



NDA 218679

COMPLETE RESPONSE

Saol International Development Limited
% Saol Therapeutics Inc
Attention: Allison Lowry
Head of Regulatory
1000 Holcomb Woods Parkway, Suite 270
Roswell, GA 30076

Dear Allison Lowry:

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

[REDACTED] for sodium dichloroacetate.

We acknowledge receipt of your major amendment dated [REDACTED] (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.

DEFICIENCY

The data presented in NDA 218679 failed to demonstrate substantial evidence of effectiveness for sodium dichloroacetate (DCA) for the treatment of pyruvate dehydrogenase complex deficiency (PDCD). We describe the rationale for this conclusion in further detail below.

You proposed to establish substantial evidence of effectiveness using two adequate and well-controlled trials: SL1009-01 and SL1009-02.

- SL1009-01, a randomized, double-blind, placebo-controlled trial, failed to demonstrate a statistically significant benefit of DCA treatment on the prespecified primary analysis for the endpoint of change from baseline in ObsRO motor in ITT population of PDCD subjects 10 months to 17 years of age (treatment difference 0.29 [95% CI: -0.62, 1.21; p=0.52] favoring placebo arm). The proposed post hoc analyses for the subgroup of subjects with Period 1 baseline ObsRO motor score ≥ 8 were deemed inappropriate to determine the presence of a DCA treatment effect. The secondary endpoint of change from baseline in plasma lactate produced estimated treatment differences that favor

DCA with a nominal two-sided p-value < 0.05. However, the changes in the baseline plasma lactate were minimal and additional clinical and nonclinical data provided did not support the observed reduction in plasma lactate as a surrogate endpoint that predicts clinical benefit in PDCD.

- SL1009-02 compared survival of subjects who received DCA in SL1009-01 to an external control derived from a published 2012 natural history study of PDCD by DeBrosse et al. The interpretability of the SL1009-02 survival analysis results is limited by the following substantial differences between treated and control groups identified during review and assessed in context of poorly defined natural history, significant clinical heterogeneity, and lack of reliable prognostic indicators for PDCD:
 - a. Methods used to ascertain the age of disease onset were not clearly defined in the protocol and statistical analysis plan for SL 1009-02; data for the disease/symptom onset variable are incomplete, and imputation protocol was inconsistently applied introducing bias against the external control group.
 - b. Observed differences in the presence of structural brain abnormalities most commonly associated with severe disease favored the DCA-treated group.
 - c. Differences in the methodologies used for diagnosis of PDCD to identify participants in the external control (i.e., enzyme activity) compared to those who received DCA in SL1009-01 (i.e., genetic diagnosis via broad exome/genome sequencing) further limited between group comparability with respect to PDCD severity favoring the DCA-treated group.
 - d. Temporal bias: potential advances in medical care due to the temporal separation (average 18 years) from the non-contemporaneous external control favoring the DCA-treated group.

Therefore, comparison between the DCA-treated group in SL1009-01 and the proposed external control cannot be used to assess the treatment effect of DCA on survival and support claims of effectiveness.

Overall, the data for two clinical trials you have provided in this application are insufficient to establish substantial evidence of effectiveness of DCA for the treatment of PDCD.

INFORMATION NEEDED TO RESOLVE THE DEFICIENCY

To address this deficiency, submit the results of at least one new adequate and well-controlled trial demonstrating the effect of DCA on clinically meaningful endpoint(s) in the intended population.

