# Today’s Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
</tr>
</thead>
</table>
| 7:30 – 7:35 AM (5 min) | Opening Remarks & Corporate Overview             | Ivana Magovčević-Liebisch, PhD, JD  
Chief Executive Officer, Vigil Neuroscience, Inc. |
| 7:35 – 7:50 AM (15 min) | TREM2 Concept in Alzheimer’s Disease              | Marco Colonna, MD  
Robert Rock Belliveau Professor of Pathology & Immunology  
Washington University School of Medicine, St. Louis, MO  
Vigil Neuroscience, Inc. Scientific Advisory Chairman |
| 7:50 – 8:30 AM (40 min) | Overview of Vigil’s Small Molecule TREM2 Agonist Program | David Gray, PhD  
Chief Science Officer, Vigil Neuroscience, Inc.  
Christian Mirescu, PhD  
Vice President, Head of Neuroimmunology, Vigil Neuroscience, Inc. |
| 8:30 – 8:45 AM (15 min) | Alzheimer’s Disease Treatment & Unmet Need        | Samuel E. Gandy, PhD, MD  
Mount Sinai Professor of Alzheimer’s Disease Research, Professor of Neurology & Psychiatry  
Associate Director of Mount Sinai Alzheimer’s Disease Research Center, NYC  
Past Chairman, National Medical & Scientific Advisory Council of the Alzheimer’s Association |
| 8:45 - 8:50 AM (5 min) | Clinical Development of VG-3297, Vigil’s Small Molecule TREM2 Agonist | David Gray, PhD  
Chief Science Officer, Vigil Neuroscience, Inc. |
| 8:50 – 9:00 AM (10 min) | Closing Remarks and Q&A Session                  |                                                                          |
Reminders

- Webcast scheduled to end at 9:00am U.S. ET
- Presentation is available in investors section under Events & Presentations at www.vigilneuro.com
- Moderated Q&A session following prepared remarks
- To submit a written question, fill out form on webcast home page
- Webcast replay available later today on Vigil website under Events & Presentations
Forward-Looking Statements

This presentation contains “forward-looking statements,” which are made pursuant to the safe harbor provisions of the federal securities laws, including the Private Securities Litigation Reform Act of 1995. Any statements that are not statements of historical fact may be deemed to be forward-looking statements. Such statements may contain words such as “may,” “might,” “will,” “could,” “should,” “would,” “expect,” “intend,” “plan,” “prepare,” “look,” “seek,” “anticipate,” “believe,” “estimate,” “predict,” “potential,” “possible,” “continue,” “ongoing” or the negative of these terms, or other comparable words.

These forward-looking statements include, among others, statements relating to: the Company’s strategy, business plans, focus and value of future milestones; the progress and timing of the preclinical development, clinical development and regulatory development of Vigil’s programs, including VGL-101 and VG-3927 and the availability of data from our clinical trials involving our product candidates and expected timing of first dosing for VG-3927; our ability to discover and build a platform of precision medicine based therapies targeting the microglia; and the patient burden of Alzheimer’s disease and potential therapeutic benefit of our product candidates. These forward-looking statements, which are only predictions, involve risks and uncertainties, many of which are beyond our control and are based on our current beliefs, expectations and assumptions regarding our business. As such, you should not place undue reliance on any forward-looking statements because such risks and uncertainties could cause actual results, performance or achievement to differ materially and adversely from those anticipated or implied in the forward-looking statements. Factors that could cause actual results to differ from those predicted in our forward-looking statements include, among others, risks and uncertainties related to conducting and reporting data analyses; product development, including delays or challenges that may arise in the development and regulatory approval of our current and future product candidates or programs; uncertainties as to the availability, analyses and timing of results and data from preclinical and clinical studies and whether results from preclinical studies and early interim data will be predictive of the results of later preclinical studies and data readouts, and other clinical trials; the timing of our ability to submit and obtain regulatory clearance for investigational new drug applications and initiate additional clinical trials; our ability to work with the FDA to successfully remove the partial clinical hold on VG-3927; our ability to initiate and complete our current and expected clinical trials; whether our cash resources will be sufficient to fund our foreseeable and unforeseeable operating expenses and capital expenditure requirements; our ability to raise additional funding on favorable terms, or at all; the rate and degree of market acceptance and clinical utility of our product candidates; the accuracy of our data analyses or estimates for the potential and market for our products; our ability, and the ability of our collaborators, to protect our intellectual property and to conduct activities for the development and commercialization of our candidates in view of third party intellectual property positions; our financial performance; our ability to retain and recruit key personnel, as well as the potential contribution of our employees and board to our growth and success as a Company; developments and projections relating to our competitors or our industry; changes in general economic conditions and global instability, in particular economic conditions in the markets on which we or our suppliers operate; changes in laws and regulations; and those risks and uncertainties identified in our filings with the Securities and Exchange Commission (SEC), including under the heading “Risk Factors” in Quarterly Report on Form 10-Q for the quarter ended June 30, 2023, and such other risks and uncertainties that may be described in other filings we make with the SEC.

