LETTER OF INTENT
DETERMINATION LETTER

DDT BMQ000096
May 14, 2021

IMI-TRISTAN Consortium
c/o Bioxydyn, LTD.
Rutherford House,
Manchester Science Park,
Pencroft Way,
Manchester M15 6SZ, UK.
Attention: Dr. Gerry Kenna

Dear Dr. Gary Kenna for the IMI Tristan Consortium:

We are issuing this letter to the IMI Tristan Consortium to notify you of our determination for the project submitted to the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP). We have completed our review of the Letter of Intent (LOI) deemed reviewable on February 25, 2021 and have determined to accept the LOI into the CDER[1] Biomarker Qualification Program.

In your next submission, a Qualification Plan (QP), you will describe the detailed approaches involved in calculation of the biomarker and threshold, describe the analytical validation plan for the biomarker measurement method, provide detailed summaries of existing data that will support the validation of the biomarker, threshold and its context of use (COU), and include descriptions of knowledge gaps and how you propose they will be mitigated. Please include detailed study protocols and the statistical analysis plan for each future planned study as part of your QP submission.

Below, we provide you with specific considerations and recommendations to help improve your preparation for, and submission of, the QP. As this biomarker development effort is refined, the submitted data, the specifics of your context of use (including the target patient population), and the design of study(ies) used in the clinical validation of the biomarker will ultimately determine which of these considerations and recommendations are most

[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.

applicable. For more information about your next submission and a QP Content Element outline, please see the BQP Resources for Biomarker Requestors web page.[2]

CONSIDERATIONS & RECOMMENDATIONS

1. Biomarker description:

Change, caused by investigational (perpetrator) drug, in Gadoxetate (victim drug surrogate) hepatocyte uptake and efflux rate constants [∆k(he) and ∆k(bh), respectively] indicating potential for drug-drug interaction when above threshold

FDA agrees with your biomarker description.

1.1 Clarify if gadoxetate ∆k(he) and ∆k(bh) above threshold will be incorporated into PBPK modelling. If so, how will this be implemented and what's the plan to validate such modeling?

2. COU Considerations

Requestor's COU Statement:
A safety (acute lack-of-harm) biomarker, employed in the development of investigational drugs (IDs) which are thought to carry an enhanced DDI risk because prior animal or in vitro human cell studies have indicated that the investigational drug (ID) is a hepatic transporter inhibitor or inducer. ∆k(he) and ∆k(bh) would be used in early phase clinical drug development. An ID whose effect on either ∆k(he) or ∆k(bh) is not below-threshold would be prioritized for an early program of clinical DDI investigations.

FDA COU Recommendation:
Safety biomarker for use, in conjunction with other drug-drug interaction assessments during drug development, to assess the potential for clinical impact of an investigational drug as an inhibitor and/or inducer of OATP1B1/1B3, NTCP, MRP2 and/or MRP3 transporters on the pharmacokinetics of drugs intended for coadministration that are substrates of those transporters and for which alteration of hepatic concentrations may differ from the plasma concentration, to inform drug-drug interaction management and prevention strategies.

2.1 In the submission you indicate the biomarker is to be used in conjunction with clinical biomarkers assessing drug-drug interaction risk profile of the investigational drug and appropriate PBPK modelling. Please indicate the clinical biomarkers you intend to use with this biomarker.

[2] https://www.fda.gov/drugs/cder-biomarker-qualification-program/resources-biomarker-requestors

2.2 We note in the LOI submission document that you reference safety and efficacy uses for this biomarker; however, drug development tool qualification allows a single COU per submission. We encourage you to limit the submission content for this LOI for any given project to focus upon a single COU in drug development. If you intend to qualify gadoxetate for an efficacy COU, that will need to be submitted as a separate LOI.

3. Analytical Considerations

3.1 In your submission, you indicate you will minimize the time between scans acquired before and after administration of the investigational drug to improve repeatability of k(he) and k(bh). However, it is unclear whether you plan to characterize k(he) and k(bh) repeatability in the absence of an investigational drug. We recommend you characterize the repeatability of k(he) and k(bh) measurements under the range of imaging conditions (e.g., field strength, imaging hardware, pulse sequence parameters) covered by your proposed biomarker so that you understand when changes in k(he) and k(bh) are within the expected variability of the measurement.

3.2 Regarding image acquisition, you state “Acquisitions can be performed on 1.5T or 3T MRI scanners from any vendor, provided the required sequences are available as products”. Please clarify whether DCE-MRI acquisitions before and after administration of the investigational drug will occur on the same imaging equipment (i.e. same manufacturer, field strength, and model). Differences in technological characteristics across MR systems (e.g. field strength, magnet homogeneity, gradient and RF subsystem capability, B1 mapping accuracy) may contribute appreciably to DCE-MRI data variability. DCE-MRI repeatability testing should be aligned with your general image acquisition approach such that it appropriately informs your threshold determination.

3.3 In your QP submission, please provide a complete description of your image acquisition process including 1) the manufacturer and model of compatible imaging equipment, 2) RF coils used, 3) the specific 3D spoiled gradient echo pulse sequence used, 4) pulse sequence parameters and timing, and 5) the specific B1 mapping protocol and post-processing methods for producing flip angle maps.

4. Clinical Considerations

4.1 The transporters responsible for gadoxetate uptake and efflux are inconsistently described throughout the LOI submission including reference to OATP1A1, which seems to be a murine transporter. Please clarify in your QP submission the human hepatic transporters for which you will provide analytical and drug development validation data.

4.2 Gadoxetate may have different affinities for the different transporters and those considerations should be addressed in your QP submission (e.g., kinetic experiments in cells or vesicles expressing the human transporters).