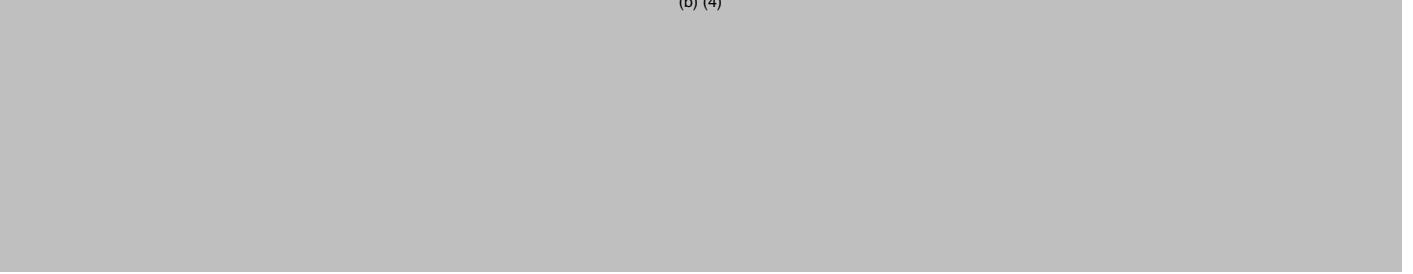
If you intend to demonstrate substantial evidence of effectiveness based on a single adequate and well controlled trial, you will also need to provide adequate confirmatory evidence substantiating the results of your adequate and well controlled trial.

ADDITIONAL APPROVABILITY ISSUES

As substantial evidence of effectiveness of DCA for the treatment of PDCD was not established in this application, we cannot conclude that the known and potential risks with DCA in your application are outweighed by its benefit(s). Therefore, for the potential benefits and risks to be adequately evaluated, the following issues, including those for premarketing risk assessment, and our recommendations for resolving those issues, must be addressed, in some manner, in the resubmission of your application.

Companion Diagnostic

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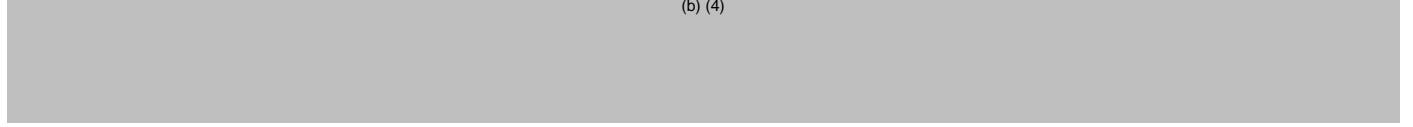


Clinical Pharmacology

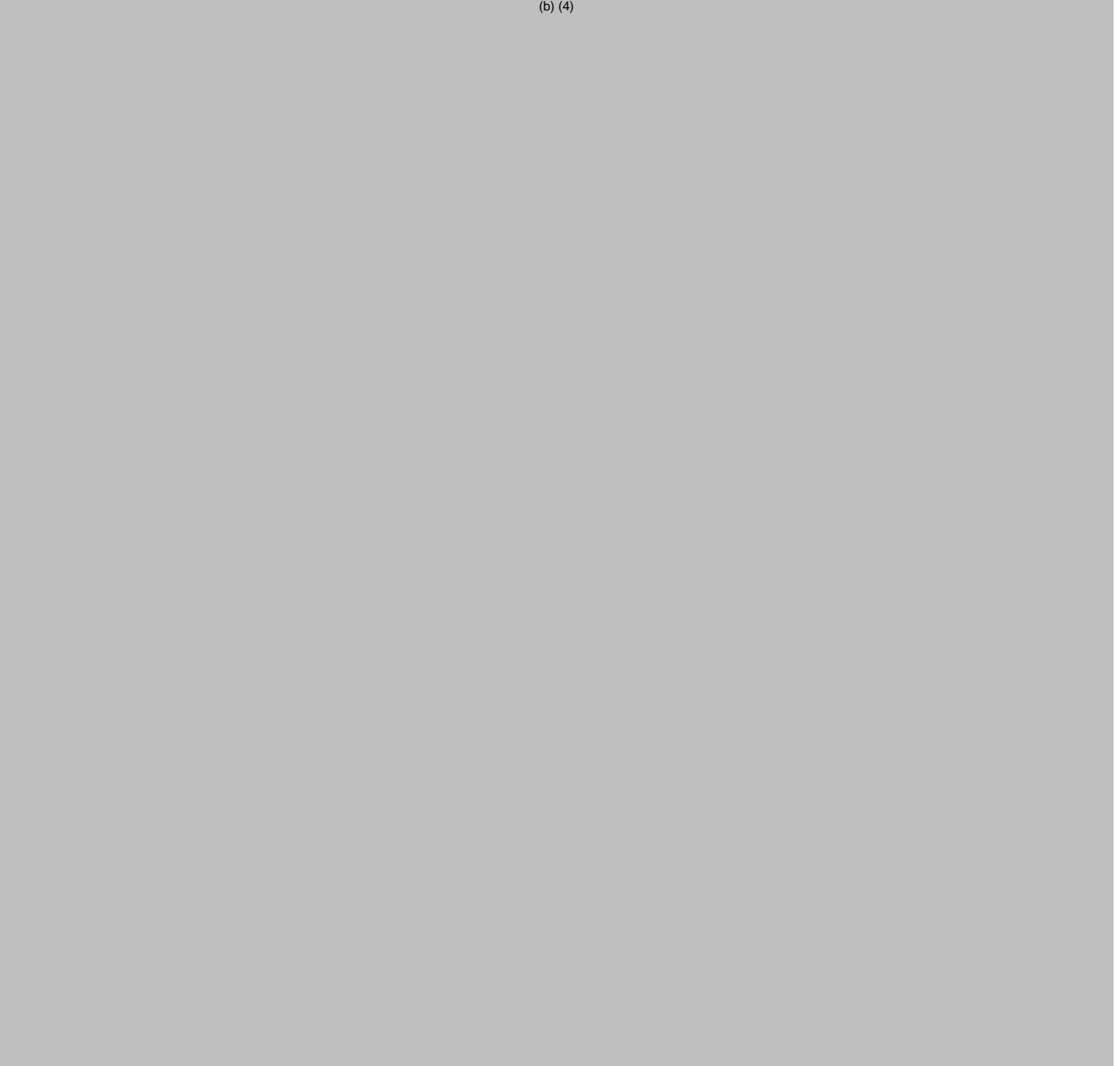
2. You have not conducted a thorough QT/QTC study to evaluate the effect of DCA on QT interval prolongation and the currently available clinical safety database in the NDA is insufficient to assess the potential effect of DCA on the QT interval. Conduct a thorough QT/QTC study to evaluate the effect of DCA on QT interval prolongation.
3. You have not evaluated the effect of food on the pharmacokinetics (PK) of DCA. Conduct a clinical trial to evaluate the effect of food on the PK of DCA.

