TRANSITION SUMMARY RESPONSE LETTER

DDTBMQ0000006

August 12, 2020

Dr. John Clay
Menarini Silicon Biosystems
3401 Masons Mill Rd., Suite 100, Huntingdon Valley, PA
19006
Dear Dr. Clay:

We are issuing this Transition Summary Response Letter to Menarini Silicon Biosystems to notify you of our decision on your transition summary for Drug Development Tool (DDT) BMQ0000006 received on May 6, 2020 by the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP).

Your proposed context of use (COU) is "CTC0 is a Response Biomarker for the early evaluation of drug product activity in mCRPC clinical trials".

FDA has completed its review and has agreed to proceed with the CDER Biomarker Qualification under the 507 DDT qualification process. Please prepare a Qualification Plan (QP) submission that addresses the scientific issues and the recommendations outlined below. A QP contains details of the analytical validation of the biomarker measurement method, summaries of existing data that will support the biomarker and its context of use (COU), and descriptions of knowledge gaps and how you propose to mitigate them. Please include detailed study protocols and the statistical analysis plan (SAP) for each study as a part of your QP submission.

When evaluating biomarkers prospectively in clinical trials, sponsors 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 intend to include analyses of these biomarkers to support regulatory decision making for a specific Investigational New Drug (IND) development program, they should prospectively discuss the approach with the appropriate CDER division.

Biomarker Considerations

Drug Development Need:

> We agree that there is a current lack of a reliable early indicator of a beneficial response to therapy for treatment of metastatic castration-resistant prostate cancer (mCRPC). This gap prolongs the drug development cycle and deprives patients access to promising, new, and life extending treatments.

Biomarker Description:

Name: Anti-epithelial cellular adhesion molecule (EpCAM and UniProtKB: P16422) positive circulating tumor cells.

This is a response biomarker, abbreviated CTC0, that registers the change in circulating tumor cell (CTC) numbers between two time points, baseline and after 12 weeks of therapy. Based on preliminary data, it appears that a favorable response to therapy is observed when patients with a CTC count >1 in 7.5 mLs of blood at baseline (detectable CTCs), are later found to have 0 CTCs (undetectable CTCs) after 12 weeks of therapy. This information will be explored further and reviewed as part on the biomarker's ongoing development.

Although a range of CTC detection technologies are available, the CellSearch CTC Test (Menarini Silicon Biosystems) is the only assay as of July 2020 that has received FDA clearance for CTC enumeration (K03158834,43 & K0733387). This assay captures and enumerates a particular class of CTCs from the total population of all CTCs, by using an Anti-EpCAM conjugated magnetic particle (ferrofluid). CTCs in this assay are strictly defined as those intact cells that are EpCAM+, have a DAPI+ nucleus surrounded by cytoplasm that is cytokeratin+ (CK+), and the CTC must also be CD45(-).

Context of Use (COU) Considerations

1.&We recommend the following clarifications to your proposed COU.

Requester's COU: *CTC0 is a Response Biomarker for the early evaluation of drug product activity in mCRPC clinical trials.*

FDA Suggested COU for continued biomarker development: *A conversion of Circulating Tumor Cell (CTC) count* in 7.5ml of blood from detectible at baseline to undetectable after 12 weeks of therapy as a response biomarker indicating preliminary and early evidence of clinical activity of therapies in mCRPC clinical trials.*
** CTC count as defined in the biomarker description*

2.&The CTC counts were determined using CellSearch, which isolates a subset of CTCs with a defined molecular signature (EpCAM+, CK+, CD45-). Other assay platforms may capture CTCs with the same or different molecular signature(s), and CTC counts can be different between methods. If another CTC measurement method will be used, please provide information RE how the new platform compares with the CellSearch system.