You should not rely upon forward-looking statements as predictions of future events or performance, or as a representation or warranty (express or implied) by us or any other person that we will achieve our objectives and plans in any specified time frame, on such specified terms, or at all. Although our management believes that the expectations reflected in our statements are reasonable, we cannot guarantee that the future results, performance or events and circumstances described in the forward-looking statements will be achieved or occur. These forward-looking statements speak only as of the date such statements are made. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.
Corporate Overview
Ivana Magovčević-Liebisch, PhD, JD
Chief Executive Officer
Vigil Neuroscience, Inc.
Vigil Neuroscience is a clinical-stage microglia-focused therapeutics company

- Founded ~3 years ago in July 2020
- Our purpose: to treat rare and common neurodegenerative diseases by restoring the vigilance of microglia, the brain’s sentinel immune cells
- Precision-based strategy for developing microglia therapeutics
- Only company known to have 2 modalities for TREM2 agonism – monoclonal antibody and small molecule
- Highly experienced, execution-focused management team and Board of Directors
- >60 highly dedicated team members
Vigil’s Precision Medicine Strategy to Target Broad Range of Neurodegenerative Diseases

- First Indication: Rare Microgliopathy (ALSP)
- Pipeline Candidates for Genetically Defined Subpopulations in Common Indications (AD)
- Further Expansion into Broader Populations in Common Indications
- Data Driven Expansion in Other Rare Microgliopathies

Apply learnings from genetically defined subpopulations to larger indications

ALSP: Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; AD: Alzheimer’s Disease
Vigil TREM2 Agonists: Differentiated Strategy & Multiple Modalities

The ONLY targeted drug candidate in development for ALSP: VGL101

The 1st & ONLY TREM2 small molecule agonist entering clinical development: VG-3927
VG-3927: Small Molecule TREM2 Agonist Well-Positioned for AD

- **First & only small** molecule TREM2 agonist entering clinical development
- **Excellent profile** as potential treatment for Alzheimer’s Disease (AD):
  - Oral dosing
  - **Superior** brain penetration & **differentiated** pharmacokinetics & MoA vs antibody-based therapeutics
    > Novel MoA potentiates TREM2 response to natural damage ligands may enable
      • **Improved potency & specificity** in active disease state
      • Potentially **more favorable safety profile**
  - Absence of Fc effector domain may limit observations of ARIA
- **Investigational New Drug (IND) is now open**
  - Phase 1 clinical trial in healthy volunteers **allowed to proceed** with partial clinical hold related to maximum exposure limit
- **Dosing in Phase 1** clinical trial in healthy volunteers to commence in **Oct 2023**
Featured Key Opinion Leaders (KOLs)

Marco Colonna, MD
Robert Rock Belliveau Professor of Pathology & Immunology
Washington University School of Medicine, St. Louis, MO
Vigil Neuroscience, Inc. Scientific Advisory Board Chairman

Samuel E. Gandy, MD, PhD
Mount Sinai Professor of Alzheimer’s Disease Research, Professor of Neurology & Psychiatry
Associate Director of Mount Sinai Alzheimer’s Disease Research Center, NYC
Past Chairman, National Medical & Scientific Advisory Council of the Alzheimer’s Association
TREM2 Concept in Alzheimer’s Disease (AD)

Marco Colonna, MD
Robert Rock Belliveau Professor of Pathology & Immunology
Washington University School of Medicine, St. Louis, MO
Vigil Neuroscience, Inc. Scientific Advisory Board Chairman
Unique Developmental Origin of the Brain Resident Immune System

Microglial-specific Markers:
- CD11b
- CD45\textsuperscript{low}
- Cx3cr1\textsuperscript{high}
- Tmem119
- FCRLS
- P2RY12
- Sall1
Microglia in Healthy & Disease States

Microglia are Key to Maintaining Normal Brain Homeostasis and Neuronal Function

Microglia surveillance of healthy brain to maintain tissue homeostasis

Microglia are Brain-resident First Responders to Acute Brain Injury

Microglia processes quickly and precisely orient to damage niche following focal photo-injury

Nimmerjahn, A et al. (2005) Science
Microglia Migration into AD's Neuropathological Amyloid Plaque Microenvironment

**Healthy Control Brain**

**Alzheimer’s Disease Brain**

- Amyloid plaque
- Insoluble ApoE
- Microglia

Colonna Lab, unpublished data
Genetics of AD Inspire the Next Generation of Microglia-Targeted Therapeutics

Expansion of AD Sequenced Genomes Identifies Rare And Novel Causal Genetic Risk Factors

AD Genetics-identified Genes Enriched in Microglia

Targeting Neuroimmunology Specifically for Alzheimer’s Disease
Distinct Genetic Links vs Inflammation Disease States

Human Genetic Underpinnings of Alzheimer’s Disease Point Directly to TREM2 with Further Validation by Multiple Pathway Interactors

Biological Substrates of Multiple Sclerosis Points to a Distinct Signature

Why All the Focus on TREM2?
Overwhelming Human Data Point to AD-risk Associated Gene, Protein & Cellular Dysfunction

Association of TREM2 Variants with AD Risk is Robust and Highly Replicated

TREM2 Mutations in AD Suggest Loss of Ligand Binding and Loss of Microglia Function

