NDA 219624

COMPLETE RESPONSE

Genzyme Corporation
Attention: Brant Hamel, PhD, RAC
Director, Regulatory Affairs
100 Morris St.
Morristown, NJ 07960

Dear Dr. Hamel:

Please refer to your new drug application (NDA) [redacted] for [redacted] (tolebrutinib) tablets.

We acknowledge receipt of your major amendments dated [redacted], which extended the goal date by three months.

We also acknowledge receipt of your amendments [redacted], which were not reviewed for this action. You may incorporate applicable sections of the 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.

A favorable benefit-risk profile could not be established for any patient subpopulation

We acknowledge Study EFC16645 demonstrated positive results in a population that you have defined as non-relapsing secondary progressive multiple sclerosis (nrSPMS). However, we have determined that a serious risk of severe drug-induced liver injury (DILI), which was identified during the conduct of your clinical trials, cannot be adequately mitigated by the proposed risk evaluation and mitigation strategy (REMS). Given the gravity of this serious and potentially fatal risk, the review of your application focused on attempting to identify a population in whom the benefit-risk assessment is favorable to support approval, such as a population of patients with multiple sclerosis (MS) that has the greatest unmet need because there are no approved therapies. We considered your proposed indication of nrSPMS, as well as the subgroups of subjects with active SPMS and non-active SPMS in Study EFC16645, to conduct benefit-risk

assessments. However, we were unable to identify a population for which the benefit could be clearly established and for which that benefit would be anticipated to outweigh the serious risk of severe DILI to support approval. We outline our reasons for this determination below.

1. **Serious risk of severe (including fatal) DILI**

   The risk of severe DILI (i.e., requiring transplant or fatal) with tolebrutinib is substantial and unusually high for drug development programs in general, and specifically for MS therapies. Our review of your premarket development program to date has identified 6 cases meeting Hy's Law criteria in the tolebrutinib Phase 3 development program out of approximately 2700 subjects, including one subject who died after requiring a liver transplant, which indicates a high level of hepatotoxic risk with tolebrutinib. Per the guidance document, *Drug-Induced Liver Injury: Premarketing Clinical Evaluation* (July 2009),[1] the presence of even a single case meeting Hy's Law criteria in the premarket development program of a drug is a signal of a high level of hepatotoxicity. Most of the drugs withdrawn from the market for hepatotoxicity have caused death or transplantation at rates so low (i.e., ≤1 per 10,000) that severe hepatotoxicity is not typically identified in the premarket development program.

   Additionally, per the guidance document referenced above, another major indicator of the potential for severe DILI is an excess of aminotransferases greater than 3 times the upper limit of normal (i.e., Temple's Corollary). In the first 6 months of double-blind treatment of Study EFC16645, 3.6% of tolebrutinib-treated subjects versus 1.9% of placebo-treated subjects experienced aminotransferases greater than 3 times the upper limit of normal.

   Therefore, based on the DILI cases (which included both fatal and non-fatal Hy's Law cases) reported in the tolebrutinib development program to date, the predicted postmarket rate of severe DILI associated with tolebrutinib is high. The predicted rate of severe DILI with tolebrutinib is at or above that of drugs which were either not approved due to the risk of DILI or were removed from the market due to DILI. The risk of DILI with tolebrutinib is idiosyncratic and greatly exceeds that observed with all other therapies approved for multiple sclerosis. Additionally, we acknowledge that DILI is a class effect of BTK inhibitors discussed in current approved labeling, but the risk of fatal DILI associated with tolebrutinib appears to be among the highest in the class. There is therefore a significant and unusually high risk of severe DILI associated with tolebrutinib.

   We considered whether the risk of DILI could be mitigated through your proposed REMS, but have determined, based on the available data, that the proposed REMS would not adequately mitigate the risk of severe DILI. We acknowledge that you changed your monitoring strategy to weekly liver monitoring following

[1] https://www.fda.gov/media/116737/download

identification of Hy's Law cases, including the fatal case of DILI, and that there have been no additional cases of DILI resulting in death or transplant following that change to date. However, additional DILI cases, including a Hy's Law case, have occurred in this limited dataset after weekly monitoring was initiated. These cases included a Hy's Law case with a rapid rise in aminotransferases, and other cases with a substantial rise in aminotransferases (greater than 10 to 60 times the upper limit of normal), some with hyperbilirubinemia. These cases predict that severe liver injury will occur in a larger population of exposed patients in a potential postmarketing setting, even with the mitigation measures described in the proposed REMS.

