



NDA 217002

COMPLETE RESPONSE

Minerva Neurosciences, Inc
Attention: Ramana Kuchibhatla, PhD
Senior Vice President and Head of Research & Development
1500 District Avenue
Burlington, MA 01803

Dear Dr. Kuchibhatla:

Please refer to your new drug application (NDA) (b) (4)
(b) (4) for (b) (4) (roluperidone) extended-release tablets.

We also refer to your amendments dated (b) (4)

Furthermore, we refer to your (b) (4)

We also acknowledge receipt of your amendments dated (b) (4)

(b) (4), which were not reviewed for this action. You may incorporate applicable sections of these amendments by specific reference as part of your response to the deficiencies cited in this letter.

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

We have concluded that your application does not provide sufficient data for the Division to approve your application for the proposed indication of treatment of negative symptoms of schizophrenia because of the following deficiencies briefly outlined below:

- (1) You have not established substantial evidence of effectiveness (SEE) for the effects of roluperidone on the negative symptoms of schizophrenia. Study MINI-101C03 (Study C03) demonstrated statistical significance on the primary efficacy endpoint. However, this study is insufficient on its own to establish SEE. The phase 3 study MIN-101C07 (Study C07) was a negative study using the pre-specified statistical analyses, regardless of exclusion of the study site with data irregularities (Study Site

(b) (4)). The Division considered your proposal that, although negative on the prespecified primary endpoint, Study C07 may contribute to SEE based on “the appropriateness of the multiplicity correction used, the consistency of results across most secondary endpoints reflecting improvement in daily function, the findings of the exposure-response modeling, the treatment effect seen beginning at Week 4, and the consistency of results between Studies C03 and C07.” However, following substantive review of Study C07, the Division concluded that the results from the posthoc analysis using a multiple testing procedure that was not prespecified and from other exploratory analyses that you proposed were not sufficiently robust to overcome the lack of a positive result on the prespecified primary analysis, the mixed results on the secondary and exploratory endpoints, and uncertainties regarding the clinical meaningfulness of the result and fitness-for-purpose of the primary endpoint.

- (2) The NDA submission lacks data on concomitant antipsychotic administration. The Division considered your position that the proposed use of roluperidone is as monotherapy for individuals who have stable positive symptoms and do not require continuous treatment with antipsychotics and, therefore, that “the information necessary to prescribers to decide how roluperidone should be used and how to manage potential risks is a topic for review and consideration of the labeling, potentially including a limitation of use, contraindications, and/or warnings.” However, the Division concluded that data regarding the impact on the safety and efficacy of roluperidone when administered with an antipsychotic would be needed to determine whether the potential benefits of roluperidone could outweigh the risks. Current standard of care treatment for schizophrenia includes ongoing treatment with antipsychotic medications. There are substantial risks associated with untreated positive symptoms, and co-administration with an antipsychotic would be expected if patients experience worsening of positive symptoms. Importantly, because antipsychotics may lead to secondary negative symptoms or improve underlying causes of secondary negative symptoms (e.g., paranoia, depression), coadministration of roluperidone with antipsychotics could result in pharmacodynamic interactions that impact safety and efficacy. It is important to understand if roluperidone provides clinically meaningful treatment of negative symptoms in the context of concomitant antipsychotic treatment
- (3) The NDA submission lacks data needed to establish that the change in negative symptoms of schizophrenia with roluperidone treatment was clinically meaningful. The evaluation of the anchor-based analyses of the effect of roluperidone on negative symptoms—as assessed by the change from Baseline to Week 12 in the Positive and Negative Syndrome Scale, Marder’s Negative Symptoms Factor Score (NSFS) and the Personal and Social Performance scale (PSP)—found that the observed change in negative symptoms was not representative of clinically meaningful within-patient improvement in either Study C03 or C07.

- (4) Schizophrenia is chronic condition for which you have proposed chronic administration of roluperidone. The submitted safety database included an inadequate number of subjects exposed to roluperidone at the proposed dose (64 mg) for at least 12 months. The safety database should be consistent with the [ICH E1](#) Guideline for the safety evaluation of drugs intended for the long-term treatment of non-life-threatening diseases.

To address these deficiencies, you must submit at least one additional positive, adequate, and well-controlled study to support the safety and effectiveness of roluperidone for the treatment of negative symptoms. You must provide additional data to demonstrate the safety and efficacy of roluperidone coadministered with antipsychotic medications, to support that observed effect on negative symptoms with roluperidone treatment corresponds to a clinically meaningful change, and to demonstrate the long-term safety of the proposed dose. The Division expects that data from U.S. subjects will contribute to these additional efficacy and safety data. We recommend that you discuss the design of any additional planned study or studies with the Agency prior to study initiation.

