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 diseases; plans to discover and develop novel therapeutics to leverage microglial biology, such as VGL101, VG-3927 and current or future product candidates, and to enable success 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 potential 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; our ability to work with the FDA to successfully remove the partial clinical hold on VG-3927; 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 that 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
Experienced & Execution-focused Team

Management

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

David Gray
PhD
Chief Science Officer

Christopher Silber
MD
Chief Medical Officer

Evan A. Thackaberry
PhD, DABT
SVP, Head of Early Development

Chris Verni
JD
General Counsel

Jennifer Ziolkowski
CPA
Chief Financial Officer

Board of Directors

Bruce Booth
DPhil
Chairman of the Board
Partner, Atlas Venture

Cheryl Blanchard
PhD
Independent Director
President & CEO, Anika Therapeutics

Suzanne Bruhn
PhD
Independent Director
President & CEO, Tiaki Therapeutics

Samantha Budd Haeberlein
PhD
Independent Director

Gerhard Koenig
PhD
Independent Director
Co-Founder, President & CEO, Arkuda Therapeutics

Ivana Magovčević-Liebisch
PhD, JD
President & CEO, Vigil Neuroscience

Mary Thistle
Independent Director

Suzanne Bruhn
PhD
Independent Director
President & CEO, Tiaki Therapeutics

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Independent Director
Co-Founder, President & CEO, Arkuda Therapeutics

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President & CEO, Vigil Neuroscience

Mary Thistle
Independent Director

Stefan Vitorovic
Co-founder & Managing Director, Vida Ventures

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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)

Data Driven Expansion in Other Rare Microgliopathies

Further Expansion into Broader Populations in Common Indications

Apply learnings from genetically defined subpopulations to larger indications

ALSP: Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; AD: Alzheimer’s Disease)

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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 AD: VG-3927

The **1st & ONLY** TREM2 small molecule agonist in clinical development

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## Our Pipeline

### Vigil Has Exclusive Rights to All Programs

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VGL101: Fully Human Monoclonal Antibody</strong></td>
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<tr>
<td>Healthy Volunteer</td>
<td>Healthy Volunteer SAD &amp; MAD Phase 1 Trial&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ALSP&lt;sup&gt;2&lt;/sup&gt;</strong></td>
<td>Phase 2 Proof-of-Concept Trial</td>
<td></td>
<td></td>
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<tr>
<td><strong>Other Leukodystrophies</strong></td>
<td>Preclinical PoC Evaluation</td>
<td></td>
<td></td>
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<tr>
<td><strong>VG-3927: Oral Small Molecule TREM2 Agonist</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Alzheimer’s Disease</td>
<td>Healthy Volunteer SAD &amp; MAD Phase 1 Trial&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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2) Additional observational Natural History Study, ILLUMINATE, in ALSP is ongoing (NCT05020743)

3) IND for VG-3927 now open; Phase 1 clinical trial in healthy volunteers allowed to proceed with partial clinical hold related to maximum exposure limit
Microglial-targeted Therapeutics
Our Initial Focus: Microglial Receptor Protein TREM2
Microglial-targeted Therapeutics: Activate & Restore Critical Regulators of CNS Health

- Microglia are sentinel immune cells in the brain
  - Sense and respond to damage signals (e.g., infection, cell debris, myelin turnover)
  - Coordinate signal-specific downstream responses
- Microglial dysfunction is associated with rare and common neurodegenerative diseases

Fujita & Yamashita Neuronal Signal 2021
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TREM2 as a Therapeutic Target

TREM2 Acts as an Environmental Sensor to Detect Cellular Damage

TREM2 is Essential for Microglial Function
VGL101 – Antibody TREM2 Agonist for Treatment of ALSP

