

Improving the lives of  
patients, caregivers and  
families through  
transformative treatments for  
neurodegenerative diseases

**(vigil)**<sup>TM</sup>  
NEURO

vigilant for **you**<sup>®</sup>

November 2024

# 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 iluzanebart (VGL101), VG-3927 and current or future product candidates, identify additional indications for our current product candidates, and to enable success in clinical development; beliefs about TREM2 agonism’s importance in ALSP & 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 and our ability to submit and obtain regulatory clearance for investigational new drug applications, initiate additional clinical trials, and submit new drug applications or biologics license applications; our ability to initiate and complete our current and expected future 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 and manufacturing 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; 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.

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.

# Overview

---

Our brain's immune system can be directed to treat neurodegeneration

We are the leaders in harnessing microglia, the brain's immune cells

We have two clinical TREM2 agonist programs in rare and common diseases

Our precision medicine strategy is central to our mission and success

# Experienced and Execution-Focused Management Team



**Ivana Magovčević-Liebisch**  
PhD, JD  
President & CEO



**David Gray**  
PhD  
Chief Science Officer



**Petra Kaufmann**  
MD, FAAN  
Chief Medical Officer



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

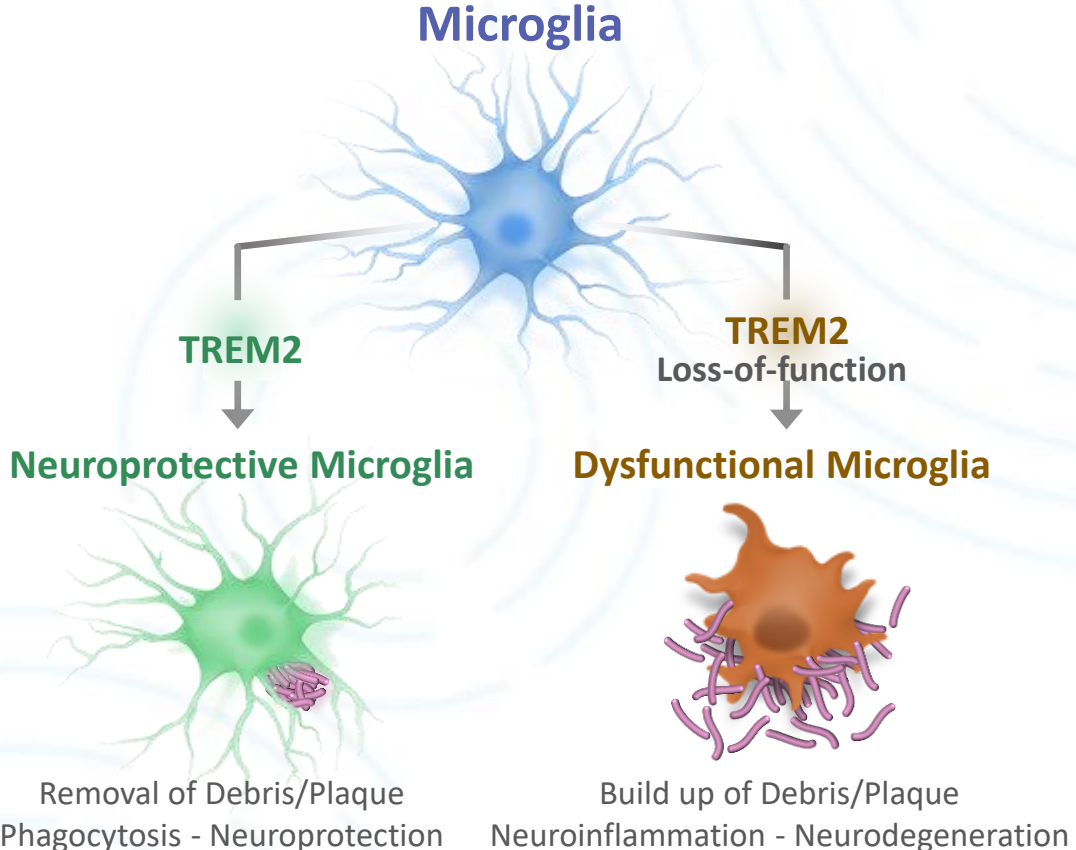
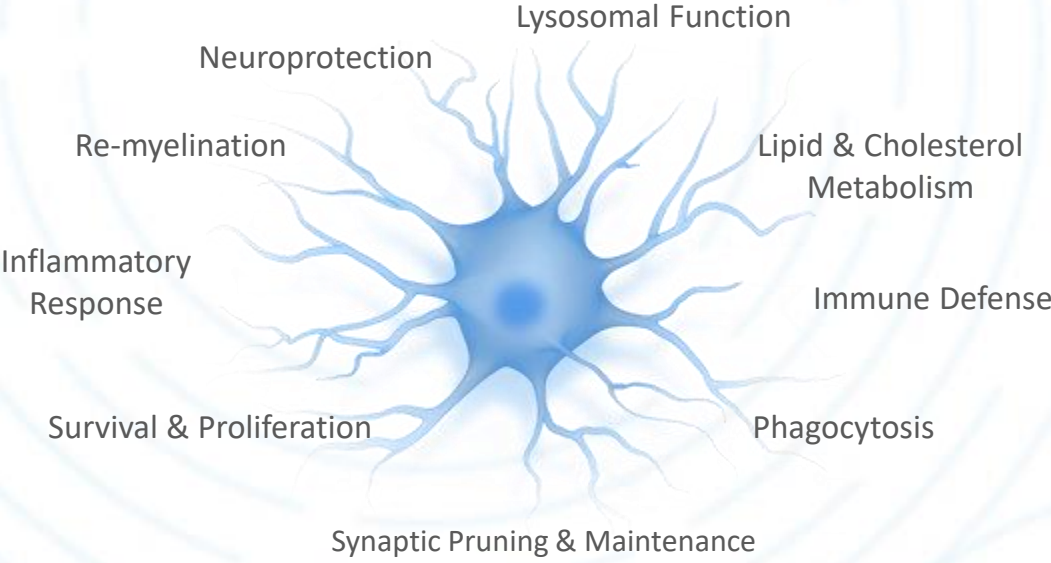


**Jennifer Ziolkowski**  
CPA  
Chief Financial Officer



# Microglia are Key to Brain's Immune System & Combatting Neuroinflammation

## Sentinel for CNS Health



**Microglial dysfunction is a driver of rare and common neurodegenerative diseases**

# Our Precision Medicine Strategy

Apply learnings from subpopulations with clear link to microglial dysfunction in additional indications



