Vigil Neuroscience
Ivana Magovčević-Liebisch, PhD, JD
President & Chief Executive Officer

JP Morgan Healthcare Conference
January 9, 2023
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: our plans to deliver precision-based therapies to improve the lives of patients and their families and to target a broad range of neurodegenerative disorders; plans to discover and develop novel therapeutics to leverage microglial biology, such as VGL101 and small molecules active against TREM2, and to enable success in ALS in clinical development; beliefs about TREM2 agonism's importance in Alzheimer's disease; beliefs about the profiles and potential, including the commercial potential, of our pipeline and the strength of our intellectual property position; our analyses and beliefs about data, including pathology and disease biomarkers and the signaling, engagement and potency as an agonism of TREM2 in microglia; plans and upcoming milestones, including estimated timelines, for our pipeline program development activities and pipeline expansion opportunities; expected timing and next steps regarding data announcement, clinical trial activities and regulatory filings and approvals; expectations regarding our ability to develop and advance our current and future product candidates and discovery programs; and the belief that we are well-positioned to execute on our mission.

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 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 and timing of results and data from preclinical and clinical studies; the timing of our ability to submit and obtain regulatory clearance for investigational new drug applications and initiate additional clinical trials; our ability to initiate and complete our current and expected clinical trials; our ability to establish and maintain collaborations, strategic relationships and supply arrangements, or that we will not realize the intended benefits from such relationships or arrangements; 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 ability and willingness of our third-party collaborators to continue research and development activities relating to 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; the effect of the COVID-19 pandemic, including mitigation efforts and economic impacts, on any of the foregoing or other aspects of our business operations, including our preclinical studies and clinical trials; 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 our most-recently filed Annual Report on Form 10-K or Quarterly Report on Form 10-Q, and such other risks and uncertainties that may be described in subsequent filings we may make with the SEC.

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Vigil Neuroscience is a clinical-stage microglia-focused therapeutics company.

Our purpose: to treat rare and common neurodegenerative diseases by restoring the vigilance of microglia, the brain’s sentinel immune cells.

We are utilizing the tools of modern neuroscience drug development across multiple therapeutic modalities as we seek to deliver precision-based therapies to improve the lives of patients and their families.
Vigil’s Mission: Restoring Microglial Vigilance to Create Disease-Modifying Treatments for Neurodegenerative Diseases

Discovering and developing novel therapeutics designed to leverage microglial biology breakthroughs that activate and restore microglial function

Precision-based development strategy first in rare microgliopathies with plans to advance into larger patient populations

First product candidates target microglial receptor protein TREM2
   Evaluating new microglial targets and indications

IPO in January 2022
   Raised ~$315M to-date
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

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

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Vigil TREM2 Agonists: Differentiated Strategy & Multiple Modalities

Vigil Neuroscience

TREM2 mAb in Development for ALSP: VGL101

The ONLY targeted drug candidate in development for ALSP

Small Molecule TREM2 Agonist in Development for Larger Indications

The ONLY TREM2 small molecule agonist in development
## Our Pipeline

### Vigil Has Exclusive Rights to All Programs

<table>
<thead>
<tr>
<th>VGL101</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
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<tr>
<td>Healthy Volunteer</td>
<td>Healthy Volunteer SAD &amp; MAD Phase 1 Trial (interim data announced)*</td>
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<tr>
<td>ALSP**</td>
<td></td>
<td>Phase 2 Proof-of-Concept Trial</td>
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<tr>
<td>Other Leukodystrophies</td>
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<td>Preclinical PoC Evaluation</td>
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### Small Molecule TREM2 Agonist Program

- Alzheimer’s Disease
  - IND-Enabling Studies

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*SAD: single ascending dose; MAD: multiple ascending dose; Phase 1 completed dosing and interim analysis for certain cohorts

** Additional observational Natural History Study, ILLUMINATE, in ALSP is ongoing (NCT05020743)
VGL101 – Antibody TREM2 Agonist for Treatment of ALSP

VGL101 is an investigational therapy and has not been reviewed or approved by any regulatory authority.
VGL101 – Human mAb Agonist of TREM2 with a Compelling Profile

