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Navidea Biopharmaceuticals Announces Publication of Study Examining Tc99m Tilmanocept Imaging of Arterial Inflammation in People with HIV

DUBLIN, Ohio--(BUSINESS WIRE)-- Navidea Biopharmaceuticals, Inc. (NYSE American: NAVB) (“Navidea” or the “Company”), a company focused on the development of precision immunodiagnostic agents and immunotherapeutics, today announced the publication of a manuscript titled “Increased Macrophage Specific Arterial Inflammation Relates Uniquely to Non-calcified Plaque and Specific Immune Activation Pathways in People with HIV: A Targeted Molecular Imaging Approach,” based on work performed at the Massachusetts General Hospital (“MGH”) and Harvard Medical School, Boston MA, and sponsored by the Company. The research, appearing in *The Journal of Infectious Diseases* (PMID: 35856671), was led by Principal Investigator Steven Grinspoon, MD, Chief of the Metabolism Unit at Mass General Hospital and Professor of Medicine at Harvard Medical School.

Persistent immune activation and downstream macrophage-specific arterial infiltration are thought to contribute to increased atherosclerotic (plaque) cardiovascular disease risk among people with HIV on anti-retroviral therapy (“ART”). In this study, Tc99m tilmanocept imaging was applied to investigate macrophage-specific arterial inflammation among participants with versus matched participants without HIV. The hypothesis was that people with HIV would demonstrate higher levels of aortic arterial inflammation in relation to atherosclerotic plaque and immune activation.

Results showed that patients with HIV on antiretroviral therapy (N=20) had significantly higher macrophage-specific arterial inflammation demonstrated by Tc99m tilmanocept than risk-matched people without HIV (N=10). Total, non-calcified, and calcified aortic plaque volume calculated from CT scans did not differ significantly between groups. Macrophage-specific arterial inflammation related to non-calcified plaque among HIV patients (and not among participants without HIV) and additionally related to levels of specific inflammatory markers. Aortic Tc99m-tilmanocept uptake was significantly higher across different uptake thresholds among participants with HIV (P=0.03) and demonstrated a steeper relationship between arterial inflammation and non-calcified plaque volume (P=0.0001 for interaction between HIV-status and plaque volume) but not calcified plaque volume (P=0.83 for interaction). Among people with HIV (and not among participants without HIV), non-calcified aortic plaque volume related directly with aortic Tc99m-tilmanocept uptake at different uptake thresholds.

Macrophage-specific arterial inflammation, quantified using a novel molecular imaging approach, was higher among patients with HIV on ART compared to matched participants of

similar atherosclerotic cardiovascular risk without HIV. Arterial inflammation related to non-calcified plaque volume only among patients with HIV. Cellular biomarkers of inflammation also related to macrophage-specific arterial inflammation. These key immune pathways may contribute to heightened cardiovascular disease risk among people with HIV and are thus of relevance to identifying novel therapies.

These data suggest increased macrophage-specific arterial inflammation of noncalcified plaque may be a mechanism of increased cardiovascular risk in people with HIV. Use of Tc99m tilmanocept imaging may help to identify future targets for novel immunomodulatory therapies to reduce atherosclerotic cardiovascular disease risk among people with HIV on ART.

Dr. Michael Rosol, Chief Medical Officer for Navidea, said, “We are pleased to have helped sponsor this important work with Dr. Grinspoon at MGH. This is another in a line of research collaborations we have had with the highest level of researchers at top tier institutions.” Dr. Rosol continued, “Today’s announcement exemplifies the broad reach of our tilmanocept platform. The development of applications of Tc99m tilmanocept as a biomarker in people with HIV could have far-reaching implications for monitoring patient treatment and making decisions about therapeutic benefit.”

Dr. Grinspoon said, “This study provides another key piece of evidence of increased arterial inflammation in relationship to monocyte and activation and key innate immune activation pathways in people living with HIV. Tilmanocept may be useful to assess novel immunomodulatory strategies to reduce inflammation and improve risk of cardiovascular disease in PWH.”

About Navidea

Navidea Biopharmaceuticals, Inc. (NYSE American: NAVB) is a biopharmaceutical company focused on the development of precision immunodiagnostic agents and immunotherapeutics. Navidea is developing multiple precision-targeted products based on its Manocept platform to enhance patient care by identifying the sites and pathways of disease and enable better diagnostic accuracy, clinical decision-making, and targeted treatment. Navidea’s Manocept platform is predicated on the ability to specifically target the CD206 mannose receptor expressed on activated macrophages. The Manocept platform serves as the molecular backbone of Tc99m tilmanocept, the first product developed and commercialized by Navidea based on the platform. Navidea’s strategy is to deliver superior growth and shareholder return by bringing to market novel products and advancing the Company’s pipeline through global partnering and commercialization efforts. For more information, please visit www.navidea.com.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends affecting the financial condition of our business. Forward-looking statements include our expectations regarding pending litigation and other matters. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, among other things: our

history of operating losses and uncertainty of future profitability; the final outcome of any pending litigation; our ability to successfully complete research and further development of our drug candidates; the timing, cost and uncertainty of obtaining regulatory approvals of our drug candidates; our ability to successfully commercialize our drug candidates; dependence on royalties and grant revenue; our ability to implement our growth strategy; anticipated trends in our business; our limited product line and distribution channels; advances in technologies and development of new competitive products; our ability to comply with the NYSE American continued listing standards; our ability to maintain effective internal control over financial reporting; the impact of the current coronavirus pandemic; and other risk factors detailed in our most recent Annual Report on Form 10-K and other SEC filings. You are urged to carefully review and consider the disclosures found in our SEC filings, which are available at http://www.sec.gov or at http://ir.navidea.com.

Investors are urged to consider statements that include the words “will,” “may,” “could,” “should,” “plan,” “continue,” “designed,” “goal,” “forecast,” “future,” “believe,” “intend,” “expect,” “anticipate,” “estimate,” “project,” and similar expressions, as well as the negatives of those words or other comparable words, to be uncertain forward-looking statements.

You are cautioned not to place undue reliance on any forward-looking statements, any of which could turn out to be incorrect. We undertake no obligation to update publicly or revise any forward-looking statements, whether as a result of new information, future events or otherwise after the date of this report. In light of these risks and uncertainties, the forward-looking events and circumstances discussed in this report may not occur and actual results could differ materially from those anticipated or implied in the forward-looking statements.

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