Rare  
Microgliopathy  
ALSP<sup>1</sup>



Data Driven  
Expansion into  
Other Rare  
Microgliopathies



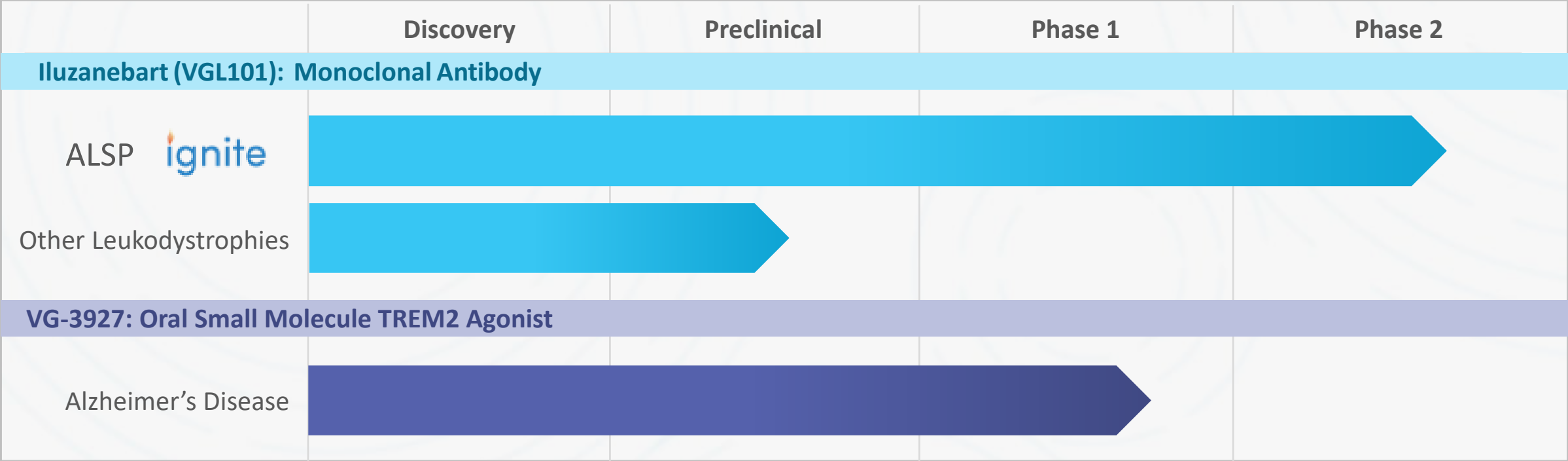
Genetic and Other  
Subpopulations in  
Common Indications  
(AD)



Expansion  
into Broader  
Populations and  
Additional  
Indications

1. ALSP: adult-onset leukoencephalopathy with axonal spheroids and pigmented glia

# Building a Robust Pipeline in Rare & Common Neurodegenerative Diseases



(vigil)<sup>TM</sup>







## Iluzanebart (VGL101)

*Iluzanebart (VGL101) is an investigational therapy and has not been reviewed or approved by any regulatory authority*



# Iluzanebart Program Overview

Product 	Opportunity 	Status 	Next Steps 
<p>Fully human monoclonal antibody targeting TREM2</p>	<p>Rare microgliopathies, such as ALSP with U.S. prevalence of &gt;19,000<sup>1</sup></p>	<p>Ongoing Phase 2 clinical trial in ALSP patients Ongoing natural history study</p>	<p>Pursue potential accelerated development pathway with FDA Report Phase 2 final analysis in 1H 25</p>



**First program to show promising clinical data on TREM2 agonism as potential therapeutic for treating neurodegenerative diseases**

1. Refer to footnote 1 on slide 18

# ALSP: Adult-Onset Leukoencephalopathy with Axonal Spheroids & Pigmented Glia

## Fatal, Rare, and Rapidly Progressive Neurodegenerative Disease

- Inherited, progressive neurological disease that affects every part of the brain
- Microglial insufficiency caused by autosomal dominant *CSF1R* gene mutations
- Average age of onset in mid-40s
- Rapid progression – incapacitated in 3-4 years; average time to death: 6-7 years
- Definitive diagnosis with genetic testing
- No approved treatment options available



Sources: Lakshmanan et al, *Neurol Genet* 2017; Hayer et al, *Neurology* 2018; Lynch et al. *J Neurol Neurosurg Psychiatry* 2016; Konno et al. *Neurol* 2018; Ahmed et al. *J Neurol Neurosurg; Psych* 2014; Papapetropoulos et al. *Front. Neurol.* 2022

# ILLUMINATE: First Natural History Study in ALSP

## Understanding ALSP and enabling regulatory success



**Observational study<sup>1</sup> of ~50 ALSP patients to model the course of the disease**

- Characterizing multiple MRI<sup>2</sup> and CSF<sup>3</sup> biomarkers
- Evaluating several clinical measures of disease progression



**Emerging relationship between biomarkers and disease progression**

- Volumetric MRI
- NfL<sup>4</sup>
- Soluble CSF1R<sup>5</sup>

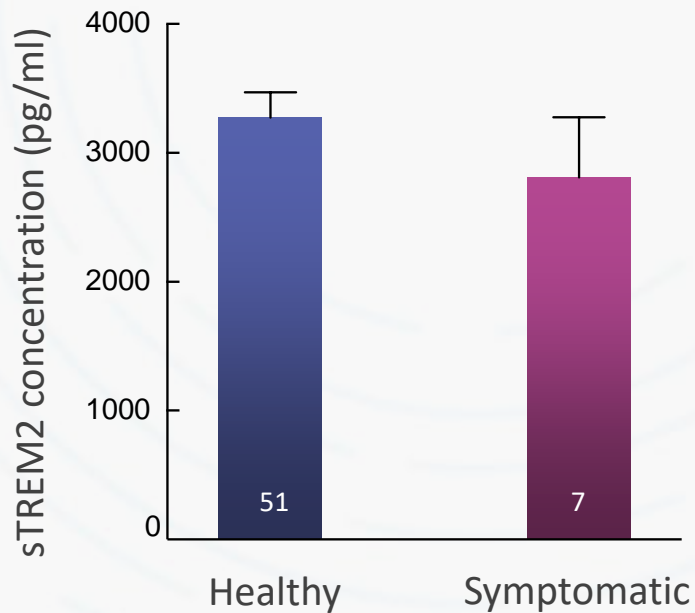


**Potential for accelerated development pathway**

1. ILLUMINATE: NCT05020743; 2. MRI: magnetic resonance imaging; 3. CSF: cerebrospinal fluid; 4. neurofilament light chain; 5. CSF1R: Colony stimulating factor 1 receptor

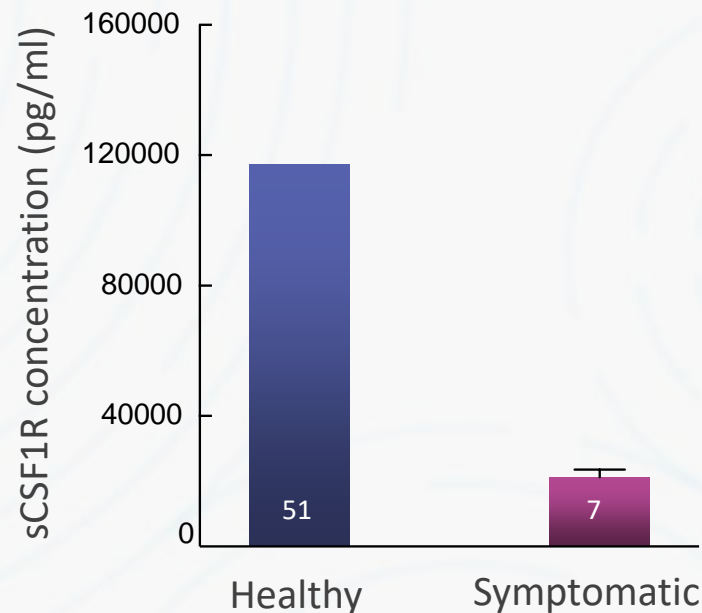
# Baseline Fluid Biomarker Levels Altered in ALSP