- **High TREM2 selectivity; induces microglial genes with sub-nanomolar potency**
- **Preclinical proof of concept in human iPSC derived microglia**
- **Favorable safety & tolerability profile with linear, dose proportional PK in HVs**
- **Dose dependent, robust & durable CNS target engagement in HVs**
- **Established manufacturing competency, strong IP position, and obtained ODD & FTD**

**Abbreviations:**
- mAb: monoclonal antibody
- iPSC: induced pluripotent stem cells
- PK: pharmacokinetics
- HVs: healthy volunteers
- ODD: Orphan Drug Designation
- FTD: Fast Track Designation

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Rationale for ALSP as Initial Indication for VGL101

Orphan, under-recognized autosomal dominant disorder with prevalence feasible for clinical development and potential commercialization

Vigil’s VGL101 program is the first and only drug candidate in development in this indication with engagement of patient and scientific community

TREM2 agonism rescues CSF1R deficiency in vitro due to the convergence of these 2 microglial receptors on a common signaling pathway

Opportunity to be first to achieve human PoC with a TREM2 agonist

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Compelling Preclinical Data for VGL101 PoM in ALSP

(A) VGL101 Rescued CSF1R Inhibition of Microglia

(B) VGL101 Preserved Microglia Morphology Despite CSF1R Ligand Withdrawal

Microglia Deficit in White Matter Regions, Cerebellum, & Cortex

Kempthorne et al. Acta Neuropathologica. 2020; A: superficial white matter (WM); B: deep WM; C: cerebellar WM; D: cortical layers VI, V & VI; E: cortical layers I, II & III

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Summary of Interim Topline VGL101 Phase 1 Data in Healthy Volunteers*

First-in-human Phase 1 SAD/MAD trial exploring safety, tolerability, PK & PD

- Favorable safety & tolerability profile demonstrated
- Human PK linearity/predictability & long half-life supports monthly dosing
- Proof of target engagement and pharmacological activity in healthy volunteers
- 1st antibody to report durability of TREM2 engagement in a clinical setting

Phase 1 data support VGL101 20 mg/kg as a pharmacologically active dose

Phase 2 IGNITE PoC trial in ALSP ongoing

*As of October 7, 2022, and includes doses up to 40 mg/kg SAD and 20 mg/kg MAD

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First Natural History Study in ALSP

The Illuminate Study Designed to Support Clinical Success in ALSP

- Ongoing first-ever natural history study of ALSP patients with *CSF1R* gene mutation
- Sample size up to 36 subjects globally
- Objectives:
  - Characterize biomarkers & clinical measures of disease progression in ALSP
  - Possibility for contemporaneous external comparator arm
- Observation period: 24 months
- Key assessments include MRI, CSF biomarkers & clinical assessments at baseline & every 6/12-month interval

Radiographic Progression Measurable at Month 6

37 yr | Female | Symptomatic ALSP MoCA at baseline / 6 mos: 15 / 9

MoCA: Montreal Cognitive Assessment

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Greater Disease Progression for Symptomatic vs Prodromal Participants at 6 Months

6-month volumetric MRI findings

Greater Disease Progression Based on Greater Reductions in Brain Tissue Volume & Greater Increases in Lesion & Ventricular Volume

| Brain Region | Prodromal (9) | Symptomatic (8/9)
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Frontal</td>
<td>-3.0 ± 1.2</td>
<td>-6.2 ± 2.4</td>
</tr>
<tr>
<td>Parietal</td>
<td>-3.8 ± 1.5</td>
<td>-5.1 ± 2.7</td>
</tr>
<tr>
<td>Corpus Callosum</td>
<td>-6.0 ± 2.6</td>
<td>-7.8 ± 3.1</td>
</tr>
</tbody>
</table>

1. No. of symptomatic participants – 8 for frontal/parietal/corpus callosum; 9 for ventricle

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Fluid Biomarker Baseline Levels Altered in ALSP Individuals

**sTREM2 Levels Comparable between Prodromal/Symptomatic & Healthy**

**sCSF1R Levels Reduced in Prodromal/Symptomatic vs Healthy**

**NfL Levels Increased in Symptomatic Reflecting Active Neurodegeneration**

Healthy: healthy volunteers from Vigil’s VGL101 Phase 1 trial; Prodromal: participants with confirmed CSF1R mutation and MRI findings in Vigil’s Natural History Study (NCT05020743); Symptomatic: subjects with CSF1R mutations and ALSP symptoms in Vigil’s Natural History Study; no. of samples for all CSF analyses: 25 (Healthy); 3 (Prodromal); 6 (Symptomatic); No. of samples for serum analysis: 67 (Healthy); 10 (Prodromal); 11 (Symptomatic); all biomarker values are in mean ± standard error of mean (SEM)
VGL101 ALSP Phase 2 Open-label Proof-of-Concept Trial Design

