Disclaimer

The private securities litigation reform act of 1995 (the act) provides a safe harbor for forward-looking statements made by or on behalf of the company. Statements in this presentation, which relate to other than strictly historical facts, such as statements about the Company’s plans and strategies, expectations for future financial performance, new and existing products and technologies, anticipated clinical and regulatory pathways, and markets for the Company’s products are forward-looking statements within the meaning of the Act. The words “believe,” “expect,” “anticipate,” “estimate,” “project,” “forecast”, “goal” “future”, “intent”, “will”, “may”, ”could” and similar expressions, as well as the negatives of thee words or comparable words, identify forward-looking statements that speak only as of the date hereof. You are cautioned that such statements involve risks and uncertainties that could cause actual results to differ materially from historical or anticipated results due to many factors including, but not limited to, the Company’s continuing operating losses and uncertainty of future profitability, uncertainty of market acceptance of its products reliance on third party manufacturers, accumulated deficit, future capital needs, uncertainty of capital funding, dependence on limited product line and distribution channels, competition, limited marketing and manufacturing experience, our ability to successfully complete research and further development of our drug candidates, the timing cost, and uncertainty of obtaining any required regulatory approvals of our drug candidates, our ability to successfully commercialize our drug candidates, and other risks detailed in the Company’s most recent Annual Report on Form 10-K and other Securities and Exchange Commission filings. You are further cautioned that the foregoing list of important factors is not exclusive. The Company undertakes no obligation to publicly update or revise any forward-looking statements.
We are a precision immuno-diagnostics and therapeutics company focused on solving the many problems presented by inflammatory conditions

We are leveraging our platform technology to create a robust pipeline of immuno-diagnostics and immuno-therapeutics
Corporate Overview

A precision immuno-diagnostics company focused on inflammatory diseases

1. Building off FDA/EMA-approved diagnostic product

2. Non-invasive imaging targeting CD206 receptors on Activated Macrophages

3. Initial focus on personalized Rheumatoid Arthritis Diagnostics

4. Proprietary Manocept™ platform applicable to multiple disease states in both Diagnostics (Dx) and Therapeutics (Tx)
# Our Diagnostics and Therapeutics Pipeline

<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Therapeutics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid Tumors Lymphatic Mapping, Sentinel Node Biopsy Dx (Lymphoseek™)</td>
<td>Oncology Therapeutic</td>
</tr>
<tr>
<td>Rheumatoid Arthritis Dx</td>
<td>Anti-Inflammatory Therapeutic</td>
</tr>
<tr>
<td>Cardiovascular Diseases Dx</td>
<td></td>
</tr>
<tr>
<td>Kaposi’s Sarcoma Dx</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preclinical/Discovery</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>FDA/EMEA-Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid Tumors Lymphatic Mapping, Sentinel Node Biopsy Dx (Lymphoseek™)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid Arthritis Dx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Diseases Dx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaposi’s Sarcoma Dx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncology Therapeutic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Inflammatory Therapeutic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Solid Tumors Lymphatic Mapping, Sentinel Node Biopsy Dx (Lymphoseek™)**
  - Sold to Cardinal
  - Navidea Seeking Partner
- **Rheumatoid Arthritis Dx**
  - Meeting with FDA held September 1
- **Cardiovascular Diseases Dx**
  - Planning Phase 2B/Phase 3, tbd with FDA
- **Kaposi’s Sarcoma Dx**
  - Planning for discussion with FDA
- **Oncology Therapeutic**
  - Ongoing pre-clinical studies
- **Anti-Inflammatory Therapeutic**
  - Ongoing pre-clinical studies

**Navidea Biopharmaceuticals, Inc.**
Our Core Tilmanocept Technology

Targeted Binding to Activated Macrophages

Best-in-class CD206 affinity allows sensitive detection of all types of activated macrophages in vivo

Disease agnostic provides robust pipeline beyond RA

FDA/EMA approved (favorable regulatory pathway)
## The Tilmanocept Difference (Diagnostics)