Gene Expression in Sporadic AD Further Validates Involvement of the TREM2 Pathway

Microglial Loss-of-Signaling Hypothesis for TREM2
TREM2-DAP12 Pathway & Its Importance Beyond AD

TREM2-DAP12 Signaling Transduction and Cellular Function in Microglia

- **Low avidity ligand state**
  - TREM2
  - DAP12
  - SYK
  - 
  - Ligand Organized TREM2 Clustering
  - Microglia Function

- **High avidity ligand state**
  - TREM2
  - DAP12
  - SYK
  - pSYK

MRI manifestations of NHD

Neuropathology in NHD patient

- **Healthy Patient**
  - NHD related astrogliosis (GFAP)

- **NHD Patient**
  - NHD associated neuronal damage (Neurofilament)
  - NHD induction of apoptosis (Casp-3 cleaved)

TREM2's Role in Microglial Activation Disease State

**Molecular Evidence**
TREM2 promotes non-inflammatory, neuroprotective microglia state

**AD Mouse Models**
TREM2 is required for neuroprotection within the amyloid plaque niche

**Human AD Validation**
Plaque-associated microglia protect neighboring neurons

Key activated processes
- Microglia chemotaxis
- Immune metabolism
- Phagocytosis

Amyloid plaque  Microglia

Preclinical Proof-of-Principle via TREM2 Agonist Antibodies
Target Validation via Pharmacological Modulation

TREM2 Agonist Antibody Reduces Neuronal Damage Locally Around Aβ Plaques

Enhanced Brain Penetration Leads to Increased Amyloid Reduction

> Control antibody

> TREM2 Antibody

*AL002

Amyloid plaque  Neuronal damage

Control tvAb  TREM2 tvAb  TREM2/TfR bsAb

Amyloid plaque

TREM2 tvAb: TREM2 tetravalent antibody
TREM2/TfR bsAb: TREM2 tetravalent antibody engineered for enhanced brain penetration
TfR: transferrin receptor epitope

Leveraging Microglia to Restore Tissue Homeostasis in AD
Evidence from Recent Anti-Aβ Therapeutics

Anti-Aβ dual binding to AD substrate and microglia

Antibody full effector function drives microglial Aβ clearance

Effector inactivated mAbs fail to engage microglia and lack efficacy

Chauraslya, A et al. (2023) Nanomedicine-Based Approaches for the Treatment of Dementia
Breakthroughs in Neuroimmunology Seed a Promising New Outlook for AD Therapeutics

Summary of Key Concepts

- Genetics of AD point to microglia as the next generation therapeutics
- TREM2 is both directly implicated as a causal gene as well as indirectly as a genetic hub
- Extensive research points to their protective role in the amyloid plaque microenvironment
- Preclinical genetic and pharmacological studies validate the TREM2 agonism for AD concept
- Recently approved anti-Aβ therapeutics provide clinical precedent that leveraging microglia can restore tissue homeostasis in AD
Acknowledgements

Washington Univ.
Marina Cella
Susan Gilfillan
Jonathan Kipnis
Igor Smirnov
David M. Holtzman
Jason Ulrich

Weizmann Institute
Ido Amit
Hadas Keren-Shaul

Brain research Institute
Niigata, Japan
Akiyoshi Kakita
Mari Tada
Masaki Takao

Mayo Clinic Rochester
Aivi Nguyen
Rachel Larsen
Eleni Costantopoulos

University of Brescia
Luigi Poliani
William Vermi
Mattia Bugatti
Andrea S Omodei

CST, Boston
Tyler Levy
Sean Beausoleil
Richard Cho

Vigil Neuroscience
David Gray
Christian Mirescu
Borislav Dejanovic
Kelley Larson

Amgen
Daniel C. Ellwanger
Samuel A. Hasson
Menno van Lookeren Campagne

Alector
Tina Schwabe
Meer Moustafa
Ilaria Tassi
Herve` Rhinn
Adiljan Ibrahim
Arnon Rosenthal
VG-3927: First & Only Small Molecule TREM2 Agonist Entering Clinical Development for Alzheimer’s Disease

David Gray, PhD
Chief Science Officer, Vigil Neuroscience, Inc.
VG-3927: First & Only Clinical Oral Small Molecule TREM2 Agonist

We Are Microglia Experts

- Outstanding & differentiated clinical candidate from world-class R&D
- Potent TREM2 agonism synergizes with natural damage ligands
- Broad and favorable modulation of neuropathology

© Vigil Neuroscience, Inc. 2023. All rights reserved.
VG-3927 Selected from High Quality Chemical Matter

Deep Understanding of MoA with Multiple Excellent Back-up Compounds

Highly Efficient and Structurally Diverse

Target Coverage in CNS via Oral Dosing

Strong Development Path

- Consistent PK across preclinical species
- CNS drug properties fully optimized
- Scalable and versatile synthetic route

\[ p\text{EC50} = \log [p\text{SYK EC50}] \] measured in HEK293T–hTREM2 cells. LogD(7.4) = Measured water/octanol partition coefficient at pH 7.4. Rat%F = percentage oral bioavailability in Wistar-Han Rats, Rat Cl = Estimated metabolic clearance rate measured in Wistar Han rats, Rat Kp = Brain to plasma partition coefficient measures in Wistar Han rats.