**Study Population**
- Patients with symptomatic ALSP related to *CSF1R* gene mutation

**Study Design**
- Open-label, up to 15 patients

**Treatment Duration**
- 12 months (with opportunity for further extension), monthly IV administration

**Outcome Assessments**
- Safety and tolerability of VGL101
- MRI-based assessment of brain volume and white matter lesions
- CSF biomarkers for neurodegeneration and target engagement
- Clinical outcome measures and PK
U.S. adult onset leukodystrophies: ~16,500 (incidence)\(^1\); ~99,000 (prevalence)\(^2\)

\(^1\) Incidence: ~5/100K; \(^2\) Prevalence: ~300/1M

U.S. ALSP*: ~1,000-2,000 (incidence); ~10,000 (prevalence)

*~10% of all adult-onset leukodystrophies\(^3\)

Potentially significant U.S. commercial opportunity

EU27+UK prevalence: ~15,000\(^4\); Japan prevalence: ~4,000\(^4\)

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\(^1\) Sassi et al Neurobiol Aging 2018; \(^2\) Ahmed et al. J Neurol Neurosurg Psych 2014; \(^3\) Lynch et al. Neurogenetics 2015; \(^4\) Assumes same prevalence as U.S.
Small Molecule TREM2 Agonist Program for Alzheimer’s Disease
**First-in-Class Small Molecule (SM) TREM2 Agonist Program**

- World-class R&D platform has produced lead compounds with highly favorable profile & unique MoA
- SM agonists are molecular glues that potentiate the TREM2 signaling response to natural ligands
- Comparable *in vivo* potency to mAbs with superior brain penetration & oral dosing

Small Molecule Program Grounded in Deep Foundational Understanding

- Highly Potent & Selective for TREM2
- MoA & Structural Biology Depth
- High Free Drug Concentration in Brain
- PK Supports Daily Oral Dosing
- Large Safety Margins in Pilot Tox Studies
- Broad IP Estate
SM Agonists Demonstrated On-Target TREM2 Activation Across Common & Rare TREM2 Variants

First-in-class pharmacology
Highly potent & selective agonist profile

Human microglia potency, TREM2 CV (WT): <5 nM
TREM2 KO microglia potency: >3,000 nM

Precision fit-for-purpose
SMs retain agonist profile across key TREM2 genetic variants

<table>
<thead>
<tr>
<th>TREM2 Variant</th>
<th>Highly Potent</th>
<th>Precision AD Rationale</th>
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<tbody>
<tr>
<td>Common Variant</td>
<td>✔</td>
<td>TREM2 Risk Variants Loss-of-function</td>
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<tr>
<td>R47H</td>
<td>✔</td>
<td>TREM2 Small Molecule Agonism</td>
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<td>R62H</td>
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<tr>
<td>H157Y</td>
<td>✔</td>
<td></td>
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<tr>
<td>T96K</td>
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Left – Human iPSC derived microglia were cultured and stimulated by varying nanomolar (nM) concentrations of a Vigil small molecule (SM) TREM2 agonist. To measure the impact of TREM2 activation, the half-maximal induction (EC50) of phosphorylated SYK (pSYK) was quantified by AlphaLISA and expressed as % increase relative to DMSO negative control (Neg Ctl). Right – To determine TREM2 specificity, pSYK was quantified in wild-type vs TREM2 KO human microglia, validating on-target signaling activation.

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SM Agonists: Molecular Glue Potentiating TREM2 Response to Natural TREM2 Ligand

First-in-class mechanism
Vigil’s SMs act as molecular glue

Sensitizing TREM2 in microglia
Vigil’s SMs potentiate TREM2 response to damage-associated ligands

Maximal TREM2 response profile

TREM2 Activation

Co-Stimulation

Control

TREM2 Ligand

Vigil SM

(SM TREM2 Agonist (Concentration, nM))

TREM2 Signaling Activation (%Max pSYK of Natural Ligand)

Sulfatide Level (Concentration, nM)

Decreasing concentrations of SM agonist

(Right panel) Cultured human iPSC derived microglia were co-stimulated with varying nanomolar concentrations (nM, x-axis) of a brain-extracted sulfoglycolipid TREM2 ligand, Sulfatide, in the absence (pink) or presence of varying levels of Vigil small molecule (SM) TREM2 agonist (cyan curves). To quantify SM potentiation of TREM2 signaling, data were normalized to and expressed as the % of maximal pSYK level induced by Sulfatide stimulation in the absence of TREM2 SM agonism (0 nM set as 100%).