<table>
<thead>
<tr>
<th></th>
<th>Manocept™</th>
<th>Key Differentiator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Activated Macrophages</td>
<td><strong>Highly specific target correlated to active inflammatory response</strong></td>
</tr>
<tr>
<td><strong>Molecular Weight</strong></td>
<td>~2-20 kilo-daltons</td>
<td><strong>Able to penetrate circulating and deep tissue macrophages while maintaining industry leading specificity</strong></td>
</tr>
<tr>
<td><strong>Backbone (BB)</strong></td>
<td>Natural and synthetic polymers</td>
<td><strong>Negligible cost and ability to achieve robust gross margin profile</strong></td>
</tr>
<tr>
<td><strong>Half life</strong></td>
<td>minutes</td>
<td><strong>Clearance limits radiation exposure, and allows for recurrence and monitoring applications</strong></td>
</tr>
<tr>
<td><strong>The Tilmanocept Difference (Diagnostics)</strong></td>
<td>$10^{-9}$ - $10^{-13}$</td>
<td><strong>Binding affinity greater than or equal to the best mAbs – highest levels of specificity but at much lower cost</strong></td>
</tr>
<tr>
<td><strong>Drug loading</strong></td>
<td>Multiple “copies” of radiolabel can be added to Tilmanocept backbone</td>
<td><strong>Increases resolution of diagnostic imaging</strong></td>
</tr>
</tbody>
</table>

Navidea Biopharmaceuticals, Inc.
Why Focus on Rheumatoid Arthritis?

+1M
Patients in the US are living with RA

$39B
$39 billion drag to the US Economy

20-50%
20-50% of patients respond adequately to any RA treatment

2nd
RA is the 2nd largest drug category globally
Why are Current Dx & Treatment Paradigms Failing?


2. Lack of biomarkers to guide treatment selection and/or monitor response

3. Development of tolerance to current therapies\(^1\)

Our Solution and Value Proposition

Quantitative Imaging of Activated Macrophages in Rheumatoid Arthritis Patients

1. Increasing evidence of the role of activated macrophages in therapy response.

2. Selecting most appropriate treatment modality for patients based upon pathotype.

3. Convenient safe, rapid, non-invasive detection.
What the Experts Think (KOL Testimonials)

“Tilmamocept not only provides the opportunity to objectively measure and follow RA disease activity in my patients’ joints, but it also may eventually predict which therapy will be most effective for that patient, a tool that is desperately needed in today’s rheumatology clinic.”

- Key Opinion Leader at a leading university with a large RA patient population

“If I had a tool that could give me early information regarding how my patient is responding to treatment, or not responding, it would be a game changer.”

L. Moreland
Chief of the Division of Rheumatology and Clinical Immunology at the University of Pittsburgh School of Medicine
Our First Rheumatoid Arthritis Indication

Quantitative Imaging with Tc 99m Tilmanocept for candidates of Anti-TNF Therapy

Choosing an Effective Therapy: Imaging before treatment

Early Indication of Treatment Effectiveness: Imaging shortly after initiation of a new Rx

Objective Therapy Monitoring Tool: Imaging later in Rx duration to evaluate effectiveness of current treatment
Tilmanocept Detects and Quantifies Disease Burden by Detecting Activated Macrophages

Activated Macrophages

- Source: vecteezy.com (brgfx)
Activated Macrophages are Typically Present in RA Joints

Normal Joint

RA Joint
Tilmanocept consistently localizes in areas of macrophage driven inflammation*

Healthy Control Joint

RA Joint

RA Patient Day 0

RA Patient Day 8

Patient exhibited reproducible localization over a 1 week period

*Select images from NAV3-31 Trial
Activated Macrophages are Important in RA Joints
Tilmanocept Localization

Objective Diagnostic Scoring

Tilmanocept localization to joints in patients with active RA

These images are quantified for determination of macrophage disease activity

3D SPECT/CT- Orange/green areas show high RA inflammation
2D Planar- Darker regions are RA inflammation
RA Diagnostic Commercial Workflow