## Baseline Soluble TREM2 Levels



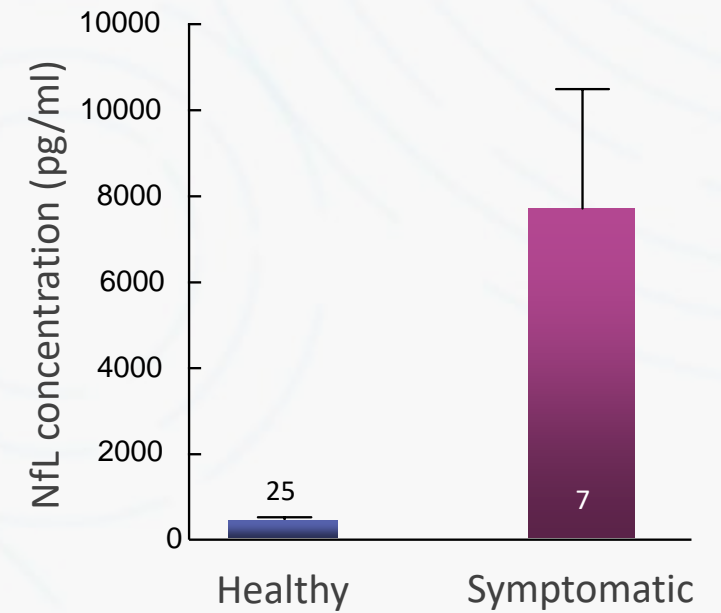
**sTREM2 levels similar across all populations**

## Baseline Soluble CSF1R Levels



**sCSF1R levels significantly reduced in symptomatic patients**

## Baseline NfL Levels



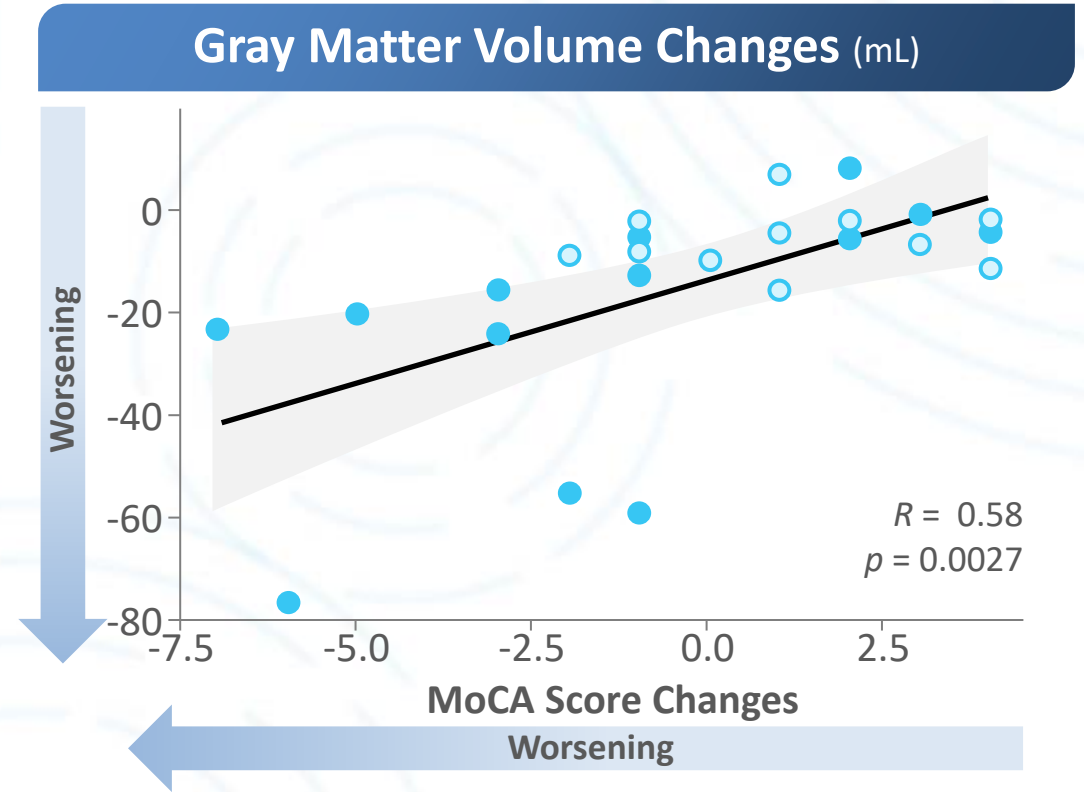
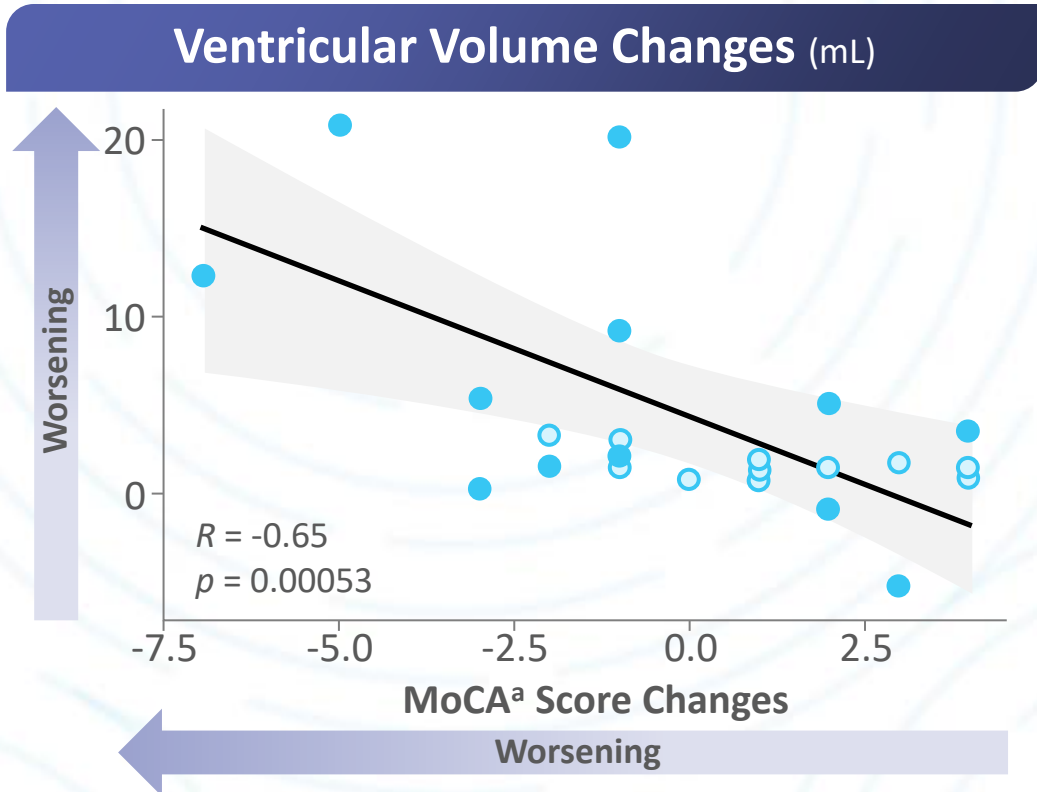
**NfL levels highly elevated in symptomatic patients**

