**UNITED STATES**
**SECURITIES AND EXCHANGE COMMISSION**
**Washington, D.C. 20549**

# FORM 8-K

**CURRENT REPORT**
**Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934**

| | |
|---|---|
| Date of Report (date of earliest event reported) | April 20, 2022 |

# NAVIDEA BIOPHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

| Delaware | 001-35076 | 31-1080091 |
|---|---|---|
| (State or other jurisdiction of incorporation) | (Commission File Number) | (IRS Employer Identification No.) |

| 4995 Bradenton Avenue, Suite 240, Dublin, Ohio | 43017 |
|---|---|
| (Address of principal executive offices) | (Zip Code) |

| | |
|---|---|
| Registrant's telephone number, including area code | (614) 793-7500 |

(Former name or former address, if changed since last report.)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

| Title of Each Class | Trading Symbol(s) | Name of Each Exchange on Which Registered |
|---|---|---|
| Common Stock, par value $.001 per share | NAVB | NYSE American |

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 or Rule 12b-2 of the Securities Exchange Act of 1934.

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

**Item 8.01 Other Events.**

On April 20, 2022, Navidea Biopharmaceuticals, Inc. (the "Company") provided an executive summary of an updated third-party asset valuation of its rheumatoid arthritis diagnostic product candidate on its corporate website, www.navidea.com. Copies of the valuation report and the press release are attached to this Current Report on Form 8-K as Exhibits 99.1 and 99.2, respectively, and are incorporated herein by reference.

On April 20, 2022, the Company issued a press release announcing the results of an interim analysis of its NAV3-32 Phase 2b Study in rheumatoid arthritis. A copy of the press release is attached as Exhibit 99.3 and incorporated herein by reference.

**Item 9.01. Financial Statements and Exhibits.**

(a) Not applicable

(b) Not applicable

(c) Not applicable

(d) Exhibits

| **Exhibit No.** | **Description** |
|---|---|
| 99.1 | Navidea Biopharmaceuticals, Inc. Valuation Report |
| 99.2 | Press Release dated April 20, 2022 |
| 99.3 | Press Release dated April 20, 2022 |
| 104 | Cover Page Interactive Data File (embedded within the Inline XBRL document) |

**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Navidea Biopharmaceuticals, Inc.

Date: April 20, 2022

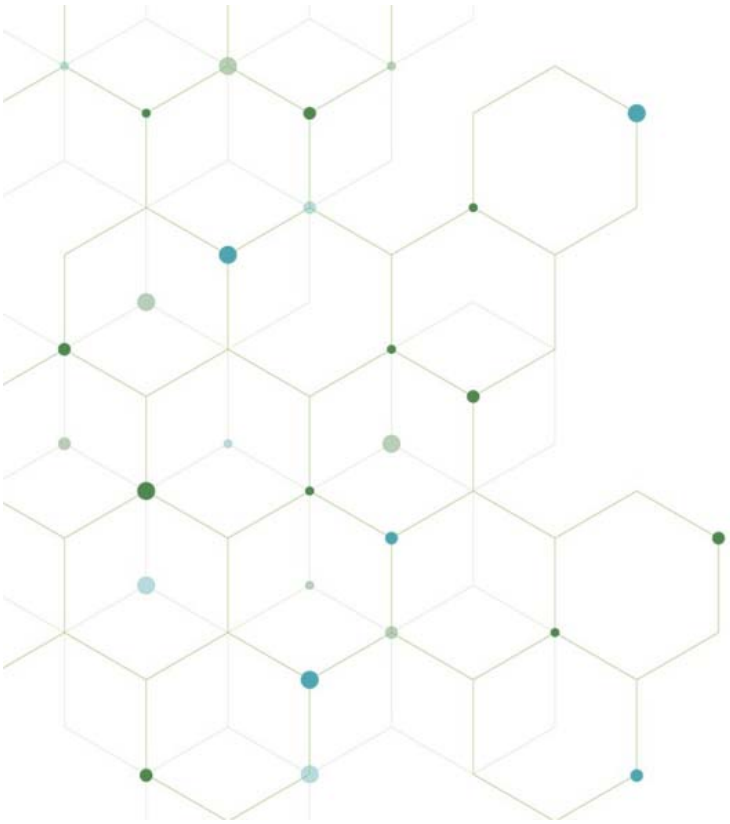
By: /s/ Michael S. Rosol
Michael S. Rosol, Ph.D.
Chief Medical Officer

**NAVIDEA BIOPHARMACEUTICALS, INC.**
**REPORT OF LIFESCI PARTNERS**
**EXPLANATORY NOTE**

Navidea Biopharmaceuticals, Inc. ("Navidea") is publicly disclosing the attached report (the "LifeSci Report") of LifeSci Partners (LifeSci Advisors, LLC), which has performed a primary U.S. market and secondary E.U. market research valuation of Navidea's advanced pipeline product Tc99m tilmanocept for prediction of treatment efficacy of anti-TNFα therapy in RA. Navidea is releasing the LifeSci Report to provide investors with information on Navidea's process for evaluating investments in its product pipeline.

