U.S. FOOD & DRUG ADMINISTRATION

LETTER OF INTENT
DETERMINATION LETTER

DDTBMQ000110
January 4, 2021

Innovative Medicines Initiative (IMI) TransBioLine
Drug-Induced Pancreas Injury (DIPI) Work Package
Attention: Dr. Lidia D. Mostovy
One Health Plaza
East Hanover, New Jersey, 07936

Dear Dr. Lidia D. Mostovy:

We are issuing this letter to Innovative Medicines Initiative – TransBioLine Drug-induced Pancreas Injury Work Package, to notify you of our determination on your proposed qualification project submitted to the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP). We have completed our review of your Letter of Intent (LOI) deemed reviewable on August 31, 2020 and have concluded to **Not Accept** it into the CDER BQP[1]. You have proposed qualification of a panel of safety biomarkers that may potentially enable detection of drug-induced acute acinar pancreas injury in phase 1 trials. Please note that the 21st Century Cures Act was signed into law in December 2016 and adds the 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 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.

We have provided comments and recommendations for further improvement of your proposed project. In addition, we have also highlighted other potential context of use cases that are likely to meet a drug development need that may benefit patients with acute, chronic, or recurrent pancreatitis. We recommend revising and resubmitting this LOI based on the following considerations:

Drug Development Need Considerations:

You have not established the need for the development of this panel within the proposed context of use (COU). The incidence of drug-induced acute pancreatitis (DIAP) is rare (i.e., accounts for

[1] In December 2016, the 21st Century Cures Act added section 507 to the Food, Drug, Cosmetic Act (FD&C Act). FDA is now operating its drug development tools (DDT) programs under section 507 of the FD&C Act.

0.1 - 2% of all acute pancreatitis cases[2, 3]), and the scope of the problem (i.e., how often therapeutic programs are discontinued because of a concern for the development of pancreatitis) remains uncertain; therefore, assessing the added value of more sensitive and specific biomarkers is challenging. In addition, it is unclear whether 1) the panel will be able to distinguish DIAP from other causes of acute pancreatitis (AP), and 2) how reliance on this proposed panel would result in an earlier diagnosis that would prevent or decrease the severity of pancreatitis. Given the nature, severity, and morbidity of AP, you have not provided information to support that the proposed panel has the ability to reduce the risk of DIAP for healthy volunteers such that it would be acceptable to rely on the proposed panel for safety monitoring or inform dose selection in phase 1 clinical trials. The clinical comments below provide additional feedback on the proposed context of use.

However, based on your LOI, the proposed panel may be appropriate for different contexts to address unmet drug development needs. For example, use of biomarkers in nonclinical studies that have improved translational prediction to human outcomes of DIAP could be beneficial, especially if those biomarkers could detect early development of AP. Likewise, more sensitive diagnostic biomarkers for early detection of acute, chronic, or recurrent acute pancreatitis that are specific to the type or etiology as well as early detection of pancreatic cancer could be useful for diagnosis of these conditions or in an assessment of response to therapy in human clinical trials.

Context of Use (COU) Considerations

Requestor's COU: *A safety biomarker or biomarker panel to aid in the detection of acute acinar pancreas injury in phase I trials where there is an a priori concern that a novel drug may induce pancreas injury (DIPI) in humans.*

FDA's comments regarding the COU: We do not agree that a biomarker panel will likely decrease the risk of acute and severe pancreatic injury in patients or healthy volunteer in phase 1 studies. Please propose a new COU based on our suggestions in the drug development need and clinical consideration sections. Please also revise your analytical and clinical plans accordingly.

Biomarker Considerations:

Requestor's Description: *A biomarker panel including circulating pancreas-specific miRNAs and the following four molecular biomarkers measured in serum and urine.*

[2] Jones, M. R., Hall, O. M., Kaye, A. M., and Kaye, A. D. (2015). Drug induced acute pancreatitis: A review. Ochsner J. 15, 45–51.

[3] Nitsche C, Maertin S, Scheiber J, Ritter CA, Lerch MM, Mayerle J. Drug-induced pancreatitis. Curr Gastroenterol Rep. 2012;14(2):131-8.