All measurements taken in CSF

Healthy: healthy volunteers from Vigil's VGL101 Phase 1 trial; Symptomatic: subjects with CSF1R mutations and  $\geq 3$  ALSP-related clinical signs or symptoms in ILLUMINATE; CSF1R: Colony Stimulating Factor 1 Receptor; CSF: cerebrospinal fluid; NfL: neurofilament light chain

# MRI Biomarkers of Disease Progression Correlate with Cognitive Decline

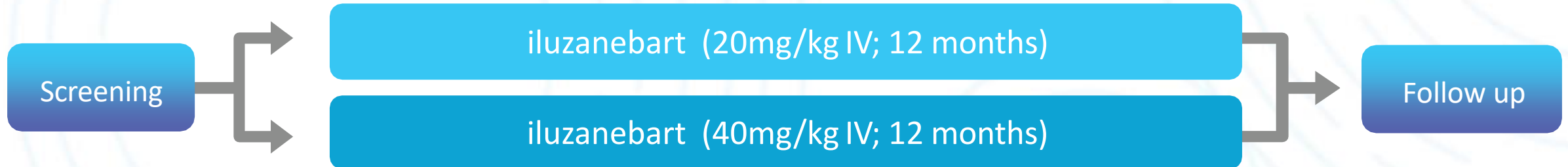
## Changes in Brain Volume Correlate with MoCA changes at 12 months



○ Prodromal ● Symptomatic

Interim analysis as of Sept. 23, 2023. Includes all study patients with 12 months of available follow-up on each measure. Plotted data are individual patient values for change from baseline to month 12. <sup>a</sup> Montreal Cognitive Assessment (MoCA) is a 30-point assessment on multiple cognitive domains, including executive function, memory, visuospatial ability, language, and attention.

# Evaluating Iluzanebart for ALSP in IGNITE Phase 2 Open-Label Trial



<b>Trial Population</b>	<ul style="list-style-type: none"> <li>Patients with symptomatic ALSP related to CSF1R gene mutation</li> </ul>
<b>Trial Design</b>	<ul style="list-style-type: none"> <li>Open-label, ~20 patients</li> </ul>
<b>Treatment Duration</b>	<ul style="list-style-type: none"> <li>12 months, IV administration once-monthly (optional long-term extension study)</li> </ul>
<b>Outcome Assessments</b>	<ul style="list-style-type: none"> <li>Safety and tolerability</li> <li>Volumetric MRI measurements of brain matter deterioration</li> <li>CSF biomarkers of target engagement and neurodegeneration, pharmacodynamics (NfL, sCSF1R, sTREM2, osteopontin)</li> </ul>

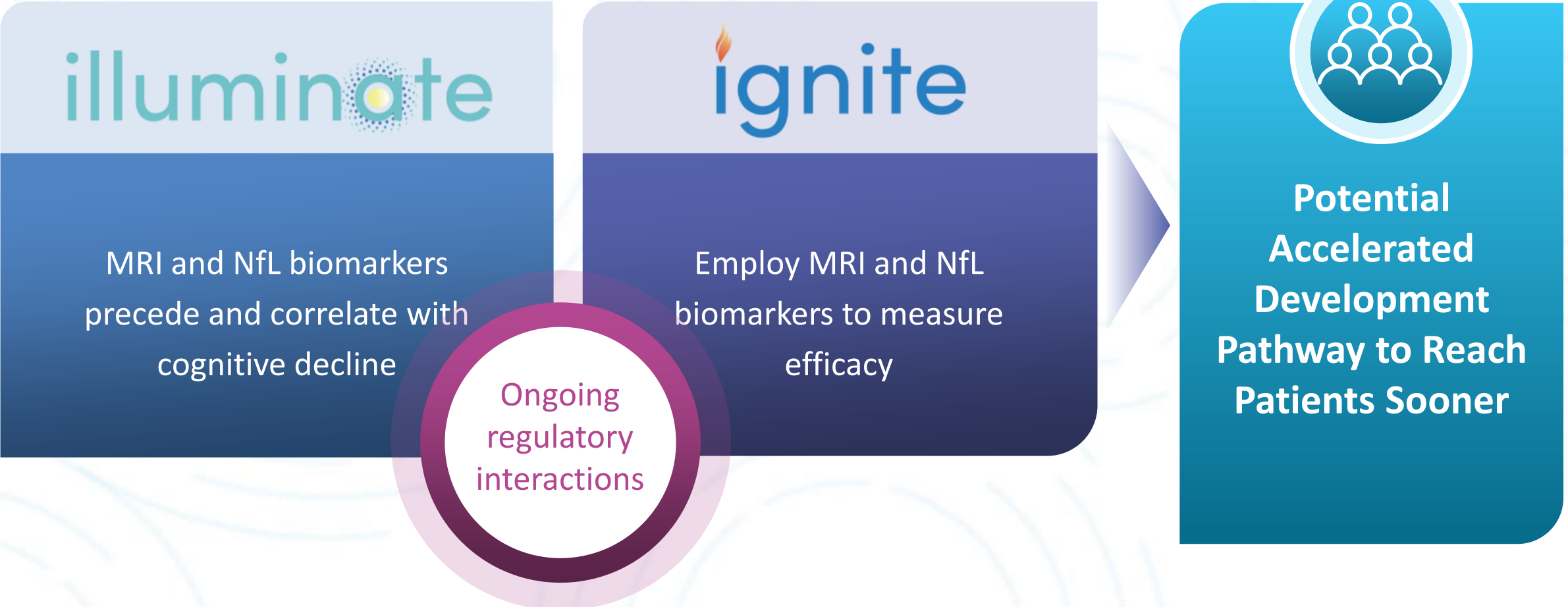
# IGNITE Phase 2 Interim Results

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

- Favorable safety and tolerability profile
- Durable effect on microglial activity biomarkers
- Changes on MRI and NfL measures in individual patients are directionally consistent with treatment effect
- Downstream pharmacological activity in the CNS, including increased CSF levels of sCSF1R