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

- Preclinical proof of concept in human iPSC derived microglia
- High TREM2 selectivity; induces microglial genes with sub-nanomolar potency
- 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 FDA ODD & FTD & EMA ODD

mAb: monoclonal antibody; HVs: healthy volunteers; ODD: Orphan Drug Designation; FTD: Fast Track Designation
1. Received positive opinion from Committee for Orphan Medicinal Products of the European Medicines Agency (EMA) on ODD for VGL101 for treatment of ALSP in Sep 2023
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 clinical 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
ALSP: A Genetically-linked Microgliopathy with Significant Unmet Need

Epidemiology
- 10% adult-onset leukodystrophies (global): ~10K patients in U.S. & ~13K patients in EU
- Mean age onset 43 years (range 18–78)

Genetics
- Autosomal dominant CSF1R gene mutations

Progression
- Incapacitated in 3-4 years; average time to death: 6-7 years

Diagnosis
- Genetic screening for CSF1R mutations, clinical criteria have low specificity

Clinical Picture/Phenotype
- Main phenotype is cognitive resembling frontotemporal dementia (FTD)
- Neuropsychiatric and motor symptoms very common including ataxia, apraxia, and pyramidal dysfunction (spasticity)
- Other neurologic symptoms include parkinsonism and epilepsy

Treatment
- No approved products and no experimental treatments
Both CSF1R and TREM2 are primarily expressed on the surface of microglia.

CSF1R is essential for microglial survival and homeostasis.

CSF1 activation of CSF1R pathway signals through phosphorylation of SYK.

TREM2 activation of TREM2 pathway signals (via DAP12) through phosphorylation of SYK.

Loss-of-function mutations in either TREM2/DAP12 or in CSF1R lead to devastating adult-onset neurodegenerative diseases with similar symptoms.

Vigil’s Approach in ALSP: TREM2 Agonism to Compensate for CSF1R Mutations and Correct Microglial Dysfunction
CSF1R Mutations Lead to Microglial Loss & Dysfunction in ALSP

IBA-1 microglia staining (brown)
Red arrows highlight microglia observed in control vs ALSP grey and white matter

Microglial loss in grey matter & white matter in ALSP patients

Control Grey Matter | ALSP Grey Matter
Control White Matter | ALSP White Matter

Int. stage ALSP: Intermediate stage ALSP (ambulatory with relatively intact cognitive function); * p < 0.05; ** p < 0.01

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Compelling Preclinical Data for VGL101 PoM in ALSP
VGL101 rescues effects of compromised CSF1R function in human microglia

(A) Removing CSF1R Ligands as a Functional Model of ALSP

<table>
<thead>
<tr>
<th>Control media (CSF1/IL-34)</th>
<th>CSF1/IL-34 withdrawal Media</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>hIgG1 isotype control</td>
</tr>
<tr>
<td>VGL101 anti-TREM2</td>
<td></td>
</tr>
</tbody>
</table>

Complete removal of ligands for CSF1R from growth media

(B) VGL101 Restored Survival & Reduced Apoptosis in Microglia in CSF1R Ligand Depletion Model

![Graph showing Microglia Viability and Caspase 3/7 activation](image)

(C) VGL101 Preserved Microglia Morphology in CSF1R Ligand Depletion Model

![Images showing microglia morphology](image)

(B): Human induced pluripotent stem cells (iPSC)-derived microglia grown in media containing CSF1 and IL-34 (Control Media) and media depleted of CSF1 and IL-34 (Withdrawal Media) with addition of immunoglobulin G control (hIgG) and VGL101 were measured for cell survival compared to Rescue Media (Microglia Viability % rescue Media as Control), ***: p=0.0001; ****: p<0.0001; and activation of Caspase 3/7 compared to Withdrawal Media (Caspase 3/7 % of Withdrawal Media), **: p=0.0075; ***: p=0.0006; (C) iPSC-derived microglia grown in media containing CSF1 and IL-34 (Control Media) and media depleted of CSF1 and IL-34 (Withdrawal Media) with no treatment and addition of CSF1R ligand, hIgG control and VGL101 were evaluated for microglia morphology – white arrowheads indicate rod-like morphology of activated microglia.
Compelling Preclinical Data for VGL101 PoM in ALSP
VGL101 rescues pharmacological inhibition of CSF1R & restores microglia viability