CLINICAL/CLINICAL PHARMACOLOGY

Roluperidone and BFB-520 are associated with concentration-dependent QTc prolongation. You have not developed a strategy sufficient to reliably identify patients in the intended population who would be at greatest risk of QT interval prolongation with roluperidone. The proposed method for identifying patients by CYP2D6 genotype and phenotype is not appropriate given that the CYP2D6 phenotype assignments used in the development program are not consistent with current phenotyping and testing standards.

To mitigate the risk of QTc prolongation, you have proposed that roluperidone should only be administered after CYP2D6 genotyping results are available and only to patients who have at least one CYP2D6 normal function allele (e.g., *1, *2, *35). You propose a contraindication in patients who lack at least one CYP2D6 normal function allele which you define as CYP2D6 intermediate and poor metabolizers (hereafter abbreviated IMs and PMs, respectively).

However, your definition of CYP2D6 IMs and PMs (patients who lack at least one CYP2D6 normal function allele) is not consistent with standard phenotype definitions, which use activity scores. In our analyses of reclassified CYP2D6 phenotype using standard phenotype definitions, CYP2D6 IMs were enrolled in Studies C03 and C07 (~33-37% of study populations) and almost all CYP2D6 IMs have an activity score equal to 1. Based on the available data, there are potential safety risks in CYP2D6 IMs across the entire range of activity scores. If the product were to be approved in the future, based on the available data, we would recommend labeling the product only in patients who are CYP2D6 normal or ultrarapid metabolizers (hereafter abbreviated NMs and

UMs, respectively) with contraindications in CYP2D6 IMs and PMs per standard phenotype definitions which use activity scores. If an indication in CYP2D6 IMs is pursued, additional pharmacokinetic (PK) and safety characterization would be needed given the narrow CYP2D6 IM population (only patients with activity score equal to 1) and sparse PK sampling in your phase 2b and phase 3 studies. In addition, due to the potential for reduced efficacy and, therefore, altered benefit-to-risk profile, we recommend analyses of safety and efficacy in CYP2D6 UMs compared to NMs.

Given that CYP2D6 genotyping is considered essential for safe and effective use of the drug, development and contemporaneous authorization of an in vitro companion diagnostic device would likely be required to ensure robust pharmacogenomic test allele coverage and test accuracy to identify patients for treatment. The proposed administration based on CYP2D6 genotype (patients must have at least one CYP2D6 normal function allele, including *CYP2D6*1*) is not appropriate given that *CYP2D6*1* is the default when tested alleles are not present (i.e., test-dependent) and there is not a proposed in vitro companion diagnostic device to ensure test rigor and accuracy.

PRODUCT QUALITY

Drug Substance

(b) (4)



Drug Product

(b) (4)



(b) (4)



BIOPHARMACEUTICS

(b) (4)



(b) (4)



NONCLINICAL

(b) (4)



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 Resources](#) and [Pregnancy and Lactation Labeling Final Rule](#) 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 correspondence dated, (b) (4), which addresses the proposed proprietary name, (b) (4). This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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:

CLINICAL PHARMACOLOGY

- (1) Roluperidone is extensively metabolized via multiple pathways (i.e., CYP as well non-CYP based mechanisms). The PK is also impacted significantly in the presence of CYP2D6 inhibitors. The impairment of hepatic function is anticipated to increase systemic exposures of roluperidone and its major metabolite, BFB-520, and may pose safety risks to patients on therapy. A dedicated safety and PK study in patients with impaired hepatic function will ultimately be warranted to adequately inform product labeling. You may consider a reduced design hepatic impairment study in patients with moderate hepatic impairment.
- (2) The radiolabeled mass balance study suggests that approximately 1% of administered oral dose of roluperidone is excreted unchanged in urine. This suggests that roluperidone undergoes substantial disposition through non-renal

mediated pathways. Given that uremic toxins could impact the non-renal mediated disposition, a dedicated safety and PK study in patients with impaired renal function will ultimately be warranted to adequately inform product labeling. We recommend that you evaluate the safety and PK of roluperidone in a reduced design renal impairment study in patients with severe renal impairment.