**Final Analysis: 1H 2025**  
12 months (all subjects: 20 mg/kg + 40 mg/kg)

# Utilizing Our Biomarker Strategy to Develop Iluzanebart





# Partnering with the Patient Community



- Valued member of the patient community
- Launched ALSPAware: a no-cost genetic testing and genetic counseling program for patients and healthcare providers in the U.S.
  - Developed with input from KOLs and patient advocacy groups
  - Designed to enable improved patient diagnosis of ALSP
- Established the world's first patient facing website, ALSPinfo.com



NORD®



Global Genes®  
Allies in Rare Disease



# ALSP: Significant Global Market Opportunity

Frequency of ALSP-causing CSF1R variants

**281 / 1 million<sup>1</sup>**

Extrapolates to **~94K** in U.S. & **~145K** in EU27 + UK<sup>2,3,4</sup>  
According to UK BioBank analysis

Diagnosing ALSP

**Up to ~16%**  
of Adult-onset Leukodystrophy patients have ALSP<sup>5,6</sup>

**ALSP is often misdiagnosed**  
including **~0.5%** of MS patients and **~0.3%** of AD patients<sup>7,8</sup>

Estimated ALSP Prevalence

**≥19,000**  
in U.S.

**≥29,000**  
in EU27 + U.K.

1. Based on frequency of pathogenic and likely pathogenic variants according to the American College of Medical Genetics criteria; Wade et al. *Neurol Gen* (manuscript accepted); 2. Assumes U.S. population of ~334M in Dec 2023 ([www.census.gov](http://www.census.gov)); 3. Assumes EU27 population of ~449M in 2023 (<http://ec.europa.eu/Eurostat>); 4. Assumes UK population of ~68M in 2024 ([www.worldpopulationreview.com/countries/united-kingdom-population](http://www.worldpopulationreview.com/countries/united-kingdom-population)); 5. Ishiguro et al. *Eu J Neurol* 2023; 6. Wade et al. *AAN* 2023; 7. Carlson et al. *ACTRIMS* 2021; 8. Sassi et al. *Neurol Aging* 2018;

(vigil)<sup>TM</sup>



## VG-3927: Next-Generation Differentiated AD Treatment

*VG-3927 is an investigational therapy  
and has not been reviewed or  
approved by any regulatory authority*

# TREM2 as Next-Generation Alzheimer's Disease Treatment



## TREM2 is an established causal link to human AD

- TREM2 mutations increase AD risk<sup>1</sup>
- High TREM2 is associated with slower AD progression<sup>2</sup>



## TREM2 is critical for microglial function

- TREM2 is a key pathology-sensing receptor on microglia<sup>3</sup>
- TREM2 signaling switches microglia into neuroprotective state<sup>4</sup>



## TREM2 AD therapeutic hypothesis<sup>5</sup>

- Direct microglia to engage their neuroprotective capability
- Can broadly counter multiple pathologies (ab, tau, etc)

**Microglia sense neuropathology and convert to neuroprotective state**

1. Guerreiro, et al. *N Engl J Med* 2013; Jonsson, et al. *N Engl J Med* 2013 2. Pereira et al. *Nat Aging* 2022; Ewers et al. *EMBO Mol Med.* 2020 3. Wang et al. *Cell* 2015 4. Keren-Shaul et al. *Cell* 2017 5. Parhizkar et al. *Nat Neurosci.* 2019; Yuan et al. *Neuron* 2016

# VG-3927: First Clinical-Stage Small Molecule TREM2 Agonist & PAM

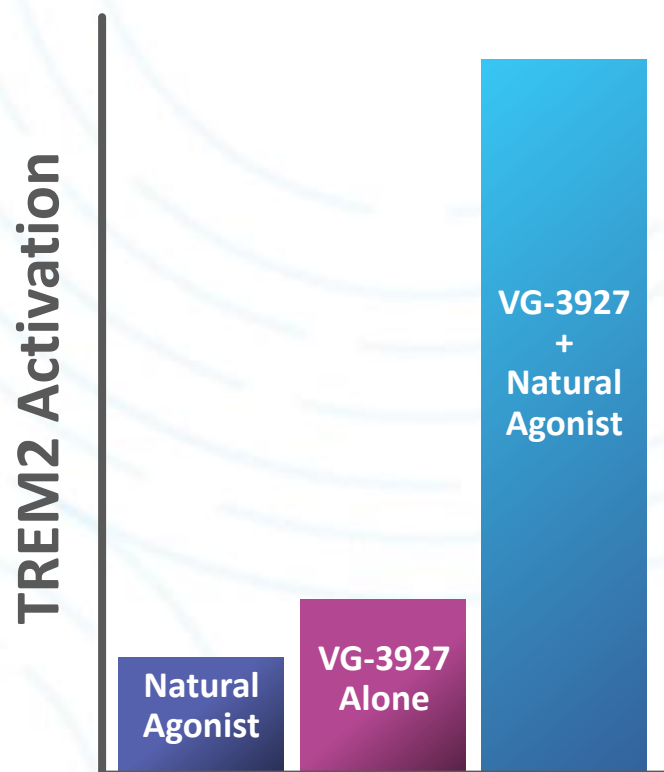
High-quality & CNS penetrant with potential to become next-generation AD treatment



# VG-3927: Potent Agonist & PAM that Synergizes with Natural TREM2 Ligands

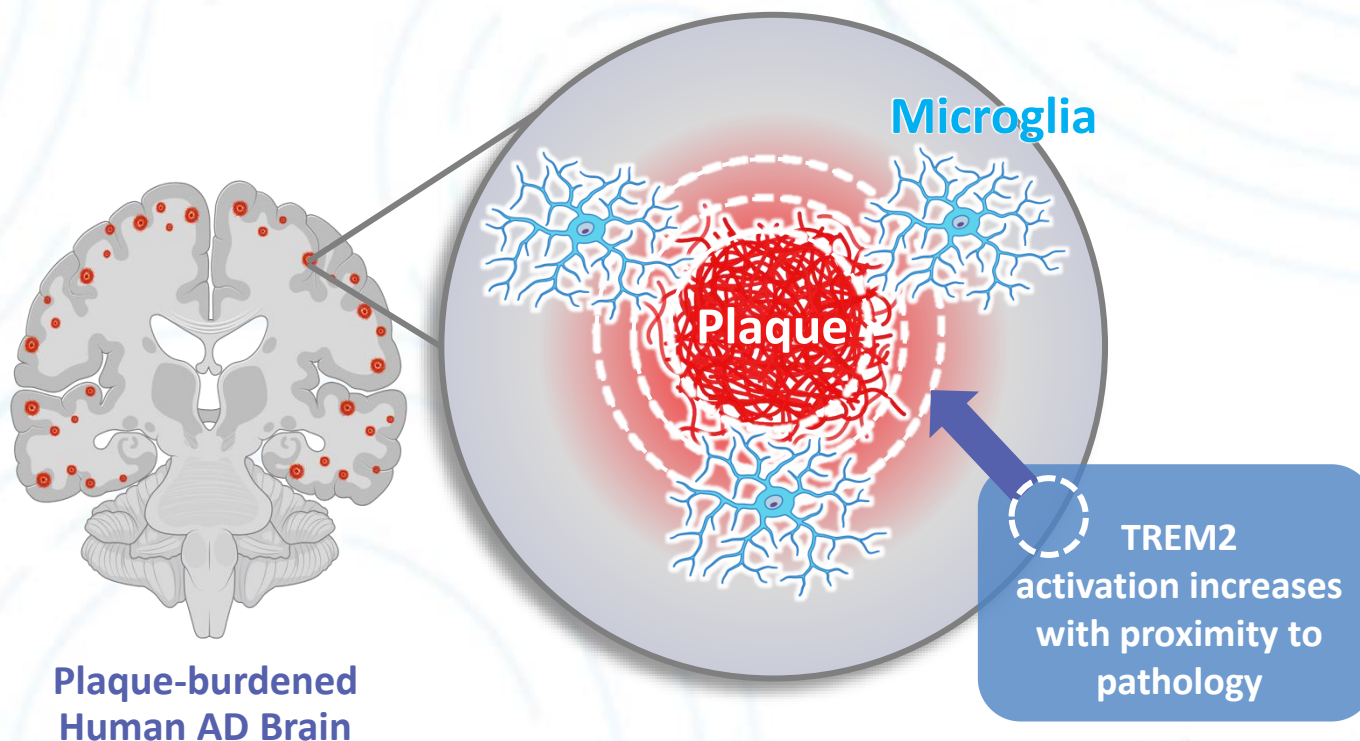
## Enhancing TREM2 function where it matters most