(A) ALSP Model based on Partial Inhibition of CSF1R via PLX5622

(B) VGL101 Rescued Microglia Viability in Haploinsufficient Model

Model partial loss-of-function state of CSF1R in ALSP by dosing inhibitor to IC50
Preclinical Evidence for VGL101 Rescue of ALSP
VGL101 promotes microglia survival & activates CSF1R signaling in patient-inspired ALSP model

(A) ALSP Model with 1 copy of Loss-of-function CSF1R Variant

Stem cell-derived microglia with loss-of-function CSF1R-I794T (one of the known ALSP-related variants)

(B) VGL101 Increased Viability of Microglia with 1794T Variant in CSF1R

(C) VGL101 Restored Downstream CSF1R Signaling* in ALSP Model

*Measuring changes in phospho-CSF1R levels

Phospho-CSF1R (pg/mL)

<table>
<thead>
<tr>
<th>Control Microglia</th>
<th>IgG neg ctrl</th>
<th>VGL101</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF1R-WT/WT variant</td>
<td>IgG neg ctrl</td>
<td>101794T</td>
</tr>
</tbody>
</table>

**** p < 0.0001

**** p < 0.0001

IgG Control VGL101

Microglia Viability (% IgG Control)

0 25 50 75 100 125 150

0 25 50 75 100 125 150

Konno et al. Neurol 2018

*p < 0.05; ** p < 0.01

CSF1R-I794T

CSF1R-WT
Summary of 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 and 40 mg/kg as pharmacologically active doses

Phase 2 IGNITE PoC trial in ALSP ongoing

As of July 7, 2023; SAD: single ascending dose; MAD: multiple ascending dose; PK: pharmacokinetics; PD: pharmacodynamics
VGL101 Demonstrated Favorable Safety & Tolerability at Doses up to 60 mg/kg SAD and MAD in Phase 1

No reports of Serious Adverse Events (SAEs) or Adverse Events (AEs) of special interest

First-in-human Phase 1 SAD/MAD trial for VGL101
- Double-blind placebo-controlled portion exploring 1, 3, 10, 20, 30, 40 and 60 mg/kg on safety, tolerability and PK
- Open-label single-arm portion exploring 3, 10, 20, 40 and 60 mg/kg on CSF biomarkers

Data on 136 healthy volunteers dosed
- Including 113 subjects dosed with VGL101 up to and including 60 mg/kg SAD and MAD

In blinded safety review of all dose cohorts, VGL101 was safe & well tolerated
- Most AEs were mild and most resolved spontaneously
  - Most common treatment-related AE was pruritus
- No serious AEs or severe treatment-related AEs were reported
- Changes in vital signs, ECG, and laboratory parameters were unremarkable

VGL101 Safety & Tolerability Supports Phase 2 Doses of 20 & 40 mg/kg in ALSP Patients
VGL101 Has Linear, Dose Proportional & Predictable PK

Single Ascending Dose Pharmacokinetics (PK)

- ~29 days half-life supporting monthly dosing interval
- Brain penetration and achieving projected CSF therapeutic exposures (0.1 – 0.2% CSF-to-serum ratio)

20 mg/kg Multiple Dose PK
(3 doses at 28-day intervals)
Proof of Target Engagement: VGL101 Demonstrated Dose Dependent, Robust & Durable sTREM2 Decreases

Percentage change in concentration of sTREM2 in cerebrospinal fluid (CSF) vs baseline