- (3) Based on our analysis, roluperidone and BFB-520 are associated with concentration-dependent QTc prolongation, which is consistent with the available nonclinical data. In any future submission, we therefore recommend that you revise your proposed label to describe the increase in QTc following the recommendations in the draft guidance for industry titled "QTc Information in Human Prescription Drug and Biological Product Labeling" (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/qtc-information-human-prescription-drug-and-biological-product-labeling>). The description of the QTc increase in section 12.2 should be based on study MIN-101C08 and analyzed using exposure-response following the recommendations described in "Scientific white paper on concentration-QTc modeling" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2017; doi 10.1007/s10928-017-9558-5) and "Correction to: Scientific white paper on concentration-QTc modeling" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2018; doi 10.1007/s10928-017-9565-6).
- (4) The submitted population PK model underpredicts Cmax of roluperidone. In your resubmission, you should refine the population PK model to improve the prediction of roluperidone Cmax.

CLINICAL

- (1) We acknowledge receipt of your (b) (4) submissions providing information about data for the ongoing Study MIN-101C18, "A Phase 1b, Inpatient Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of the Coadministration of Roluperidone and Olanzapine in Adult Subjects with Moderate to Severe Negative Symptoms of Schizophrenia." These submissions will not be reviewed in the current cycle because of the limited time remaining before the PDUFA date and the inability of these submissions to impact the overall regulatory decision-making related to this application.

However, we note that Study MIN-101C18 protocol is designed to evaluate the concomitant administration of roluperidone and olanzapine. As communicated in our Advice Letter sent to (b) (4) on (b) (4), although the protocol would provide short-term PK information regarding the coadministration of olanzapine and roluperidone, it does not appear to fully address the Division's concerns about the lack of data regarding the coadministration of antipsychotics and roluperidone because the duration of treatment is too short, the sample size is too small, and because the clinical population intended to use this drug is likely to be prescribed a

range of antipsychotic medications. In addition, washing out effective antipsychotic medications and other psychotropic medications that may be prohibited per your protocol may introduce confounding effects on the proposed safety and exploratory efficacy outcomes in addition to placing subjects at risk for decompensation.

CLINICAL OUTCOME ASSESSMENTS

(1) We would expect additional validity evidence in order to conclude that the NSFS and the PSP measures are fit-for-purpose in this context of use. Specifically:

- Qualitative evidence from patients and caregivers, demonstrating that the items contained in the NSFS and the PSP score are important, comprehensive, and relevant to patients who experience predominant negative symptoms of schizophrenia. We note that the documentation provided regarding clinician endorsement is considered to be complete.
- Development of a conceptual framework for each measure, mapping the key concepts to each clinical outcome assessment (COA) item.
- Clinically meaningful change analyses utilizing anchors that measure severity and/or change in overall negative symptoms of schizophrenia and overall personal and social functioning, versus severity in overall symptoms of schizophrenia.
- Additional psychometric analyses or evidence from the literature demonstrating that key measurement properties are adequate in the NSFS score and the PSP as follows:
 - NSFS and PSP
 - Provide details regarding the exact method and model by which the intraclass correlation coefficients (ICCs) are derived
 - Provide details regarding the methods by which the kappa values are determined (e.g., Cohen's kappa or Fleiss kappa)
 - Provide evidence of inter- and intra-rater reliability at clinical sites for the NSFS and PSP.

– NSFS

- Provide a clear scoring algorithm and rationale, and description of scoring methods
- Provide clear evidence of known-groups validity in this context of use
- Provide analyses to demonstrate that item-level changes are consistent across items rather than changes being confined to a specific grouping of items (N, mean, median, standard deviation, minimum, maximum, and % missing). Include change in each NSFS item score from baseline by treatment arm and at Baseline, Week 4, and Week 12 (e.g., IR sent July 18, 2023, Request #6: item-level changes).

– PSP

- Conduct factor analyses to demonstrate the dimensionality of the PSP
- Provide the rationale regarding the cut-off for dichotomization of the PSP total score based on disease severity (i.e., dichotomizing the CGI-S into disease severity based on scores of 1 to 3 for “mild or less” and scores of 4 to 7 for “at least moderate”).

- (2) In a future study we recommend qualitative interviews (exit interviews) to assess meaningful change that is important to patients and/or caregivers to inform whether the amount of change purported to be meaningful via your meaningful change analyses is confirmed.
- (3) We expect evidence demonstrating best practices (e.g., [Wild et al. 2005](#)) are employed for translation of all COAs (e.g., copies of translation certificates).
- (4) When centralized raters are used to derive the PSP total score, we expect detailed information regarding derivation of the scores (e.g., via electronic automation, by each rater, via centralized, blinded raters) and details regarding the PSP score mapping (e.g. description of exact content of materials provided to the centralized rater(s) such as chart notes, domain scoring sheet).

PRODUCT QUALITY

Drug Product

(b) (4)

(b) (4)

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 drug 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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