A Phase 1, First-in-human, Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Intravenous Dose Study of a Novel TREM2 Agonist (VGL101) in Healthy Volunteers (HVs)

Spyros Papapetropoulos, Andreas Meier, Ryan O’Mara, Andrew Marsh, Kelly Neelon, Raj Rajagovindan, Evan Thackaberry, David Stiles

Vigil Neuroscience, Inc., Watertown, Massachusetts, USA

AAN Annual Meeting 2023 | Boston, MA USA | 24 April 2023

Disclosure(s): Andreas Meier is an employee of Vigil Neuroscience
Study conducted and funded by Vigil Neuroscience
VGL101: Fully Human mAb TREM2 Agonist

VGL101 is a fully human IgG1 monoclonal antibody designed to activate triggering receptor expressed on myeloid cells 2 (TREM2), a key microglial receptor protein

- Binds to the extracellular Ig-like domain of TREM2 with high binding affinity
- Activates intracellular kinase, Spleen Tyrosine Kinase (SyK), downstream of receptor binding with nanomolar potency
- Being developed for the treatment of rare genetically defined neurodegenerative diseases caused by microglial deficiency (microgliopathies)
  - Currently in a Phase 2 proof-of-concept trial for the treatment of Adult-onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP) – a primary microgliopathy
- Presenting interim Phase 1 data on safety, tolerability, PK and PD for VGL101 in healthy volunteers
ALSP Overview

**Adult-onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP)**

- **Rare autosomal dominant neurodegenerative disorder caused by mutation in the **CSF1R** gene**
  - Primarily causing degeneration of brain white matter
  - Previously known as pigmentary orthochromatic leukodystrophy (POLD) and hereditary diffuse leukoencephalopathy with spheroids (HDLS)
    > ALSP now preferred term as it recognizes the hallmark pathophysiology of both the axonal spheroids (swelling) and abnormal microglia
  - Accounts for ~10% of adult onset leukodystrophy

- **Adult-onset with rapid disease progression**
  - Heterogeneous phenotype including cognitive, motor and neuropsychiatric symptoms – prone to mis-diagnosis
  - Incapacitation 3-4 years from disease onset
  - Average time to death: 6-7 years

- **No approved therapies**
CSF1R & TREM2 Convergence Supporting VGL101 Utility in ALSP

TREM2 Agonism Rescues CSF1R Deficiency

- **CSF1R** is a trophic receptor for microglia
  - Regulates downstream processes similar to TREM2
  - ALSP is caused by **CSF1R** deficiency
  - **CSF1R** and TREM2 pathways converge on SYK protein kinase
  - Convergence of pathways provides the biological rationale for compensating **CSF1R** deficiency with TREM2 agonism

- **VGL101** mediated rescue of **CSF1R** deficiency
  - Pretreatment of iPSC-derived microglia induces **CSF1R** mediated decreased microglial viability
  - Addition of VGL101 restored viability back to untreated levels

iPSC-derived microglia grown in media treated with control (Vehicle), CSF1R inhibitor alone (PLX5622), CSF1R inhibitor plus immunoglobulin G control (PLX5622+IgG), or CSF1R inhibitor plus VGL101 (PLX5622+VGL101) were measured for microglia viability compared to Vehicle (Microglia Viability (% of Vehicle)). ****: p<0.0001
VGL101 Clinical Development for ALSP

**Natural History Study**
- 24-mo observational, multicenter study in ALSP patients with confirmed CSF1R mutations
- Characterize biomarkers & clinical measures of disease progression in ALSP
- Possibility for contemporaneous external comparator arm

**Phase 1 SAD & MAD in HVs**
- Phase 1 SAD & MAD trial in healthy volunteers Characterize safety, tolerability, PK and PD of VGL101
- Inform dose selection for Phase 2 proof-of-concept trial in ALSP patients

**Phase 2 in ALSP Pts**
- Phase 2 proof-of-concept in ALSP patients with confirmed CSF1R mutations
- Characterize safety, tolerability, PK, effects on MRI, fluid biomarkers and clinical outcome measures of VGL101

NHS (illuminate), ClinicalTrials.gov Identifier: NCT05020743
Phase 1, ClinicalTrials.gov Identifier: NCT05677659
**VGL101 Phase 1 Trial**

**Study design & status as of Oct 7, 2022**

- **Cohorts with data included in interim analysis**

- **Randomized, double-blind, placebo-controlled, SAD & MAD IV-dosing trial of a novel TREM2 agonist (VGL101) to evaluate safety, tolerability, PK, PD of VGL101 in healthy volunteers**

- **ClinicalTrials.gov Identifier: NCT05677659**

*40mg/kg cohort was only included for safety and was not included in the PK or PD for this readout*
Methods and Demographics

Primary Objectives

- To determine the safety and tolerability of single- and multiple-ascending intravenous (IV) doses of VGL101 in healthy adult participants
  - Part A is a randomized, double-blind, single-ascending dose (SAD) study in healthy adult participants.
  - Part B is a randomized, double-blind, multiple-ascending dose (MAD) study in healthy adult participants
  - Healthy volunteers, males and females between 18 to 55 years of age