1. Rheumatologist Orders Imaging

2. Radiologist Acquires Images

3. Images Analyzed by Navidea’s Core Lab

4. Report informs:
   • The Likely Efficacy of Anti-TNF Rx
   • Early Indication of Effectiveness of Anti-TNF Rx
   • Monitoring Treatment Efficacy

Source: vecteezy
US RA Market Opportunity is Large & Untapped

Includes:
(1) Initial label
(2) Early guidance of more effective RA Tx
(3) Therapy-indiscriminate treatment response

Quantitative imaging with Tc 99m Tilmanocept for candidates of anti-TNF therapy

Potential with Expanded Label
$>1$ bn

Initial Label
$500$ mm
The Goal of Our Ongoing and Upcoming RA Studies*

- Confirm reproducibility (NAV3-31 P2B)
- Correlate with Immuno-histochemistry (NAV3-32 P2B)
- Establish Normative Database (NAV3-35 P2B)
- Establish Predictive Capacity of Tx Response (NAV3-33 P3)

*Specific trial designs are under discussion

Navidea Biopharmaceuticals, Inc.
## Encouraging Analyses of NAV3-31

### Overview of results of 3 arm phase 2B Trial for our Rheumatoid Arthritis Diagnostic

<table>
<thead>
<tr>
<th>Arm</th>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1</td>
<td>healthy controls imaged on day 0</td>
<td>• confirmed the repeatability, reproducibility, and stability of Tc99m tilmanocept imaging</td>
</tr>
<tr>
<td>Arm 2</td>
<td>active but stable RA patients imaged day 0 and day 8</td>
<td>• further established the quantitative determinants of healthy joints vs. those with RA-involved inflammation</td>
</tr>
<tr>
<td>Arm 3</td>
<td>anti-TNF alpha patients imaged pre-treatment (day 0), week 5, week 12, and week 24</td>
<td>• Tc99m tilmanocept imaging from baseline to week 5 was predictive of clinical outcome in 90% of patients at 12 weeks and 86% at 24 weeks.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Results also support the hypothesis that, in a subset of RA patients, the baseline scan alone can be a reliable predictor of non-responsiveness to anti-TNF alpha therapy.</td>
</tr>
</tbody>
</table>
Tc99m Tilmanocept Prediction of Treatment Response
Arm 3 NAV3-31

Legend

<table>
<thead>
<tr>
<th>Responder</th>
<th>Non-Responder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tc99m tilmanocept imaging can provide early prediction of treatment efficacy
RA Path to NDA Submission

1. FDA discussion & review of Phase 3 meeting held September 1
2. Begin Phase 3 Fourth Quarter 2021
3. NAV3-32 Phase 2b correlation of imaging to biopsy readout ongoing
   • not on critical path for FDA approval
4. Aim for completion of Phase 3 by end of 2023
5. NDA submission to follow
Our Diagnostics Pipeline

Cardiovascular Disease (CVD)
92 million Americans living with Cardiovascular disease
Ph 2 Study ongoing

Kaposi Sarcoma (KS)
Orphan Disease that is highly life threatening in a minority of patients
Ph 2 Study ongoing
CVD is Another Blockbuster Dx Opportunity

CVD is the leading cause of death in the US

1 in 3
U.S. Adults are living with Cardiovascular Disease

= 92 M Americans
Ongoing CVD Phase 2 Trial at Mass General

Evaluating imaging and detection of vulnerable plaque

- Phase 1 study completed
- Published J Infection Diseases 16 Jan '17
- Additional study funded to expand to IV administration
Timanocept as CVD Detection Tools

Detecting High Risk Plaque

Atherosclerosis is an Activated Macrophages Mediated Disease

Activated Macrophages are Potential Markers of CVD Risk and Response to Therapy
Therapeutics Optionality

Leveraging our core Manocept platform to deliver therapeutics.
Therapeutics Concept

