinical outcome assessments early in the development program to the extent possible. Sponsors should consider both qualitative and quantitative evidence to provide a clear rationale and justification on the method(s) (including

any proposed score transformations) used to derive the COA score(s). Sponsors should also consider whether their target population will have sufficient symptom severity and/or functional limitations, and how this may affect their proposed analyses and the instrument's ability to measure a clinically meaningful within-patient score change. Sponsors may want to explore designating individual item scores as endpoints as it appears that the PKDD and PKDIA are being influenced by a subset of items (e.g., tiredness and shortness of breath), with some items reflecting no change at all.

4 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:
There have been multiple communications with the applicant regarding the adequacy of the clinical outcome assessments (COAs), which included advice on the following:

- [redacted](b) (4)):
    - Advised measuring disease-specific symptoms separately from disease impacts.
    - Recommended to submit qualitative study protocol
    - Advised that the PKDIA might be more appropriate for use as an exploratory measure to provide supportive information.
    - Discouraged psychometric evaluation of the Pyruvate Kinase Deficiency Diary (PKDD) and Pyruvate Kinase Deficiency Impact Assessment (PKDIA) in a pivotal trial to determine its scoring, psychometric properties, and threshold for meaningful within-patient change as it would be applied to trial data intended to demonstrate treatment efficacy.

- Advice Letter dated August 14, 2017 (IND 119825[3]):
    - Recommended limiting the items in the PKDD to the most important concepts elicited from patients.
        - Recommended measuring signs and symptoms of most importance for improvement (i.e., tiredness, jaundice, and bone pain, shortness of breath).
        - Recommended to use a verbal rating scale with the "jaundice" item [redacted](b) (4).
        - Recommended inclusion of a "tiredness at worst" item.
        - [redacted](b) (4)
        - Indicated that additional qualitative work may be needed to further establish content validity of the tool if modified based on the suggestions above.
    - Recommended additional qualitative work to identify the most important impacts to improve to help guide in the concept selection for the PKDIA.
    - Recommended to provide details on PKDD and PKDIA scoring. For a PKDD total symptom score, recommended to exclude [redacted](b) (4).

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2 [redacted](b) (4)

[3] The development of the PKDD and PKDIA continued under IND 119825.

- Meeting Minutes (Pre-NDA) dated April 14, 2020 (IND 119825):
    - Indicated that a final qualitative report was needed to support evidence of content validity of the PKDD and PKDIA before review of the psychometric analysis plan.

      Reviewer's comment(s): *At this stage, the applicant did not have a final scoring algorithm for the PKDD and PKDIA and planned to test multiple scoring approaches using data from Study AG348-C-006 to derive the final scoring algorithm.*

Previous COA Reviews:

- (b) (4)
- C2017176 IND 119825 Patel (DAARTS Reference ID: 4147901)
- C2020123 IND 119825 Illoh (DAARTS Reference ID: 4586680)

Disease Background:
Pyruvate kinase deficiency is a rare nonspherocytic chronic hemolytic anemia. It is an autosomal recessive disease that is caused by mutations in the *PKLR* gene that result in defective red blood cell (RBC)-specific form of pyruvate kinase (PKR).

Pyruvate kinase deficiency has a variable clinical presentation, ranging from a mild to life-threatening condition, and can be associated with severe, debilitating comorbidities. Patients suffer from lifelong nonspherocytic hemolytic anemia marked by additional acute hemolytic crises during infections, episodes of stress, pregnancy, and aging. Symptoms can be fatigue, tachycardia, shortness of breath, jaundice, and bone changes associated with extramedullary hematopoiesis.

Investigational Product:
Mitapivat (also known as mitapivat sulfate and AG-348) is a first-in-class, orally bioavailable, potent, allosteric activator of wild-type PKR and a range of mPKR enzymes. Mitapivat acts by allosterically binding to the PKR tetramer and enhancing its affinity for PEP, thereby restoring the conversion of PEP + ADP to pyruvate + ATP. Mitapivat thus targets the underlying enzymatic defect that causes hemolysis in pyruvate kinase deficiency by restoring PKR activity.

Materials reviewed:

- AG348-C-006 Clinical Study Report
- AG348-C-006 Statistical Analysis Plan
- PRO evidence dossier
- Applicant's Response to Information Requests (October 25 and 28, 2021)

5 CLINICAL OUTCOME ASSESSMENT REVIEW

5.1 Clinical Trial Population

The target population for Study AG348-C-006 were adults (>18 years) with pyruvate kinase deficiency who were not regularly receiving transfusions. The following definition was used for subjects who were not regularly receiving transfusions: no more than 4 transfusion

episodes in the 12-month period up to the first day of study treatment and no transfusions in the 3 months before the first day of study treatment.

Eligible participants must have an average screening hemoglobin (Hb) concentration of ≤100 g/L (10 g/dL; 6.21 mmol/L).

A complete list of the inclusion and exclusion criteria is summarized in the clinical study protocol and report for Study AG348-C-006.

5.2 Clinical Trial Design

Study AG348-C-006 is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mitapivat in not-regularly-transfused adults with pyruvate kinase deficiency. The study consisted of a Dose Optimization Period (Part 1) followed by a Fixed Dose Period (Part 2).

A total of 80 participants were randomized in the study, with 40 in the mitapivat arm and 40 in the placebo arm. Seventy-nine (98.8%) participants completed the study.

5.3 Endpoint Position, Definition, and Assessment Schedule

A description of the intended placement of the COA in the endpoint hierarchy (primary and key secondary endpoints), including the endpoint definition and assessment schedule for Study AG348-C-00 is provided below.

Primary endpoint

- The Hb response, defined as a ≥15 g/L (1.5 g/dL; 0.93 mmol/L) increase in Hb concentration from baseline that is sustained at 2 or more scheduled assessments at Weeks 16, 20, and 24 during the Fixed Dose Period.

Ranked secondary COA efficacy endpoints

- Change from baseline in the PKDD weekly mean score
- Change from baseline in the PKDIA weekly score

Subjects completed the PKDD and PKDIA and several other measures during screening and at varying intervals according to the schedule of assessments.

- The PKDD was collected daily during Screening (up to 6 weeks) and daily throughout Part 1 and Part 2 (24 weeks).
- The PKDIA was collected on the first day of Screening (+1 day) and at weekly intervals (±1 day) until Day 1 of Part 1. During Part 1 and Part 2, the PKDIA was collected at Weeks 4, 8, 12, and 24. In addition, the PKDIA was collected at Weeks 16 and 20.

The PKDD and PKDIA were completed at the end of each day by the participants.

Reviewer's comment(s):

- *For the PKDD, PKDIA, LDH, and haptoglobin endpoints, the Hochberg testing procedure (Hochberg, 1988) will be used with 2-sided α=0.05 if all 4 endpoints*

higher in the hierarchy achieved statistical significance. Four 2-sided p-values for PKDD, PKDIA, LDH, and haptoglobin endpoints will be ordered from largest to smallest and compared to a set of critical values. The comparison will be conducted sequentially by comparing the largest p-value to α, then the second-largest p-value to α/2, then the third largest p-value to α/3, and the fourth largest p-value to α/4, until a p-value for an endpoint is smaller than the corresponding critical value, whereupon the Hochberg procedure provides a conclusion of statistically significant effect of mitapivat compared to placebo for that endpoint and all endpoints with smaller p-values.

- *Other COAs (EQ-5D-5L, SF-12v2, The Functional Assessment of Cancer Therapy-Anemia [FACT-An]– "Additional Concerns," and Patient Global Impression of Severity [PGIS]) in the study were collected on the first day of Screening (+1 day) and at weekly intervals (±1 day) until Day 1 of Part 1. In Parts 1 and 2, the PGIS were collected at Weeks 4, 8, 12, and 24; and the EQ-5D-5L, SF-12v2, and FACT-An were collected at Weeks 12 and 24.*

5.4 Targeted Clinical Outcome Assessment-Related Labeling Claim(s)

The sponsor has proposed the following specific targeted COA-related labeling claims:

Reviewer's comment(s):

- *The data from Study AG348-C-006 demonstrated that mitapivat had statistically significant improvement in the selected secondary efficacy patient-reported outcome (PRO) endpoints compared with placebo. Despite achievement of statistical significance in both instruments, there are concerns regarding the reliability of the scores analyzed as part of the endpoints. Further, there were minimal observed score changes, if any, when looking at the item-level data at the raw score scale (e.g., some item scores reflect less than one category change on the raw score scale).*

- *From a COA perspective, the PKDD and PKDIA measure some important aspects of pyruvate kinase deficiency symptoms and associated functional impacts.* (b) (4)

  - *If PRO data are labeled from the PKDD, we recommend a description of the items that are driving the total score to avoid misleading claims as well as any important limitations regarding the interpretability of the data.*
  - *For the PKDIA, the regulatory utility of this data is questionable. The PKDIA includes concepts that might be influenced by factors beyond the treatment (e.g., interference with leisure activities, negative impact on relationships).*

5.5 Clinical Outcome Assessment(s)

5.5.1 Clinical Outcome Assessment Description(s)

Pyruvate Kinase Deficiency Diary (PKDD)

The PKDD is a 7-item PRO instrument designed to assess the signs and symptoms of pyruvate kinase deficiency. Items are rated on multiple response scales. Six items are rated using an 11-point numeric rating scale (NRS) ranging from 0 ("No or not at all sign/symptom") to 10 ("Extremely or worst possible or high sign/symptom). One item (Item 3-jaundice) is rated on a five-point verbal rating scale (VRS) that ranges from 0 ("No yellow eyes and/or skin") to 4 ("Very severe yellow eyes and/or skin"). Item 4 (bone pain) also contains a "Not experience" response option for participants who have never experienced this symptom. Item 5 (shortness of breath) contains a "Not applicable" response option, as well as an option for those participants who avoided the activity due to the inability to perform moderate physical activity. The recall period is "today (from the time you woke up this morning to the time you are completing this questionnaire)."

Pyruvate Kinase Deficiency Impact Assessment (PKDIA)

The PKDIA is an 8-item PRO instrument designed to assess the impacts of pyruvate kinase deficiency. Seven items are rated on an 11-point NRS ranging from 0 ("None of the time" or "Not at all difficult") to 10 ("All of the time" or "Extremely difficult"). One item (Item (b) (4)-need for additional rest or sleep) uses a 5-point VRS that ranges from 0 ("No additional rest or sleep") to 4 ("A lot of additional rest or sleep"). The recall period is the previous 7 days.

Reviewer's comment(s):
The PKDIA was generated initially as a 12-item PRO measure based on cognitive interviews. The applicant indicated that modeling of the reduced item response set showed that not all items performed well in measuring a single latent construct, and so the item set was reduced from twelve to eight items. Refer to section 5.5.3 regarding what items are included in the total score, as well as the concerns related to the appropriateness of item response theory (IRT) for the scoring. Note that all twelve items were administered in Study AG348-C-006.

5.5.2 Conceptual Framework(s)

The conceptual frameworks for the instruments are shown in Figures 2 and 3 (shown on next page).