*Cautionary Note Regarding Forward-Looking Statements.* Some of the statements made in the LifeSci Report represent 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. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, among other things, the fact that the valuation by LifeSci Partners of Navidea's Tc99m tilmanocept pipeline product is subject to and based on numerous assumptions about the commercial success of the product, expected associated costs, and the outcome of various risks, including results of clinical trials, that could affect the timetable for revenues, among other assumptions, and that actual outcomes are likely to vary from such assumptions, which would result in variations from the possible results set forth in the LifeSci Report. Any such statements about possible outcomes for Navidea's product are subject to other risk factors detailed in Navidea's most recent Annual Report on Form 10-K and other SEC filings. You are urged to carefully review and consider the disclosures found in Navidea's SEC filings, which are available at http://www.sec.gov or at http://ir.navidea.com.

You are cautioned not to place undue reliance on any forward-looking statements, any of which could turn out to be incorrect. Navidea undertakes 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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# RA U.S. and EU Primary and Secondary Research Valuation

April 2022

Navidea® BIOPHARMACEUTICALS

# Executive Summary

Tc-Tilmanocept represents a potential multi-billion opportunity to fill key unmet needs in RA for the U.S. and EU

| | |
|---|---|
| **Diagnostics Landscape** | • Tc-Tilmanocept is positioned to be the first therapeutic-guiding diagnostic with **physician-perceived reliable predictive power** in RA, a disease that impacts ~1.9 M adult patients in the U.S. and ~3.7 M across Europe<br>• A novel RA radiopharmaceutical diagnostic is expected to **price between ~$850 (EU) and ~$1,300 (U.S.)** |
| **Physician Feedback on Tc-Tilmanocept** | • Physicians expressed **enthusiasm for Tc-Tilmanocept** in RA, particularly for **baseline prediction of response** to anti-TNF therapies, and anticipated use in the **majority of 2L+ patients** when initiating new lines of therapy; however, use in 5 week and annual follow-up settings may grow with increased data and comfort |
| **Base-case Valuation Outputs** | • Assuming **~55% and ~8%** share in 2L+ LoT switch and 1L incident patients, respectively, 5 week follow-up in **~35%** of baseline patients, and annual follow-up in **~15%** of baseline patients, **peak revenue may reach ~$1.2 B** in the U.S. and EU in 2036; considering costs and a ~52% POS, **rNPV may reach ~$1.1 B** |
| **Upside Valuation Outputs** | • Upside scenario assumes ACR / EULAR guideline inclusion boosts baseline use in **incident patients by ~45%, 5 week testing to ~60%** of baseline patients, and **annual follow-up to ~40%** of baseline patients, resulting in **~$2.6 B in peak revenue (2036) and an rNPV of ~$2.2 B across the U.S. and EU** |
| **Future Opportunities** | • Multiple opportunities remain to unlock further Tc-Tilmanocept value in RA, including **label expansion**, **patient advocacy campaigns** to increase **diagnosis rates**, **marketing efforts** to **bolster preference share**, and **registration as a biomarker** |



RA: Rheumatoid Arthritis; 1L: First-line; 2L: Second-line; 2L+: Second-line and Beyond; LoT: Line of Therapy; ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; POS: Probability of Success; rNPV: Risk-adjusted Net Present Value.

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Navidea Biopharmaceuticals Tc-Tilmanocept U.S. Valuation Assessment

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# Project Overview

# Project Overview

Navidea Biopharmaceuticals Tc-Tilmanocept U.S. Valuation Assessment

## Key Project Goals

- Conduct primary and secondary market research to characterize the current (and evolving) market environment, KOL feedback on Product X, and the expected revenue potential for Product X
- Evaluate KOL receptivity to Product X's target product profile to gauge anticipated adoption and utilization within RA
- Bolster Navidea's utilization assumptions for its commercial revenue forecast for Product X based on primary market research

### Market Landscape

Develop insights on **current market dynamics** (e.g., patient journey, competitive landscape, etc.) for **diagnostics in RA across the U.S. and EU**

### U.S. Primary Market Research

Understand the current & future RA diagnostic landscape and **anticipated utilization of Product X** based on primary research with academic and community physicians

### Commercial Forecast

Develop a comprehensive **Excel-based commercial forecast model** to project the year-over-year commercial potential of Product X in the U.S. and EU

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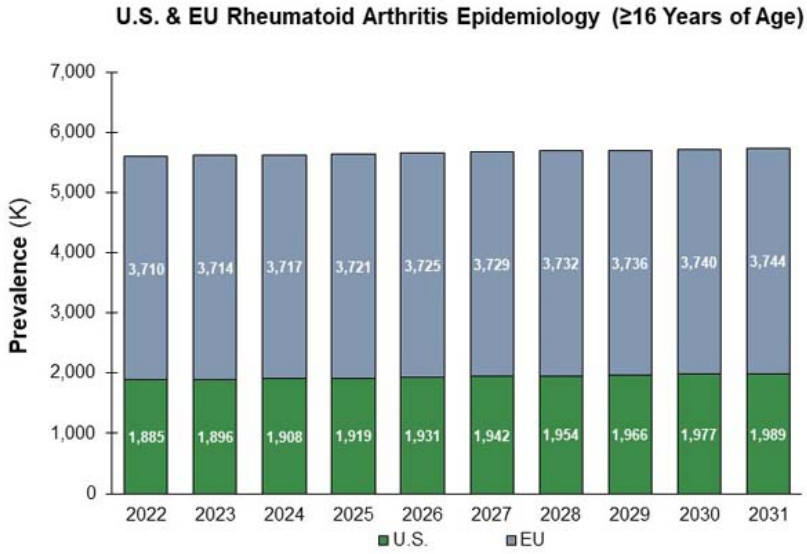
# Rheumatoid Arthritis Landscape