Therefore, even with the implementation of weekly monitoring, the predicted postmarket rate of severe DILI associated with tolebrutinib remains substantial. The benefit-risk assessment must assume that there will be severe and potentially fatal cases of DILI in the postmarketing setting, even with a REMS requiring weekly laboratory monitoring.

2. Uncertainties regarding benefit in disease subpopulations

Your enrollment criteria defined the targeted population for the proposed indication of nrSPMS, which does not align with the current multiple sclerosis (MS) course descriptor paradigm.[2] Enrolled subjects could have either non-active SPMS (i.e., no clinical relapses and no inflammatory MRI activity) for which there are no approved therapies, or active SPMS (i.e., no clinical relapses but evidence of inflammatory MRI activity) which is considered a relapsing form of MS (RMS) and for which there are approved therapies.

Because of the lack of historical MRI data collection in the study, we were unable to retrospectively determine whether the subjects enrolled in Study EFC16645 had active or non-active SPMS based on the information included in your submission. We acknowledge that you attempted to retrospectively obtain historical MRI data to characterize enrolled subjects, which was submitted in a response to information request dated (b) (4). However, these data are of limited interpretability due to selection bias, as the data were only able to be collected from subjects who elected to enroll in and remained in the open-label extension study (Study LTS17043), and reflected <40% of the enrolled population in Study EFC16645. The lack of historical MRI data collection during the study limits this assessment to the baseline MRI, which is a single timepoint that is not likely to adequately characterize a subject's recent clinical course and disease activity. Nonetheless, we conducted additional analyses to better characterize a potential treatment effect of tolebrutinib in subjects based on their baseline MRI.

[2] Lublin FD, et al. Neurology. 2014 Jul 15;83(3):278-86. doi: 10.1212/WNL.0000000000000560. Epub 2014 May 28.

Subgroup analyses of Study EFC16645 indicate that the observed treatment effect was greater in subjects who had T1 gadolinium-enhancing (GdE) lesions at baseline (i.e., active SPMS), which comprised 13% of the enrolled population. For subjects with GdE lesions at baseline, the hazard ratio (HR) (95% confidence interval [CI]) for the primary endpoint was 0.346 (0.183, 0.656), and without GdE lesions at baseline was 0.777 (0.601, 1.006). This subgroup analysis suggests that the treatment effect is largely driven by the small group of subjects with active SPMS based on their baseline MRI scan, a population for which there are approved therapies.

Additionally, the observed treatment effect in Study EFC16645 was greater in subjects who had not received a prior MS therapy, which comprised approximately 25% of the study population. The treatment effect was substantially diminished in subjects who had tried two or more prior MS therapies. For the primary endpoint, the HR (95% CI) based on number of prior MS therapies is as follows: subjects with no prior MS therapies 0.392 (0.241, 0.638); subjects with one prior MS therapy 0.649 (0.407, 1.034); subjects with two or more prior MS therapies 0.902 (0.643, 1.265). These observations raise concerns regarding the consistency of any potential benefit across all patients with nrSPMS, which needs to be weighed against the known substantial risk of DILI. We also note that patients with SPMS in the United States would typically have been treated with at least one approved MS therapy for RMS prior to reaching the secondary progressive phase of MS.

We acknowledge that these analyses do not allow definitive conclusions about efficacy in these subgroups; however, the analyses raise substantial uncertainties about the SPMS population that is more likely to benefit from tolebrutinib. Given the serious and unusually high risk of severe DILI, it is critical to have certainty about efficacy in a population in whom this level of DILI risk could be considered acceptable.

3. Insufficient evidence of effects on slowing disability accumulation independent of relapse activity

Additionally, there are uncertainties about the analyses that you have provided to support the claim included in your proposed indication statement regarding slowing disability accumulation independent of relapse activity.

We acknowledge the data submitted as confirmatory evidence, including post hoc analyses of disability accumulation independent of relapse activity from two Phase 3 studies in the RMS population (Studies EFC16033 and EFC16034) that did not meet their primary endpoint. Though the concept of disability accumulation independent of relapse activity is of interest, it remains an emerging construct with multiple limitations. There are no widely accepted criteria for defining disability accumulation independent of relapse activity. There are

also limitations in both the analysis methods and the interpretability of the submitted post hoc analyses. Additionally, it is unclear whether this concept represents the same pathophysiology or has the same clinical implications for both nrSPMS and RMS, especially in later stages of the disease.

There are also significant limitations in the understanding of the underlying pathophysiology of progression in MS and the potential for BTK inhibitors to address this pathophysiology, which limit the ability of a mechanistic rationale to provide confirmatory evidence for this application.