Platform for Therapeutics that target CD206+ (and CD209 dendritic cells) Activated Macrophages

**GPS**

Mannose Moiety
With One Hardwired Address - CD206 Activated Macrophages

**Delivery**

Manocept™ Backbone

**Targeted Payload**

Immune-modulators,
Chemotherapeutics, Tc99,
Other Isotopes
# Therapeutics Pipeline

<table>
<thead>
<tr>
<th><strong>1000 CLASS</strong></th>
<th><strong>2000 CLASS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>(Oncology/Fibrosis)</em></td>
<td><em>(Anti-inflammatory)</em></td>
</tr>
<tr>
<td>Killing TAMs &amp; Altering the Tumor Microenvironment to Enhance Immunotherapies</td>
<td>Altering Activated Macrophage Function &amp; Treating the Mechanism of Disease</td>
</tr>
<tr>
<td>Depleting Through Apoptosis</td>
<td>Inhibiting Inflammatory Activity</td>
</tr>
<tr>
<td>Depletes disease causing M2 Macrophages</td>
<td>Targeted steroid converts M1 to M2</td>
</tr>
</tbody>
</table>
Therapeutics Program Focus

Aberrant macrophages are associated with several major disease states

Current Programs

**Inflammation**
Aberrant activated macrophages can drive excessive inflammation and autoimmune diseases (RA, OA, Lupus, MS, Myocarditis, Uveitis)

**CNS**
Improper clearance of certain compounds are responsible for macrophage driven inflammation seen in Alzheimer disease and implicated in MS, Parkinson’s, Lipid Storage, and CNS diseases.

**Cancer**
Tumors convert anti-tumor macrophages to pro-tumor macrophages, called Tumor Associated Macrophages (TAMs). TAMs inhibit the endogenous immune system from effectively fighting the tumor and also drive angiogenesis.

Pipeline

**Fibrosis**
Overactive M2 macrophages are a key driver of fibrosis (NASH, Nephropathies, Fibrotic Disorders).

**Cardiovascular**
Lipid-containing macrophages can exacerbate atherosclerosis, an inflammatory condition

**Infectious Disease**
The macrophage acts as an incubator in certain infectious diseases (HIV, TB, Assorted Drug Resistant Bacteria)
Key Management

Michael Rosol  
Chief Medical Officer

Prior to Navidea, Dr. Rosol served as Associate Director in the Clinical and Translational Imaging Group at Novartis Institutes for BioMedical Research from Nov 16 to Dec 18, and as Head of its Translational Imaging Group from 2012-2015.

He was also Senior Director of Business Development at Elucid Bioimaging, Inc. where he drove adoption of its Computer-Aided Phenotyping applications from May 16 to Nov 16, and CSO of MediLumine, Inc. from Oct 2015 to May 2016,

Dr. Rosol holds a PhD from Boston University School of Medicine.

William Regan  
Chief Strategy Officer and Chief Compliance Officer

Served as Principal of Regan Advisory Services (RAS) consulting on all aspects of regulatory affairs within pharma, biotech and diagnostic imaging business, including PET, contrast agents and radiopharmaceuticals

Prior to RAS, managed radiopharmaceutical manufacturing, quality assurance, pharmaceutical technology and regulatory affairs at Bristol-Myers Squibb (BMS).

Served as global regulatory head for BMS’ Medical Imaging business

Michel Mikhail  
Chief Regulatory Officer

Prior to joining Navidea, Dr. Mikhail worked in global regulatory consulting for various pharmaceutical and biotech companies from January 2016 through September 2021. Before acting as a consultant, Dr. Mikhail served in senior regulatory executive roles at BioNTech AG, Fresenius Kabi, Ranbaxy Europe Ltd. (now SunPharma), Pharmacia & Upjohn (now Pfizer), Knoll AG (now Abbvie), SmithKline Beecham (now GlaxoSmithKline), and Boehringer Ingelheim.

Dr. Mikhail holds a Ph.D. from the University of Paris and a Dr. Med. Vet. from the University of Hannover.