**Single Ascending Doses (SAD)**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg/kg</td>
<td>-10% ± 2%</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>-20% ± 3%</td>
</tr>
<tr>
<td>20 mg/kg</td>
<td>-30% ± 4%</td>
</tr>
<tr>
<td>40 mg/kg</td>
<td>-40% ± 5%</td>
</tr>
<tr>
<td>60 mg/kg</td>
<td>-50% ± 6%</td>
</tr>
</tbody>
</table>

**2 Days After Single Dose**

- 3 mg/kg (n=6)
- 10 mg/kg (n=6)
- 20 mg/kg (n=6)
- 40 mg/kg (n=6)
- 60 mg/kg (n=6)

**Multiple Ascending Doses (MAD)**

(3 doses at 28-day intervals)

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg/kg</td>
<td>-10% ± 2%</td>
</tr>
<tr>
<td>20 mg/kg</td>
<td>-20% ± 3%</td>
</tr>
<tr>
<td>40 mg/kg</td>
<td>-30% ± 4%</td>
</tr>
</tbody>
</table>

**28 Days After 3rd/Final Monthly Dose**

- 10 mg/kg (n=6)
- 20 mg/kg (n=6)
- 40 mg/kg (n=4)

As of July 7, 2023
sTREM2: soluble TREM2; CFB: change from baseline (pre-dose levels); SEM: standard error of mean
*p-value < 0.05 (t-test)

For the SAD cohorts, sTREM2 levels were reduced 14 days after dosing (P<0.05) with VGL101 at doses of 10 mg/kg and above
Meier et al ANA 2023 Poster M151
Proof of Pharmacology: VGL101 Shows Durable sCSF1R Increases

Percentage change in concentration of sCSF1R in cerebrospinal fluid (CSF) vs baseline

As of July 7, 2023
sCSF1R: soluble CSF1R; CFB: change from baseline (pre-dose levels); SEM: standard error of mean
*p-value < 0.05 (t-test)
For the MAD cohorts, sCSF1R levels were increased 2 days after 3rd/final monthly dose with 20 mg/kg VGL101 (P<0.05)
Meier et al ANA 2023 Poster M151
Proof of Pharmacology: VGL101 Shows Durable Osteopontin Increases

**Percentage change in concentration of osteopontin in cerebrospinal fluid (CSF) vs baseline**

### Single Ascending Doses (SAD)

- **2 Days After Single Dose**

  - 3 mg/kg (n=6)
  - 10 mg/kg (n=6)
  - 20 mg/kg (n=6)
  - 40 mg/kg (n=6)
  - 60 mg/kg (n=6)

### Multiple Ascending Doses (MAD)

(3 doses at 28-day intervals)

- **28 Days After 3rd/Final Monthly Dose**

  - 10 mg/kg (n=6)
  - 20 mg/kg (n=6)
  - 40 mg/kg (n=4)

---

As of July 7, 2023

CFB: change from baseline (pre-dose levels); SEM: standard error of mean

*p-value < 0.05 (t-test)

Meier et al ANA 2023 Poster M151
First Natural History Study in ALSP

The Illuminate Study
Setting Up for Clinical Success in ALSP

- Ongoing first-ever natural history study of ALSP patients with CSF1R gene mutation
- Sample size up to 50 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

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ILLUMINATE: NCT05020743; MoCA: Montreal Cognitive Assessment
Greater Disease Progression for Symptomatic vs Prodromal Participants at 6 Months

Finite brain volume results in inverse relationship between brain tissue volume and white matter lesion/ventricle volumes

**REDUCTION in Brain Tissue Volume**

<table>
<thead>
<tr>
<th>Disease Progression</th>
<th>Frontal</th>
<th>Parietal</th>
<th>Corpus Callosum</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Change in Brain Tissue Volume from Baseline</td>
<td>Prodromal (9)</td>
<td>Symptomatic (8)</td>
<td>Prodromal (9)</td>
</tr>
<tr>
<td>[Graph showing reduction in brain tissue volume]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**INCREASE in Lesion And Ventricle Volume**