# U.S. & EU Rheumatoid Arthritis Epidemiology (≥16 Years of Age)

RA has a prevalence of ~0.7% and ~0.6% of the population ≥16 years of age in the U.S. and EU, respectively




In the U.S., rheumatoid arthritis (RA) has an **incidence of ~40 per 100 K** and a **prevalence of ~0.7%** of the population over 16 years of age, with an annual growth rate of ~0.6%

Similar to the U.S., EU-based secondary publications suggest RA has an **incidence of ~35 per 100 K** and a **prevalence of ~0.6%** of the population over 16 years of age, with an annual growth rate of ~0.1%

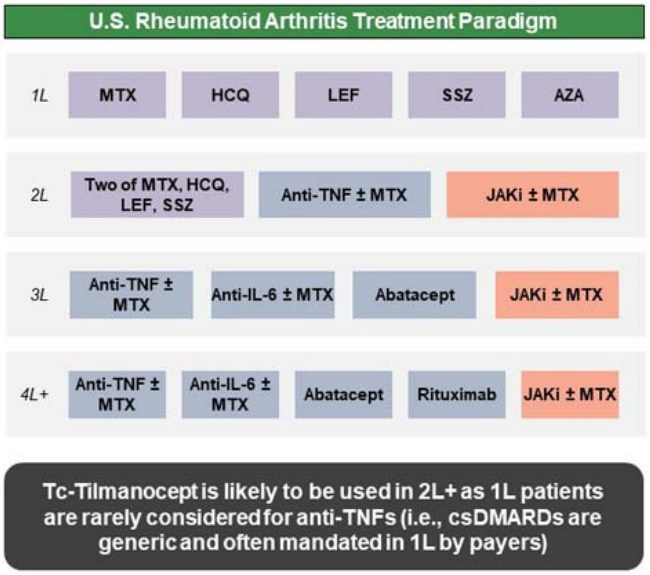
Notably, these prevalence assumptions **only include adult RA patients and not juvenile RA** under the age of 16, which is estimated to **impact ~300 K patients in the U.S. alone**



Source: Almutairi. Rheum Int. 2020; Eriksson. Arthritis Care Res. 2013; Prakken. The Lancet. 2011; Myasoedova. Rheumatoid Arthritis Clinical Studies. 2010; Zlatkovic-Svenda. Annals of the Rheumatic Diseases. 2016;75:643; EULAR Horizon 2020 Framework Programme; Alamanos. Current Rheumatology Reviews. 2005; The World Bank, Europa; UN Statistics; Census Bureau International Data Base.

# Rheumatoid Arthritis Treatment Paradigm

Anti-TNFs are used in the 2L+, but patients may switch TNFs and receive them across multiple lines of therapy




**Tc-Tilmanocept is likely to be used in 2L+ as 1L patients are rarely considered for anti-TNFs (i.e., csDMARDs are generic and often mandated in 1L by payers)**

**1L** — **MTX often prescribed** with NSAIDs / GCs for rapid symptom relief; ineligible patients **receive alternative single-agent csDMARDs**

**2L** — The ~70% of patients who do not achieve remission after 3 – 6 mo. often **progress to anti-TNFs/-JAKs** or a combo of two csDMARDs

**3L** — The ~80% of patients who fail 2L often receive **alternative anti-TNFs/JAKs**; select patients receive IL-6 inhibitors or abatacept

**4L** — **The ~85% of patients refractory to 3L progress to 4L**, where prescribing is guided by treatment history and highly variable

**EU-Specific Findings**

- **EU treatment guidelines (i.e., EULAR) outline a very similar treatment progression to that of the U.S.** (i.e., csDMARD utilized alone for all 1L patients, adding a bDMARD or tsDMARD in combo if refractory)
- **EU patients are even less likely to get a 1L biologic** given increased cost-sensitivity vs. the U.S.

LifeSci Partners

Source: LifeSci Physician Interviews (N=15); ACR Guidelines; EULER Guidelines; UpToDate; GlobalData. **DMARD: Disease-modifying Antirheumatic Drug; b: Biological; cs: Conventional Synthetic; ts: Targeted Synthetic.** GC: Gluco-corticoid; MTX: Methotrexate; HCQ: Hydroxychloroquine; LEF: Leflunomide; SSZ: Sulfasalazine; AZA: Azathioprine.

