



NDA 210862

COMPLETE RESPONSE

Biohaven Therapeutics, Ltd.
c/o Biohaven Pharmaceuticals, Inc.
Attention: Marianne Frost, MA
Senior VP, Regulatory Affairs and Operations
215 Church Street
New Haven, CT 06510

Dear Marianne Frost:

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

for (b) (4) (troriluzole) capsules.

We acknowledge receipt of your major amendments dated (b) (4), which extended the goal date by three months.

We also acknowledge receipt of your amendment dated (b) (4). The new nonclinical studies submitted in the amendment were not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

CLINICAL AND STATISTICAL

The Agency initially raised concerns with your proposal to conduct Study 206-RWE, an externally controlled study comparing data from Study 206 to natural history controls at a (b) (4). We noted that such a study would likely be inadequate to provide substantial evidence of effectiveness, particularly with consideration that Study 206, the randomized, double-blind, placebo-controlled study, failed on all primary and secondary endpoints in the pre-specified analysis population. The Agency noted that "the proposed natural history data source does not appear to be fit-for-purpose, and the externally controlled analyses will likely generate results that are difficult to interpret and subject to biases due to the baseline differences between the study subjects and external control subjects".

Although the Agency provided feedback on the design of the protocol and statistical analysis plan for Study 206-RWE (b) (4), we continued to express concerns that the post hoc, externally controlled study alone seemed inadequate to demonstrate substantial evidence of effectiveness because the study would not be blinded or prespecified, would include previously analyzed data, and would be susceptible to residual confounding due to unmeasured differences in subjects from Study 206 compared to the natural history

cohorts. We also reiterated these concerns at the (b) (4), during which we stated that Study 206-RWE was not considered to be an adequate and well-controlled investigation, and therefore, it would not be capable of providing the primary support for demonstration of substantial evidence of effectiveness.

Given the seriousness and rarity of spinocerebellar ataxia, the Agency determined that the NDA should be filed to allow for thorough review of the data. After a comprehensive and detailed review of the submission, we have determined that substantial evidence of effectiveness has not been established for troriluzole for the treatment of spinocerebellar ataxia. A detailed discussion of the deficiencies follows.

- I. Study 206-RWE cannot be considered an adequate and well-controlled investigation, as defined in CFR 314.126, to support effectiveness due to design flaws and fundamental methodological limitations that have introduced bias into the study.**
 - 1. Limited comparability between trial subjects and external controls and residual biases:** Several factors undermined the reliability of the Clinical Research Consortium for the Study of Cerebellar Ataxia natural history study (CRC-SCA) as a control arm in Study 206-RWE. The propensity score matching could not address important factors that could affect disease progression such as baseline supportive treatments, comorbidities, and geographic factors, which were not measured and therefore could not be matched. E-values as low as 1.1 to 1.3, indicate that even modest unmeasured confounding could eliminate statistical significance. Of note, when matching included 1-year progression rates to better control for baseline disease trajectory differences, the treatment effect became statistically nonsignificant at both Year 2 and Year 3 ($p=0.3849$ at Year 3), suggesting that the observed benefits may be entirely attributable to baseline differences rather than true treatment effects. The comparison between progression rates at 1 year in subjects randomized to placebo in Study 206 and CRC-SCA controls revealed significant differences favoring placebo (particularly in SCA1 and SCA2 genotypes), providing direct evidence of confounding that undermines confidence in CRC-SCA as a control arm and in the results of Study 206-RWE.
 - 2. Site overlap, selection and expectations biases:** Two-thirds of CRC-SCA natural history sites (12 of 18) were also among the 21 U.S. sites that conducted Study 206. This overlap of study sites creates significant potential for multiple biases. First, selection bias may occur because Study 206 had strict eligibility criteria while CRC-SCA had minimal restrictions. At sites simultaneously participating in both studies, we cannot rule out that Study 206 screening failures might be enrolled in the CRC-SCA population creating potential for systematic selection biases. Second, expectation bias likely occurred because the same unblinded investigators, examiners, and raters

- assessed both populations with knowledge of study enrollment. This knowledge could unconsciously influence disease severity ratings. Although the impact of these biases on the observed treatment effect of troriluzole cannot be reliably quantified, these biases add substantial uncertainty to the study results in addition to other unmeasured confounders.
3. **Substantial Missing Data:** There was a substantial amount of missing data in Study 206-RWE, with 52% of troriluzole-treated subjects and 79% of CRC-SCA controls missing Year 3 functional Scale for the Assessment and Rating of Ataxia (f-SARA) data for the primary efficacy analysis. Non-completers in the troriluzole group had significantly higher baseline disease severity (worse f-SARA scores: 5.4 versus 4.7, $p=0.0335$). The Jump-to-Reference (J2R) analysis, which assumes treatment benefits are lost when subjects discontinue, and was a pre-specified sensitivity analysis, showed the 3-year result became statistically non-significant ($p=0.1023$ instead of $p=0.0301$). Therefore, the treatment effect observed on the primary analysis of Study 206-RWE is unreliable, because of the extremely large percentage of missing data, combined with evidence of informative censoring (missingness was not random), and lack of robustness under plausible missing data assumptions.
 4. **Systematic Timing Bias:** Critical timing discrepancies existed between studies, with CRC-SCA using 365-day periods compared to 336-day periods for Study 206, resulting in CRC-SCA subjects being assessed progressively later (up to 90 days at Year 3). When timing was properly aligned in sensitivity analyses, the results failed to achieve nominal statistical significance, ($p=0.0997$), indicating that the 90-day timing difference in the assessment may not fully explain the entire observed benefit but accounted for a statistically meaningful portion of the effect.
 5. **Measurement Methodology Differences:** The primary outcome assessment differed fundamentally between the study populations in Study 206 and CRC-SCA. Study 206 used direct f-SARA administration using the validated 16-point scale with standardized instructions and trained raters while CRC-SCA used the original 40-point SARA scale, and these scores were subsequently mapped to f-SARA equivalents using a predetermined conversion algorithm. This mapping process introduced notable measurement differences, including increased variability in the mapped f-SARA gait subscores and overall f-SARA total scores compared to the directly measured f-SARA in the troriluzole group, suggesting that the statistical assumptions of homogeneous variance-covariance structures across the two studies underlying your primary MMRM efficacy analysis is not appropriate.
 6. **Lack of Pre-specification:** The primary analysis of Study 206-RWE is based on the comparison of Year 3 data from Study 206 (randomization phase and open-label extension) to natural history controls from CRC-SCA. The protocol