3.&The proposed CTC0 response biomarker was exclusively derived from the development trials of four studies of androgen-receptor (AR) targeted agents, but in only one study of a non-AR targeted agent. The CTC Conversion" from >1 CTCs at baseline to 0 CTCs after 12 weeks of therapy is found to be associated with a favorable response to this specific class of treatment regimen. Whether or not such a response biomarker is valid for other investigational drug products such as those with a different mechanism of action (MoA) is unknown and would require additional clinical trial data. As your biomarker development effort continues, your COU should specify the therapeutic product(s) or product classes for which CTC0 response biomarker has been validated in clinical trials.

4.&Please clarify whether your CTC comparison with baseline is for 12- or 13-weeks post therapy.

Analytical Considerations:

5.&FDA cleared CellSearch has a LOD of 1.2 CTC/7.5 mL blood, which was established through spiking SK-BR-3 breast cancer cell line. You state that CellSearch can discriminate between a CTC count of 0 or 1 in 7.5 mL blood from prostate cancer patients. However, from the data included in the 510(k) submissions, the test was not analytically validated at levels lower than 5 CTC/ 7.5mL.

a.&Should CTC samples be shipped to a central laboratory for CTC testing, shipping validation studies should be performed to define the shipping and storage conditions, and the length of time for which that CTC count is stable.

b.&CV% should be determined at varying CTC levels (e.g., 0, 1 CTC per 7.5 mL of blood) for the entire procedure – blood sampling, storage, shipment, antibody-staining, isolation and numeration.

c.&Assay variability must be taken into consideration in data analysis and interpretation.

6.&We recommend the patient breakdown (distribution) with each count (1, 2, 3, 4) and corresponding outcome (i.e. is there clinical support that patients with lower # of CTCs have better prognosis?).

7.&Please provide studies that support the analytical validation of CellSearch at levels lower than 5 CTC/ 7.5mL.

Clinical Considerations:

8.&CellSearch may capture only a particular class of CTCs from the total population of all CTCs. Thus, the proposed CTC0 derived from CellSearch may not be applicable to all metastatic castration resistant prostate cancer patients. Additional biochemical marker(s) may need to be incorporated for validity in all mCRPC patients for a more generalized COU claim.

9.&Data for CTC0 may be adequate as an early response biomarker in early-phase trials and could potentially be helpful for determination of breakthrough therapy designation. Since it is not clear that the CTC0 endpoint reflects clinical benefit for the patient, the COU is not intended to include use of CTCO as an endpoint to support marketing approval.

10. Use as a primary endpoint in a registrational trial would likely require ODAC discussion and potentially additional supportive data.

11. CTC0 concept does not appear to address the cases that are associated with high baseline CTC counts and a significant drop but ≥1 after 12-week therapy. Clarify how a favorable or non-favorable response would be determined in those cases.

Statistical Considerations:

12. Provide baseline CTC distribution as a continuous variable and as a 3-category (0, 0 < baseline CCT < 5, ≥ 5) variable by registration trial. In addition, provide correlation analysis between baseline CTC and baseline PSA for each of the 5 registration trials.

13. The statistical analysis plan (SAP) needs to be included in your qualification plan submission.

14. In the SAP, specify the value for a predictive accuracy measure (e.g., C-index) to be considered as strong or acceptable prediction and provide justification. In addition, specify analyses to explore whether baseline characteristics affect the correlation between the proposed biomarker and overall survival.

When you prepare for your QP submission, thoroughly review the questions above and address them line by line following the numbering above or you may refer to the sections in your QP where your responses are found. The summary of your responses may be added to the appendix section of your QP.

The following weblinks contain the contents to include in your submission to reach the next milestone (Qualification Plan): https://www.fda.gov/drugs/cder-biomarker-qualification-program/resources-biomarker-requestors and the submission portal: CDER NETGEN Portal. Please Contact **CDER's Biomarker Qualification Program (BQP)** (**CDER-BiomarkerQualificationProgram@fda.hhs.gov**) should you have any questions (refer to **DDTBMQ0000006**).

Sincerely,

Christopher L. Leptak -S

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