**Key:** csDMARD bDMARD tsDMARD

# Clinical Unmet Needs

KOLs are most interested in biomarkers for prediction of response to therapy and disease severity

| Key Unmet Needs | | |
|---|---|---|
| 1 | **Predictive Treatment Response:** A predictive test that can determine a patient's response to therapy, to help inform prescribing decision making across multiple available therapeutic classes in RA | *"Predicting response to treatment is currently a black box. All we can do is cycle through therapies, which takes time. For RA patients, time is cartilage and bone."* |
| 2 | **Prognostic Biomarkers:** Physicians desire a highly specific test (e.g., predictive biomarkers) that can distinguish more severe forms of RA to help inform management | *"I would love to see biomarkers that can categorize who is more at risk for more severe RA, especially those who are at risk for progressive lung disease."* |
| 3 | **Novel Therapeutics:** KOLs note interest in a novel therapies that can provide benefit to refractory RA patients (e.g., new MOA, non-immunosuppressive, and/or orally administered) | *"There are patients who have failed every line of therapy. It would be nice if there was a new class of drugs that was safe and could help these patients."* |

Source: LifeSci Physician Interviews (N=15).

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# U.S. Physician Feedback on Tc-Tilmanocept

# Summary of Physician TPP Feedback

Rheums were interested in Product X, citing its predictive power and exceptional safety as key highlights

## Indication / Trial Design

**Physician Perception:** Negative — Neutral — Positive

- Physicians were enthusiastic about using Product X in RA **patients considered for biologics**, most often **patients in the 2L+**
- They expressed greater interest in Product X as a **predictor of response at baseline**, rather than early response at 5 weeks

## Efficacy

**Physician Perception:** Negative — Neutral — Positive

- **Specificity was identified as a key endpoint** to ensure beneficial therapies are not withheld
- Respondents perceived Product X's specificity and sensitivity to be **clinically meaningful**


## MOA / ROA

**Physician Perception:** Negative — Neutral — Positive

- Rheumatologists were **unfamiliar with CD206** expressing activated macrophages in RA, suggesting a **need for physician education**
- ROA was considered **less convenient** than other diagnostic modalities, but convenience would only limit use if more convenient options exhibited **similarly strong predictive power**

## Safety

**Physician Perception:** Negative — Neutral — Positive

- Rheumatologists were **most enthusiastic** about Product X's **safety and tolerability profile**
- Physicians were impressed by Product X's **real-world safety record in cancer**, indicating safety would be **no issue in implementing Product X in RA**

# Product X Patient Eligibility

Rheums viewed most 2L+ switch patients as eligible for Product X, along with select 1L and prevalent patients

**Patient Eligibility for Product X**

**1L Incident Pts. Considered for Anti-TNFs:** Physicians estimated ~10% of 1L patients exhibit particularly severe disease or are MTX ineligible (e.g., women of childbearing age, those who refuse alcohol cessation) and therefore considered for anti-TNFs and Product X

*"Anti-TNFs may be used in a small percentage of 1L patients, mostly due to contraindications to MTX, though I also consider patients with particularly inflammatory disease if insurance will cover it."*

**2L+ LoT Switch Patients:** Respondents identified 2L+ LoT switch patients as the key patient population for Product X, given the vast majority of 2L+ patients are considered for anti-TNFs aside from the few with history of infections, organ dysfunction, or cancer

*"Almost all patients are considered for anti-TNFs after failing MTX. It's only those with renal or liver issues, past infections, or fear over a family history of cancer who may go elsewhere."*

**Prevalent RA Patients:** While incident / LoT switch patients were identified as the key eligible population, select physicians expressed interest in annual follow-up among prevalent patients who originally received it in the incident / LoT switch setting (N=3)

*"I like the idea of imaging for sub-clinical synovitis over time. Even if patients feel good, the disease can progressively damage their joints."*



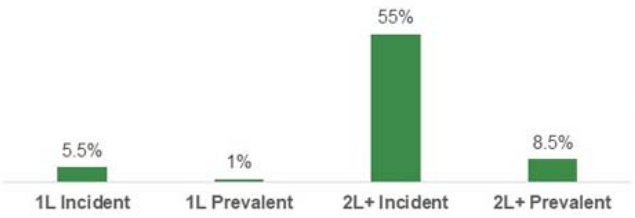
Source: LifeSci Physician Interviews (N=15).
MTX: Methotrexate; LoT: Line of Therapy.

# Product X Preference Share

Physician-stated preference share estimates suggest a majority of 2L+ incident patients may receive Product X

**Product X Baseline Preference Share**

*(Represents Patients Ordered At Least 1 Diagnostic Annually)*




**~35%**

**5 Week Early Prediction of Response Testing:** Physicians estimated ~35% of patients initially ordered Product X would repeat testing at 5 weeks, predominantly in severe patients and/or those with no sign of response

**~15%**

**Annual Follow-up Testing:** ~15% of patients originally ordered Product X at baseline may receive annual follow-up testing, with most physicians desiring additional data in the follow-up setting to support use

- Preference share assumptions are based off physician-stated estimates and reactions to **Product X's base-case TPP**
- **Physician willingness to order Product X was highest for 2L+ incident patients**, though physicians noted interest in Product X among the minority of 1L patients considered for anti-TNFs
- Of those who receive Product X at baseline, **~35% of patients may receive a 5-week follow-up** test and **~15% may receive annual follow-up testing** based on the presented TPP, though additional data in the follow-up setting and experience with Product X may boost follow-up utilization over time