Figure 1. Conceptual framework for PKDD

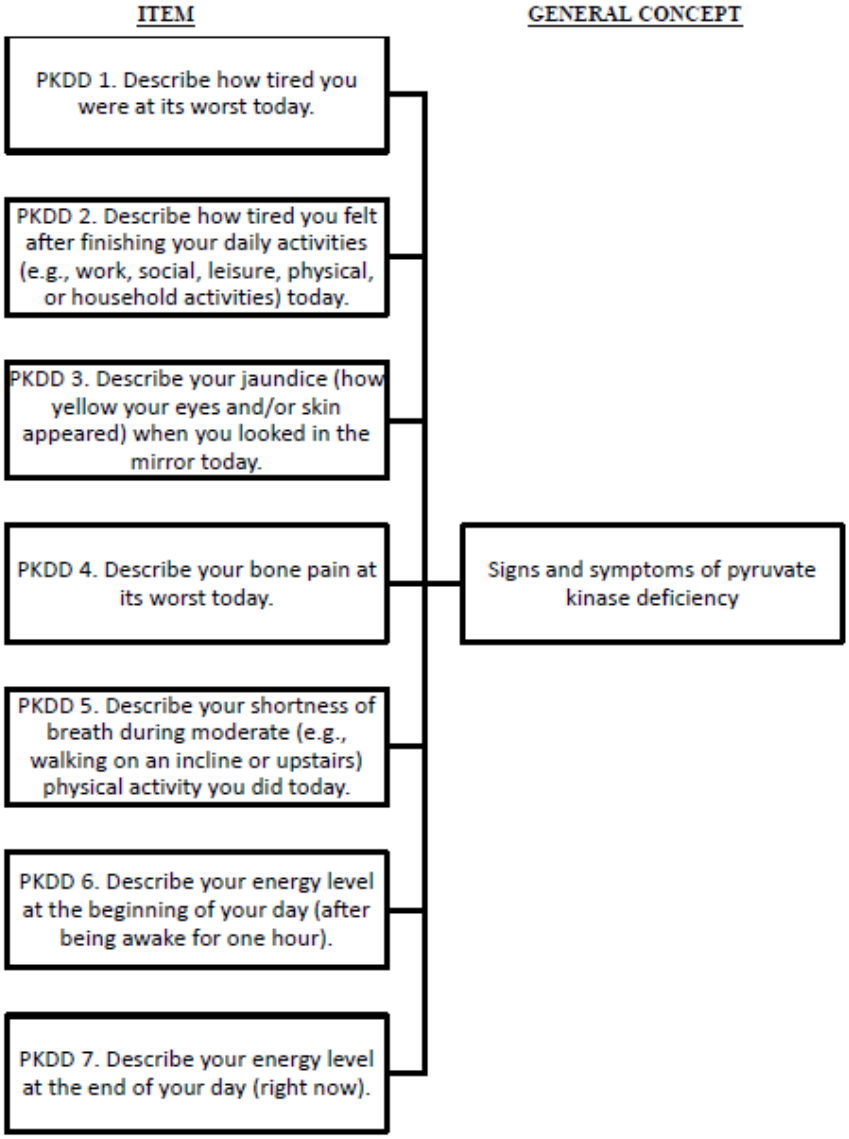
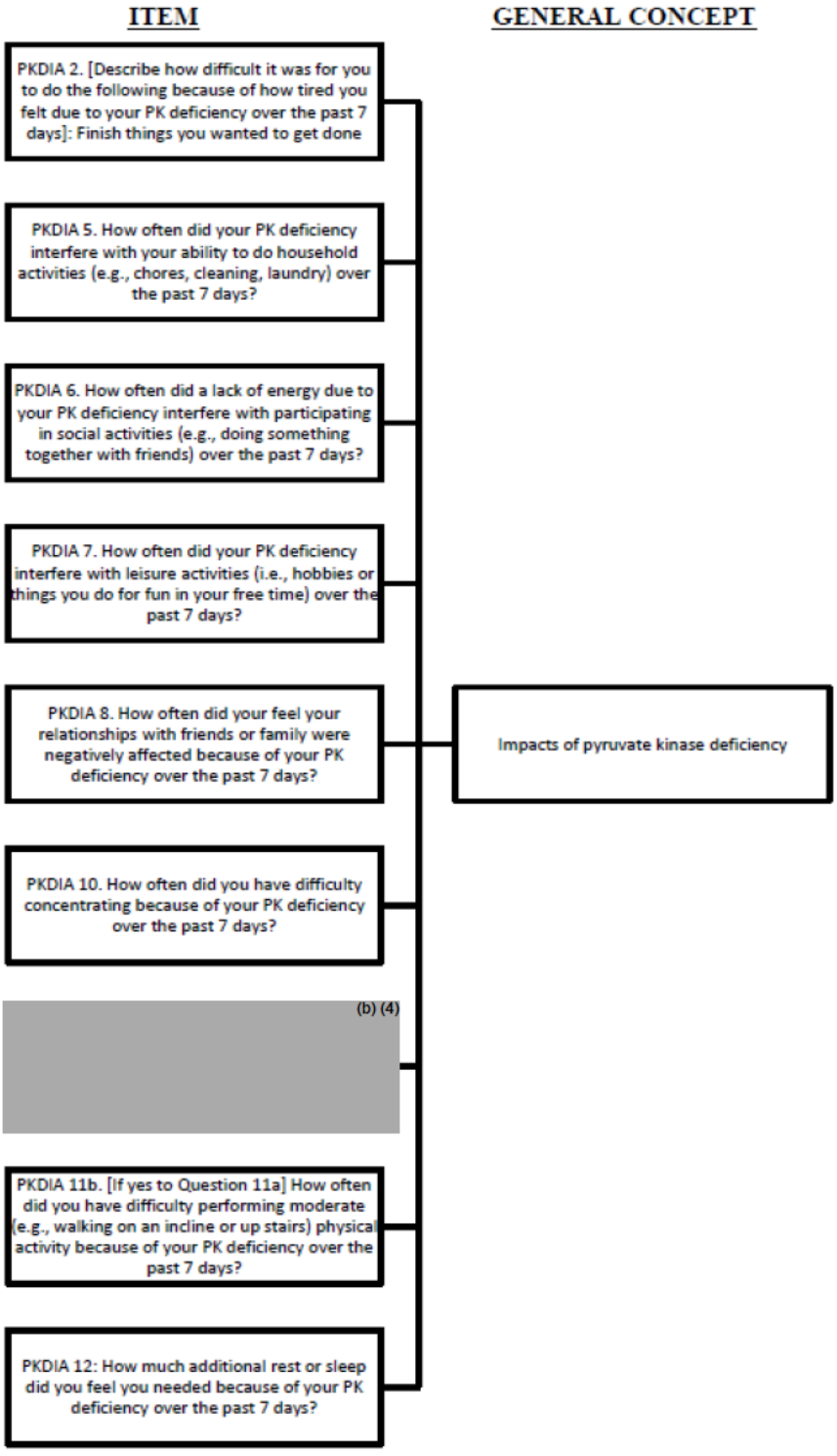


Figure 2. Conceptual Framework for PKDIA



5.5.3 Scoring Algorithm

For evaluating scoring for the PKDD and PKDIA, an IRT modeling approach was utilized using a graded-response model (GRM) framework. For the PKDD, the fit statistics were *R*MSEA < 0.01

(<0.01, 0.132), *S*RMR = 0.15, TLI > 0.99, *C*FI> 0.99. For the PKDIA, the fit statistics were *R*MSEA = 0.159 (0.117, 0.200), *S*RMR =0.18, TLI = 0.89, *C*FI= 0.91.

PKDD
The PKDD generates a total score based on a T-score. The score ranges from 25-76, with higher scores indicating greater symptom severity.

For the endpoint, a weekly average score was computed. The weekly average scoring includes Items 1, 2, 3, 4, 5, 6, and 7. Scores are produced by first reverse keying Items 6 and 7 (regarding energy levels) for each study day by subtracting the observed score from 10 so that higher scores represent worse signs and symptoms of PK deficiency for all PKDD items. Next, the response options for Items 1, 2, 4, 5, 6, and 7 are collapsed by dividing the observed value by 2 and rounded down to the nearest integer. If the observed value equals 10, 1 is subtracted from the divided score before rounding down to the nearest integer (e.g., [10/2]- 1). This process reduces the 0-10 ratings to a 0-4 scale. Once the preceding steps have been completed, PKDD items can be summed for each daily administration to create a daily PKDD sum score; a scoring table has been provided in Appendix C. The next step is to convert the daily PKDD sum score to a T-score via the scoring table. These daily PKDD T-scores can then be averaged across a study week which includes at least four administration days.

PKDIA
The PKDIA generates a total score based on a T-score. The score ranges from 30-76, with higher scores indicating greater negative impact.

For the endpoint, a weekly average score was computed. PKDIA scoring includes Items 2, 5, 6, 7, 8, 10, 11b, and 12 (item numbering from original version of PKDIA). Scores are produced by first collapsing response options for Items 2, 5, 6, 7, 8, 10, and 11b in the same manner used for the PKDD weekly average score, i.e., observed values are divided by 2 and rounded down to the nearest integer, if the observed value equals 10 then 1 is subtracted from the divided value and rounded down. Next, all items are summed for each administration and a scoring table (see Appendix C) is used to convert PKDIA summed scores to T-scores.

Reviewer's comment(s):
The four PKDIA items excluded from scoring were difficulty starting things due to feeling tired (Item 1), feeling bothered by appearance (Item 3), receiving unwanted attention (Item 4), and impact on work or school (Item 9). Item 11a was also removed, but Item 11b remained in the final version.

The applicant noted the following regarding the methods for the scoring algorithms:

- *Rating scales were collapsed due to a lack of responses in some categories. Additionally, response distributions were skewed on the 11-category response scale which resulted in sparse responses for some rating categories in the upper end of the response scale.*
- *The division by 2 described in the scoring algorithm aids in facilitation of programming the collapsing of categories from the 0-10 response scale to a 0-4 response scale.*

- *A scoring table was created to leverage the scaling properties of IRT scores with respect to empirically determining scores on the latent variable continuum using information in the data.*

In discussion with the Patient-focused Statistical Support team (PFSST), the proposed scoring algorithms had major issues as the scoring algorithms adopt multiple score transformations, which are unjustified and result in difficulties in the final T-score interpretation., and the following was concluded:

1. *The rescaling from the 0-10 NRS to a 0-4 VRS appears to be arbitrary.*
2. *The T-score is a linear transformation of the Z-score, which is constructed using item response theory (IRT) scoring. While acknowledging the benefit and advantage of using IRT scoring as compared with the conventional classical test theory (CTT) scoring, the PFSST reviewer cannot agree with using IRT scoring to support the PKDD- and PKDIA-based endpoint calculations due to the small sample size (n=80), the lack of detailed information on IRT scoring, and the unclear rationale of the scoring tables. Specifically,*
    a. *The small sample size could result in large measurement error in the IRT calibration, which can further contribute to pervasive uncertainties in IRT scoring. This is well-known limitation for IRT scoring. For example, as shown in Table 10 on page 62/3673 of the COA evidence dossier, item slopes for some of the items are very large (e.g., item 1 a1 = 5.65), which may indicate large standard errors. Note that the Sponsor did not provide standard error estimates or Fisher information at each score level in the COA dossier.*
    b. *Based on the applicant's justification of the scoring tables, the Z-score represents expected a posterior (EAP) score derived from the R package mirt (i.e., each response pattern has one corresponding EAP score). The applicant further states that "each EAP score in column 2 of the [scoring] table represents the most probable theta level across all possible response pattern combinations for that single scale-level sum score". This IRT scoring method of transforming a raw sum score to a latent factor score appears to resemble a PROMIS scoring table[4]. However, without details on the exact transformation, the Agency cannot fully assess the sponsor's methodology. Furthermore, the PFSST reviewer was unable to find relevant literature to support the Sponsor's scoring approach. Therefore, the resulting latent factor scores (Z-scores) and corresponding T-scores are challenging to interpret.*

Given these concerns, PFSST recommends against the use of T-scores for efficacy analyses (b) (4) (b) (4) *. The raw scores are more interpretable.*

[4] https://www.healthmeasures.net/index.php?option=com_content&view=article&id=180&Itemid=994

5.5.4 Content Validity

The applicant has completed the following activities to develop the PKDD and PKDIA instruments:

- literature review
- expert input
- patient input (concept elicitation and cognitive interviews)

A summary of the results for each activity is described below. Refer to the PRO evidence dossier for full details regarding the methodology and results of each activity.