Secondary Objectives

- Characterize the single-dose and the multiple dose serum pharmacokinetics (PK) and pharmacodynamics (PD) of VGL101 IV in healthy adult participants
- Assess immunogenicity of single- and multiple-ascending IV doses of VGL101 in healthy adult participants
- Evaluate PK of VGL101 in cerebral spinal fluid (CSF) after single doses and multiple doses
  - Additional open-label SAD and MAD cohorts for the collection of CSF in healthy adult participants

Demographics

- 82 healthy volunteers have been dosed in the ongoing first-in-human Phase 1 SAD/MAD trial
  - 68 participants received VGL101
  - 14 participants received placebo

Data as of 07 October 2022
VGL101 Phase 1 Preliminary Safety Data

Favorable safety & tolerability profile at doses up to 40 mg/kg (SAD) & 20 mg/kg (MAD)

- In blinded preliminary safety review of completed cohorts, VGL101 was generally safe and well tolerated
  - Across cohorts AEs reported as at least possibly related to IP
    - were mild except one moderate AE of dysequilibrium
    - AEs reported in ≥2 subjects included headache, throat tightness, elevated mood, and pruritus
  - AEs resolved without intervention
  - No report of serious adverse events
  - No clinically meaningful abnormalities in
    - Vital signs
    - Electrocardiograms
    - Laboratory parameters
  - Protocol-specified stopping criteria were not met

(Data as of 07 October 2022)

IP, investigational product; SAE, serious adverse event; AE, adverse event
VGL101 Phase 1 PK Data: SAD and MAD

Well-characterized linear & dose proportional PK after single dose & predictable PK with repeat dosing

- ~27 days half-life supporting monthly dosing interval
- Brain penetration and achieving projected CSF therapeutic exposures (0.1 – 0.2% CSF-to-serum ratio)

Data as of 07 October 2022

*Data on 30 mg/kg dose available for up to 28 days post-dose; terminal data not available as of 07 October 2022
VGL101 Phase 1 PD Data: Absolute Changes in CSF sTREM2

Dose dependent, robust and durable sTREM2 decreases, suggesting proof of target engagement

- Soluble TREM2 (sTREM2) is the most proximal biomarker of TREM2 receptor engagement

Single Ascending Doses (n=18)

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg/kg SAD</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg SAD</td>
<td></td>
</tr>
<tr>
<td>20 mg/kg SAD</td>
<td></td>
</tr>
</tbody>
</table>

Change from Baseline pg/ml (±SEM) in sTREM2

-2,100 -1,200 -600 -300 0 600 900 1,200

Days Following Single Dose

- Baseline
- 2
- 14

20 mg/kg Multiple Dose (3 doses at 28-day intervals; n=6)

Change from Baseline pg/ml (±SEM) in sTREM2

- Baseline
- 2
- Days Following 3rd/Final Dose
- 28

SEM: Standard Error of Mean; Baseline: Pre-dose Levels; *p-value < 0.05

Data as of 07 October 2022
VGL101 Phase 1 PD Data: Absolute Changes in CSF sCSF1R

Durable sCSF1R increases, suggesting proof of pharmacology

- Soluble CSF1R (sCSF1R) is a distal biomarker of microglial activation

<table>
<thead>
<tr>
<th>Single Ascending Doses (n=18)</th>
<th>20 mg/kg Multiple Dose (3 doses at 28-day intervals; n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change from Baseline pg/ml ±SEM in sCSF1R</strong></td>
<td><strong>Change from Baseline pg/ml ±SEM in sCSF1R</strong></td>
</tr>
<tr>
<td>Days Following Single Dose</td>
<td>Days Following 3rd/Final Dose</td>
</tr>
<tr>
<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>28</td>
</tr>
</tbody>
</table>

**Dose Group**
- 3 mg/kg SAD; n=6
- 10 mg/kg SAD; n=6
- 20 mg/kg SAD; n=6

SEM: Standard Error of Mean; Baseline: Pre-dose Levels; *p-value < 0.05
VGL101 Phase 1 Trial

Conclusions

- **Generally safe and well-tolerated at doses up to 40 mg/kg SAD and 20 mg/kg MAD**
  - Safety & tolerability to date support further dose escalation and Phase 2 initiation in patients with ALSP
- **PK shows linear, predictable characteristics across doses and a half-life that support monthly dosing**
- **Demonstrated proof of target engagement and pharmacological activity based on dose dependent, robust and durable reductions in sTREM2 following repeat dosing**
  - Showed increases in sCSF1R levels which were durable following repeat dosing
  - 1st antibody to report durability of TREM2 engagement in a clinical setting
- **Data supports continued development of VGL101**
  - Safety, tolerability, PK/PD data from Phase 1 trial support 20 mg/kg as a pharmacologically active dose
  - Phase 1 healthy volunteer trial exploring higher doses of VGL101 ongoing
  - Phase 2 proof-of-concept trial in ALSP patients ongoing

Data as of 07 October 2022
Thank You