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# U.S. Valuation Assumptions

# Revenue and Cost Assumptions Summary

## Select Revenue Assumptions

- **Addressable Patients:** Adults >16 years with diagnosed RA
- **Overall RA Treatment Rate:** ~94%
- **Prevalent Patients U.S.(2024)/EU (2025):** ~1.9 M/~ 3.7 M
- **Preference Share:** 55% in 2L patients switching therapies in base case scenario *(Note: Based on U.S. primary research)*

  80% in upside scenario
- **Annual Tests per Patient:** 1 – 2
- **Compliance:** 90%
- **Launch Year U.S./EU:** 2024/2025

## Select Cost Assumptions

- **R&D and Regulatory Expenses:** Ongoing P2B & P3; NDA filing
- **SG&A:** high 20% range
- **CAPEX:** low single digit % of sales
- **Corporate tax rate:** 21%
- **Discount rate:** 12% (*Cost of capital estimates assume Navidea partners with a mid-to-large size company for RA commercialization)*
- **Probability of Technical and Regulatory Success (PTRS**): Phase II: 100% Phase III: 68.4% Approval: 80.3% Commercialization: 95% (*Development risk assumptions based on historical precedence by stage for NMEs in autoimmune diseases reported in published literature (Hay. Nature. 2014). Assumes Tc-Tilmanocept has already succeeded Phase 2 based on data to-date.)*

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# Valuation Output and Strategic Considerations

# Tc-Tilmanocept Base-case Revenue Projections (U.S. and EU)

Tc-Tilmanocept may generate ~$735 M and ~$505 M in 2036 annual revenue in the U.S. and EU, respectively

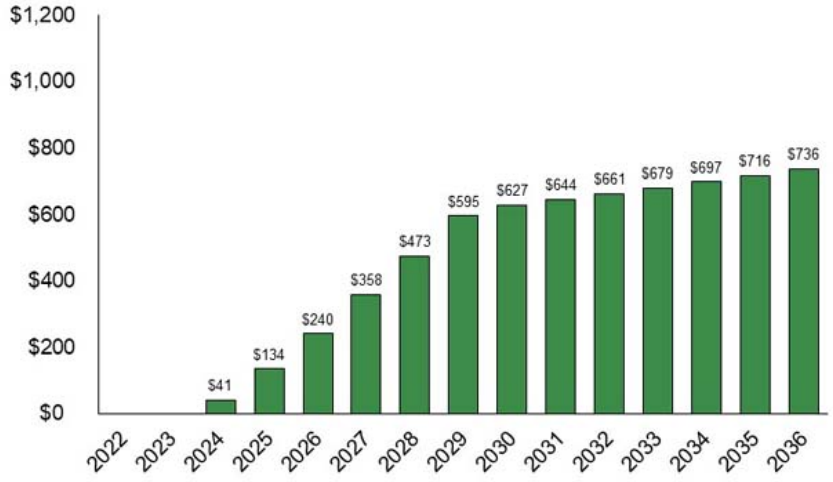
**Base-case U.S. and EU Projected Net Revenue** ($M)


| U.S. and EU Base-case Outputs | 2036 Peak Sales: $1.2 B | Aggregate Sales (2022 – 2036): $11.7 B | Probability Of Success: 52% | rNPV (2022 – 2036): $1.1 B |
|---|---|---|---|---|

rNPV: Risk-Adjusted Net Present Value.

# Tc-Tilmanocept Base-case Revenue Projections (U.S. only)

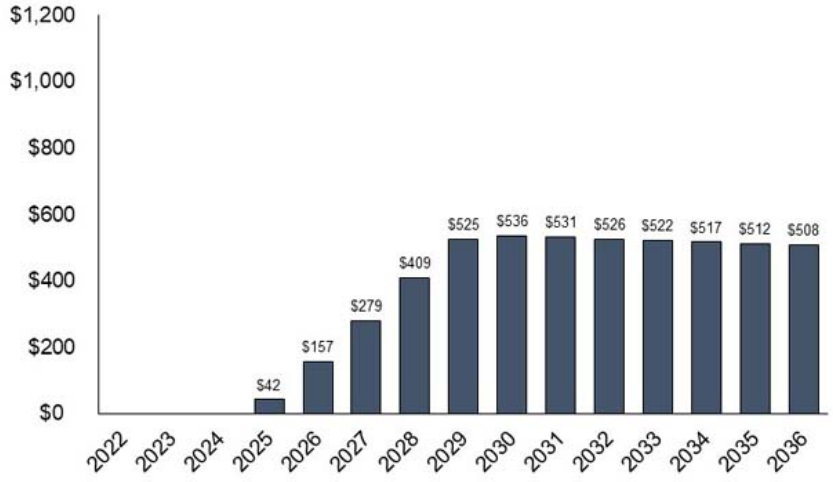
With base-case assumptions, Tc-Tilmanocept may generate ~$735 M in annual U.S. revenue by 2036




| U.S. Base-case Outputs | |
|---|---|
| 2036 Peak Sales | ~$735 M |
| Aggregate Sales (2022 – 2036) | ~$9.2 B |
| Probability of Success (PoS) | ~52% |
| rNPV (2022 – 2036) | ~$600 M |