Literature Review

- The applicant conducted a literature review to identify signs, symptoms, and impacts commonly experienced by participants with PK deficiency. The targeted review was conducted using select materials (e.g., summary of patient advisory board meeting, patient survey results). A total of seven materials were selected for inclusion in the extensive review and data extraction process. Refer to Section 2.1 of Appendix A in the Development of Patient-Reported Outcome Measures for Adults with Pyruvate Kinase Deficiency: Report for a complete list of materials reviewed.

- The primary symptoms reported by participants in the literature included fatigue, tiredness, exhaustion, lethargy, jaundice, bone pain, and body pain.

- The primary impacts found in the literature included impacts on activities of daily living, completing household activities, changing or modifying daily schedules due to over-exertion, wearing makeup or clothes to conceal appearance concerns, difficulties concentrating, feeling angry or frustrated, missing work and/or school, impacts on relationships with family and friends, and difficulties playing sports.

- Based on the materials reviewed, two preliminary hypothesized conceptual frameworks were developed: one specific to the signs and symptoms of PK deficiency (Figure 1 of Appendix A in the Development of Patient-Reported Outcome Measures for Adults with Pyruvate Kinase Deficiency: Report) and one specific to the impacts of PK deficiency on patients (Figure 2 of Appendix A in the Development of Patient-Reported Outcome Measures for Adults with Pyruvate Kinase Deficiency: Report).

Expert input

- Input was obtained by one PRO specialist and two clinical experts on the study documents to be used for the concept elicitation interviews, including the eligibility criteria and the interview guide.

- Input was also obtained from the PRO specialist, the two clinical experts, and a PK deficiency patient advocate during item generation for the PKDD and PKDIA.

Patient Input

Concept elicitation

- Twenty-one participants were interviewed. About half of the interviews (n=10, 47.6%) were conducted in the United States while the others were conducted in Germany (n=4, 19%) and the Netherlands (n=7, 33.3%). In the United States (US), four subjects (19%) were from the Amish community. The majority of the participants were white (n=10, 47.6%), non-Hispanic or Latino (n=10, 47.6%), and female (n= 11, 52.4%) with a mean age of 40 years (range: 19 to 58 years). Most participants were transfusion independent (n=16, 76.2%), while five were transfusion dependent (23.8%).

- A total of 38 unique signs and symptoms of PK deficiency were reported. All concepts were spontaneously reported by at least one participant (4.8%). Among the 38 signs and symptoms spontaneously reported and currently experienced, saturation was achieved for all but one concept (i.e., yellow diarrhea).

- The most frequently reported sign, yellow eyes, was reported by 19 subjects (90.5%), and all but one subject reported the concept spontaneously. Other frequently reported signs and symptoms (defined as reported by 11 or more subjects [≥52.4%]) included fatigue (n=15, 71.4%), low energy (n=13, 61.9%), and shortness of breath (n=13, 61.9%). Somewhat frequently reported signs and symptoms (defined as reported by 6-10 subjects [28.6-47.6%]) included increased heart rate (n=9, 42.9%), bone pain (n=8, 38.1%), exhaustion (n=8, 38.1%), pale skin (n=7, 33.3%), and dizziness/lightheadedness (n=6, 28.6%).

  Reviewer's comment(s): *The applicant reports that there were no major differences in the signs and symptoms reported by ~25% or more participants from the US, Germany, or the Netherlands.*

  Although participants reported experiencing fatigue, they described it in the context of being tired.

- Of the signs and symptoms for which ≥25% of participants provided a bothersome rating (on an 11-point numeric rating scale (NRS) that ranged from 0 ("not at all bothersome") to 10 ("extremely bothersome")), the most bothersome symptom was yellow skin (n=8; $\bar{x}$=4.9; SD=3.2; range=0.0-9.0) followed by yellow eyes (n=6; $\bar{x}$=3.3; SD=2.5; range=0.0-8.0).

- Of the signs and symptoms for which ≥25% of participants provided severity ratings (on an 11-point NRS that ranged from 0 ("no [symptom]" to 10 ("[symptom] as bad as you can imagine")), the most severe symptom was yellow eyes (n=6; $\bar{x}$=7.2; SD=1.6; range=5.0-9.0), followed by yellow skin (n=9; $\bar{x}$=6.9; SD=2.1; range=4.0-10.0).

  Reviewer's comment(s): *While jaundice was reported frequently and most severely in the qualitative study, this symptom did not have sufficient severity at baseline in Study AG348-C-006.*

- The signs/symptoms that appear to be of most importance to PK deficient patients for improvement include tiredness (n=8, 38.1%), followed by yellow skin (n=5, 23.8%) and bone pain (n=4, 19.0%). Yellow eyes and fatigue were also named by four subjects (19.0%) each.

- A total of 59 unique impacts of PK deficiency emerged from the concept elicitation interviews and were divided into 9 categories (i.e., activities of daily living, appearance, cognitive, emotional, leisure activity, physical, sleep, social, and work or school). All impacts were spontaneously reported by at least one subject (4.8%). Among the 59 impacts spontaneously reported and currently experienced, saturation was achieved for all but two concepts (i.e., pregnancy complications and envy).

- The most frequently reported impact was the need for additional rest (n=18, 85.7%). Two other physical impacts were also reported: difficulty with exercise or sports (n=16, 76.2%) and getting sick easily and/or often (n=14, 66.7%).

  Reviewer's comment(s): *The applicant reported that participants attributed their difficulty with exercise/sports to shortness of breath, tiredness, and/or bone pain.*

- Other frequently reported impacts (defined as reported by 11 or more subjects [≥52.4%]) included negative impact on appearance (n=13, 61.9%), receiving unwanted attention (n=12, 57.1%), and negative impact on social activities (n=11, 52.4%). Somewhat frequently reported impacts (defined as reported by 6-10 subjects [28.6-47.6%]) included: feeling concerned (n=10, 47.6%), difficulty walking (n=9, 42.9%) difficulty climbing stairs/walking uphill (n=8, 38.1%), negative impact on leisure activities (n=8, 38.1%), negative impact on work or school performance (n=8, 38.1%), feeling annoyed (n=7, 33.3%), difficulty with household activities (n=7, 33.3%), missing work or school (n=6, 28.6%), and lack of motivation (n=6, 28.6%).

  Reviewer's comment(s): *The applicant reported that there were no major differences in the most frequently and somewhat frequently reported impacts reported by participants from the US, Germany or the Netherlands. All but one of the most frequently or somewhat frequently reported impacts was reported in the US, Germany and the Netherlands. Negative impact on work or school performance was reported by subjects in the US and the Netherlands only.*

- Of the impacts for which ≥25% participants provided difficulty ratings (on an 11-point NRS that ranged from 0 ("not at all difficult") to10 ("extremely difficult")) the following were reported: difficulty with exercise/sports (=5.2; SD=2.0; range=2.0-8.0), the need for additional rest (=5.4; SD=2.2; range=2.5-10.0), getting sick easily/often (=7.8; SD=2.0; range=4.0-10.0), negative impact on social activities (=6.1; SD=2.6; range=2.0-9.0), and unwanted attention (=4.1; SD=1.8; range=1.0-6.0).

- Based on concept elicitation interviews, the 11-item PKDD and 8-item PKDIA were generated.

Cognitive interviews

- Twenty participants were interviewed. Eighteen (90%) of the participants were the same participants from the concept elicitation interviews. Among the participants interviewed, half (n=10, 50%) were conducted in the US while the others were conducted in the Netherlands (n=7, 35%) and Germany (n=3, 15%). Four subjects (20%) self-identified as Amish, although one (5.0%) of these subjects did not live a traditional Amish lifestyle. Half of the participants were white (n=10, 50%) and non-Hispanic or Latino (n=10, 50%). The majority of the participants were female (n= 11, 55%) with a mean age of 43 years (range: 21 to 78 years).

- Regarding PKDD,
  - In general, the PKDD was well understood by participants. Overall, all participants (n=20, 100.0%) demonstrated the ability to understand the PKDD instructions as intended. Additionally, at least 75.0% of subjects (n=15) or more, interpreted each item as intended.
  - The most notable issues related to interpretation were in regard to relevance and attribution issues. To remedy issues with relevance, Item (b) (4) (difficulty concentrating) was removed from the PKDD and instead added to the PKDIA measure. To remedy issues with appropriate attribution, Item (b) (4) (starting things) and Item (b) (4) (finishing things) were modified to more clearly direct subjects to consider these items in terms of their energy level. (b) (4)
  - Participants did not consistently understand Item (b) (4) (additional rest/sleep). The phrase "feel you needed" was added to the item to better direct subjects to consider only how much additional rest or sleep they felt they needed but not the amount of additional rest or sleep they physically took.
  - Participants understood and appropriately used the recall period, "over the past day (from the time you woke up to the time you are completing this questionnaire," as most subjects found it easy to respond over the past day (n=16, 80.0%) and an accurate description of their symptom experience (n=14, 70.0%). (b) (4)
  - Participants encountered minimal issues interpreting and using each item's response options, as the number of subjects who misinterpreted any given item's response did not exceed 20.0% of the sample (n=4 subjects). Response option selections were also evenly distributed across items.
  - The most common issues related to response option interpretation including difficulty selecting the corresponding response option to their described experience, and difficulty differentiating between two response options.
  - Item (b) (4) (shortness of breath) response options were updated to provide a clearer distinction between the non-NRS options, and also to remain consistent with response option structure included in the PKDIA.

- Regarding the PKDIA,
  - In general, the PKDIA was well understood by participants. Overall, all participants (n=20, 100.0%) demonstrated the ability to understand the PKDIA instructions as intended, and at least 85.0% of subjects (n=17) or more, interpreted each item as intended.
  - [redacted] Additionally, [redacted] (household activities) was relocated to appear earlier in the measure with the other "activity" related items to improve the organization and flow of the measure, and subsequent item numbering was adjusted accordingly.
  - [redacted].

Reviewer's comment(s):
Overall, tiredness, jaundice, and shortness of breath items from the PKDD appeared to be supported by the qualitative data. The applicant reported that bone pain (Item [redacted] and [redacted] were found to be less relevant and experienced by fewer participants than other concepts, however, the margin was not large enough to support removal of these items, and they were retained for further exploration during planned psychometric validation.

Regarding the PKDIA, the qualitative summary report lacks information on the most important impacts of PK deficiency to improve. The applicant was previously recommended to ask patients what the most important impacts are associated with pyruvate kinase deficiency to improve to help guide their concept selection for this instrument. The PKDIA includes concepts that might be influenced by factors beyond the treatment (e.g., interference with leisure activities, negative impact on relationships, additional rest or sleep). This reviewer seeks Clinical input with regard to the clinical relevance of these concepts, as well as the regulatory utility of such concepts.

Based on FDA feedback conveyed in the Advice Letter dated August 14, 2017, the following changes were made by the applicant prior to administration in Study AG348-C-006:

PKDD

- *An item assessing tiredness at its worst was added to the PKDD.*
- [redacted]
- *Response options for the item assessing jaundice were revised [redacted] to a 5- point VRS.*
- *The item assessing [redacted] was removed.*
- *Items were reordered and renumbered to improve flow.*

PKDIA

- [redacted] (b) (4)
- *Items were renumbered.*

The applicant did not conduct additional qualitative work after the suggested modifications were made to the instruments, therefore it is unknown whether the addition of the tiredness at its worst item and the changes made to response options for the item evaluating jaundice were relevant to and understood by patients.