© Vigil Neuroscience, Inc. 2023. All rights reserved.
VG-3927: Entering Phase 1 with Excellent Product Profile

- **TREM2 EC\(_{50}\):** < 0.003 µM
- **TREM1 selectivity:** > 50,000-fold
- **Clean profile (evaluated in ~350 off-target assays)**

**Highly Potent & Selective for TREM2**

- **SIF solubility:** 83 µM
- **MDCK Papp:** >10 cm\(^{-6}\)/s
- **MDCK PGP ER:** ~0.5

**Good Permeability and Solubility**

- **PK consistent with QD dosing**
- **CSF exposure ≈ free plasma**
- **No CYP inhibition liability**
- **No TDI risk**

**Compelling PK profile**

- **Well tolerated with sufficient safety margins to support Ph1**
- **hERG margin:** > 3,500-fold

**Favorable Safety Profile**

EC\(_{50}\): half maximal effective concentration; PK: pharmacokinetics; QD: once-daily; CSF: cerebrospinal fluid; CYP: cytochrome P450 enzymes; TDI: time-dependent inhibition; hERG: human ether-a-go-go-related gene; SIF: stimulated intestinal fluids; MDCK Papp: Madin-Darby canine kidney apparent permeability; PGP ER: P-glycoprotein efflux ratio

© Vigil Neuroscience, Inc. 2023. All rights reserved.
Establishing VG-3927 for Development in AD

Pharmacological & Clinical Translation

**VG-3927 Pharmacological Profile**

- TREM2 engineered systems
- Human iPSC microglia monocultures
  - High-throughput profiling
  - Therapeutically relevant target cells

**VG-3927 Functional & Model System Profile**

- Human CNS tri-culture platform
- Mouse neurodegenerative disease models
- Biologically diverse human CNS model system
- Established preclinical AD transgenic mice
- Nonhuman primate profiling
- ID and validation of translational biomarkers
VG-3927: Potent & Selective TREM2 Agonist

VG-3927 – Highly Selective Agonist for TREM2 Over TREM1

VG-3927 Signaling in Human Microglia is Fully Dependent on TREM2

DOSO: dimethyl sulfoxide
VG-3927: Potent TREM2 Agonist in Neurodegenerative Disease-Associated TREM2 Variants

Supports Precision-based Clinical Development

Vigil Precision AD Strategy

Vigil Precision AD Strategy

VG-3927 Potency Across Notable AD-risk Variants of TREM2

<table>
<thead>
<tr>
<th>TREM2 Variant</th>
<th>Highly Potent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Variant</td>
<td>✔</td>
</tr>
<tr>
<td>R47H</td>
<td>✔</td>
</tr>
<tr>
<td>R62H</td>
<td>✔</td>
</tr>
<tr>
<td>H157Y</td>
<td>✔</td>
</tr>
<tr>
<td>T96K</td>
<td>✔</td>
</tr>
</tbody>
</table>
VG-3927 Potentiates Signaling of Damage-associated Ligands

**Damage-associated Ligand: Sulfatide**

### TREM2 Signaling Activation

- **High**
- **Low**
- **CTL**

### Potentiation of TREM2 Activation

**VG-3927**

### Focusing Efficacy in Pathological Microenvironments

Plaque-burdened AD State

<table>
<thead>
<tr>
<th>Sulfatide Level (Concentration, nM)</th>
<th>TreM2 Signaling Activation (% Max pSYK of Natural Ligand)</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>TreM2 Signaling Activation (Control)</td>
</tr>
<tr>
<td>100</td>
<td>TreM2 Signaling Activation (Low)</td>
</tr>
<tr>
<td>320</td>
<td>TreM2 Signaling Activation (High)</td>
</tr>
<tr>
<td>1000</td>
<td>TreM2 Signaling Activation (AD State)</td>
</tr>
</tbody>
</table>

CTL: control; Low: VG-3927 at 2 nM; High: VG-3927 at 125 nM

© Vigil Neuroscience, Inc. 2023. All rights reserved.
TREM2 AD-risk Variants Are Loss of Function & Impact Signaling

**Example: R47H Leads to Defective Sensing of Sulfatide**

**TREM2 R47H Variant**

**Mutation Impact:**
- Missense in ligand binding domain
- Loss of TREM2 response to sulfatide (damage-associated ligand)

**TREM2 Activation (CV vs R47H Variants)**

![Graph showing TREM2 activation](image)

**Genotype Impact on TREM2 Activation**

- **CV:CV**
  - Normal Sulfatide Response
- **CV:R47H**
  - Partial LoF
- **R47H:R47H**
  - Full LoF

**Note:**
- TM: transmembrane domain; ICD: intracellular domain; CV: common variant; LoF: loss of function
VG-3927 Restores TREM2 Response to Damage-associated Ligand in R47H

**Rescues Signaling Impairment in AD-risk Variant**

- TREM2-R47H defective response to damage-associated ligand (sulfatide)
- VG-3927 rescues signaling and response to sulfatide
- Similar effects observed in TREM2 R62H AD-risk variant