Biomarker Protein	HUGO ID
Trypsinogen Activation Peptide (TAP)	HGNC: 9475
Carboxypeptidase A1 (CBPA1)	HGNC: 2296
Carboxypeptidase A2 (CBPA2)	HGNC: 2297
Carboxypeptidase B Activation Peptide (CAPAP)	HGNC: 2299

FDA's questions for continued development of the biomarker description: You have provided several studies suggesting a link between the increase in the four chosen biomarkers and onset of pancreatic injury. However, since acute pancreatic injury is rare and the relationship of these biomarker levels to the pathological pathway for pancreatic injury is not well understood, we are concerned that any correlation between injury and biomarker levels could be due to other factors and not necessarily directly related to pancreatic injury. In addition, at this point, we are unable to comment on the ability of miRNAs to detect pancreatic injury as you have not provided us with a list and information on the potential measurement methodology. To overcome this challenge, we recommend you provide a robust justification to support why specific biomarkers that will be included in the proposed panel are able to predict pathologic changes in the pancreas.

We have the following comments and recommendations related to the analytical, clinical, and statistical aspects of your proposed program.

Analytical Considerations

1. At this time, you are exploring multiple methods of measurement and protein-matrix combinations and do not have a list of miRNAs that will be used. By the time you are ready to submit the qualification plan, we suggest finalizing the list for methods, matrices, and biomarkers you will be measuring and at a minimum, provide information for your measurement method's characterization even if you haven't completed the complete analytical validation.

2. You provided your analytical validation plan for the learning phase and the validation phase for the proposed biomarkers (trypsinogen activation peptide (TAP), carboxypeptidase A1 (CPA1), carboxypeptidase A2 (CPA2) and carboxypeptidase B activation peptide (CAPAP) in urine and EDTA plasma by IP-LC-MS/MS) and micro RNAs (by NGS for the learning phase and RT-qPCR for the validation phase). However, the development of the biomarker(s) is still in the early phase and key details of the final biomarker(s) are still unknown. The types of studies ultimately needed to demonstrate that the selected biomarker(s) can be used as stated in the COU will depend on the type of biomarker (e.g., whether this will be a composite biomarker or whether the individual results from each biomarker will be interpreted), how the result will be interpreted (e.g., looking for a change from baseline, using medical decision points), the sample types (urine, plasma, liquid biopsy), the methods used to measure the biomarkers, the patient population(s), the measuring range, etc. We offer the following recommendations for your development plan and for the types of information that should be provided in a future BQP

submission:

a. We have questions about the validation plan and report described for the NGS method that will be used to select the miRNAs to move forward for qualification. For example:

   i. You did not describe your protocol for miRNA library preparation including details of how you plan to assess miRNA quality before the start of library generation and how you plan to eliminate DNA contamination prior to library preparation.

   ii. The generation of the miRNA sequencing data is dependent on your bioinformatics pipeline; however, you have not described the pipeline or described how you have validated all steps from sequence generation to final result.

   iii. You have not described the quality control thresholds for the method or how you plan to validate the abundance of rare transcripts (as needed).

   iv. It is not clear to us whether you are using the same samples that you have used to validate the method for the testing that you will conduct in the learning phase. The NGS method seems to have been validated using “human platelet-poor EDTA plasma (PPP) samples” but it is not clear if the learning phase samples are also PPP samples.

   v. In your report, you have described ligation bias that leads to reduced accuracy in the detection of specific miRNA sequences, which are under- or over-represented as a proportion of total reads due to varying ligation efficiency. However, you have not described how you plan to account for or control this bias.

   vi. You have not discussed amplification induced bias associated with your NGS method. It is our understanding that you will start with very small amounts of biological materials (e.g., cell-free RNA) which will involve whole transcriptome amplification for miRNA. You should make sure that you have controls in place to ensure that there is uniform amplification of all the miRNA targets.

