LOI DECISION LETTER

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Dear Dr. Kranzler:

We have completed our review of your Letter of Intent (LOI) submission of April 2, 2018, requesting qualification of the rs678849 biomarker. We have decided to **Not Accept** it into the CDER Biomarker Qualification Program. Please note that the 21st Century Cures Act was signed into law in December 2016, and adds new section 507 to the Federal Food, Drug, and Cosmetic Act (FD&C Act) concerning the qualification of drug development tools (DDTs). FDA now operates its biomarker DDT program under the section 507 provisions. As stated in section 507(a)(2)(B), an LOI submission may not be accepted based upon factors which include scientific merit.

In summary, our decision was based on the following:

- While your biomarker may have utility in clinical management of patients, there is not a clear understanding of its use as a predictive biomarker to aid in drug development.

The data that you provided are interesting, however, appear premature to support the use of rs678849 to enrich study populations investigating new buprenorphine formulations for treatment of opioid use disorder. The underlying pathophysiology and mechanism of action for this very common single nucleotide polymorphism (SNP) that leads to the difference in treatment response observed between European and African Americans remains unclear. We encourage and support your continued efforts to further elucidate the role of this genomic biomarker or as one of a panel of biomarkers in the pathophysiology of opioid use disorder and its treatment. This biomarker may result in the development of a useful clinical tool for the

management of opioid use disorder or, should more supportive scientific evidence become available, in its use as a drug development tool.
The comments and questions in this letter represent CDER's scientific considerations related to the proposed biomarker and COU. If you choose to continue development of this tool for regulatory use, we recommend that you fully address these considerations prior to resubmission.

Biomarker Considerations

Requestor's Biomarker Description: *rs678849 is a (an intronic) SNP in the OPRD1 gene, the gene encoding the delta-opioid receptor.*

1. We agree with your proposed biomarker description.

Drug Development Need and Context of Use (COU) Considerations

Requestor's COU: *Predictive biomarker to enrich clinical studies of new buprenorphine drugs in self-identified African American patients diagnosed with opioid use disorder who are less likely to test positive for concurrent opioid drug use during the study.*

2. The proposed COU describes the use of the genomic biomarker rs678849 as a predictive biomarker for the development of buprenorphine in a sub-population.
    a. The utility of developing rs678849 as a predictive biomarker to enrich clinical trials of buprenorphine is uncertain. Your presentation of the data indicates that the presence of the biomarker in other population subsets does not appear to have the same effect. This inconsistency may indicate that there may be adjunctive elements to this biomarker which are responsible for or contribute to the observed effect in the African American sub-population. These contributory elements and their effects have not been described.
    b. Thus far, demonstration of clinically significant differences to buprenorphine compared with placebo have not been challenging, thereby abrogating the need for enrichment in clinical trials of buprenorphine. Enrichment is typically not necessary in the development of generic formulations of buprenorphine as the regulatory requirement is the demonstration of bioequivalence, and these studies are typically small.
    c. The proposed biomarker may have the best utility in the clinical management of opioid misuse, to provide guidance on the selection of a treatment regimen for individual patients. However, the clinical decision of a treatment regimen between methadone and buprenorphine treatment is complex. The medications are used in very different treatment paradigms/settings and may be more or less desirable or accessible depending upon individual patient circumstances. These factors may influence choice of regimen more than any biomarker-based prediction of medication response. The clinical application of a biomarker is outside the regulatory drug development tool space.

As a drug development tool,

3. Please provide information on the current knowledge about *OPRD1* pharmacogenomics. Include information on other *OPRD1* variant(s) that may be in linkage disequilibrium with rs678849 and/or on *OPRD1* rs678849 haplotype(s). Include a description of the association(s) of these variant(s) and haplotype(s) with other diseases/conditions. Provide justification for developing rs678849 as a single SNP marker rather than other *OPRD1* variant(s) and haplotype(s) as a biomarker(s) for regulatory use.

4. Publicly available experimental and *in silico* data indicates that rs678849 is not a functional regulatory variant for *OPRD1* and does not influence its expression in normal tissues. Please describe why rs678849, a common variant in different ethnic populations, is associated with buprenorphine treatment response in African Americans only, and why the CC genotype effect is inverted for buprenorphine vs. methadone treatment response in African Americans.

Analytical Considerations

5. It is not clear whether a TaqMan Predesigned SNP Genotyping Assay or a TaqMan Custom SNP Genotyping Assay will be used for determining subjects' *OPRD1* genotype, and whether such an assay has FDA 510(k) clearance. According to the assay manual, the Custom SNP Assays are not covered by the TaqMan Assays QPCR guarantee which provides the quality assurance and performance of the assay. Please clarify which TaqMan Genotyping Assay (i.e., Predesigned vs. Custom) will be used and whether such assay is FDA cleared. Provide validation information for the assay including analytical performance characteristics such as accuracy, sensitivity, specificity, and reproducibility of the assay.

6. Although we do not recommend acceptance of this proposed biomarker into the Biomarker Qualification Program at this time, the LOI decision does not preclude further development of this biomarker or the development of a potential *in vitro* diagnostic device. If you choose to seek FDA clearance or approval of such an *in vitro* diagnostic device, we encourage you to work closely with the Agency. For more information on working with FDA to meet marketing requirements for medical devices, please refer to the following web page:
https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm

   You may also find the Division of Industry and Consumer Education (DICE) helpful for general questions on medical devices:
https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ContactDivisionofIndustryandConsumerEducation/default.htm

Clinical Considerations

7. While you plan to conduct a 16-week trial using a recently approved extended-release buprenorphine with monthly dosing (except for the first 7 – 10 days) in your proposed study, a flexible daily dosing approach presumably using a different formulation was used for the 24-week study conducted by Crist et al. (*Neuropsychopharmacology* 2013;38:2003-10). Discuss how you plan to take into consideration the use of different drug products, dosing regimens, and study durations in the study design of your future study(ies).

8. We recommend that you analyze the efficacy results on a by-patient basis over time (responder, partial responder, non-responder) rather than using group mean results at each time point.

9. You propose to use a sublingual buprenorphine product followed by an extended-release buprenorphine product. We recommend that you use the products approved by the FDA and check the labeling information available at "Drugs@FDA." When drafting the full study protocol, refer to the approved product labeling regarding information on dosing regimen, dosing recommendation in specific patient population such as patient with hepatic impairment, and dosing recommendation for patients on co-medications with drug interaction potential.

Statistical Considerations

10. You propose to conduct the clinical study to confirm preliminary findings from the two previous studies, one of which is from Crist et al., and from the meta-analysis combining the data from the final 8 weeks of the two studies. Please provide adequate justification for your proposal including a sample size of 200 subjects and define the criteria that will be used as confirmation of the current findings.

We want to emphasize that this decision not to accept rs678849 into CDER's Biomarker Qualification Program is not a final decision about that biomarker. You may submit a new LOI with a revised COU for review that contains the requested clarification and additional supportive scientific data and information recommended herein.

Please note that the Biomarker Qualification Program also issues a Letter of Support (LOS) for promising biomarkers which have not yet been accepted into the CDER Biomarker Qualification Program. CDER works to encourage the early identification of novel biomarkers that may address important drug development needs. The LOS is intended to enhance the visibility of these novel biomarkers, make public FDA's support for continued development, and encourage data sharing and collaboration. More information about submission of a LOS request is available at;
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm602478.htm

If you have questions, please contact Chris Leptak (christopher.leptak@fda.hhs.gov) through email.

Sincerely,

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