---

**VG-3927 Fully Restores Compromised Signaling in AD-risk Variant**

<table>
<thead>
<tr>
<th>Log [Sulfatide] (M)</th>
<th>Relative pSYK Induction (% Max induction of TREM2&lt;sup&gt;CV&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-10</td>
<td>0</td>
</tr>
<tr>
<td>-9</td>
<td>100 (&lt;10%)</td>
</tr>
<tr>
<td>-8</td>
<td>200 (56%)</td>
</tr>
<tr>
<td>-7</td>
<td>300 (322%)</td>
</tr>
<tr>
<td>-6</td>
<td>400 (343%)</td>
</tr>
<tr>
<td>-5</td>
<td>500 (334%)</td>
</tr>
</tbody>
</table>

**TREM2 Activation**

- **High**:
  - 343% Treasure: VG-3927 Synergy
  - 322% Treasure: VG-3927 Synergy
  - 334% Treasure: VG-3927 Synergy

**CV:CV**

- 100% Treasure: Control
- 56% Treasure: Low: VG-3927 at 1 nM
- <10% Treasure: High: VG-3927 at 100 nM

**CTL: control; Low: VG-3927 at 1 nM; High: VG-3927 at 100 nM**
VG-3927 Acts as a Molecular Glue to Stabilize TREM2 Complex

**Novel Mechanism of Action**

Higher molecular weight band reveals novel receptor ligand complex

Neg CTL: negative control; DMSO: dimethyl sulfoxide; KO: knock-out; PAGE: polyacrylamide gel electrophoresis; iMGLs: induced pluripotent stem cell-derived microglia; HEK: human embryonic kidney

© Vigil Neuroscience, Inc. 2023. All rights reserved.
**VG-3927 Orchestrates Multi-Protein Interaction to Trigger Signaling**

**Unique Molecular Glue Mechanism of Action**

- **Unassembled Inactive TREM2 Receptor Complex**
  - TREM2
  - DAP12
  - SYK
  - SYK

- **VG-3927 TREM2 SM for AD**
  - Proximity-induced fluorescence
  - Fluorescence signal generated by TREM2-DAP12 proximity

- **Minimal TREM2 and DAP12 Interaction at Baseline**
  - VG-3927 Brings Together Both Signaling Partners
  - TREM2 clusters and utilizes DAP12 to initiate downstream signaling
  - VG-3927 coordinates these protein-protein interactions

**Quantification of TREM2-DAP12 Interaction**

- CTL
- VG-3927

© Vigil Neuroscience, Inc. 2023. All rights reserved.
Establishing VG-3927 for Development in AD

Pharmacological & Clinical Translation

VG-3927 Pharmacological Profile

- TREM2 engineered systems
- Human iPSC microglia monocultures

High-throughput profiling

VG-3927 Functional & Model System Profile

- Human CNS tri-culture platform
- Mouse neurodegenerative disease models
- Nonhuman primate profiling

Biologically diverse human CNS model system
Established preclinical AD transgenic mice
ID and validation of translational biomarkers

© Vigil Neuroscience, Inc. 2023. All rights reserved.
VG-3927: First & Only Small Molecule TREM2 Agonist Entering Clinical Development for Alzheimer’s Disease

Christian Mirescu, PhD
Vice President, Head of Neuroimmunology, Vigil Neuroscience, Inc.
Establishing VG-3927 for Development in AD

Pharmacological & Clinical Translation

VG-3927 Pharmacological Profile

TREM2 engineered systems
High-throughput profiling

Human iPSC microglia monocultures
Therapeutically relevant target cells

VG-3927 Functional & Model System Profile

Human CNS tri-culture platform
Biologically diverse human CNS model system

Mouse neurodegenerative disease models
Established preclinical AD transgenic mice

Nonhuman primate profiling
ID and validation of translational biomarkers

© Vigil Neuroscience, Inc. 2023. All rights reserved.
Vigil Human CNS Platform Combines Neurons, Astrocytes & Microglia

Human iMGL Monoculture Platform

- Pharmacology in disease-relevant human cells
  - Microglial pharmacology
  - Target selectivity
  - Fine mapping agonism

Human CNS Tri-culture Platform

- Bridge to a predictive human translational system
  - Vigil’s fully human translational cell model
  - Understand interactions between diverse CNS cells
  - Complementary with mono-culture applications

iMGL: induced pluripotent stem cell (iPSC)-derived microglia
VG-3927 Functional Profiling in CNS Tri-Culture Platform

Platform Application: Understand VG-3927 Downstream Biology & Human Neuroprotective Actions

<table>
<thead>
<tr>
<th>Neurons</th>
<th>Astrocytes</th>
<th>Microglia</th>
</tr>
</thead>
</table>

VG-3927 Modulates Established Target Engagement Biomarker

- VG-3927 Modulates Established Target Engagement Biomarker

Mobilizing microglia response with a favorable, non-inflammatory profile

- Boosting of neuroprotective markers
- Plus countering inflammation-induced neurodegeneration

© Vigil Neuroscience, Inc. 2023. All rights reserved.
VG-3927: Enhances Signals of Microglia Mobilization