   vii. We caution you that if the NGS method used in the learning phase is not well validated or fit for purpose, you run the risk of moving forward miRNAs for qualification that are not meaningful. If you are planning to confirm the result obtained using the NGS method during the learning phase using RT-PCR method described in your LOI (prior to moving forward with qualification using independent samples), please consider the questions about the validation of that method provided below (for example items 5d and 5e).

b. In your future BQP submission, please provide a detailed description of the biomarker(s) including the methods used to measure each of the biomarkers, a description of the metrological traceability for the measurements, how the biomarker(s) will be interpreted, any medical decision points, the validated matrix type(s), and whether the biomarker(s) are qualitative or quantitative.

c. In the submission, provide a detailed description of all reagents and all steps needed to obtain the results.

d. It is not clear if you are consistently using one sample type for validation and testing. As discussed above in item 2a, the validation documents for the NGS method describes the use of PPP samples while the protocols on "Isolation of total RNA from blood serum/plasma samples" describes that both serum and plasma samples will be used for the isolation of miRNA. Plasma and serum could have different levels of circulating miRNA and should be validated separately. For the studies for the qualification phase, it is described that urine and plasma samples will be collected from the patients. It is not clear if the validated plasma type will be consistently used for the testing for qualification. You should make sure to validate all sample types you intend to use during the qualification phase of testing and provide a clear description of the sample types used in your future submission.

e. You should also make sure to test samples following validated and consistent preanalytical steps for all methods needed to generate the results. For example, you should make sure the tube types used to collect samples for testing are validated; that all samples are handled and stored under validated conditions for all steps needed (e.g., for RNA preparation, for cDNA generation for RT-PCR, etc.); and that all centrifugation/mixing/heating steps needed, etc. are done under consistent and validated conditions. The samples in the clinical studies should undergo the same preanalytical steps as the samples used in the analytical validation; otherwise, information would need to be provided to show the difference in preanalytical steps wouldn't affect the results.

f. For the RT-PCR method, you did not describe the validated method used for normalization and this should be described in your future submission.

g. It is our experience that some methods can have significant batch-to-batch (or lot-to-lot) performance differences and this can complicate interpretation of results from studies. We recommend that you develop strategies to assess each batch (or lot) needed for your testing to make sure that you are generating consistent results irrespective of testing batch/lot.

h. You should provide detailed protocols used to validate the selected biomarker(s) (and any composite biomarker, as needed) including a description of the purpose of each study and the conclusions drawn from the study. The protocols should include the

following: the method(s) and instrument(s) used, all reagents needed and all steps needed (including all preanalytical steps), the specimen type (e.g., urine, plasma, native samples, contrived samples, quality control material) including a description of the tube type used, the specific concentrations of each target biomarker in that sample (and that of the composite, as needed), the number of samples tested, the number of replicates tested for each sample, the number of days, the number of operators, the number of reagent lots used, any reference materials used, and all quality control materials used (including internal and normalization controls). All studies should be conducted using stable samples (i.e., stored and handle using validated conditions for all steps needed, see item 2e). The sample type and matrix type should reflect the clinical samples that will ultimate be used and native patient samples should be used whenever possible (and especially around important medical decision levels). In general, we find the following Clinical and Laboratory Standards Institute (CLSI) guidelines helpful when designing your validation studies: C62 "Liquid Chromatography-Mass Spectrometry Methods"-First Edition and other applicable guidelines such as EP05-A3 "Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline-Third Edition"; EP06-A "Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline" and EP17-A2 "Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline-Second Edition". You should also include your rationale for the performance parameters evaluated and those not evaluated. For example, for quantitative methods, we recommend an evaluation of linearity as described in the above referenced guideline.

i. For analytical specificity, you only described an evaluation of hemolysis for the RT-qPCR method. We recommend that you conduct a risk analysis and consider the technology of the specific testing methods, your patient population and identify and evaluate any potential interfering compounds relevant to the technology and the patient population. We recommend that you consider the recommendations in EP07-A3 "Interference Testing in Clinical Chemistry, Third Edition" and EP37 "Supplemental Tables for Interference Testing in Clinical Chemistry" and provide your rationale for the potential interferents tested and the concentrations evaluated.