Additional advice that was conveyed to the applicant that was not implemented:

- *Based on the qualitative findings and discussion with Clinical, the applicant was recommended to measure tiredness, jaundice, and bone pain as the core signs/symptoms of PK deficiency with the inclusion of shortness of breath (n=13, 61.9%). For the remaining signs/symptoms, the applicant was recommended to exclude from the total score. This did not preclude the applicant from measuring these other signs/symptoms for exploratory purposes.*
- *Score jaundice separately from the other symptoms as jaundice is a sign.*
- *Limit the items in the PKDIA to the most important impacts elicited from patients.*
- *Provide details on scoring of the PKDD and PKDIA.*

5.5.5 Other Measurement Properties

The applicant evaluated the psychometric properties of the PKDD and PKDIA using data from Study AG348-C-006. The analysis population to evaluate the measurement properties of the instruments were 80 subjects. The blinded data from the full analysis set was the basis for all validation analyses. Baseline PKDD and PKDIA assessments were available for 77 and 78 patients, respectively.

Reviewer's comment(s):

- *The applicant was discouraged to conduct psychometric evaluation of instruments in a pivotal trial to determine its scoring, psychometric properties, and threshold for meaningful change as it would be applied to trial data intended to demonstrate treatment efficacy ([redacted] (b) (4)).*

A summary of the psychometric findings for each instrument is provided below. For more details on the methodology and results of these analyses, refer to the Appendix C of the PRO evidence dossier.

PKDD

- The median change from baseline in select PKDD items are shown in Table 1.

Table 1. Median (range) change from baseline in individual PKDD items 1, 4, and 5 (weekly average raw scores) for Study AG348-C-006

PKDD	**Baseline**		**Week 24**		**Change from Baseline to Week 24**	
	Placebo (n=40)	Mitapivat (n=40)	Placebo (n=40)	Mitapivat (n=40)	Placebo (n=40)	Mitapivat (n=40)
Tired Worst	5.3 (0, 9)	6.3 (0, 9)	5.3 (0, 10)	4.8 (0, 8)	-0.1 (-5, 5)	-1.3 (-6, 2)
Jaundice	1.7 (0, 3)	1.5 (0, 3)	1.1 (0, 4)	1.0 (0, 3)	0.0 (-2, 1)	-0.2 (-2, 1)
Bone Pain Worst	0.7 (0, 6)	0.1 (0, 8)	0.8 (0, 5)	1.0 (0, 6)	-0.1 (-5, 5)	0.0 (-5, 3)
Shortness of Breath	3.8 (0, 9)	2.6 (0, 8)	2.7 (0, 7)	1.4 (0, 7)	-0.4 (-5, 2)	-1.1 (-4, 2)

Reviewer's comment(s): *When looking at the individual raw daily scores, this reviewer noted minimal change was observed in the items (see Table 3 in Appendix E). Therefore, the applicant was requested to provide median weekly average raw scores for items 1 (tiredness at worst), 3 (jaundice) 4 (bone pain), and 5 (shortness of breath). These were the initial items previously recommended to the applicant to measure as they appear to represent the core pyruvate kinase deficiency symptoms based on patient input and Clinical input. Based on Table 7, this reviewer notes that there may be insufficient symptom severity for jaundice and bone pain.*

- 3.17% ─ 53.06% of participants endorsed the least severe category responses at baseline across PKDD items (i.e., participants reporting no symptoms). For PKDD item 4 (bone pain), 41.3% of participants endorsed the least severe category response at baseline. Additionally, about 22% of the participants found this item to be not applicable (i.e., chose "not applicable" response option).

Reviewer's comment(s): *The applicant reported that the responses were skewed right such that respondents tended to use the lower ends of the response options. This observed skewness was most extreme in Items 3 (jaundice) and 4 (bone pain). The finding for bone pain is consistent to the qualitative findings in that it was demonstrated to be less relevant and experienced by less participants than other concepts.*

This reviewer has concern regarding this approach taken. Based on discussion with PFSST the applicant has not justified this approach. Therefore, the results of the psychometric analyses are difficult to interpret since they are based on this scoring approach.

- Inter-item correlations >0.80 were shown for PKDD Item 1 (tiredness at worst) and Item 2 (daily activities) (ρ=0.84). For the other PKDD items, the correlations were mostly low to moderate (ρ=0.06 to 0.58).

- For assessment of internal consistency reliability of the PKDD, the ω coefficient[5] was 0.86.

- For assessment of test-retest reliability[6] of the PKDD, the intra-class correlation coefficient (ICC) was 0.94.

  Reviewer's comment(s): *The quantitative report did not specify how the applicant defined a stable analysis population for the assessment of test-retest reliability.*

- For assessment of convergent validity of the PKDD, low to strong correlations (|r|=-0.30 to 0.72) were observed between the PKDD scores and various patient-reported assessments, such as the PKDIA, PGIS, FACT-An, EQ-5D-5L (UK and US versions), SF-12 Mental Component Score, and SF-12 Physical Component Score.

- For assessment of known-groups validity, the PKDD scores observed across the PGIS subgroups showed better PKDD scores (lower scores) on average for the patient subgroups with no pyruvate kinase deficiency signs/symptoms than subgroups with greater levels of severity at baseline to Week 24. There was an exception where the highest level of the PGIS was endorsed by only one patient, and that one patient did not score higher than the mean of the next-lowest PGIS group. The effect size for the analysis was $\eta^2 = 0.274$.

  Reviewer's comment(s): *This reviewer notes that the PGIS has intrinsic limitations for use as a reference measure to evaluate known-groups validity in that its response categories may not define clinically distinct groups. The PGIS is not measuring symptom severity but the global impact of pyruvate kinase deficiency ["PK deficiency affected me"].*

  Overall, it is difficult to assess the other measurement properties of the PKDD based on the scoring approach used (see Section 5.5.3 of this review) and insufficient sample size for some of the analyses (e.g., known groups validity). Additionally, there is a lack of detail for some of the methodology used for some of the analyses (e.g., test-retest reliability). Some of the approaches used are also questionable (e.g., inadequate reference measures). This reviewer notes that the applicant did not evaluate responsiveness.

  The results from the IRT model are not presented as it is difficult to interpret the results due to insufficient sample size.

PKDIA

- The median change from baseline in select PKDIA items are shown in Table 2.

[5] Internal consistency was measured by taking the empirical internal reliability estimates of the model. This approach is similar to that posed by McDonald with his Coefficient ω. Coefficient ω differs from the often-used Coefficient α in that it takes the factor structure established within a model into account.
[6] Test-retest reliability was computed using the ICC (2,1) based on weekly scores from screening, just prior to baseline—i.e., days -14 to -8—as compared to baseline values.

Table 2. Median (range) change from baseline in individual PKDIA item raw scores for Study AG348-C-006

PKDIA	**Baseline**		**Week 24**		**Change from baseline**	
	Placebo (n=40)	Mitapivat (n=40)	Placebo (n=40)	Mitapivat (n=40)	Placebo (n=40)	Mitapivat (n=40)
Tired Finish Things	4.0 (0, 9)	6.0 (0, 10)	4.0 (0, 9)	3.0 (0, 10)	0.0 (-6, 5)	-1.0 (-6, 3)
Interfere Household Activities	3.0 (0, 9)	3.0 (0, 9)	3.0 (0, 8)	1.5 (0, 8)	0.0 (-6, 6)	-1.0 (-6, 4)
Interfere Social Activities	4.0 (0, 9)	3.0 (0, 8)	3.5 (0, 10)	2.0 (0, 8)	0.0 (-5, 4)	-1.0 (-7, 6)
Interfere Leisure Activities	4.0 (0, 9)	4.0 (0, 8)	4.0 (0, 10)	1.5 (0, 9)	0.0 (-7, 5)	0.0 (-5, 4)
Relationships Negatively Affected	3.0 (0, 10)	2.0 (0, 8)	1.5 (0, 10)	0.5 (0, 8)	0.0 (-6, 4)	-1.0 (-6, 3)
Difficulty Concentrating	3.0 (0, 10)	4.0 (0, 9)	3.0 (0, 8)	2.0 (0, 9)	0.0 (-7, 6)	-1.0 (-5, 4)
Difficulty Physical Activity	3.5 (0, 9)	3.0 (0, 10)	3.0 (0, 7)	2.0 (0, 10)	0.0 (-5, 4)	-1.0 (-6, 6)
Additional Rest/Sleep	2.0 (0, 4)	2.0 (0, 4)	2.0 (0, 4)	1.0 (0, 3)	0.0 (-2, 3)	-1.0 (-2, 1)

- 10.26% ─ 34.62% of participants endorsed the least severe category responses at baseline across PKDIA items (i.e., participants reporting no impact).

  Reviewer's comment(s): *The applicant reported that the responses were skewed right such that respondents tended to use the lower ends of the response options. The applicant adopted the same approach with the PKDD and collapsed categories.*

- Inter-item correlation was high (r=0.84) for PKDIA Item 6 (interfere social activities) and Item 7 (interfere leisure activities), while correlations were mostly low to moderate (r=0.14 to 0.78) for the other PKDIA items.

- For assessment of internal consistency reliability of the PKDIA, the coefficient was observed to be $\omega = 0.90$.

- For assessment of test-retest reliability[5] of the PKDD, the ICC was 0.87.

- For assessment of convergent validity of the PKDIA, moderate to strong correlations (|r|=0.50 to 0.82) were observed between the PKDIA scores and various patient-reported assessments, such as the PKDIA, PGIS, FACT-An, EQ-5D-5L (UK and US versions), SF-12 Mental Component Score, and SF-12 Physical Component Score.

- For assessment of known-groups validity, the PKDIA scores observed across the PGIS subgroups showed better PKDIA scores (lower scores) on average for the patient subgroups with no PKD impacts than subgroups with greater levels of impacts at baseline to Week 24. The effect size for the analysis was $\eta^2 = 0.508$.

  Reviewer's comment(s): *This reviewer notes that the sample size may have been too small for the study population to accurately establish known-groups validity.*

  Overall, this reviewer notes the following:
  - *Minimal change was seen on all items of the PKDD and PKDIA items with most items not being experienced by subjects at baseline.*

- *The internal consistency reliability of the PKDD and PKDIA were within acceptable range.*
- *There was a lack of description for how the applicant defined a stable analysis population for the assessment of test-retest reliability.*
- *The applicant evaluated the measurement properties of the original version (i.e., 12-item version) of the PKDIA, therefore making the findings difficult to review and interpret.*
- *The proposed scoring algorithms for the PKDD and PKDIA adopt multiple score transformations, which are unjustified and result in difficulties in the final score interpretation. Additionally, the small sample size (n=80) can result in large measurement error in IRT item calibration, which contributes to pervasive uncertainties in IRT scoring*

5.5.6 Interpretation of Meaningful Within-Patient Score Changes

The applicant proposed that a 5- to 8-point reduction in the PKDD and a 6- to 10-point reduction in the PKDIA are meaningful within-patient score changes. However, due to the minimal changes observed in the instruments the applicant's proposed thresholds for meaningful within-patient score change was not fully reviewed. Further, there were limitations with the anchor used for anchor-based analyses, specifically the Patient Global Impression of Severity (PGIS) asked about global impact ("Today, my PK deficiency affected me") and does not correspond to concept of the target COAs which limits the interpretability of the anchor-based analyses.