Potentiation of TREM2 Activation

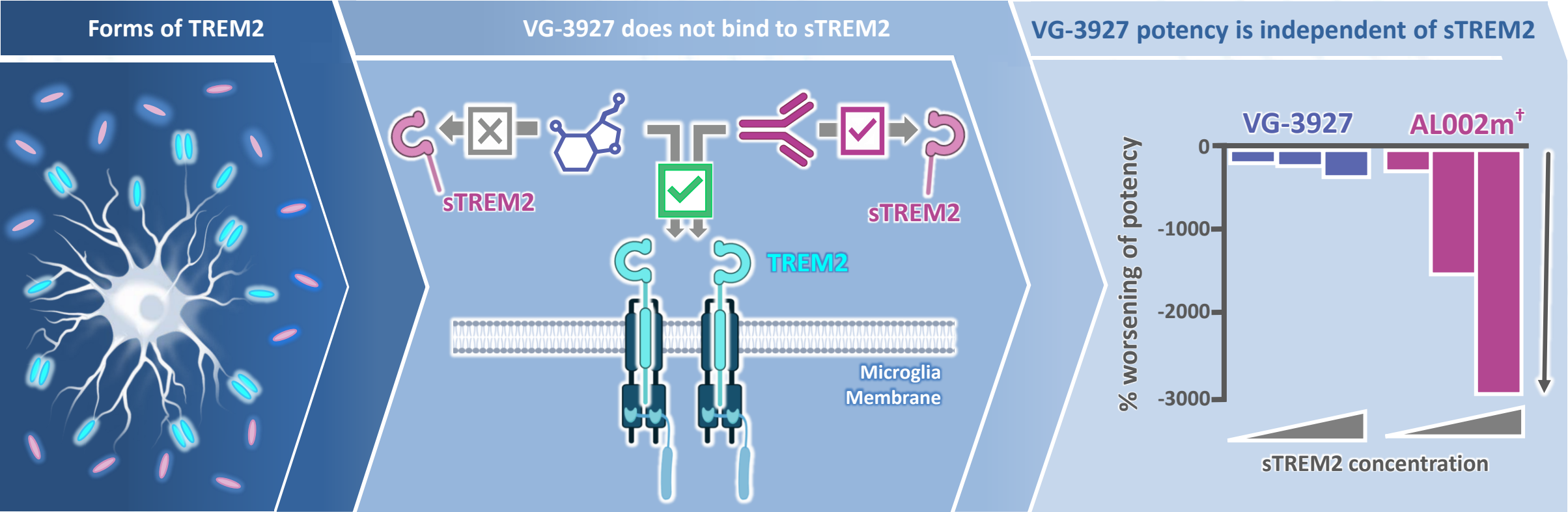


Based on internal preclinical data




Potential for enhanced efficacy directly at site of neurotoxicity



# Lack of sTREM2 Binding Differentiates VG-3927 from AL002m<sup>†</sup>



 Soluble TREM2 (sTREM2)  
 TREM2

 On-target microglia agonism  
 Confirmed off-target interaction  
 No interaction

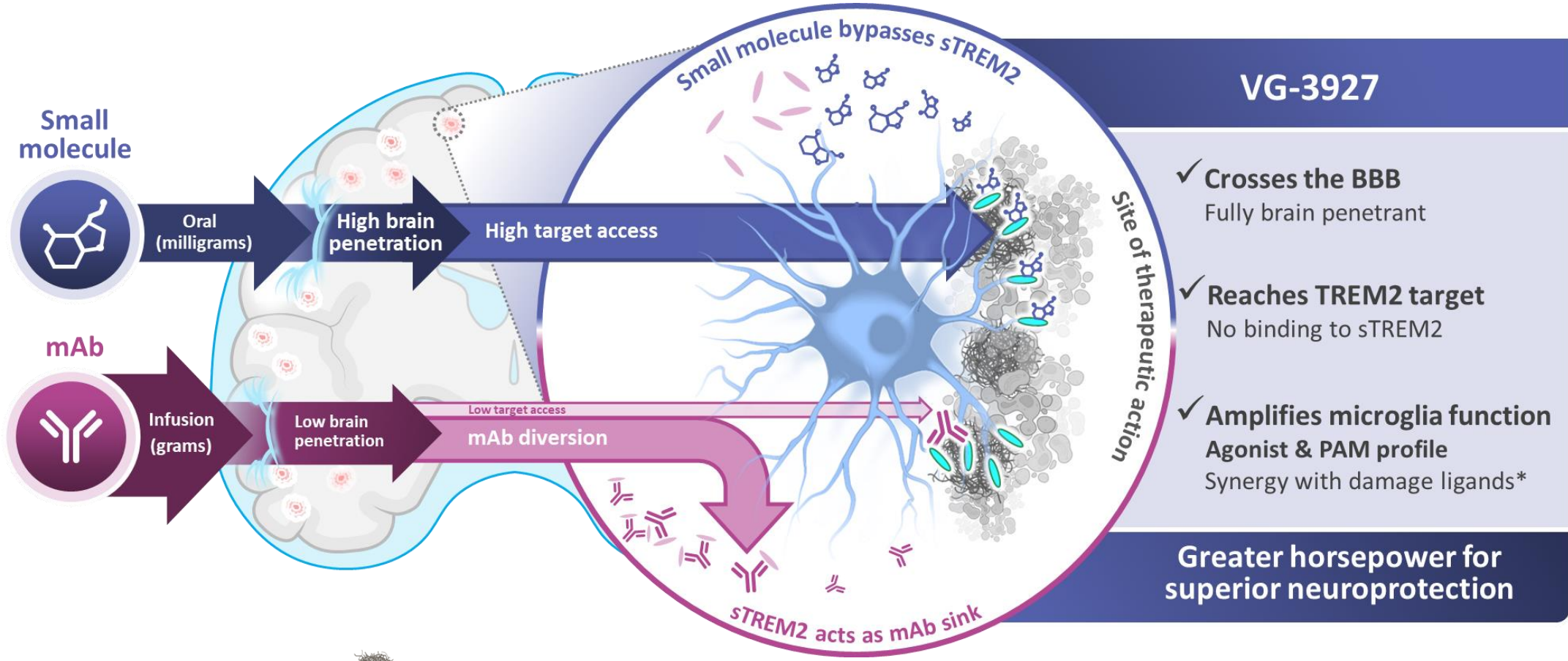
Right: To measure the signaling potency (EC<sub>50</sub>) of VG-3927 and AL002m in human monocytic THP1 cells, phosphorylation of DAP12 was measured across a range of TREM2 agonist and soluble TREM2 extracellular domain (sTREM2) concentrations. The graph represents the EC<sub>50</sub> increase (worsening of potency) for each TREM2 agonist.