<table>
<thead>
<tr>
<th>Disease Progression</th>
<th>White matter lesion*</th>
<th>Ventricle</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Change in Brain Tissue Volume from Baseline</td>
<td>Prodromal (9)</td>
<td>Symptomatic (7)</td>
</tr>
<tr>
<td>[Graph showing increase in lesion and ventricle volume]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Findings measure percent change from baseline – prodromal begin with a lower baseline vs. symptomatic; absolute change in WML volume for symptomatic is >3x greater than prodromal

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Fluid Biomarker Baseline Levels Altered in ALSP Individuals

**sTREM2**

- **CSF**
  - Healthy: 3000 pg/ml ± 100 pg/ml
  - Prodromal: 3000 pg/ml ± 100 pg/ml
  - Symptomatic: 3000 pg/ml ± 100 pg/ml

**sCSF1R**

- **CSF**
  - Healthy: 12 pg/ml ± 4 pg/ml
  - Prodromal: 4 pg/ml ± 2 pg/ml
  - Symptomatic: 4 pg/ml ± 2 pg/ml

**NfL**

- **CSF**
  - Healthy: 2000 pg/ml ± 100 pg/ml
  - Prodromal: 2000 pg/ml ± 100 pg/ml
  - Symptomatic: 2000 pg/ml ± 100 pg/ml

- **Serum**
  - Healthy: 60 pg/ml ± 10 pg/ml
  - Prodromal: 60 pg/ml ± 10 pg/ml
  - Symptomatic: 60 pg/ml ± 10 pg/ml

**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, ~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

---

**VGL101 (12 months, IV administration of 20mg/kg)**

- **Interim Analysis:** 6 months (n=6) 20mg/kg

**VGL101 (12 months, IV administration of 40mg/kg)**

- **Primary Analysis:** 6 months (all subjects) 20 mg/kg + 40 mg/kg
- **Final Analysis:** 12 months (all subjects) 20 mg/kg + 40 mg/kg

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Building Toward Success in ALSP Clinical Development

Ongoing Patient & KOL Engagement

- **Natural History Study**
  - Enrollment ongoing

- **Phase 1 Clinical Trial in Healthy Volunteers**
  - Trial Complete

- **Phase 2 Clinical Trial investigating VGL101 in ALSP Patients**
  - Enrollment ongoing

- **Genetic Testing and Counseling Program for Patients and HCPs**
  - Ongoing

Data Presented at ANA (Sep 2023)
U.S. adult onset leukodystrophies: \( \sim16,500 \) (incidence)\(^1\); \( \sim99,000 \) (prevalence)\(^2\)

\(^1\) Incidence: \( \sim5/100K \); \(^2\) Prevalence: \( \sim300/1M \)

U.S. ALSP*: \( \sim1,000-2,000 \) (incidence); \( \sim10,000 \) (prevalence)

*\( \sim10\% \) of all adult-onset leukodystrophies\(^3\)

Potentially significant U.S. commercial opportunity

EU27+UK prevalence: \( \sim15,000 \)^4; Japan prevalence: \( \sim4,000 \)^4

---

VG-3927 – Small Molecule TREM2 Agonist for Alzheimer’s Disease
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

---

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

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

Supports Precision-based Clinical Development

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**

- Low: VG-3927 at 2 nM
- High: VG-3927 at 125 nM

**Potentiation of TREM2 Activation**

- VG-3927 + Sulfatide

**Focusing Efficacy in Pathological Microenvironments**

- Plaque-burdened AD State

---

**Note:**

- CTL: control
- Low: VG-3927 at 2 nM
- High: VG-3927 at 125 nM
TREM2 AD-risk Variants Are Loss of Function & Impact Signaling

Example: R47H Leads to Defective Sensing of Sulfatide

TREM2\textsuperscript{R47H} Variant

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

---

TREM2 Activation (CV vs R47H Variants)