Reviewer's comment(s): *This reviewer requested empirical cumulative distribution function (eCDF) curves by treatment arm for StudyAG348-C-006 using raw scores, however the eCDF interpretation has limitations, e.g., same data used for efficacy, not adjusted for covariates.*

Overall, it is unclear what constitutes a meaningful within-patient score change(s) in the PKDD and PKDIA weekly mean scores.

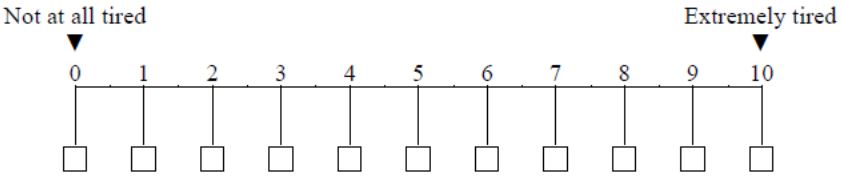
6. APPENDICES

Appendix A: PKDD
Appendix B: PKDIA
Appendix C: PKDD and PKDIA Scoring Algorithms
Appendix D: PGIS
Appendix E: Item-level analyses for PKDD (daily score)

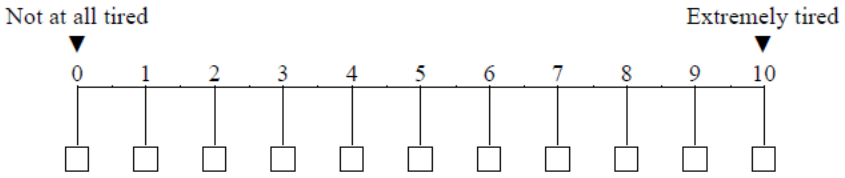
Appendix A: PKDD

Instructions: Please answer the following questions based on your experience with Pyruvate Kinase (PK) Deficiency **today (from the time you woke up this morning to the time you are completing this questionnaire)**. Please select the box corresponding to the number that best describes you.

1. Describe how **tired** you were at its worst today.



2. Describe how **tired you felt after finishing your daily activities (e.g., work, social, leisure, physical or household activities)** today.



3. Describe your **jaundice** (how **yellow your eyes and/or skin** appeared) when you looked in the mirror today.

   ☐0 No yellow eyes and/or skin

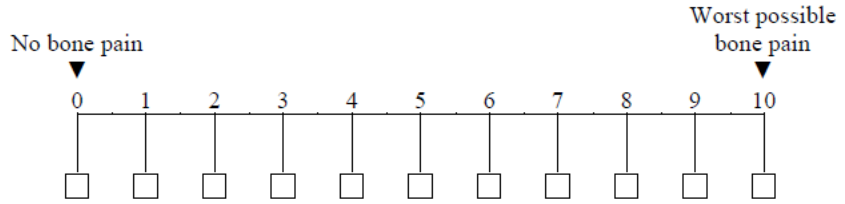
   ☐1 Mild yellow eyes and/or skin

   ☐2 Moderate yellow eyes and/or skin

   ☐3 Severe yellow eyes and/or skin

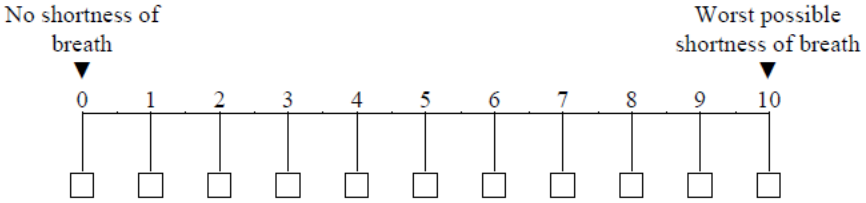
   ☐4 Very severe yellow eyes and/or skin

4. Describe your **bone pain** at its worst today.



   ☐ I have never experienced bone pain

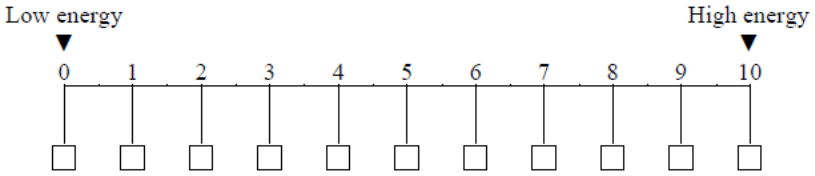
5. Describe your **shortness of breath** during moderate (e.g., walking on an incline or upstairs) physical activity you did today.



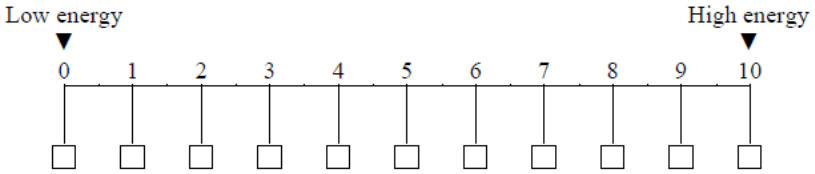
   ☐ I avoided this activity because it was too difficult for me to do moderate physical activity

   ☐ Not applicable, because I did not have the opportunity to do moderate physical activity

6. Describe your **energy level at the beginning of your day (after being awake for one hour)**.



7. Describe your **energy level at the end of your day (right now)**.



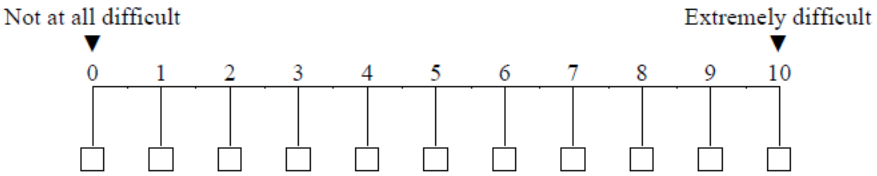
Appendix B: PKDIA

*Items not included in scoring are presented in gray.

Describe how difficult it was for you to do the following **because of how tired you felt** due to your PK deficiency over the past 7 days:

(b) (4)

2. **Finish things you wanted to get done**



(b) (4)

(b) (4)

5. How often did your PK deficiency interfere with your ability to do **household activities (e.g., chores, cleaning, laundry)** over the past 7 days?

None of the time All of the time

0 1 2 3 4 5 6 7 8 9 10

6. How often did a lack of energy due to your PK deficiency interfere with participating in **social activities (e.g., doing something together with friends)** over the past 7 days?

None of the time All of the time

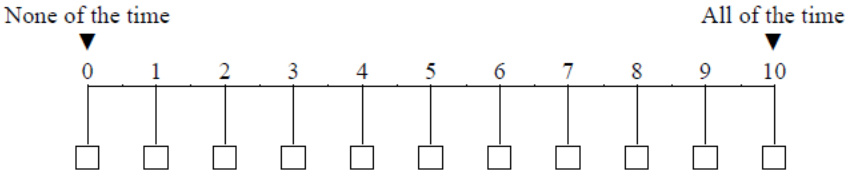
0 1 2 3 4 5 6 7 8 9 10

7. How often did your PK deficiency interfere with **leisure activities (i.e., hobbies or things you do for fun in your free time) over the past 7 days**?

None of the time All of the time

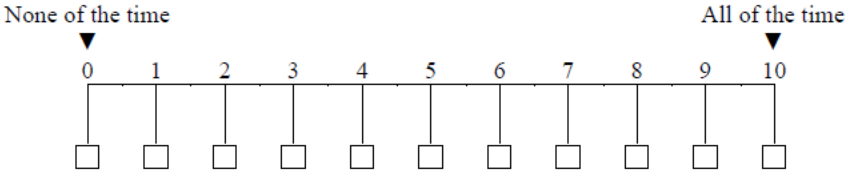
0 1 2 3 4 5 6 7 8 9 10

8. How often did you feel **your relationships with friends or family were negatively affected** because of your PK deficiency over the past 7 days?



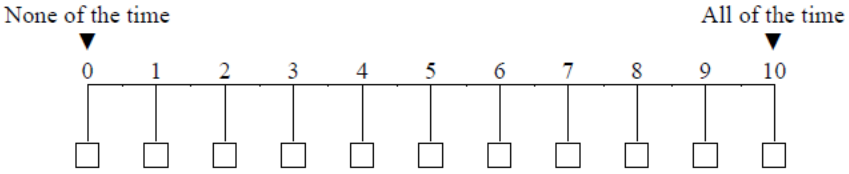
(b) (4)

10. How often did you have **difficulty concentrating** because of your PK deficiency over the past 7 days?



(b) (4)

11b. [redacted] (b) (4) How often did you have difficulty performing **moderate (e.g., walking on an incline or up stairs) physical activity** because of your PK deficiency over the past 7 days?



12. How much **additional rest or sleep did you feel you needed** because of your PK deficiency over the past 7 days?

- ☐0 No additional rest or sleep
- ☐1 A little additional rest or sleep
- ☐2 Some additional rest or sleep
- ☐3 Quite a bit additional rest or sleep
- ☐4 A lot of additional rest or sleep

Appendix C: PKDD and PKDIA Scoring Algorithms

(b) (4)

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Appendix E: Item-level analyses for PKDD (daily score)

Table 3. Median (range) change from baseline in individual PKDD item raw scores (daily score) for Study AG348-C-006

PKDD	**Baseline (Day 1)**		**Day 168**		**Change from Baseline to Day 168**	
	Placebo (n=40)	Mitapivat (n=40)	Placebo (n=40)	Mitapivat (n=40)	Placebo (n=40)	Mitapivat (n=40)
Tired Worst	6.0 (0, 9)	6.0 (0, 10)	5.0 (0, 10)	4.0 (0, 9)	1.0 (-6, 5)	-2.0 (-7, 1)
Daily Activities	5.0 (0, 9)	6.0 (0, 10)	5.0 (0, 10)	4.0 (0, 10)	0.0 (-7, 4)	-1.0 (-7, 1)
Jaundice	2.0 (0, 4)	1.0 (0, 3)	1.0 (0, 4)	1.0 (0, 3)	0.0 (-2, 2)	0.0 (-2, 1)
Bone Pain Worst	0.0 (0, 8)	0.0 (0, 10)	0.0 (0, 4)	0.0 (0, 6)	0.0 (-5, 3)	0.0 (-4, 3)
Breathe Activities	0.5 (0, 9)	2.0 (0, 8)	1.0 (0, 7)	1.0 (0, 9)	0.0 (-6, 5)	-1.0 (-7, 5)
Energy Beginning	6.0 (1, 10)	5.0 (1, 9)	6.0 (1, 10)	5.0 (1, 10)	0.0 (-5, 6)	1.0 (-5, 5)
Energy End	4.5 (1, 10)	4.0 (0, 9)	5.0 (0, 10)	5.0 (0, 9)	0.0 (-4, 7)	1.0 (-3, 4)

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/s/

MIRA J PATEL
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SELENA R DANIELS
12/23/2021 06:41:47 AM

DAVID S REASNER
12/23/2021 06:53:57 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 17, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216196
Product Name, Dosage Form, and Strength:	Pyrukynd (mitapivat) tablets, 5 mg, 20 mg, 50 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Agios Pharmaceuticals, Inc
FDA Received Date:	June 17, 2021
OSE RCM #:	2021-1227
DMEPA 2 Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for Pyrukynd (mitapivat) tablets, Agios Pharmaceuticals, Inc submitted NDA 216196 for Agency review. This review evaluates the proposed Pyrukynd prescribing information (PI), Patient information, carton labeling, and container label for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, Patient Information, container label, carton labeling for Pyrukynd to identify deficiencies that may lead to medication errors and other areas of improvement. We identified areas of the proposed PI, container label, and carton labeling identified areas that can be modified to improve the clarity of the information presented. For the Division, we note the PI can be improved for readability and accessibility of information. For the Applicant, we recommend improving the format of the expiration date, add a declaration of the net quantity of contents for each individual blister card container label, and the usual dosage statement on the carton labeling can be improved.