Nonclinical

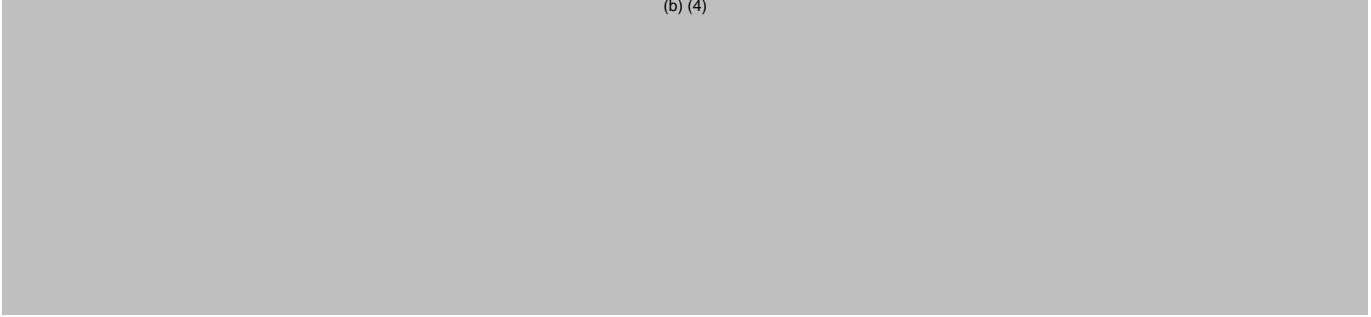
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PRESCRIBING INFORMATION

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 Resources⁵ and Pregnancy and Lactation Labeling Final Rule⁶ 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

The review of your proposed proprietary name has been terminated due to the deficiencies with the application as described in this letter. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter. If you do not have a conditionally acceptable proprietary name, you may submit a Request for Proprietary Name Review to your IND.

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.

⁵ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

⁶ <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

- 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*.

If you have any questions, contact [REDACTED]

(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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