



NDA 220049

COMPLETE RESPONSE

PTC Therapeutics, Inc.
Attention: Aparna Geddam, MS
Director, Global Regulatory Strategy
500 Warren Corporate Center Drive
Warren, NJ 07059

Dear Aparna Geddam:

Please refer to your new drug application (NDA) (b) (4)

or vatiquinone oral capsules, (b) (4).

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL/BIOSTATISTICS

1. After a detailed review of your application, we have concluded that the data do not demonstrate substantial evidence of effectiveness (SEE) for vatiquinone in the treatment of Friedreich's Ataxia (FA). You proposed to meet the evidentiary standard based on a single adequate and well-controlled study with confirmatory evidence. The single controlled trial supporting this application, PTC742-NEU-003-FA (MOVE-FA), is not capable of serving as a single adequate and well-controlled study, with or without confirmatory evidence (CE), to provide SEE. The deficiencies in the data are outlined below:
 - MOVE-FA failed to demonstrate a statistically significant difference between vatiquinone and placebo for the prespecified primary endpoint of change from baseline to week 72 in the modified Friedreich's Ataxia Rating Scale (mFARS). Change from baseline in mFARS is an outcome measure that is considered by FDA to be an acceptable primary endpoint to assess clinically meaningful change in how a patient with FA functions.
 - MOVE-FA also failed to demonstrate a statistically significant difference between vatiquinone and placebo for the prespecified key secondary efficacy endpoints.

- You have proposed that the nominally significant results of the prespecified exploratory analyses of the Upright Stability Subscale (USS) of the mFARS provide evidence of effectiveness of vatiquinone in FA. Although we acknowledge the clinical relevance of the upright stability assessments to patients with FA, this was an exploratory endpoint and the observed treatment difference was small (-1.26) with a modest nominally significant p-value ($p=0.02$). The clinical meaningfulness of the treatment difference is uncertain. Further, there are concerns with some statistical observations regarding handling of missing data and baseline imbalances that limit the strength of the findings.
 - There were baseline imbalances in age of onset of FA and baseline mFARS score that were small; however, given the small treatment difference in the USS at Week 72, they have the potential to impact the interpretability of these results. At baseline, the placebo group had more subjects with younger age of onset (94% of subjects in placebo group versus 87% of subjects in vatiquinone group had disease onset before 14 years old). Given that younger age of onset is associated with more rapid disease progression, subjects in the placebo group may have worsened more quickly over the time period of the trial, which could have biased results to favor vatiquinone. Additionally, baseline disease severity appeared slightly worse in the placebo group, evidenced by a 1.7-point higher baseline mFARS score and a 1.1-point higher baseline USS score in the placebo group (higher scores on mFARS and its subscales represent greater functional impairment). The clinical meaningfulness of the slight imbalances in baseline mFARS scores are unclear; however, if subjects in the placebo group were even slightly more impaired at baseline, it would make the results at Week 72 more difficult to interpret.
 - Additionally, the results were not robust to missing data from three subjects were excluded from the ITT or mITT populations because no postbaseline mFARS scores were obtained. Exclusion of subjects postrandomization can introduce bias because subjects who do not adhere to the treatment may differ from those who do adhere in known and unknown ways, which may impact the study results. A tipping point analysis was performed by adding back the three excluded subjects by incrementally increasing 1 point/step for their change from baseline to Week 72 USS score, progressing from best case to worst case scenarios. The p-values in this analysis ranged from .02 to .16 and did not remain below 0.05 across the entire range of clinically plausible assumptions for the three subjects.

- Overall, the nominally significant findings on the USS are not sufficiently statistically robust or persuasive to overcome the limitations of the clearly negative findings on the prespecified analyses of the primary and secondary endpoints.
- Additionally, the observed benefit on USS in the 72 week MOVE-FA trial was not independently substantiated by the natural history comparison studies, in which long-term treatment in the open-label extension was compared to natural history and saw no benefit on the USS after 3 years of treatment with vatiquinone compared to the natural history cohorts.
- You have also reported a nominally significant difference on the Modified Fatigue Impact Scale (MFIS) compared to placebo at 72 weeks; however, the Division has concerns with the interpretability of this outcome assessment. The Division has long-considered the MFIS not suitable as an endpoint capable of providing supportive evidence of efficacy given a potential for recall bias with a 4-week recall period for symptoms, and the vagueness of some items, not all of which are direct measures of fatigue. Additionally, the MFIS was also an exploratory endpoint, which was similarly not prespecified and not part of the multiplicity plan to control the family-wise error rate.

The overall persuasiveness of the findings on the USS, a nominally significant exploratory endpoint, in the setting of negative results on an acceptable clinically meaningful primary endpoint and key secondary endpoints are not sufficient to establish the effectiveness of vatiquinone for the treatment of FA.

2. Although the ability to use confirmatory evidence depends first on the presence of a single adequate and well-controlled study, which you do not have, we also reviewed the real-world evidence and biomarker data submitted as confirmatory evidence.
 - The real-world evidence submitted as confirmatory evidence included two studies that compared the change in total mFARS scores among subjects treated long-term with vatiquinone to subjects from the FACOMS natural history study. The two studies showed a statistically significant difference in total mFARS score after year 3 (Study 1) or year 2 (Study 2) in subjects treated with vatiquinone compared to natural history cohorts. The findings are suggestive of a benefit on symptom progression with chronic treatment; however, we again note that the differences in USS between the treated subjects and natural history cohorts were small and not statistically significant. There are strengths and limitations to the analyses of the real-world data and the Division would be willing to consider whether these submitted analyses could contribute to confirmatory evidence in the setting of a positive adequate and well-controlled study.

- The mechanistic and biomarker data submitted as confirmatory evidence in this application are insufficient to serve as CE. Important limitations include indirect measurement of GSH levels and the very low number of subjects with FA that had biomarker data available for analysis. Should you choose to resubmit the NDA in future, we encourage you to submit relevant biomarker data in patients with FA acquired as per FDA's regulatory standards to serve as confirmatory evidence of effectiveness. The Division would be willing to consider whether additional relevant biomarker data could contribute to CE in the setting of a positive adequate and well-controlled study.

To address these deficiencies, data from a positive, adequate, and well-controlled study will be needed to establish the effectiveness of vatiquinone in the treatment of subjects with FA. We are willing to work with you on the design of such a study. A potential path would be to conduct a prospective randomized, controlled study in pediatric subjects with FA with change from baseline in USS as a primary endpoint.

NONCLINICAL/PRODUCT QUALITY

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(b) (4)

To address these deficiencies, you must conduct adequate studies to qualify the multiple drug substance and drug product impurities identified above.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources¹ and Pregnancy and Lactation Labeling Final Rule² websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

² <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to our correspondence dated, (b) (4), which addresses the proposed proprietary name, (b) (4). This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

- (1) Describe in detail any significant changes or findings in the safety profile.
- (2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
- (3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
- (4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

- (5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
- (6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
- (7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

The submitted population pharmacokinetics (PK) model underpredicts C_{\max} of vatiquinone. In your resubmission, you should refine the population PK model to improve the prediction of vatiquinone C_{\max} .

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact

(b) (4)

Sincerely,

{See appended electronic signature page}

(b) (4)

Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (4)

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