23 <sup>†</sup>AL002m is an internally synthesized mAb that, based on Alector's publicly available information, we developed to be structurally equivalent to AL002



# VG-3927: Next-Generation Small Molecule AD Therapy

## Superior Neuroprotection v. Monoclonal Antibodies (mAbs)



- Soluble TREM2 (sTREM2)
- TREM2
- Plaques
- Cellular damage

BBB = blood-brain barrier  
PAM = positive allosteric modulator  
\* E.g. amyloid-β, cell debris, ApoE





# Small Molecule TREM2 Preclinical Functional Activity On-Par with Lecanemab But Not Matched by AL002m<sup>†</sup>

*In vivo* functional assay comparing ability to increase phagocytosis of AB plaque



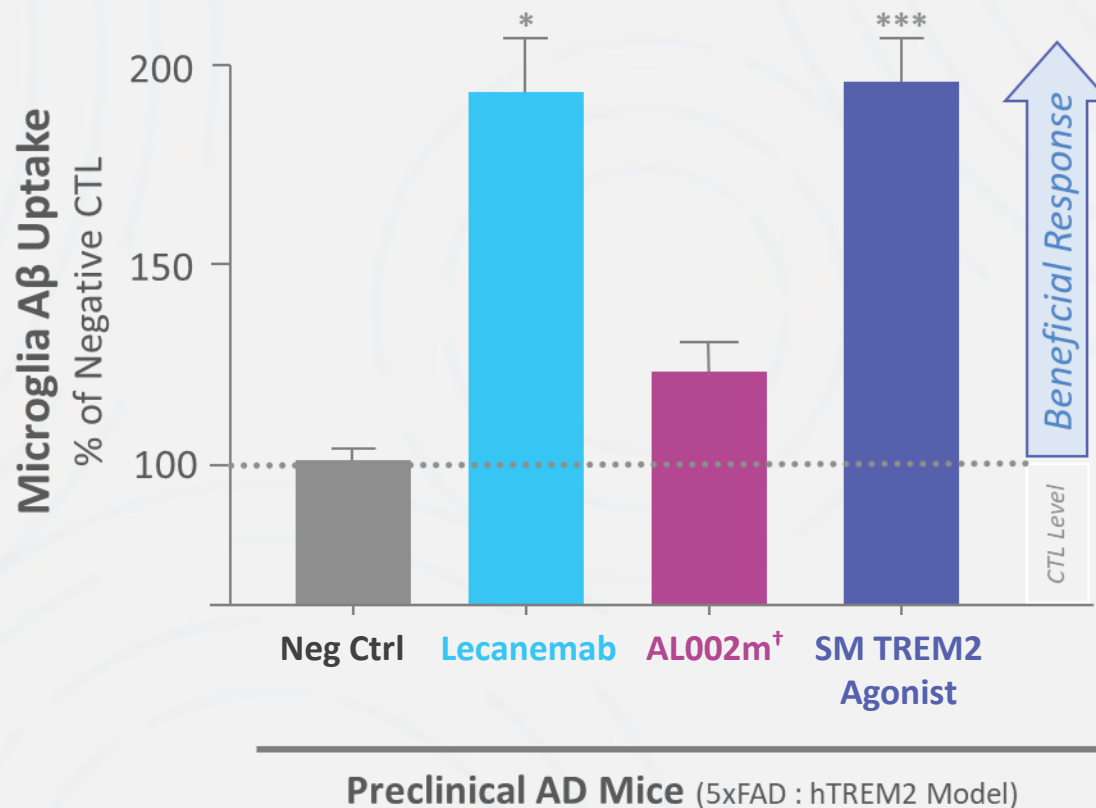
**Vigil**  
SM TREM2 Agonist  
*Oral delivery*



**Lecanemab**  
Anti-A $\beta$   
*IP injection*



**AL002m<sup>†</sup>**  
Anti-TREM2  
*IP injection*



<sup>†</sup>AL002m is an internally synthesized mAb that, based on Alector's publicly available information, we developed to be structurally equivalent to AL002

Right: Engulfment of pathological A $\beta$  aggregates in aged plaque-bearing humanized TREM2 mice (5xFAD:hTREM2) was measured via flow cytometry. Proportions of A $\beta$ <sup>+</sup> microglia (via methoxy-X04 labeling) were analyzed and graphed relative to negative control (Neg Ctrl, set to 100%). Differentiated TREM2 agonist responses were observed between oral dosing of a TREM2 small molecule agonist (30mg/kg po) vs systemic injection of AL002m (30mg/kg ip). The TREM2 small molecule functional increase in microglia A $\beta$  uptake was indistinguishable from a high dose of the therapeutically validated reference lecanemab (150mg/kg ip). \* indicates  $p < 0.05$ , \*\*\* indicates  $p < 0.001$  compared to Neg Ctrl.

# VG-3927: Greater Horsepower with Differentiation on ARIA

---



- ✓ Low oral dose (milligrams v. grams); lower systemic exposure
- ✓ No Fc region; ARIA has only been observed in mAbs with Fc
- ✓ Shorter half-life; flexibility to mitigate ARIA if observed

# VG-3927 Phase 1 Trial: Safety, Tolerability, and PK/PD Interim Data Support Continued Development in AD



## Ongoing Phase 1 Trial

- Double-blind placebo-controlled SAD/MAD study exploring safety, tolerability, PK, and PD\*
- 80 healthy volunteers enrolled, 60 received VG-3927 across multiple SAD and MAD cohorts (as of Jun 2024)
- Initiated single-dose biomarker cohort of AD patients, including some participants who carry TREM2 or other disease-related variants



## Interim Analysis

- Demonstrated predictable PK supportive of once-daily dosing
- Significant and dose-related reduction in sTREM2 levels observed demonstrating clinical proof-of-target engagement and an increase in osteopontin/secreted phosphoprotein 1 (SPP1) after repeat dosing
- All adverse events (AEs) were mild/moderate, and all resolved without intervention; no serious AEs reported\*\*