**Favorable, Non-inflammatory Profile**

**Enhancement of Microglia Migration Signal**

- IP-10 Increase

**Suppression of Pro-inflammatory Cytokines**

- IL-1β Reduction

- VG-3927 Tunes Microglial Secreted Factors

* denotes p<0.05

* denotes p=0.01; ** denotes p=0.001
VG-3927 Reduces Established Neurodegeneration Biomarkers

**Reduction of Extracellular NfL & Tau**

**VG-3927’s Impact on Key Neurodegeneration Biomarkers in Humans**

**VG-3927 Reduces Extracellular NfL Accumulation in Human Tri-cultures**

**VG-3927 Reduces Extracellular Tau Accumulation in Human Tri-cultures**

**ANOVA**

\[ Treatment, p<0.0001 \]

**ANOVA**

\[ Treatment, p<0.0001 \]

© Vigil Neuroscience, Inc. 2023. All rights reserved.
VG-3927 Protects Against Inflammation-Induced Astrogliosis

**TREM2 Agonism Activates Anti-inflammatory Benefit**

**GFAP: Marker of Astrogliosis**

**VG-3927 Reduces Astrogliosis Biomarker (GFAP) in Human CNS Tri-cultures**

**Neurodeg Stimulus**

LPS/IFNy

**Neuro-inflammation**

**Neurodegeneration**

Extracellular NfL and Tau

**Astrogliosis**

Extracellular GFAP

**Human iPSC Astrocyte**

Extracellular GFAP

Healthy state

Intracellular GFAP

Damage state

LPS: lipopolysaccharide; IFNy: interferon-gamma; GFAP: glial fibrillary acidic protein
VG-3927 Protects Against Biomarkers of Inflammation-Induced Neurodegeneration

TREM2 Agonism Activates Anti-inflammatory Benefit

VG-3927 Suppresses Extracellular NfL & Tau Accumulation in LPS Model

ANOVA Treatment, p<0.05

© Vigil Neuroscience, Inc. 2023. All rights reserved.
Establishing VG-3927 for Development in AD

Pharmacological & Clinical Translation

**VG-3927 Pharmacological Profile**

- TREM2 engineered systems
- Human iPSC microglia monocultures

High-throughput profiling

**VG-3927 Functional and Model System Profile**

- Human CNS tri-culture platform
- Mouse neurodegenerative disease models
- Nonhuman primate profiling

Biologically diverse human CNS model system

Established preclinical AD transgenic mice

ID and validation of translational CSF biomarkers

---

© Vigil Neuroscience, Inc. 2023. All rights reserved.
VG-3927: Functionally Active in AD State

VG-3927 & VGL101 mAb Activate Neuroprotective Genes Similarly

Mouse Amyloidosis Model
VG-3927 Oral Dosing

VG-3927 Recapitulates TREM2 Antibody Gene Signatures

VG-3927 Activates Protective Microglia Gene Signatures

Model: SxFAD AD (mut APP/PS1) + hTREM2
Exploring VG-3927 Therapeutic Effects in Aβ Plaque-bearing Mice

**Initial Pilot Study**

**VG-3927 Effects in Humanized TREM2 AD Mouse Model**

**Intervention**: Post-plaque deposition  
**Initial age**: 4.5 month-old 5xFAD-hTREM2 mice

**Daily Dosing for 6 Weeks**  
**VG-3927**  
10mpk  
QD

**Disease-modifying Effects of VG-3927 on Aβ Pathology & AD-related Hallmarks**

- **Vehicle**
- **VS**
- **VG-3927**

- **Amyloid plaques**
- **Microglia**

47

© Vigil Neuroscience, Inc. 2023. All rights reserved.
VG-3927 Reduces Aβ Pathology in Plaque-bearing Mice

**Preliminary Effects Following 6 Weeks of Oral Dosing**

**VG-3927**

- Trend toward reducing plaque area and insoluble Aβ
- Additional potential to reduce plaque-associated ApoE

[Bar charts showing VG-3927 Effects on Aβ Plaque Area (Immunohistology from Brain Slices) and VG-3927 Effects on Insoluble Aβ\(_{1-42}\) (Biochemistry of Brain Homogenates).]
VG-3927 Reduces Neuropathology-associated Aggregated ApoE

**Preliminary Effects Following 6 Weeks of Oral Dosing**

- **No Change in Soluble ApoE Functional Form**
- **Reduced Aggregated ApoE Pathological Form**

**Working Model of VG-3927 Modulation of AD-related Pathology**

- **Aβ-ApoE Complexes**
- **VG-3927 Synergy**
- **Intracellular space of non inflammatory TREM2 activated microglia**
- **Extracellular neuropathological microenvironment**
- **VG-3927 microglia clearance**
Confirmation of Oral Bioavailability, Brain Penetration & CNS Target Engagement

