



NDA 219195

COMPLETE RESPONSE

Applied Therapeutics, Inc.
% Quantum Regulatory Solutions, LLC
Attention: Mark A Ammann, PharmD
President
5047 West Main Street, PMB 305
Kalamazoo, MI 49009

Dear Dr. Ammann:

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

for govorestat.

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

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.

You submitted data from an 18-month, randomized, double-blind, placebo-controlled trial (Trial AT-007-1002) with confirmatory evidence of the drug effect on plasma galactitol from nonclinical studies and clinical studies to establish substantial evidence of effectiveness of govorestat for the treatment of classic galactosemia (CG) in adults and pediatric patients 2 years of age and older. Based on our review of the data, we are unable to conclude there is substantial evidence of effectiveness.

TRIAL AT-007-1002:

Data Quality Issues of the Efficacy Measurements: The review of the submitted datasets, documents, and inspections of the Sponsor and the clinical investigator who enrolled 42 of 47 subjects in the trial identified major systemic data quality issues related to study conduct, data management, and data replicability for the Clinical Outcome Assessments (COAs). These issues included improperly implemented COAs, unresolved COA efficacy data discrepancies, and inadequate processes and procedures for appropriate data management, including deletion of COA source records. Because of these findings, the accuracy, traceability, and reliability of the COA-based primary outcome data generated in Trial AT-007-1002 cannot be assured. As such, the Agency could not rely on these data to determine govorestat's efficacy.

Efficacy Results: Even if the serious data quality issues were not present, Trial AT-007-1002 failed to achieve the prespecified criterion for statistical significance on global testing of three prespecified primary endpoints of the Oral and Written Language Scales Oral Expression (OWLS-OE), the Vineland-3 Socialization domain, and the NIH Cognitive Battery (NIH-CB) comparing govorestat to placebo using protocol version 17/SAP 3.0, the version the Agency considered prespecified for the purpose of hypothesis testing. Further analyses of the individual primary and secondary efficacy endpoints did not demonstrate convincing evidence of treatment effect. The trial also failed to meet the pre-specified criterion for statistical significance on the primary endpoints based on the protocol version 18/SAP 5.0 (OWLS Oral Expression Test, OWLS Listening and Comprehension Test, BASC-Behavioral Symptoms Index, and BASC-Activities of Daily Living domain).

CONFIRMATORY EVIDENCE:

Clinical efficacy findings of Trial AT-007-1002 aside, govorestat's effect on plasma galactitol seen in Trials AT-007-1002 and AT-007-1001 and its correlation with clinical outcomes is inadequate as confirmatory evidence for the reasons below:

- a. Based on the extensive review of the published literature and nonclinical data, the Agency determined that, while galactitol may play a role, there is limited evidence for galactitol being a major pathogenic driver of CG and that other metabolites and pathogenic pathways may also contribute to the neurobehavioral manifestations of GC.
- b. In addition to significant technical limitations and design flaws of the submitted nonclinical studies that preclude a reliable assessment and interpretation of the results, the review and analyses of the submitted nonclinical studies did not identify robust, consistent, and sustained effect of changes in galactitol in response to govorestat treatment on neurobehavioral outcomes in animals.
- c. The correlation analyses of plasma galactitol and clinical outcomes, using various measurements of plasma galactitol and methods of analysis, at different time points, suggest overall weak and inconsistent associations.

ACCELERATED APPROVAL:

The discussion under the Confirmatory Evidence section above describing the limitations of the evidence to support the role of galactitol in the pathogenesis of the CG applies to the consideration of galactitol as a reasonably likely surrogate endpoint (RLSE) for the purpose of accelerated approval. Further, if plasma galactitol were shown to be the key mediator of the pathogenesis of CG sufficient to be considered a RLSE, it is not clear what magnitude of galactitol reduction would reasonably predict

clinical benefit. In the submitted data, treatment with govorestat resulted in only modest reductions in plasma galactitol.

In summary, the Agency concludes the currently available evidence does not support plasma galactitol as a reasonably likely surrogate endpoint for CG.

INFORMATION NEEDED TO RESOLVE THE DEFICIENCIES:

Provide substantial evidence of effectiveness for govorestat for the treatment of CG. Given the significant data quality issues with the efficacy endpoints in Trial AT-007-1002 and efficacy results outlined above, conduct at least one new adequate and well-controlled trial demonstrating an effect of govorestat on clinically meaningful endpoint(s) in subjects with CG. If you intend to demonstrate substantial evidence of effectiveness based on the single adequate and well controlled trial plus confirmatory evidence framework, consider conducting a well-designed and adequately powered nonclinical efficacy study in an animal model of CG demonstrating a robust effect of govorestat treatment at exposures relevant to humans, assessed using validated assays, on clinically relevant neurobehavioral outcomes, histopathology, and metabolic markers of CG. Evaluation of a clinically relevant functional endpoint(s) should be considered. Depending on the robustness of the results and the demonstrated relevance to the effects observed in animals to those observed in your clinical trial, the nonclinical study data could be considered confirmatory evidence, along with all other potential sources of confirmatory evidence. Refer to the FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence*.^{1,2}

Regarding galactitol as a reasonably likely surrogate endpoint (RLSE) for the purpose of accelerated approval, you will need to (1) provide strong mechanistic evidence for the role of galactitol as the major mediator in the pathogenesis of the neurobehavioral symptoms of CG, (2) adequately and comprehensively address evidence from published literature regarding plausible alternative toxic metabolites/pathophysiologic mechanisms of disease, and (3) determine and provide evidence to support a galactitol reduction response threshold that would be reasonably likely to predict clinical benefit. For accelerated approval, you will need to provide substantial evidence of effectiveness of govorestat on the RLSE based on adequate and well controlled clinical investigation(s) and confirmatory evidence, if one single adequate and well controlled trial is being considered as primary evidence.

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

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

² <https://www.fda.gov/media/172166/download>

Prescription Drug Labeling Resources³ and Pregnancy and Lactation Labeling Final Rule⁴ 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.⁵

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 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.

³ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

⁴ <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

⁵ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

- 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:

1. The submitted study using rat blood is insufficient to support the proposed claim in the Prescribing Information of the effect of govorestat on serum creatinine using the colorimetric assay. We recommend obtaining clinical data at relevant concentrations in order to support the proposed claim.
2. Review of nonclinical data has (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*.^{7,8}

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

⁶ <https://www.fda.gov/media/71921/download>

⁷ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁸ <https://www.fda.gov/media/172311/download>

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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