We provide recommendations for the Division in Section 4.1 and recommendations for Agios in Section 4.2 below.

4 CONCLUSION & RECOMMENDATIONS

Our review of the proposed container label, carton labeling, and PI for Pyrukynd (mitapivat) identified areas for improvement to promote the safe use of this product from a medication error perspective. We provide our proposed recommendations for the Division in Section 4.1 below and in Section 4.2 for the Agios Pharmaceuticals, Inc.

4.1 RECOMMENDATIONS FOR DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Highlights of Prescribing Information

1. Dosage and Administration

a. Due to the complex dose escalation schedule and taper schedule, we recommend you consider revising the second bullet to read "See Full Prescribing Information for dose titration and taper schedule. (2.1)".

B. Full Prescribing Information

1. Dosage and Administration Section

a. As the tablets are to be swallowed whole we recommend adding a statement in Section 2.1. We recommend adding "Swallow PYRUKYND tablets whole. Do not split crush, chew or dissolve the tablets."

b. For patients on a maintenance regimen (last row in Table 1), it is unclear how often Hb level should be assessed. We recommend you clarify how often to assess Hb level in the Maintenance row of Table 1.

2. How Supplied/Storage and Handling Section

a. As currently presented, the How Supplied is tedious to read. We recommend you consider presenting this information in a Table to improve readability. For example,

PYRUKYND (b) (4) Packs			
Tablet Strength	**Tablet Description**	**Imprint**	**NDC**
5 mg	Round, blue, film-coated tablets	"M5" printed on one side	71334-205-05
20 mg	Round, blue, film-coated tablets	"M20" printed on one side	71334-210-20
50 mg	Oblong, blue, film-coated tablets	"M50" printed on one side	71334-215-50

PYRUKYND Taper Packs				
Tablet strength(s)	**Blister Wallet Configuration**	**Tablet Description**	**Imprint**	**NDC**
5 mg	5 mg blister wallet containing 7 tablets	round, blue, film-coated tablets	"M5" printed on one side	71334-220-11
20 mg and 5 mg	20 mg blister wallet containing 7 tablets 5 mg blister wallet containing 7 tablets	round, blue, film-coated tablets round, blue, film-coated tablets	"M20" printed on one side "M5" printed on one side	71334-225-12
50 mg and 20 mg	50 mg blister wallet containing 7 tablets 20 mg blister wallet containing 7 tablets	oblong, blue, film-coated tablets round, blue, film-coated tablets	"M50" printed on one side "M20" printed on one side	71334-230-13

4.2 RECOMMENDATIONS FOR AGIOS PHARMACEUTICALS, INC

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. The format for the expiration date, MMYYYY, can be improved. To minimize confusion and reduce the risk for deteriorated drug medication errors, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Blister Wallet Container Labels

1. As currently presented, the Blister Wallet Monthly Packs denote the day of the week, i.e. 'SUN', 'MON', 'TUE', etc. However, it is possible that a patient may begin Pyrukynd on any day of the week, not just Sunday. Therefore, we recommend you replace 'SUN', 'MON', 'TUE', etc with Day 1, Day 2, etc.

2. We recommend adding "Recommended Dosage: See prescribing information" as currently presented this information is missing.

C. Carton Labeling

1. To ensure consistency with the Prescribing Information, revise the statement, "(b) (4)

[redacted] (b) (4) ” to read “Recommended Dosage: See prescribing information.”

2. As currently presented, the Usual dosage statement, “Do not split, crush, chew, or dissolve the tablets.” appears on the back panel. We are concerned this statement might be overlooked on the back panel. Therefore, we recommend revising this statement to read, “Swallow tablets whole. Do Not split, crush, chew, or dissolve the tablets.” and moving this statement to the principal display panel.

3. “[redacted] (b) (4) ” appears on the bottom right corner of the carton labeling. This is unnecessary; therefore, we recommend you delete the statement, “[redacted] (b) (4) ” from the carton labeling.

4. As currently presented, net quantity of the 20 mg/5 mg and 50 mg/20 mg Carton Taper Packs read, “[redacted] (b) (4) , we recommend revising the net quantity to read as follows:

   Contains: Two 7-day blister wallets with 7 tablets per wallet:

5 mg	20 mg
7 tablets per wallet	7 tablets per wallet

5. As currently presented [redacted] (b) (4)
   We recommend removing [redacted] (b) (4) .

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pyrukynd received on June 17, 2021 from Agios Pharmaceuticals, Inc.

Table 2. Relevant Product Information for Pyrukynd

Initial Approval Date	N/A
Active Ingredient	mitapivat
Indication	For the treatment of adult patients with pyruvate kinase deficiency
Route of Administration	Oral
Dosage Form	tablets
Strength	5 mg, 20 mg, 50 mg
Dose and Frequency	PYRUKYND is taken (b) (4) with or without food. (b) (4) swallowed whole. Do not split, crush, chew, or dissolve the tablets. **Recommended Dose** The starting dose for PYRUKYND is 5 mg taken orally twice daily. To gradually increase hemoglobin (Hb) (b) (4)

Table 1: Dose Titration Schedule

Duration	Dose Titration	
Day 1 to Week 4	• 5 mg twice daily	
Assess Hb level every 4 weeks	**If Hb level is below normal range**	**If Hb level is within normal range**
Week 5 to Week 8	• Increase to 20 mg twice daily and maintain for 4 weeks	• Maintain 5 mg twice daily
Week 9 to Week 12	• Increase to 50 mg dose twice daily and maintain	• Maintain current dose (5 mg twice daily or 20 mg twice daily)
Maintenance	• If hemoglobin level decreases, consider uptitration to the maximum of 50 mg twice daily as per the above schedule	

	• If a dose reduction is required then reduce to the next lower dose level, 20 mg twice daily or 5 mg twice daily

Missed Dose

If a dose of PYRUKYND is missed by 4 hours or less, administer the dose as soon as possible. If a dose of PYRUKYND is missed by more than 4 hours, do not administer a replacement dose, and wait until the next scheduled dose. Subsequently, return to the normal dosing schedule.

Interruption or Discontinuation

To (b) (4) the risk of acute hemolysis, avoid abrupt interruption or discontinuation of PYRUKYND. Taper the dose to gradually discontinue the medication (see Table 2). Monitor patients for signs of acute hemolysis (b) (4) worsening of anemia.

Table 2: Dose Taper Schedule

Current Dose	Dose Taper Schedule		
	Day 1-7	Day 8-14	Day 15
5 mg twice daily	5 mg once daily	Discontinue	N/A
20 mg twice daily	20 mg once daily	5 mg once daily	Discontinue
50 mg twice daily	50 mg once daily	20 mg once daily	Discontinue

Abbreviations: N/A = not applicable.

How Supplied	(b) (4)

	(b) (4)
Storage	Store at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F) *[see USP Controlled Room Temperature]*. Store the blister (b) (4) in the original carton until use.
Container Closure	(b) (4) blister film material, with aluminum lid stock comprised of (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 16, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, “mitapivat”, “IND 119825”, and “NDA 216196”. Our search identified 0 previous label and labeling reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Pyrukynd labels and labeling submitted by Agios Pharmaceuticals, Inc.

- Container labels received on October 20, 2021
- Carton labeling received on October 20, 2021
- Prescribing Information (Image not shown) received on June 17, 2021, available from \\CDSESUB1\evsprod\nda216196\0001\m1\us\proposed-labeling.docx

G.2 Label and Labeling Images

14 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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CLINICAL INSPECTION SUMMARY

Date	November 15, 2021
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief/ Division Director Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Hyon-Zu Lee, Pharm.D., Clinical Analyst Tanya Wroblewski, M.D., Medical Team Leader Ann Farrell, M.D., Division Director Courtney Hamilton, Pharm.D., Regulatory Health Project Manager Division of Nonmalignant Hematology (DNH) Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
NDA	NDA 216196
Applicant	Agios Pharmaceuticals, Inc.
Drug	Pyrukynd™ (mitapivat [AG-348])
NME	Yes
Division Classification	Allosteric activator of wild-type red blood cell-specific form of pyruvate kinase enzyme
Proposed Indication	Treatment of adult patients with pyruvate kinase deficiency
Review Type	Priority
Consultation Request Date	June 29, 2021
Summary Goal Date	November 30, 2021
Action Goal Date	February 10, 2022
PDUFA Date	February 17, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Studies AG348-C-006 and AG348-C-007 were submitted to the Agency in support of a New Drug Application for the drug mitapivat, proposed as treatment of adult patients with pyruvate kinase deficiency. Two clinical investigators (Hanny Al-Samkari, M.D. and Andreas Birkedal Glenthoj, M.D.) were inspected for Study AG348-C-006 and Study AG348-C-007. The sponsor (Agios Pharmaceuticals, Inc.) was also inspected for oversight of the above studies.

The study data derived from the above two clinical investigator sites are considered reliable. Sponsor's monitoring and oversight of Study AG348-C-006 and Study AG348-C-007 appeared adequate. The study data submitted to the Agency for assessment appeared acceptable in support of the proposed indication.

II. BACKGROUND

Pyruvate kinase deficiency is a rare inherited autosomal recessive chronic non-spherocytic hemolytic anemia; diagnosis is typically based on the exclusion of more common causes of hemolysis, followed by the demonstration of reduced pyruvate kinase enzymatic activity and the detection of mutations in the PKLR gene. Patients with pyruvate kinase deficiency suffer from lifelong non-spherocytic hemolytic anemia. Common symptoms and signs of lifelong hemolytic anemia are fatigue, shortness of breath, tachycardia, jaundice, and bone changes associated with extramedullary hematopoiesis. In addition to lifelong chronic hemolytic anemia, patients are at risk of severe acute hemolytic anemia resulting from increased hemolysis during infections, stress, aplastic crisis associated with parvovirus, and pregnancy. Patients with pyruvate kinase deficiency are at risk of long-term complications associated with hemolysis such as gallstones in about two out of three patients), liver iron overload in approximately three out of five patients, osteoporosis in about one out of six, thrombotic complications in about one out of seven patients, and pulmonary hypertension in approximately one out of five patients.

Mitapivat is an allosteric activator of wild-type PKR (red blood cell -specific form of pyruvate kinase) and a range of mutant PKR enzymes. The proposed commercial formulations for mitapivat are 5 mg, 20 mg, and 50 mg, round or oblong, blue, film-coated, immediate-release tablets for oral administration.

For this NDA under the PDUFA program review, Studies AG348-C-006 and AG348-C-007 were part of the FDA submission to support the proposed indication. DNH requested inspections for two study sites and sponsor, in part, based on their ongoing review of the totality of the applicant's submitted clinical data to the application.

Study AG348-C-006

Study AG348-C-006 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled efficacy and safety study of orally administered mitapivat compared with placebo in subjects with pyruvate kinase deficiency who were not regularly receiving blood transfusions. Mitapivat tablets were supplied as 5 mg, 20 mg, or 50 mg strength oral tablets.

The primary objective of the study was to evaluate the efficacy of treatment with mitapivat compared with placebo in increasing hemoglobin concentrations.

The primary endpoint was hemoglobin concentration measures were collected to support efficacy assessments. All the red blood cell parameters, haptoglobin, and lactate dehydrogenase values were collected to support additional efficacy assessments.