**Favorable PK & PD Demonstrated in Non-Human Primates (NHPs)**

Translation Biomarker Path to Clinic

CSF Biomarker of TREM2 Target Engagement

**CSF Drug Levels**

**PK Timecourse (hours)**

**CSF Drug Levels (nM)**

**CSF Biomarker of TREM2 Target Engagement**

**VG-3927 CNS Exposures**

**PK Following Single Oral Dose**

**Reduction of sTREM2 in NHP CSF**

**Relative Change from Pre-dose Levels**

**Cynomolgus Monkey**

po: “per os” or oral dosing
Establishing VG-3927 for Development in AD

**Pharmacological & Clinical Translation**

### VG-3927 Pharmacological Profile
- TREM2 engineered systems
- Human iPSC microglia monocultures
  - High-throughput profiling
  - Therapeutically relevant target cells
  - ✓

### VG-3927 Functional and Model System Profile
- Human CNS tri-culture platform
- Mouse neurodegenerative disease models
- Biologically diverse human CNS model system
- Established preclinical AD transgenic mice
- Nonhuman primate profiling
- ID and validation of translational CSF biomarkers
  - ✓

© Vigil Neuroscience, Inc. 2023. All rights reserved.
VG-3927: First & Only Clinical Small Molecule TREM2 Agonist for AD

Broad modulation of neuropathology by harnessing microglia

VG-3927, TREM2 SM for AD

- Phase 1 dosing in healthy volunteers to commence in Oct 2023
- Differentiated TREM2 agonist
  - Highly potent and selective
  - Orally bioavailable and brain penetrant
- TREM2 natural ligand boosting
- Broad modulation of neuropathology

© Vigil Neuroscience, Inc. 2023. All rights reserved.
Alzheimer’s Disease Treatment & Unmet Need

Samuel E. Gandy, PhD, MD
Mount Sinai Professor of Alzheimer’s Disease Research,
Professor of Neurology & Psychiatry
Associate Director of Mount Sinai Alzheimer’s Disease Research Center, NYC
Past Chairman, National Medical & Scientific Advisory Council of the Alzheimer’s Association
Alzheimer’s Disease (AD)

- Progressive degenerative disease
- Most common cause of dementia in elderly
- Progressive memory loss, impaired thinking, disorientation, language problems, mood disturbances
- Complete dependence in advanced stages

Multiple Pathophysiological Mechanisms Underly Alzheimer’s Disease

β-amyloid Plaques
Tau Tangles
Inflammation
Neurodegeneration

AD Presents a Significant Unmet Medical Need

- An estimated 6.7 million Americans are living with Alzheimer’s disease\(^1\)
  - 1 in 9 people, age 65 and older has AD
  - Accounts for 60-80% of all dementia cases
  - Increasing incidence due to an aging population
  - 7th leading cause of death

- Enormous societal and economic burden
  - Long duration of illness and time spent in a state of severe disability & dependence
  - >11 million Americans provide unpaid care for a family member or friend with AD & other dementia

- Delaying the onset and progression of AD by 1 year may result in 9.2 million fewer cases in global burden by the year 2050\(^2\)

---

Current Treatment Options for AD

Symptomatic Treatment
- Cholinesterase inhibitors and NMDA antagonists to improve symptoms
- Does not impact brain pathology or modify the disease course
- Offers modest clinical benefit but effects wane over time due to disease progression

Anti-Aβ Monoclonal Antibodies
- Aβ lowering immunotherapies
- 22-30% slowing in clinical decline
- Administered by intravenous infusion once or twice a month
- Can cause ARIA (brain edema, microbleeds), a common side effect that requires MRI monitoring

Unmet need remains for therapeutics with improved safety and efficacy that address broader AD disease pathophysiology

ARIA - Amyloid-Related Imaging Abnormalities
Anti-Aβ mAbs with Efficacy Are Associated with ARIA

- Transient radiographic finding, occurs early in the treatment course
- Monitorable by MRI surveillance
- Managed by dose titration and dose suspension

<table>
<thead>
<tr>
<th>Anti-Aβ mAbs</th>
<th>Efficacy on CDR-SB</th>
<th>Aβ plaque removal</th>
<th>ARIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective at Lowering Aβ Plaques(^1^)-(^3^)</td>
<td>~22-30% slowing</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Do Not Lower Aβ Plaques(^4^)-(^5^)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Small Molecule Modality Offers the Potential to Mitigate ARIA Liability

CDR-SB: Clinical Dementia Score Sum-of-Boxes; ARIA - Amyloid-Related Imaging Abnormalities
Unmet Needs & Key Opportunities in AD Therapeutics

- Greater Efficacy
  - Efficacy limited to ~30% slowing in clinical decline

- Improved Safety
  - ARIA a common side effect, requires MRI monitoring
  - Immunogenicity

- Access
  - Intravenous infusions once/twice monthly

- Combination Therapy
  - Address broader biology of the disease beyond Aβ
Human Genetics Motivates Targeting Microglia for Next-gen AD Therapeutics

>30% of AD-risk Genes Are Expressed by Microglia

Lane et al European Journal of Neurology (2017)
Human Genetics & Disease Models Suggest Optimizing Microglia Function May Be Beneficial

- AD-related TREM2 variants exhibit impaired ligand binding & partial loss-of-microglia function
- Genetic mutations associated with reduced microglia function also implicated in other genetic forms of neurodegeneration