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SM Agonists Recapitulate TREM2 mAb Effects in AD Mouse Model

Vigil’s oral SM TREM2 glue resembles IV mAb TREM2 agonist signature in AD mouse model
Enhances protective microglial signature

Adult transgenic SxFAD mice engineered to co-express human TREM2 were dosed either orally with Vigil Small Molecule TREM2 agonist or intravenously with a TREM2 agonist monoclonal antibody in the context of amyloid plaque burden. Additional mice were dosed with negative controls to determine the relative gene expression changes (Log2 fold-change) in brain associated with TREM2 activation. Subsequently, individual gene expression responses were X-Y plotted and correlated between each modality. SxFAD Alzheimer’s mouse model: APP Swedish (K670N, M671L), Florida (I716V), and London (V717I) plus PSEN1 (M146L and L286V)
Path Forward to Clinical Translation for SM TREM2 Agonist

Path to Phase 1 target engagement
SM TREM2 agonist reduced sTREM2 levels (vs baseline) in CSF of NHP

In vivo CNS target-engagement profiling post-oral dosing of SM TREM2 Agonist

Cynomolgus Macaque Non-Human Primates (NHPs)
Vigil’s SM TREM2 Agonists – Clear Path to AD Clinical Development

- **High-quality chemistry**
  Highly potent & selective molecules

- **First-in-class innovation**
  Molecular glue potentiating TREM2 natural ligands

- **Translation to AD models**
  On-target biology and potentiation with disease state

- **Path to clinical translation**
  NHP CSF target engagement biomarker

**IND Submission & Initiate Phase 1**

**2H 2023**

- Identify genetically-defined AD sub-populations with microglia dysfunction
- Conduct comparative biomarker studies in HV & AD subpopulations

**Select population with microglia dysfunction & increased PoS for development**

**Initiate Phase 2 in AD with Small Molecule**

**Enabling precision medicine-approach in AD**

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Corporate Overview
Long-term Strategy: Microglial Function Implicated in Multiple Neurodegenerative Diseases

Current areas of interest
Future opportunities

ALS
~30K
Epilepsy*
~70K
PD
~1M
MS
~1M
FTD
~60K
ALSP
~10K
cALD
~3-4K
Krabbe
~1K
MLD
~4-5K
AD
~6M

Prevalence estimates for U.S. *Lennox-Gastaut & Dravet Syndromes (i.e., rare epilepsies)
cALD: Cerebral Adrenoleukodystrophy; MLD: Metachromatic Leukodystrophy, AD: Alzheimer’s Disease, FTD: Frontotemporal Dementia; MS: Multiple Sclerosis; PD: Parkinson’s Disease; ALS: Amyotrophic Lateral Sclerosis.

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## 2022 – 2023 Achieved & Anticipated Milestones

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<thead>
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<th>Milestone</th>
<th>Quarter/Year</th>
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<tbody>
<tr>
<td>Initiate Phase 2 clinical trial with VGL101 in ALSP</td>
<td>Q4 2022</td>
</tr>
<tr>
<td>Report full data analysis for Phase 1 clinical trial with VGL101 in healthy volunteers</td>
<td>2H 2023</td>
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<tr>
<td>Report VGL101 six-month interim data from Phase 2 proof of concept in ALSP</td>
<td>2H 2023</td>
</tr>
<tr>
<td>Submit IND and initiate clinical development for small molecule TREM2 agonist</td>
<td>2H 2023</td>
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Vigil is Well-positioned to Execute on Our Mission

- Microglial biology is rapidly becoming a new frontier for CNS drug discovery
- TREM2 deficiency leads to microglial dysfunction and drives neurodegeneration
- We are an experienced and passionate team of innovators
- Our vision is a brighter tomorrow for people with devastating neurodegenerative diseases