These limitations are highlighted by the recent negative topline results from Study EFC16035 in primary progressive multiple sclerosis (PPMS), which failed to demonstrate a benefit of tolebrutinib on the primary endpoint of 6-month composite confirmed disability progression (cCDP).

The Division has determined that the data are insufficient to support a claim of slowing disability accumulation independent of relapse activity, particularly in the context of the significant risk of DILI, because of the reliance on post hoc analyses; the uncertainties regarding the concept of disability accumulation independent of relapse activity; the limitations of the mechanistic rationale; and the negative results of Study EFC16035 on cCDP.

4. No study subpopulation was identified with a favorable benefit-risk profile

The Division considered the issues cited above in the benefit-risk assessment for the proposed indication of nrSPMS. As previously noted, the nrSPMS population includes both active and non-active SPMS. The benefit-risk assessments for these SPMS subpopulations differ due to the availability of approved therapies for RMS that is inclusive of active SPMS. Because of the heterogeneity of the broader population defined in the clinical trials as nrSPMS, we determined that the benefits did not outweigh the risk of severe DILI in this population.

The Division considered the benefit-risk assessment for the active SPMS population. We acknowledge that this subgroup was not pre-defined in the enrolled population; however, the population of enrolled subjects with baseline GdE lesions would be considered to have active SPMS. There were much larger treatment effects in the population with baseline GdE lesions than in those without baseline GdE lesions. We also acknowledge that there are limitations to this subgroup analysis due to lack of historical MRI data to more fully characterize an active SPMS population compared to a non-active SPMS population. However, given the availability of approved therapies for RMS that do not have the same magnitude of DILI risk, the Division determined that the benefits would not be anticipated to outweigh the risk of DILI for the general population of active SPMS. The Division also considered whether there was a population within the active SPMS population that may have an unmet need,

such as those that have experienced disability progression despite treatment with approved therapies, that could potentially support a favorable benefit-risk assessment. However, Study EFC16645 was not designed to assess the benefit of tolebrutinib in active SPMS in patients who experienced disability progression despite treatment with approved MS therapies. Furthermore, the data showed diminished treatment effects in subjects who had been on one or more prior MS therapies than in those who had not received any prior MS therapies.

The Division then considered whether the data could support approval for non-active SPMS, for which there are no approved therapies and therefore different benefit-risk considerations. We acknowledge that this subpopulation was not pre-defined in the enrolled population; however, the Division was willing to show flexibility to consider narrowing the indication to a population for which there are no FDA-approved therapies, and for which there is a significant unmet medical need. However, even when applying flexibility, the Division considered the data (described under item 2 above) insufficient to establish substantial evidence of effectiveness for non-active SPMS given the uncertainties raised by the diminished treatment effects in the subgroup analysis of subjects without baseline GdE lesions; the inability to rely on the post hoc analyses from the two negative Phase 3 studies in RMS; and the negative topline results from Study EFC16035 in PPMS. As discussed in the FDA draft guidance document, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019),[3] therapies with greater risks may require a greater magnitude and certainty of benefit to support approval. The Division determined that, given the substantial uncertainties regarding efficacy, the potential for benefit in this population was inadequate to overcome the identified risk of severe DILI.

Overall, substantial evidence of effectiveness has not been established in a clinically identifiable population for whom the benefits potentially outweigh the risks.

Potential next steps

To address the deficiencies in your application, we are open to having further discussion with you to identify a population for whom the potential benefits of your drug may outweigh the serious risk of severe DILI. This discussion would need to be supported by additional analyses of the safety data from the recently completed Study EFC16035 and the ongoing extension Study LTS17043 to characterize the impact of weekly liver safety monitoring on the incidence of severe DILI.

[3] https://www.fda.gov/media/133660/download

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[4] and Pregnancy and Lactation Labeling Final Rule[5] 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.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[6]

CARTON AND CONTAINER LABELING

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

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) OR FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

We acknowledge receipt of your proposed REMS included in your submission dated (b) (4), and amended on (b) (4), which contains a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for (b) (4) (tolebrutinib), if it is approved, to ensure that the benefits of the drug outweigh the risks of DILI. The REMS, should it be approved, will create enforceable obligations.

We have determined that your proposed REMS does not adequately mitigate the risk of DILI. Because your application cannot be approved without an approved REMS, you must revise your proposed REMS and submit it as part of your response to the deficiencies cited in this letter. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

[4] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[5] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
[6] https://www.fda.gov/industry/fda-data-standards-advisory-board/structured-product-labeling-resources

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.

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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