j. You described acceptance criteria for some of your current protocols. However, it is not clear how these were developed and if they are adequate to support the COU. We recommend that you consider what performance is needed to support the COU of the biomarker(s) and determine acceptance criteria for validation studies based on the performance you determine necessary for this use. We recommend that you define acceptance criteria for each analytical validation study in the context of the cumulative effect that different sources of error, including bias or systematic differences as well as imprecision, instability, etc., have on the performance of each biomarker and any composite you plan to develop. You should define acceptance criteria for each parameter such that your total analytical error for each biomarker or for any planned

composite does not preclude the determination of clinically meaningful differences in the biomarker(s).

Clinical Considerations

3. Although you have stated that there is a critical need to prevent delays in drug development and termination of potentially promising programs due to concern for DIAP you have not provided information to support this assertion. Provide examples of programs that were halted due to concern for the development of pancreatitis or drug classes in which your panel could potentially be of benefit.

4. You describe the proposed panel as intended to facilitate the development of drugs for which programs would otherwise be halted due to concern for the development of DIAP. You will need to provide rationale to support that availability of the proposed panel could result in early detection or intervention to prevent or decrease the severity of the event (i.e., pancreatitis) such that the risk is mitigated for exposing healthy volunteers to a drug with potential pancreatic toxicity in early phase clinical trials.

5. Your proposal to utilize samples from patients with acute pancreatitis to support the use of the proposed biomarker panel to assess for potential DIAP needs further clarification. You will need to provide information to support a similar presentation, physiologic response, or anticipated clinical course including onset and duration of illness between patients with acute pancreatitis secondary to multiple etiologies and those specific to DIAP.

6. Please provide information as to whether the panel will be able to distinguish DIAP from other causes of pancreatic injury.

7. Should the proposed biomarker panel have improved measurement properties over standard laboratory evaluations, there may be a role for the development of this panel under an alternative context of use.

Statistical Considerations

8. As part of your Qualification Plan, please include a Statistical Analysis Plan (SAP) that describes the statistical methods you intend to use to support qualification of candidate biomarkers. Our preliminary statistical comments can be found below. We may have additional comments on your planned approach at the time of submission of the SAP.

    a. Although you are at a stage of exploring potentially useful biomarkers, it is not clear how the proposed ANOVA analyses will be utilized.

    b. We acknowledge that you plan to generate the SAP for the confirmatory phase after the data analysis is completed in the learning phase. Clarify whether the datasets

proposed for confirmatory evaluation are sufficient to target the proposed success criteria following the acceptance of your proposed context of use stated in your LOI. If the statistical power is not adequate, additional studies should be planned. In addition, since multiple selected biomarkers from the learning phase will be evaluated in the confirmatory phase, your SAP should discuss potential multiplicity problem.

Please address each of the specific considerations and recommendations and any data requests cross-referencing the numbered list above in a separate addendum to your next LOI submission.

When evaluating biomarkers prospectively in clinical trials, requesters are encouraged to submit study data using Clinical Data Interchange Consortium (CDISC) standards to facilitate review and utilization of data. Data sharing and the capability to integrate data across trials can enhance biomarker development and utilization. If sponsors plan to use the biomarker prior to qualification to support regulatory review for a specific Investigational New Drug (IND), New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) development program, they should prospectively discuss the approach with the appropriate CDER or CBER division.

The BQP encourages collaboration and consolidation of resources to aid biomarker qualification efforts. Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Dr. Lidia D. Mostovy (lidia.mostovy@novartis.com), the point of contact for this project.

We recommend scheduling a teleconference to clarify the content of this letter. Please contact the CDER Biomarker Qualification Program via email at CDER-BiomarkerQualificationProgram@fda.hhs.gov with reference to DDTBMQ000110 in the subject line. For additional information and guidance on the BQP please see the program's web pages at the link below.[4]

Sincerely,

Christopher L. Leptak -S

Digitally signed by Christopher L. Leptak -S
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[4] https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/cder-biomarker-qualification-program

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