Study AG348-C-006 was conducted in a total of 46 study sites in multiple countries. The first subject enrolled on October 1, 2018 and the calendar date the last subject completed was on October 9, 2020. Approximately 80 study patients were enrolled in Study AG348-C-006.

Study AG348-C-007

Study AG348-C-007 was a Phase 3, multicenter, single-arm, open-label efficacy and safety study of orally administered mitapivat in subjects with pyruvate kinase deficiency who were regularly receiving blood transfusions. The study consisted of a Dose Optimization Period (Part 1) followed by a Fixed-Dose Period (Part 2).

The primary objective of the study was to evaluate the efficacy of treatment with mitapivat, as assessed by the reduction in transfusion burden.

The primary endpoint of this study was the proportion of subjects who achieved a reduction in transfusion burden, defined as at least a 33% reduction in the number of red blood cell units transfused during the 24 weeks of Part 2 compared with the historical transfusion burden standardized to 24 weeks (standardized control period). Transfusion burden (number of RBC units received over a 24 - week period) was assessed based on the transfusion information collected in Part 2 of the study.

This study was conducted in 20 countries. The calendar date the first subject enrolled was on June 26, 2018. The calendar date last subject completed was on November 12, 2020.

III. RESULTS (by site)

1. **Hanny Al-Samkari, M.D. /Study AG348-C-006/Site 840104**
   Massachusetts General Hospital
   55 Fruit Street, MA 02114

   Inspection dates: August 23 to 27, 2021

   For this study, ten subjects were consented and screened, ten subjects were enrolled. Of the randomized subjects, all ten subjects completed the treatment phase of the study.

   Study files assessed included a review of the Institutional Review Board approvals and informed consent documentation, delegation log, screening and enrollment log, monitoring log and monitoring reports, case report forms, and test article control records. The site audit also involved an evaluation of subject source records medical history, progress notes, laboratory results, blood sample records, ancillary procedures, imaging records and reports, adverse event and serious adverse event documentation, and subject-specific protocol deviation records.

   Source records were reviewed for ten enrolled subjects. The reviewed source records included medical history, eligibility criteria, randomization, protocol-required procedures, adverse events, serious adverse events, and primary endpoints. No discrepancies were noted.

   Source records for the enrolled study patients were examined and verifiable for primary efficacy data against the data line listings. No under-reporting of adverse events was found.

2. Andreas Birkedal Glenthoj, M.D./ Study AG348-C-006 and Study AG348-C-007 /Site 208101

Department of Hematology
Herlev University Hospital
Herlev Ringvej 75
2730 Herlev Denmark

Inspection dates: October 4 to 8, 2021

For Study AG348-C-006, a total eight patients were screened, and seven subjects were enrolled. All the enrolled study patients completed the treatment phase of the study.

For Study AG348-C-007, a total of six subjects were screened and six subjects were enrolled. All six study patients completed the treatment phase of the study.

The following regulatory documents were assessed: Ethics Committee approval letters and correspondence, monitoring reports, informed consent forms, subject medical records, financial disclosure reports, case report forms, subject questionnaires and diaries, dosing records, scans, independent reviewer imaging, site signature and responsibility logs, and site training documentation. The selected subjects' records were audited for eligibility, treatment assignment, blinding and disposition, genetic and laboratory samples and analyzes, protocol adherence, adverse event reporting, efficacy data, and concomitant medications.

A review of all enrolled subjects' records was conducted for both clinical investigations. Source records evaluated, as described, for the enrolled study patients were examined and verifiable for primary endpoint data against the data line listings. No discrepancies were noted. There was no evidence of under-reporting of adverse events or protocol deviations.

3. Agios Pharmaceuticals, Inc.
88 Sidney Street
Cambridge, MA 02139

Inspection dates: September 7 to 16, 2021

The inspection assessed the application sponsor's oversight responsibilities for Study AG348-C-006 and Study AG348-C-007.

The inspection included review of the trial master files, organizational charts, standard operating procedures, operational manuals, contracts. transfers of obligations, site monitoring, case report forms, handling of adverse events, data collection, and how the sponsor brought non-compliant sites into compliance. Information was also obtained concerning procedures for selection of clinical investigators, monitoring procedures and frequency, and other monitoring-related activities, test articles, and test accountability records.

The FDA audit found that sponsor provided adequate oversight, monitored these study sites and performed its responsibilities according to the FDA regulatory requirements. No evidence of comprehensive under-reporting of adverse events to the Agency was found.

In general, the oversight of Study AG348-C-006 and Study AG348-C-007 appeared adequate.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H.
Branch Chief, Good Clinical Practice Assessment Branch and
Division Director, Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 216196
Submission Number	001
Submission Date	6/17/2021
Date Consult Received	7/6/2021
Drug Name	Mitapivat
Indication	Treatment of adult patients with pyruvate kinase deficiency
Therapeutic Dose	50 mg BID
Clinical Division	DCN
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 7/6/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review dated 05/17/2019 under IND119825 in DARRTS (link);
- Previous IRT review dated 07/06/2020 under IND119825 in DARRTS (link);
- QT Evaluation report checklist (Submission 0001; link);
- Investigator's QT study report (Submission 0001; link); and
- Draft label (Submission 0001; link)

1 SUMMARY

No significant QTc prolongation effect of mitapivat was detected in this QT assessment.

The effect of mitapivat was evaluated in Study AG348-C-014, a Phase 1, randomized, single-dose, placebo-controlled study in healthy adult subjects. The highest dose that was evaluated was 300 mg under fasted condition, which is expected to provide 6-fold coverage of the therapeutic exposure (50 mg BID) and provides >2-fold coverage of the known high clinical exposure scenario (i.e., 1.7-fold increase in the presence of strong CYP3A inhibitor); therefore, waiving the need of a separate positive control. Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that mitapivat is associated with clinically relevant increases in the QTcF interval (refer to section 4.5) – see Table 1: Point Estimates and the 90% CIs (FDA Analysis) for overall results. The findings of this analysis are further supported by the available nonclinical data (sections 3.1.2), by-time analysis (section 4.3) and categorical analysis (section 4.4).

Table 1: Point Estimates and the 90% CIs (FDA Analysis)

Treatment	Concentration (ng/mL)	ΔΔQTcF (msec)	90% CI
Mitapivat 100 mg	2324.2	1.7	(1.2, 2.2)

Mitapivat 300 mg	7455.0	3.3	(2.0, 4.5)

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

The sponsor did not provide QT related language in the proposed label under Submission 0001 (link). The IRT proposes the following language for the Division's consideration. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology At a dose 6 times the maximum recommended dose, mitapivat does not prolong the QT interval to any clinically relevant extent.
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

The CSS-IRT reviewed the QT assessment proposal previously (dated 05/17/2019 and 07/06/2020 in DARRTS). There has been no major changes to the QTc assessment plan.

Study AG348-C-014 is a phase 1 randomized, single-dose, double-blinded, placebo-controlled, 4-period, crossover, food-effect study in 31 healthy adult subjects under fasted and fed conditions. Study treatments were 1) placebo, fasted; 2) mitapivat 100 mg, fasted; 3) mitapivat 100 mg, fed; and 4) mitapivat 300 mg, fasted. The supratherapeutic dose (300 mg) provided exposures that are about 6-fold higher for both AUC and Cmax when compared to 50 mg BID dosing of mitapivat. Data from the 3 fasted treatment groups were included in the QT assessment. The primary analysis is concentration-QTc analysis of QTcF.

Highlight of clinical pharmacology: After repeated (50 mg BID) dosing, steady state Cmax is predicted to be 965 ng/mL. The Cmax of mitapivat was observed at 1.5 hours post-dose for both mitapivat 100 and 300 mg dose groups with minimal accumulation,

and the Cmax of AGI-8702 (a mitapivat metabolite) of was observed at 2 and 3 hours post-dose for the mitapivat 100 and 300 mg dose groups, respectively. Mitapivat does not undergo significant accumulation at steady-state irrespective of dose. The highest exposure scenario known at this time is with co-administered with a potent CYP3A4/5 inhibitor itraconazole (4.7-fold increase in AUC and 1.7-fold increase in Cmax). The sponsor has a hepatic impairment study pending.

3.1.2 Nonclinical Safety Pharmacology Assessments

In vitro automated and manual patch clamp assays for potential hERG inhibition:

- Non-GLP automated patch clamp: both mitapivat and AGI-8702 IC50 >10 μm
- GLP manual patch clamp: mitapivat IC50 29.4 μM; IC20 8.6 μM
- No dedicated GLP manual patch clamp for AGI-8702

Reviewer's comment: *The plasma protein binding of mitapivat was 97.7% and was concentration independent. The ratio between hERG IC50 (29.4 uM) and free $C_{max,ss}$ at the 50 mg BID dose (0.05 uM) is ~590-fold.*

The sponsor reports a lack of effect on electrocardiography, heart rate and waveform intervals in GLP cardiovascular assessment in radiotelemetry-instrumented cynomolgus monkeys (single nasogastric administration of 10, 25, and 75 mg/kg) or in multiple GLP general toxicology cynomolgus monkey studies (up to 9-month, up to 100 mg/kg BID).

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for mitapivat was based on exposure-response analysis. Please see section 3.2.3 for additional details.

Sponsor presented by-time analysis results for all biomarkers (QTcF, HR, PR and QRS).

Reviewer's comment: *FDA reviewer's by-time analysis results are similar to the sponsor's by-time analysis results.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (>100 beats/min), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *FDA reviewer's analysis results are similar to the sponsor's analysis results.*

3.2.3 Exposure-Response Analysis

A linear mixed-effects model was used to assess concentration-QTc relationship, in which both mitapivat and AGI-8702 (metabolite) were chosen as concentration. The results of the sponsor's analysis show an absence of significant QTc prolongation.

Reviewer's comment: *In the reviewer's linear mixed-effects model, only mitapivat was used because mean AGI-8702 (metabolite) concentration is less than 10% of those of mitapivat at corresponding time points, and mitapivat and AGI-8702 have similar PK profiles. The result based on the model is same as that of sponsor's.*

3.2.4 Safety Analysis

No treatment-related TEAEs Grade 3 or higher were reported during the study, and no SAEs were reported during the study. No subjects discontinued from the study due to a TEAE. There were no cardiac AEs reported.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., unexplained syncope, seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period.

The mitapivat 100 mg treatment group was labeled as "Mitapivat 100 mg and placebo in fasted" and the mitapivat 300 mg treatment group was labeled as "Mitapivat 300 mg fasted" in the figures in this section.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).