# Tc-Tilmanocept Base-case Revenue Projections (EU only)

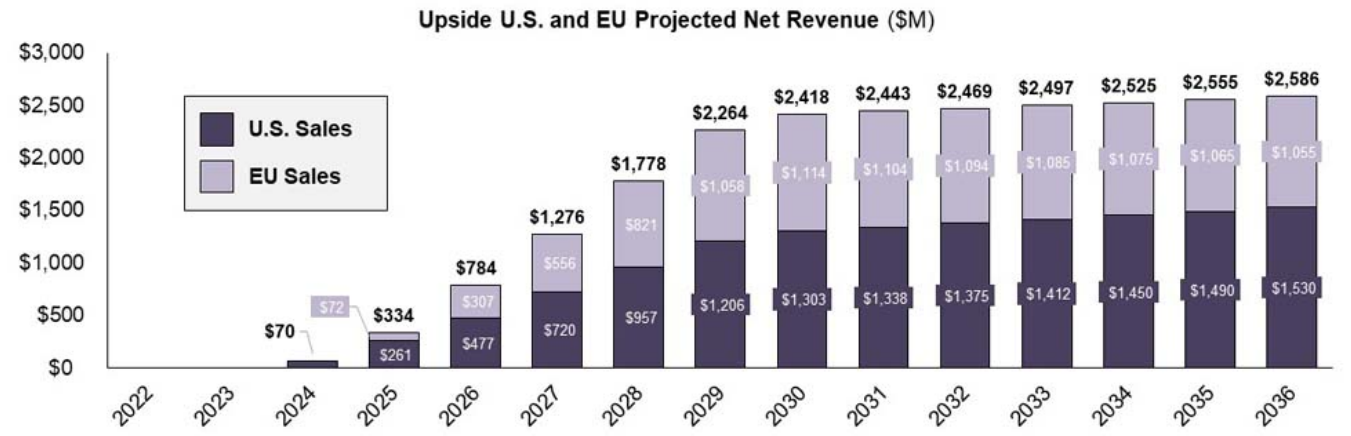
With base-case assumptions, Tc-Tilmanocept may generate >$500 M in annual EU revenue by 2029




| EU Base-case Outputs | |
|---|---|
| 2030 Peak Sales | ~$535 M |
| Aggregate Sales (2022 – 2036) | ~$5.1 B |
| Probability of Success (PoS) | ~52% |
| rNPV (2022 – 2036) | ~$450 M |

# Tc-Tilmanocept Upside Revenue Projections (U.S. and EU)

If Tc-Tilmanocept is incorporated into ACR/EULAR guidelines, 2036 U.S. / EU sales may approach ~$2.6 B




| U.S. and EU Upside Outputs | 2036 Peak Sales: $2.6 B | Aggregate Sales (2022 – 2036): $24.0 B | Probability Of Success: 52% | rNPV (2022 – 2036): $2.2 B |
|---|---|---|---|---|

rNPV: Risk-Adjusted Net Present Value.

# Aggregate rNPV for Tc-Tilmanocept in RA (U.S. and EU)

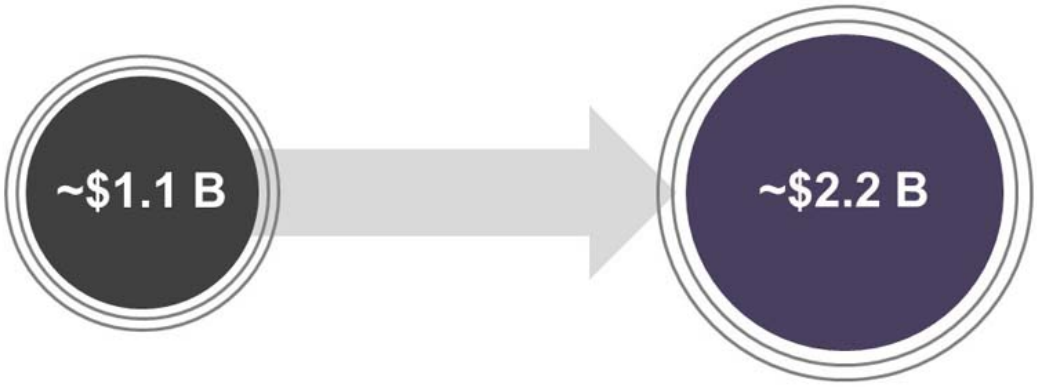
Accounting for revenue, costs, and risk, base-case rNPV may reach ~$1.1 B with upside potential of ~$2.2 B

## Base-case rNPV

*1L Incident Preference Share:* ***5.5% (U.S. and EU)***
*1L Prevalent Preference Share:* ***1% (U.S. and EU)***
*2L+ Incident Preference Share:* ***55% (U.S. and EU)***
*2L+ Prevalent Preference Share:* ***8.5% (U.S. and EU)***

## Upside rNPV

*1L Incident Preference Share:* ***8% (U.S. and EU)***
*1L Prevalent Preference Share:* ***3.5% (U.S. and EU)***
*2L+ Incident Preference Share:* ***80% (U.S. and EU)***
*2L+ Prevalent Preference Share:* ***35% (U.S. and EU)***



# Opportunities to Expand Future Commercial Potential

Multiple levers remain to unlock further Tc-Tilmanocept value in RA

### Expansion to Juvenile RA in the U.S.

Label expansion to Juvenile RA in patients <16 years of age may increase total diagnosed prevalence by ~300 K patients in the U.S.