## Upcoming Milestone

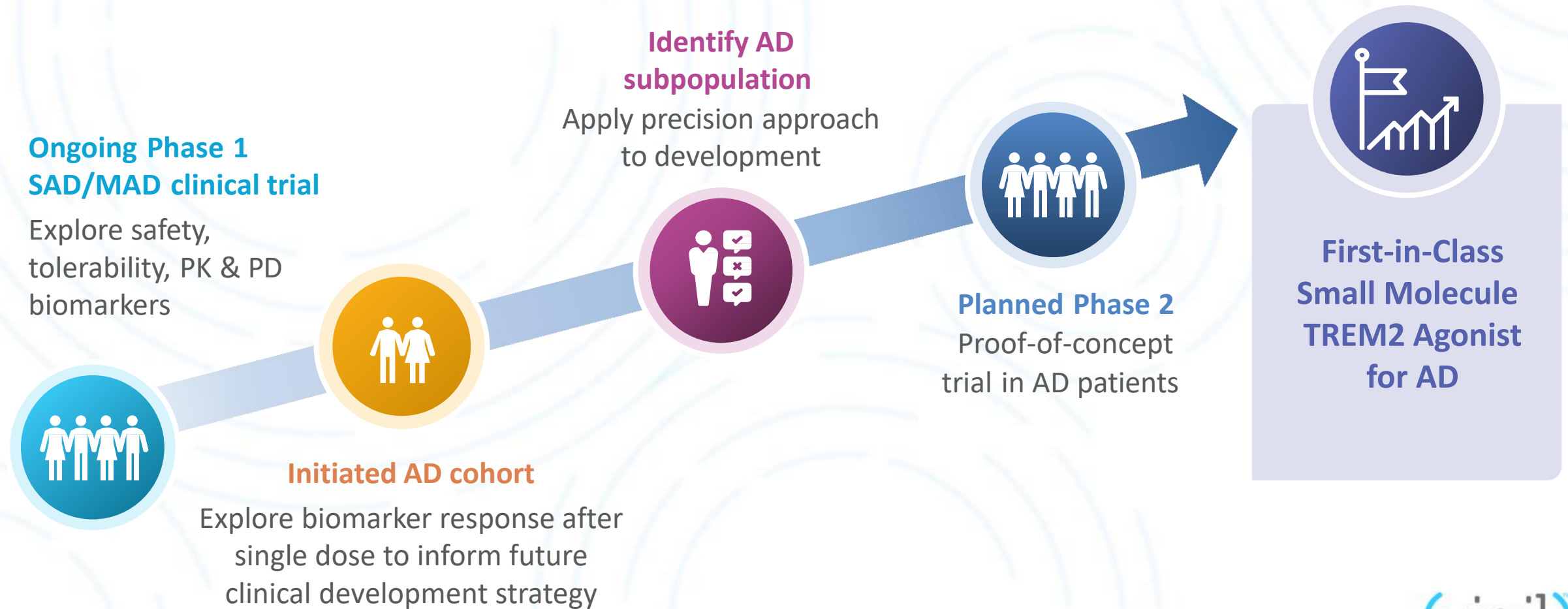
Complete Phase 1 data, including data from AD cohort, planned for Q1'2025

\*Pharmacokinetics and pharmacodynamics

\*\*As of Interim Analysis data cut from July 2024

# VG-3927: Precision Medicine Development Strategy for AD

Leveraging precision-based approach to increase probability of success in AD drug development



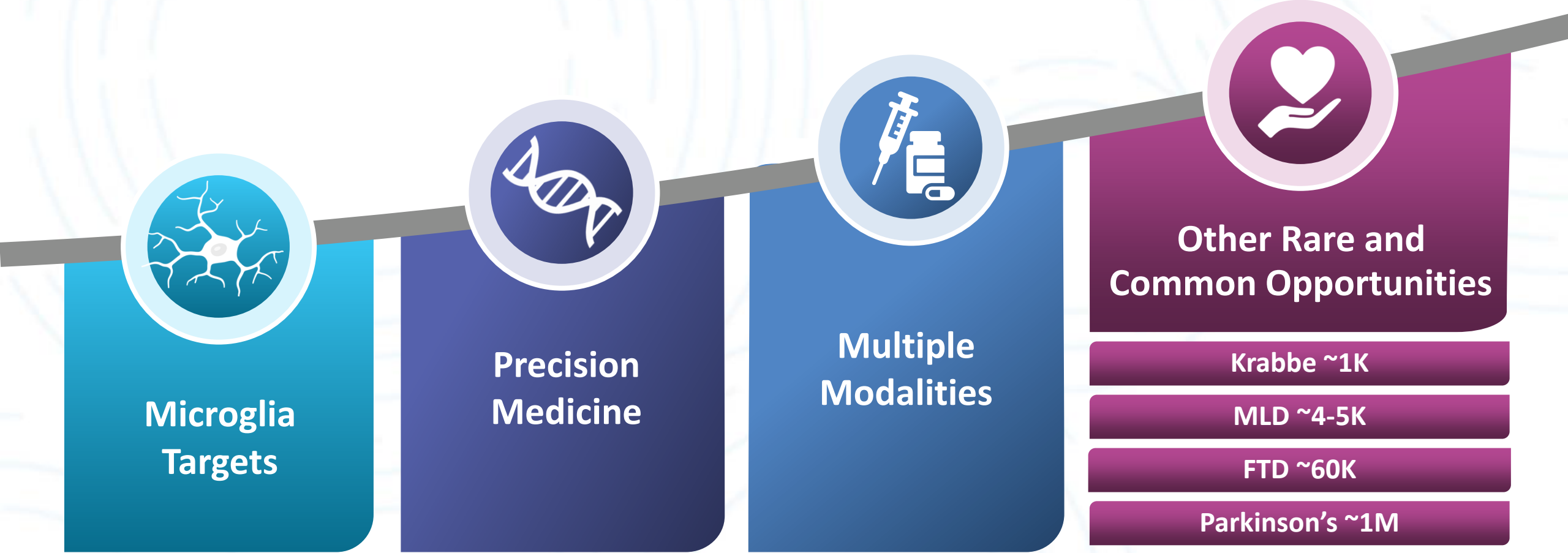
(vigil)<sup>TM</sup>



Looking Ahead

# Our Precision Medicine Strategy

Apply learnings from subpopulations with clear link to microglial dysfunction in additional indications



# Recent Accomplishments & Anticipated Milestones



## Iluzanebart (VGL101)

- ✓ Pursue potential accelerated development pathway with FDA
  - Phase 2 final analysis expected in 1H 2025



## VG-3927

- ✓ Reported Phase 1 interim HV data in July 2024
  - Complete Phase 1 data, including AD cohort, planned for Q1 2025
  - Multiple PoC presentations and abstracts at medical conferences

# Overview

---

Our brain's immune system can be directed to treat neurodegeneration

We are the leaders in harnessing microglia, the brain's immune cells

We have two clinical TREM2 agonist programs in rare and common diseases

Our precision medicine strategy is central to our mission and success



Thank You



vigilant for **you**®