Based on pSYK Activation

- **TREM2\textsuperscript{CV}**
- **TREM2\textsuperscript{R47H}**
- **TREM2\textsuperscript{CV/R47H}**

Genotype Impact on TREM2 Activation

- **CV:CV** (100%)
- **CV:R47H** (56%)
- **R47H:R47H** (Full LoF, <10%)

---

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

VG-3927 Fully Restores TREM2 R47H Defect

- Relative pSYK Induction (% Max induction of TREM2<sup>Cv</sup>):
  - CTL (control)
  - Low: VG-3927 at 1 nM
  - High: VG-3927 at 100 nM

- TREM2 Sulfatide Response (% CV:CV control):
  - CV:CV: 100%
  - CV:R47H: 56%
  - R47H:R47H: <10%

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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

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VG-3927 Orchestrates Multi-Protein Interaction to Trigger Signaling

Unique Molecular Glue Mechanism of Action

Unassembled Inactive TREM2 Receptor Complex

VG-3927 TREM2 SM for AD

Minimal TREM2 and DAP12 Interaction at Baseline

VG-3927 Brings Together Both Signaling Partners

Quantification of TREM2-DAP12 Interaction

- TREM2 clusters and utilizes DAP12 to initiate downstream signaling
- VG-3927 coordinates these protein-protein interactions

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VG-3927 Functional Profiling in CNS Tri-Culture Platform

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

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

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VG-3927: Enhances Signals of Microglia Mobilization

**Favorable, Non-inflammatory Profile**

**Enhancement of Microglia Migration Signal**

- IP-10 Increase
- VG-3927 Tunes Microglial Secreted Factors

**Suppression of Pro-inflammatory Cytokines**

- IL-1β Reduction

* denotes p<0.05
** denotes p<0.01; *** denotes p<0.001

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VG-3927 Reduces Established Neurodegeneration Biomarkers

Reduction of Extracellular NfL & Tau

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

Extracellular NfL & Tau
Damage state

Intracellular NfL & Tau
Healthy state

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

ANOVA
Treatment, p<0.0001

Extracellular NfL (% Baseline)
0 50 100 150 200 250
1 2 3 4

Days Post-Treatment

Vehicle VG-3927

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

ANOVA
Treatment, p<0.0001

Extracellular Tau (% Baseline)
0 100 200 300 400
1 2 3 4

Days Post-Treatment

Vehicle VG-3927

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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: 5xFAD AD (mut APP/PS1) + hTREM2

Amyloid-beta (Aβ)  ▢  Microglia (Iba1)

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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

- 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
VG-3927: First & Only Clinical Small Molecule TREM2 Agonist for AD

Broad modulation of neuropathology by harnessing microglia

- **First & only** small molecule TREM2 agonist in clinical development
-Harnesses neuroprotective activity of microglia via highly-potent & specific TREM2 agonism
-Genetically guided precision-based clinical strategy to de-risk drug development

Differentiation profile to potentially address AD therapeutic needs

- Highly potent, selective, orally bioavailable and brain penetrant
- 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

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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 commenced in Oct 2023
- Interim topline data expected 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
Corporate Overview
## Achieved & Anticipated Milestones

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Target Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submit IND for VG-3927, oral small molecule TREM2 agonist</td>
<td>Q4 2022</td>
</tr>
<tr>
<td>Report full data analysis for Phase 1 trial with VGL101 in healthy volunteers</td>
<td>Q3 2023</td>
</tr>
<tr>
<td>Begin Phase 1 dosing of VG-3927 in healthy volunteers</td>
<td>Oct 2023</td>
</tr>
<tr>
<td>Report VGL101 six-month interim data on six patients from Phase 2 proof-of-concept trial, IGNITE, in ALSP</td>
<td>Q4 2023</td>
</tr>
<tr>
<td>Report VG-3927 interim Phase 1 data readout in healthy volunteers</td>
<td>Mid-2024</td>
</tr>
</tbody>
</table>
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.

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THANK YOU