and statistical analysis plan (SAP) for Study 206-RWE were designed with knowledge of unblinded data of both Study 206 and the natural history data from CRC-SCA and EUROSCA, as well as with knowledge of prior analyses comparing Study 206 with the natural history data. Specifically, (b) (4), you presented results from an analysis of the 3-year OLE phase from Studies 206 and 201 compared to external controls from EUROSCA and CRC-SCA cohorts, using a matching-adjusted indirect comparison (MAIC) analysis. You have stated that the protocol and statistical analysis plan for Study 206-RWE were “prespecified”, based on the argument that the analysis included data on 21 subjects whose year 3 data in the open-label extension of Study 206 had not yet been analyzed at the time of the drafting of the protocol and SAP for Study 206-RWE. We do not agree that this constitutes “prespecification”.

Prespecification of statistical methods prior to analyzing data is critical to reduce bias and maintain study integrity by ensuring that the choice of the statistical analysis methods is not influenced by knowledge of the data. We acknowledge that Study 206-RWE uses analyses that are modified from these prior MAIC analyses, including new data from 21 subjects, and added supplemental analyses to evaluate potential biases. However, the SAP for Study 206-RWE was drafted in 2024, with prior knowledge of the results of the MAIC analyses presented to the Agency in 2023. In addition, the source data used in Study 206-RWE and the prior MAIC analyses largely overlap, and the same outcome measure was evaluated at the same time points. This is not consistent with the FDA draft guidance for industry, *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (February 2023)*, that recommends finalizing study protocols and selecting external control arms before initiating externally controlled trials and greatly affects the strength of evidence from the study because unconscious and conscious biases may be introduced.

It is our position that neither the design of Study 206-RWE nor the hypotheses underlying the SAP-specified analyses can be considered “prespecified” and that significant biases have influenced the study results.

Collectively, these issues suggest the potential for significant biases in the estimation of efficacy of troriluzole that cannot be reliably quantified or corrected. The treatment difference of -0.79 observed on the f-SARA at Year 3 ($p=0.0301$) between the troriluzole-treated group and the CRC-SCA cohort is of uncertain clinical meaningfulness. The treatment effect is not sufficiently large or robust to overcome the concerns with the multiple methodological limitations identified above. Therefore, 206-RWE is unable to serve as an adequate and well-controlled study that can contribute to substantial evidence of effectiveness.

II. Methodological issues preclude the ability to use the secondary efficacy analyses of Study 206-RWE and post hoc analyses of Study 206 as confirmatory evidence.

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 data that you proposed as confirmatory evidence.

1. **Secondary efficacy analyses of Study 206-RWE:** These analyses suffer from the same fundamental limitations as the primary efficacy analysis. The treatment effect observed in the troriluzole-treated group compared to the CRC-SCA cohort, at Year 2 and Year 1, is smaller than the effect observed at Year 3 and insufficient to overcome the multiple methodological limitations as described in Section I.

Additionally, the European Integrated Project on Spinocerebellar Ataxias (EUROSCA) demonstrated significantly faster disease progression rates compared to North American populations. This combined with limited baseline data availability, which prevents adequate adjustments and assessments, renders EUROSCA, either alone or in combination with the CRC-SCA, inadequate as an external control.

2. **Post hoc SCA genotype 3 subgroup analyses of Study 206:** Study 206 failed to achieve statistical significance on its prespecified primary endpoint of the f-SARA at 48 weeks. Post hoc subgroup analyses in the SCA genotype 3 population were not prespecified. When accounting for multiple comparisons and applying the prespecified covariates to the statistical model, the results were not statistically or clinically persuasive.
3. **Fall Risk Analysis of Study 206:** Your analysis of fall risk reduction based on adverse event reporting does not support effectiveness. The analysis was not prespecified. Moreover, the data suffers from multiple significant limitations. Inspections identified systematic under-reporting of adverse events and incorrect coding of fall events in the original adverse event dataset. It was also identified that investigators were instructed to only record falls that resulted in injury which likely led to underreporting of falls. When using the corrected dataset with an appropriate statistical model (which may still not capture all falls that occurred), the difference in relative risk reduction between troriluzole-treated subjects and controls did not achieve nominal statistical significance.

In order to address these deficiencies, you will need to provide data from an adequate and well-controlled study that demonstrates an effect on a clinically meaningful endpoint in order to establish the effectiveness of troriluzole for the treatment of spinocerebellar ataxia. We recommend that you meet with the Division to discuss the evidence that will be needed to support a future NDA for the treatment of SCA with troriluzole.

NONCLINICAL

(b) (4)

ADDITIONAL COMMENTS:

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

Reassess and propose the dosage modifications for relevant intrinsic and extrinsic factors.

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.

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

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>

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.

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

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

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)

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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