U.S. FOOD & DRUG ADMINISTRATION

LETTER OF SUPPORT

DDTBMQ000118

August 25, 2021

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Dear Dr. Rasmussen:

We are issuing this Letter of Support to the three-way consortium consisting of Bristol Myers Squibb, the University of Pennsylvania, and Nordic Bioscience to encourage the further study of the biomarker PRO-C6 representative of a fragment released during formation of type VI collagen, which also harbors a signaling molecule (endotrophin). PRO-C6 is a proposed prognostic biomarker[1] to provide an objective measure of risk of outcomes in clinical trials of patients with heart failure with preserved ejection fraction (HFpEF).

Heart failure causes substantial mortality and morbidity and has major effects on physical function and quality of life. HFpEF is a highly heterogeneous and complex syndrome. The past decade has seen a great effort on elucidating the underlying mechanisms; however, the disease pathology remains complex and largely unknown. Patients likely to have heart failure with preserved ejection fraction are those with typical demographics (e.g., elderly, female, and comorbidities), a preserved left ventricular ejection fraction (LVEF) on a standard echocardiography, and other easily detectable findings such as elevated natriuretic peptides (NT-proBNP) or atrial fibrillation[2]. However, risk assessment based on these and other available parameters has not led to new therapies. Selection of a more homogenous patient population may be key to solve this issue. The proposed PRO-C6 biomarker is intended to be used to enrich HFpEF clinical trials with a more homogenous group of patients who are more likely to experience outcomes.

We support your plan to study PRO-C6 as a prognostic biomarker to be used to enrich HFpEF clinical trials with patients who are more likely to experience outcomes. To date, published and non-published information show that the PRO-C6 biomarker may be linked to fibrosis and inflammation. These biological processes are assumed to be of relevance during the development of cardiovascular outcomes. Based on experience with use of PRO-C6 in several cross-sectional and longitudinal studies, early analyses suggest that PRO-C6 may be associated with outcomes. Furthermore, PRO-C6 may provide added prognostic information when used with standard

[1] A prognostic biomarker, as defined by the BEST Resource, is "used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest. " BEST is located at https://www.ncbi.nlm.nih.gov/books/NBK338448/

[2] Pieske, B. et al. *European Heart Journal 40, 3297–3317 (2019)*. doi: 10.1093/eurheartj/ehz641

parameters, such as NT-proBNP and the MAGGIC risk score. PRO-C6 is currently being investigated in various cohorts from different continents to demonstrate its clinical utility.

The plan to study the PRO-C6 biomarker for prognostic enrichment is consistent with the FDA's guidance document "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products"[3]. The ability to identify patients at greater risk for events can reduce the sample size needed to show an effect in an outcome study. Greater experience with the use of PRO-C6 as a biomarker in HFpEF clinical trials is needed to determine its clinical utility for prognostic enrichment and study design considerations. We further encourage the investigation of the proposed biomarker to determine the prognostic potential.

The biomarker is currently being measured by a hand-held enzyme-linked immunosorbent assay (ELISA). All measurements are performed at the facilities of Nordic Bioscience by trained personnel to ensure that data is only released when adhering to predefined acceptance criteria. Current efforts are being undertaken to validate the assay for the proposed prognostic context of use and move the assay to a robust, automated platform.

Strong emphasis on applying good scientific, laboratory, and software development practices for quality control and validation of PRO-C6 is imperative. If, after further research, PRO-C6 is formally proposed as a biomarker for qualification, analytical validation of the assay measuring PRO-C6, and validation of potential algorithms containing PRO-C6, should be performed to support the clinical validation of PRO-C6 as a prognostic enrichment biomarker.

We encourage exploration of the biomarker PRO-C6 as a prognostic biomarker to be used to enrich HFpEF clinical trials with a more homogenous patient subset who are more likely to experience outcome. We will consider data collection on this biomarker to be exploratory in nature. We believe data sharing and integrating data across trials can foster an accelerated path for HFpEF in drug development programs. If sponsors intend to include analyses of this biomarker to support regulatory decision making for a given IND drug development program, they should prospectively discuss the approach to these analyses with the appropriate CDER review division. Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Daniel Guldager Kring Rasmussen (dgr@nordicbio.com) or view Nordic Bioscience's webpage (www.nordicbioscience.com).

Sincerely,

[3] https://www.fda.gov/media/121320/download

Jeffrey N. Siegel -S

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