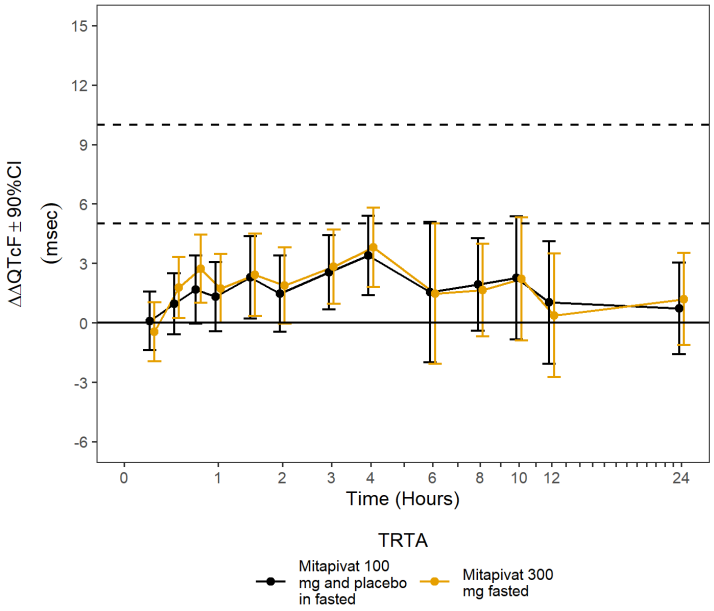


Table 2: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔQTcF (msec)	90.0% CI (msec)
Mitapivat 100 mg	31 / 29	4.0	3.4	(1.4, 5.4)
Mitapivat 300 mg	31 / 29	4.0	3.8	(1.8, 5.8)

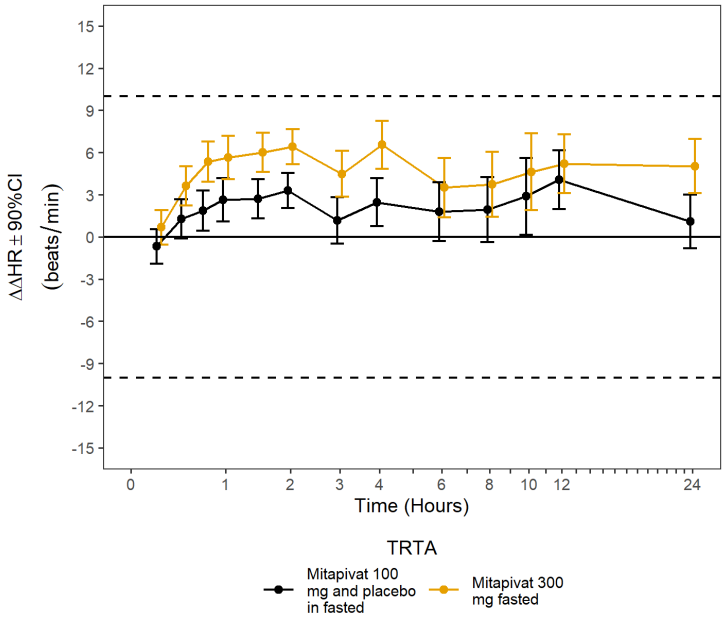
4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

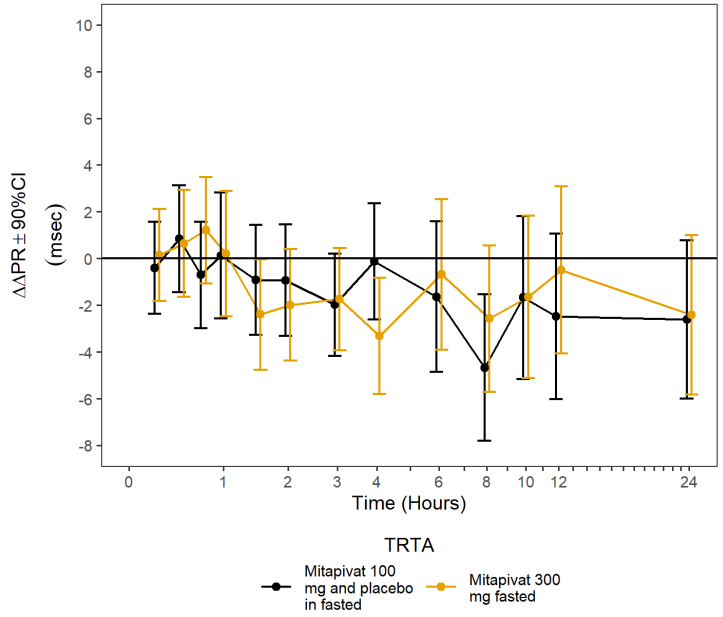
Figure 2: Mean and 90% CI of ΔΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

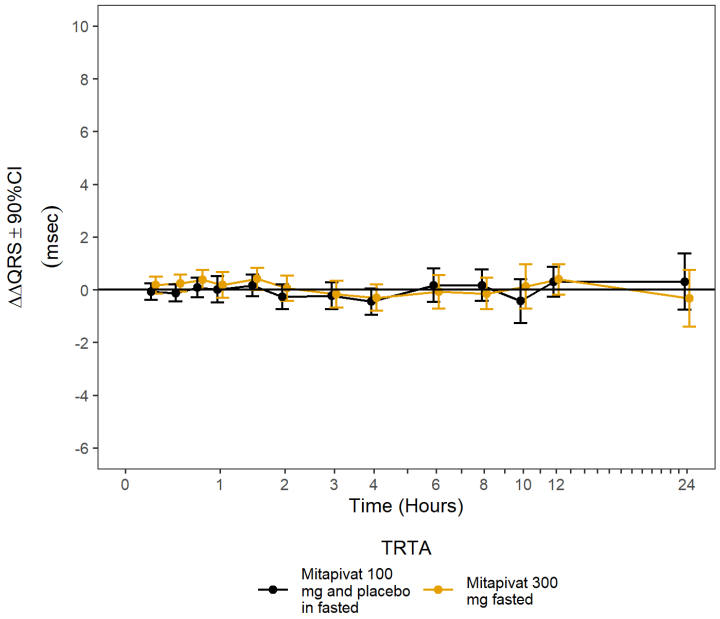
Figure 3: Mean and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects experienced QTcF greater than 450 msec and/or ΔQTcF greater than 30 msec in any of the dose levels of mitapivat.

4.4.2 HR

None of the subjects experienced HR greater than 100 beats/min in any of the dose levels of mitapivat.

4.4.3 PR

None of the subjects experienced PR greater than 220 msec with and without 25% increase over baseline in any of the dose levels of mitapivat.

4.4.4 QRS

None of the subjects experienced QRS greater than 120 msec with 25% increase over baseline in any of the dose levels of mitapivat.

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model need to be evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔΔQTcF; and 3) absence of a nonlinear relationship.

Figure 2 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTcF, and supports the use of a linear model.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)

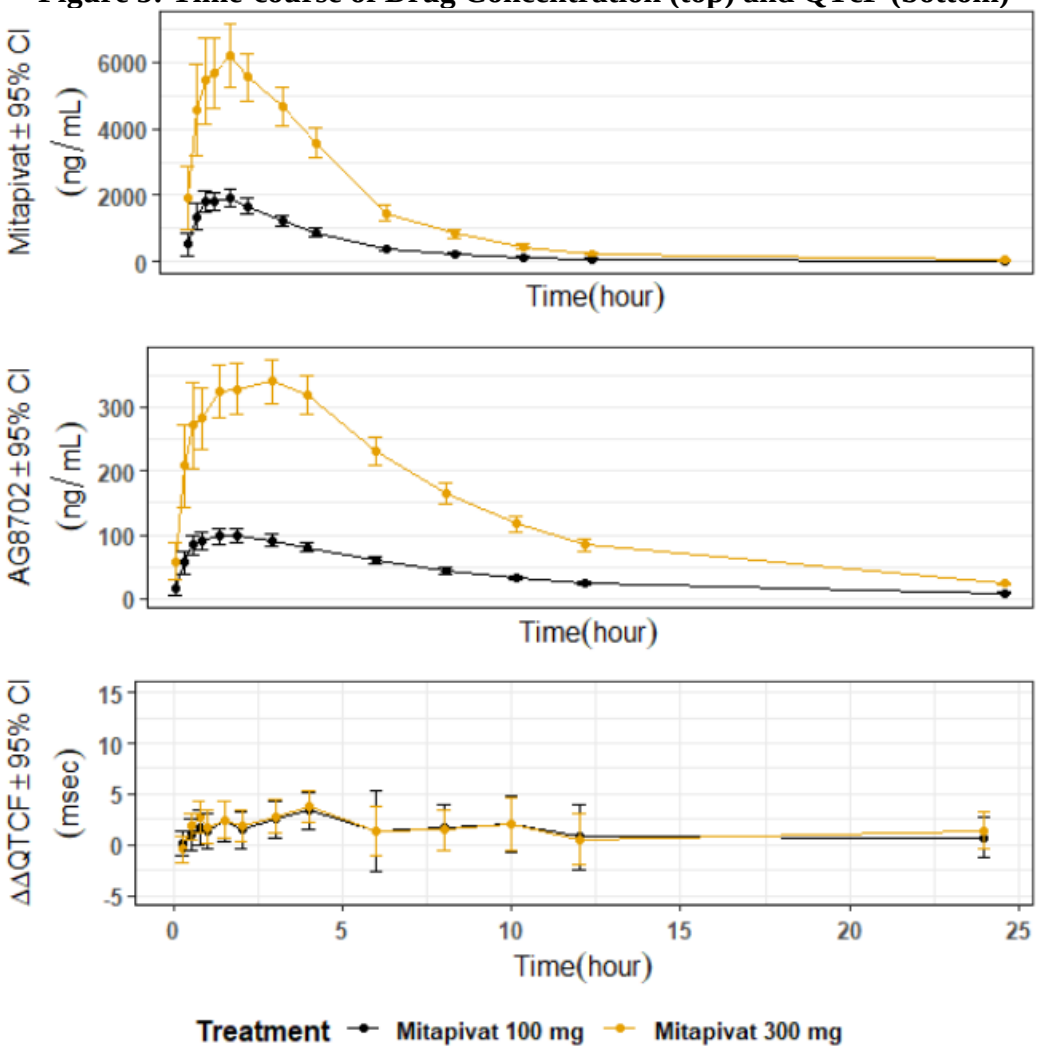
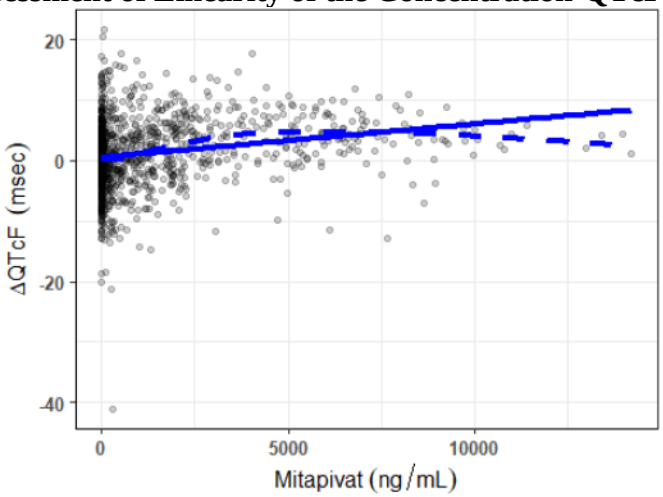
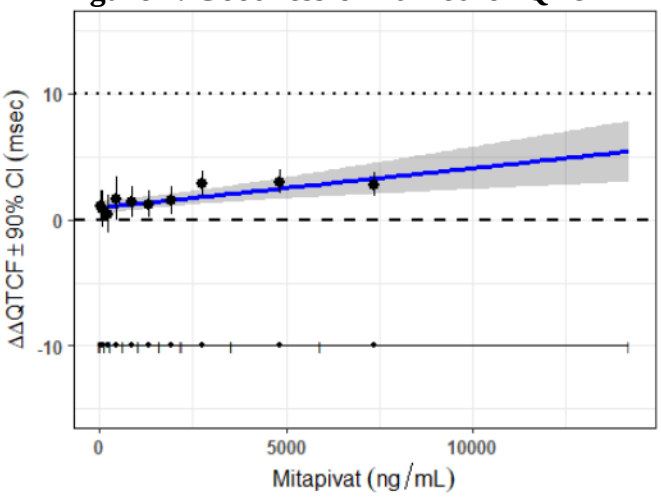


Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 1.

Figure 7: Goodness-of-fit Plot for QTcF



4.5.1.1 Assay Sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

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/s/

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