### Increased RA Diagnosis Rate

Patient advocacy campaigns and clinical breakthroughs may improve RA's diagnosis rate and increase the diagnosed prevalence

### Increased Follow-up Testing

Increasing comfort with Tc-Tilmanocept and additional data to support follow-up testing may boost the number of tests patients receive over time

### Increased Adoption

Marketing campaigns may drive adoption of Tc-Tilmanocept through guideline inclusion and physician preference

### Label Expansion to Other RA Drugs

Label expansion for therapeutic-guiding information across RA therapeutic classes will likely drive increased preference share

### Registration as a Biomarker

FDA/EMA registration for use as a biomarker of CD206 expression in RA joints may spur its use in clinical trials with pharma partners and support its inclusion in guidelines

Source: Prakken. The Lancet. 2011.

**Exhibit 99.2**

# Navidea Biopharmaceuticals Announces Updated Third-Party Asset Valuation of Tc99m Tilmanocept for Indications in Rheumatoid Arthritis for U.S. and EU Markets

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 results of an updated third-party asset valuation of its Rheumatoid Arthritis ("RA") diagnostic product candidate for both the U.S. and EU markets.

The Company engaged the independent third-party valuation firm, LifeSci Consulting (LifeSci Partners), to perform a U.S.-focused primary market research valuation and a secondary market analysis for the EU of its advanced pipeline product Tc99m tilmanocept for prediction of treatment efficacy of anti-tumor necrosis factor alpha ("TNFα") therapy in RA. A summary of the valuation report and the assumptions on which it is based is available on the Company's website, www.navidea.com. The U.S. market evaluation has been updated from the December 2021 press release using primary information from academic and high-volume health care provider rheumatologists obtained through questionnaires and interviews (primary research).

The Company is advancing its program evaluating Tc99m tilmanocept imaging, a radiopharmaceutical that selectively targets the CD206 receptor expressed on activated macrophages, for indications in RA. A previously completed Phase 2B study demonstrated results in support of the hypotheses that Tc99m tilmanocept imaging can provide robust, quantitative imaging in healthy controls and in patients with active RA, and that this imaging can provide an early indicator of treatment efficacy in patients with active RA. The Company's active Phase 3 trial will evaluate the ability of Tc99m tilmanocept imaging to serve as an early predictor of treatment response in RA patients switching to an anti-TNFα therapy.

The valuation report used cited research and assumptions believed to conform to industry best practices. Under base-case assumptions that are discussed in the report, peak combined U.S. and EU sales could reach $1.2 billion annually, and in the upside scenario peak annual U.S. and EU sales could reach $2.6 billion. Rheumatologist feedback included recognition of the need for a tool that would enable treatment response prediction. Opportunities for added value include possible indication expansion to other classes of RA therapeutics, registration of Tc99m tilmanocept imaging as a biomarker of activated macrophages in the joints of patients with RA, and expansion into additional geographic areas.

Dr. Michael Rosol, Navidea's Chief Medical Officer, said, "This report provides an updated third-party assessment of the potential commercial value of Tc99m tilmanocept in both the U.S. and EU markets. As with our earlier release, we present this in the spirit of transparency, while also giving investors a view into the company's internal rigor in evaluating investments in the product pipeline." Dr. Rosol continued, "We believe we are on the right path to bringing a valuable tool to bear to meet a large unmet medical need in patients with RA. Success would mean that we can provide rheumatologists and those suffering with RA a noninvasive, quantifiable, early indicator of whether or not an anti-TNFα treatment is working. This could bring enormous benefit to these patients by assisting physicians in putting them on the right course of treatment much earlier than is possible today."

**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 fact that the valuation by LifeSci Partners of our Tc99m tilmanocept pipeline product is subject to and based on numerous assumptions about the commercial success of the product, expected associated costs, and the outcome of various risks, including the outcome of clinical trials, that could affect the timetable for revenues, among other assumptions, that actual outcomes are likely to vary from such assumptions, resulting in variations from the possible results set forth in the valuation report; 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.

**Investor Relations Contact**

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**Exhibit 99.3**

# Navidea Biopharmaceuticals Announces Positive Preliminary Results of Its Ongoing Phase 2B Study Comparing Tc99m Tilmanocept Imaging with Histopathology of Joints from Patients with Rheumatoid Arthritis

*Data support hypothesis that Tc99m tilmanocept imaging can differentiate fibroid pathotype of rheumatoid arthritis from non-fibroid pathotypes*

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 preliminary results from the ongoing NAV3-32 Phase 2B study titled, "A Comparison of Tc99m Tilmanocept Quantitative Imaging With Immunohistochemical (IHC) Analysis of CD206 Expression in Synovial Tissue From Subjects Clinically Diagnosed With Rheumatoid Arthritis (RA)." Preliminary results on the first eleven patients indicates that quantitative Tc99m tilmanocept uptake in the hands and wrists of patients is proportional to the amount of macrophage involvement in an individual rheumatoid arthritis ("RA") patient's joint inflammation. Additionally, Tc99m tilmanocept uptake in RA-inflamed joints was able to discretely differentiate patients with the fibroid pathotype (i.e., low macrophage involvement) from those having either the diffuse myeloid or lympho-myeloid pathotypes of RA (i.e., higher macrophage involvement).