4.3 Considering that the inhibition potency of an investigational may be substrate dependent, there is a question on how gadoxetate may represent other drug substrates on the transporters of interest. Please clarify how this potential substrate-dependent inhibitory effect of an investigational drug will be accounted for when the biomarker you proposed is applied to assessment of drug-drug interaction risk.

4.4 Include in your QP the results of in vitro experiments of gadoxetate with proposed perpetrator drugs of OATP1B1, OATP1B3, NCTP, MRP2 and MRP3 and include probe substrates of those transporters for comparison.

4.5 When conducting in vitro studies, clarify whether gadoxetate is to be used as the substrate with the investigational drug to account for probe substrate specificity in the inhibition/induction experiments or how substrate specificity will be accounted for.

4.6 You proposed to conduct a study in healthy subjects and patients with cholestasis and pruritus to quantify the effect of a single dose of rifampin on Δk(he) and Δk(bh) for gadoxetate. Rifampin inhibits OATP1B1, OATP1B3, and MRP2. Please clarify whether you plan to conduct other human study to evaluate the impact of MRP3 or NTCP inhibition on Δk(he) and Δk(bh).

4.7 FDA has issued a safety communication[3] related to gadolinium-based contrast agents (GBCAs). Gadoxetate is characterized as a linear GBCA and can lead gadolinium retention in the body. GBCAs are primarily excreted via the kidneys but some of each administered dose is retained in the body long term. FDA is requiring changes to the labeling of all GBCAs to include a Warning and Precautions. Please describe your approach to demonstrating the short and long-term safety of repeat administrations of gadoxetate for measurement of this biomarker in the patients. Please describe any safety measures taken as part of the protocol.

4.8 Rifampin is a potent inhibitor of OATP1B1/3. It is useful to also evaluate the effect of other OATP1B1/3 inhibitors that are less potent than rifampin on Δk(he) and Δk(bh) for gadoxetate, to support validation of the biomarker. The following website contains some OATP1B1/3 inhibitors for your reference, https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#transporter

> Please note that this is not a comprehensive list. You may propose other OATP1B1/3 inhibitors not in the list.

[3] https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-gadolinium-based-contrast-agents-gbcas-are-retained-body#:~:text=Gadolinium%20retention%20has%20not%20been,to%20outweigh%20any%20potential%20risks.&text=However%2C%20trace%20amounts%20of%20gadolinium,in%20the%20body%20long%2Dterm.

It is also desirable to conduct a study with another inhibitor(s) of MRP2 besides rifampin to provide further evidence that the biomarker will be responsive to perpetrators.

4.9 In the clinical study(ies) you propose to conduct to validate the utility of the biomarker, please clarify if you plan to also include other drug substrates of the affected transporters (e.g., OATP1B1/3, MRP2) to measure plasma concentration changes of those substrates, to explore the relationship of gadoxetate Δk(he) and Δk(bh) and pharmacokinetic change of substrate drugs that are likely to be co-administered with investigational drugs.

4.10 The proposed study with a single dose of rifampin may reflect the impact of inhibition of transporters. Please clarify whether you plan to conduct a study with multiple doses of rifampin to evaluate the effects of induction of transporters on the Δk(he) and Δk(bh) for gadoxetate.

4.11 Provide an updated version in your QP submission of the Figure 1 flowchart in the LOI submission delineating the scope of this submission and COU and please clarify:

- whether the clinical study with gadoxetate can be combined with other ongoing trials (and if so, which trial(s)) or would be conducted as standalone clinical studies,

- whether the results would indicate a need for further clinical drug-drug interaction studies or if you propose the use of gadoxetate replaces the need for a clinical DDI study,

- where this qualification effort begins and ends, specifically indicating in your QP submission the scope of this qualification effort in the figures and diagrams so they are consistent with the text,

- while we acknowledge PBPK modeling may be applied before conducting clinical study of an investigational drug with gadoxetate to inform study design, it seems more accurate to replace the text in the yellow box (PBPK model informed DCE-MRI…) with conducting clinical study of investigational drug and gadoxetate.

4.12 Please provide the complete study protocol(s) for planned studies intended to validate the biomarker and COU. Also please provide an additional figure showing the clinical study design you propose for validation clinical studies (including frequency/timing of inhibitor/substrate dosing, measurements, timing of washout, etc.).

5. Statistical Considerations

5.1 Please include the statistical analysis plan (SAP) in the QP. The SAP should include description of how the threshold used to identify investigational drug-drug interaction risk will be derived. Please also provide a complete description of the threshold including, for example, its use globally, site-specific, and individualized for each patient. Please include

how the potential for variability of the threshold in different populations (e.g., transporter polymorphisms, sex, race or age) will be assessed.

6. General Considerations

6.1 The submission lacks a glossary characterizing terms, acronyms, and abbreviations. These include T_1, T_2 and T_1 Maps and many others. Please provide a glossary in an Appendix or clarify in footnotes to improve clarity and readability.

6.2 The Tristan protocol is mentioned several times in the submission but is not referenced. Please provide the Tristan protocol or an easily accessed reference to it in the next submission.

6.3 Throughout the submission there is content describing efforts outside the scope of this qualification effort. While we want to understand your ultimate goals, we ask that you limit the description of ultimate goals to a labelled subsection on future goals and focus the main content upon the qualification effort that is the subject of the submission.

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 QP 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 individuals or groups (academia, industry, government) that would like to join in this effort, have information or data that may be useful can contact Dr. Gerry Kenna (email: gerry.kenna@bioxydyn.com).

Should you have any questions or if you would like 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 DDT BMQ#000096 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

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[4] https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/cder-biomarker-qualification-program