<table>
<thead>
<tr>
<th>Gene</th>
<th>Condition Associated with Gene Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREM2</td>
<td>NHD/PLOSL Increase risk for AD</td>
</tr>
<tr>
<td>TYROBP/DAP12</td>
<td>NHD/PLOSL</td>
</tr>
<tr>
<td>CSF1R</td>
<td>ALSP</td>
</tr>
</tbody>
</table>

TREM2 Agonism Enhanced Barrier Function and Phagocytosis Resulting in Reduced Neuronal Loss in *in vitro* and Animal Models of AD

NHD – Nasu Hakola; PLOSL - Polycystic Lipomembranous Osteodysplasia; FTD – Frontotemporal Dementia; ALSP - Adult-onset Leukoencephalopathy with Axonal Spheroids Pigmented Glia
Golde T. *Neuron* (2019); Lewcock JW et al. *Neuron* (2020); Wang S et al *JEM* 2020
TREM2-R47H Variant Carriers Exhibit Faster Decline & Worse Cognition Compared to Non-Carriers

**Individuals with AD**
- Carriers
- Noncarriers

1.67 CDR-SB/year
1.37 CDR-SB/year

23% faster decline in carriers $p=0.02$

**Cognitively Normal Elderly**

VG-3927: Well-Positioned for Clinical Development in AD

- Orally bioavailable brain penetrant small molecule
- Potent and highly TREM2-specific
- Potentiates TREM2 response to natural damage ligands across different AD-associated genetic TREM2 variants
- Optimal balance of promoting neuroprotective function and suppressing proinflammatory activity of microglia
- Preliminary data showing impact on AD pathophysiology in an animal model of AD
- Clear target engagement in non-human primates
VG-3927 Has Potential to Address Unmet Needs & Opportunities in AD

Drive greater efficacy
- Boosting microglial repair functions
- Impact broader disease pathophysiology

Mitigate ARIA
- No Fc-mediated interactions
- Specificity of response to disease microenvironment
- Favorable kinetic profile vs mAbs

Greater Efficacy

Improved Safety

Access

Combination Therapy

• Convenient oral option vs i.v. infusion of immunotherapies

• Small molecule optimal for combination therapy and AD prevention paradigms
Clinical Development of VG-3297, Vigil’s Small Molecule TREM2 Agonist

David Gray, PhD
Chief Science Officer
Vigil Neuroscience, Inc.
VG-3927 Phase 1 Trial in Healthy Volunteers

**Trial Population**
- Healthy volunteers (HVs) including an elderly cohort

**Trial Design**
- Double-blind, placebo-controlled
- Single (SAD) & multiple (MAD) ascending dose cohorts

**Treatment Duration**
- VG-3927 or placebo (oral dosing)
- SAD – single dose
- MAD – once daily for 14 days

**Pharmacodynamics (PD)** based on CSF biomarkers (sTREM2, sCSF1R, osteopontin)
VG-3927: Early-stage Clinical Strategy to De-risk Development for AD

Phase 1
Healthy Volunteers
- Safety, tolerability, PK & PD
- SAD/MAD in healthy volunteers includes an elderly cohort in MAD
- Target engagement: based on CSF levels of sTREM2; downstream PD: based on sCSF1R and osteopontin in CSF
- Dosing to commence in Oct 2023
- Interim data on SAD/MAD cohorts in mid-2024

Phase 1b
AD Patients
- Safety and proof-of-pharmacology in symptomatic AD patients
- Characterize pharmacology in genetic subpopulations including disease associated TREM2 variant carriers to inform patient population for future clinical development

Phase 2/PoC
AD Patients
- Phase 1b to inform on target AD population and study design to assess safety and proof-of-concept in symptomatic AD patients
Closing Remarks

Ivana Magovčević-Liebisch, PhD, JD
Chief Executive Officer
Vigil Neuroscience, Inc.
VG-3927: Differentiated Oral TREM2 Agonist with De-risked Precision-based Clinical Strategy for AD

- **First & only** small molecule TREM2 agonist entering clinical development
- Harnesses **neuroprotective activity of microglia** via highly-potent & specific TREM2 agonism
- **Differentiated** profile to potentially address AD therapeutic needs:
  - **Unique MoA** (potentiation of TREM2 response to natural damage ligands) for **improved efficacy & safety**
  - Activates microglia with **broad non-inflammatory profile**
  - Absence of Fc-effector domain & **favorable PK for ARIA mitigation/management**
  - **Amenable** to future combination treatment regimens
  - **Convenient & patient-friendly** oral dosing
- Genetically guided precision-based clinical strategy to **de-risk** drug development
VG-3927 Small Molecule TREM2 Agonist Milestones

- Submit IND for VG-3927, oral small molecule TREM2 agonist  
  Q3 2023

- Begin Phase 1 dosing of VG-3927 in healthy volunteers  
  Oct 2023

- Report interim Phase 1 SAD/MAD data of VG-3927 in healthy volunteers  
  Mid-2024
Vigil is Well-positioned to Execute on Our Mission

Our vision is a brighter tomorrow for people with devastating neurodegenerative diseases

We are an experienced and passionate team of innovators

TREM2 deficiency leads to microglial dysfunction and drives neurodegeneration

Microglial biology is rapidly becoming a new frontier for CNS drug discovery