The primary objective of this study is to assess the relationship between joint-specific tilmanocept uptake values and the pathobiology of RA-involved joint tissue. This is being accomplished by taking biopsy samples from joints of patients with RA following imaging with Tc99m tilmanocept. The images are being evaluated using Navidea's proprietary imaging analysis method to determine the amount of Tc99m tilmanocept uptake in the joint to be biopsied. The biopsy tissues are being evaluated by a pathologist using immunohistochemical ("IHC") staining to determine the cellular composition, including macrophage content, in the inflammatory tissue of the RA-involved joint. The cellular composition of RA-inflamed joints is known to vary between patients and is frequently separated into one of three pathotypes termed fibroid, diffuse myeloid, and lympho-myeloid. Knowledge of an individual RA patient's pathotype may be clinically important because it may predict to which RA therapy a patient is likely to respond. It is Navidea's hypothesis that the imaging signal will correlate with the number and density of activated macrophages in the joints of RA patients, and that this imaging signal can provide important information about not only the disease status of the patient, but also indicate which pathotype of RA that the patient has. Enrollment is to continue until a minimum of four patients of each of the three pathotypes- fibroid, diffuse myeloid, and lympho-myeloid- have been enrolled and had both assessable imaging and biopsy performed.

At the current time, a total of eleven patients have had Tc99m tilmanocept imaging followed by synovial tissue biopsy in an inflamed joint of their hands or wrists. Quantitative image analysis was performed prior to biopsy. Image analyses conducted before the biopsies has been able to separate the subjects into at least 2 distinct and nonoverlapping classes of subjects. Seven of the subjects had relatively lower levels of Tc99m tilmanocept uptake. All seven of these subjects were found to have the fibroid pathotype. Of the remaining 4 subjects, 3 had the diffuse myeloid pathotype and 1 had the lympho-myeloid pathotype. Furthermore, those subjects with either the diffuse myeloid or lympho-myeloid pathotypes had, on average, more than 3 times more Tc99m tilmanocept uptake as the average subject with the fibroid pathotype. The pathologist who evaluated these biopsies was blinded to the imaging results prior to completing their report. These early results support the hypothesis that those patients with low levels of Tc99m tilmanocept localization in their hand and wrist joints have the fibroid pathotype of RA, and those with higher levels of localization are representative of one of the other two pathotypes.

Dr. Michael Rosol, Chief Medical Officer for Navidea, said, “We are encouraged by these preliminary results. They support one of our main hypotheses- that the joints of patients with the pathotype of RA involving low levels of synovial macrophages, the fibroid pathotype, have low levels of Tc99m tilmanocept uptake, while those with the other pathotypes have relatively higher levels.” Dr. Rosol continued, “We believe that this Phase 2B study is critical for establishing the definitive relationship of our imaging readout to the underlying pathobiology of an RA-involved joint, as well as to assess our hypothesis that we can use Tc99m tilmanocept imaging to classify RA subtype. This information may further assist physicians to determine what type of therapy might be most beneficial for a given patient earlier and more noninvasively than is currently possible. This study will also be important for us as we seek to achieve qualification with the FDA of CD206 as a biomarker for RA.”

The Company will hold a business update conference call today, Wednesday, April 20, 2022, at 5:00 p.m. (EDT). Chief Medical Officer Dr. Michael Rosol will host the call and webcast.

To participate in the first call and webcast, please refer to the information below:

Event: Navidea Business Update – Company Strategy and Clinical Update

Date: Wednesday, April 20, 2022

Time: 5:00 p.m. (EDT)

U.S. & Canada Dial-In: 877-407-0312

International Dial-In: +1 201-389-0899

Conference ID: 13729076

Webcast Link: https://www.webcast-eqs.com/navidbioph20220420/en

A live audio webcast of the conference call will also be available on the investor relations page of Navidea’s corporate website atwww.navidea.com. In addition, the recorded conference call can be replayed and will be available for 90 days following the call on Navidea’s website.

RA is a chronic disease affecting over 1.3 million Americans and as much as 1% of the worldwide population[1]. If the product is successfully developed, Navidea would expect to play a major role in the management of RA patients worldwide.

1. https://www.rheumatoidarthritis.org/ra/facts-and-statistics/

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These forward-looking statements include, but are not limited to, statements about preliminary data from Navidea's ongoing clinical trials. Data from the NAV3-32 Phase 2B clinical trial are preliminary and will require confirmation in additional patients as well as further analyses to draw any clinical conclusion. Preliminary data from Navidea's clinical trials that it announces or publishes from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

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