Today's Agenda

4:30 - 4:35 PM (5 min)
Opening Remarks and Corporate Overview
Ivana Magovčević-Liebisch, PhD, JD
President & Chief Executive Officer, Vigil Neuroscience, Inc.

4:35 - 5:05 PM (30 min)
Presentation of Iluzanebart (VGL101) Interim Data from Phase 2 IGNITE Study in ALSP & Ongoing ILLUMINATE Natural History Study
David Gray, PhD
Chief Science Officer, Vigil Neuroscience, Inc.

5:05 - 5:15 PM (10 min)
ALSP Disease Overview & Perspective on Interim Results
David S. Lynch, MD, PhD
Consultant Neurologist, National Hospital for Neurology & Neurosurgery, Queen Square & UCL Institute of Neurology, London
Clinical Lead, Inherited White Matter Disorders Highly Specialist Service, NHS England

5:15 - 5:30 PM (15 min)
Closing Remarks and Q&A Session

Reminders

- Webinar scheduled to end at 5:30pm 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"

(vigil)

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 including demonstrating favorable safety and tolerability profiles and achieving therapeutic benefits for patients; beliefs about TREM2 agonism's importance in ALSP and 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 design and 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 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.

Corporate Overview
Ivana Magovčević-Liebisch, PhD, JD
Chief Executive Officer
Vigil Neuroscience, Inc.

Overall Summary

IGNITE & ILLUMINATE interim analyses provide further support for continued development of iluzanebart (VGL101) as potential ALSP therapy

- ILLUMINATE NHS continues to provide important insights and a rich dataset on biomarkers and clinical measures of disease progression in ALSP
  - Totality of data, including longitudinal progression observed on selected MRI measures and clinical endpoints, support engagement with regulatory authorities

- IGNITE Phase 2 interim analysis provides further support on safety and PK/PD profiles, and clinical strategy for VGL101 in ALSP
  - Favorable safety and tolerability data
  - CNS target engagement and downstream pharmacological activity consistent with VGL101 Phase 1 data for 20 mg/kg; increases in sCSF1R CSF levels, a key biomarker of ALSP disease pathology
  - Directionally supportive changes at 6 months for individual subjects on MRI and NfL biomarkers of disease progression

- Quality and consistency of data support continuation of IGNITE and ILLUMINATE without modification

- Vigil plans to engage with FDA to initiate discussions regarding potential accelerated development pathway for VGL101

- Data on all patients in 20 mg/kg and 40 mg/kg cohorts at 6 months expected in Q3 2024

Vigil Neuroscience

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
- First company to show clinical data on TREM2 agonism as potential therapeutic approach in patients with neurodegenerative disease
- >60 highly dedicated team members

Featured Key Opinion Leader (KOL)

David S. Lynch, MD, PhD
Consultant Neurologist, National Hospital for Neurology & Neurosurgery, Queen Square & UCL Institute of Neurology, London
Clinical Lead, Adult Inherited White Matter Disorders Highly Specialist Service, NHS England
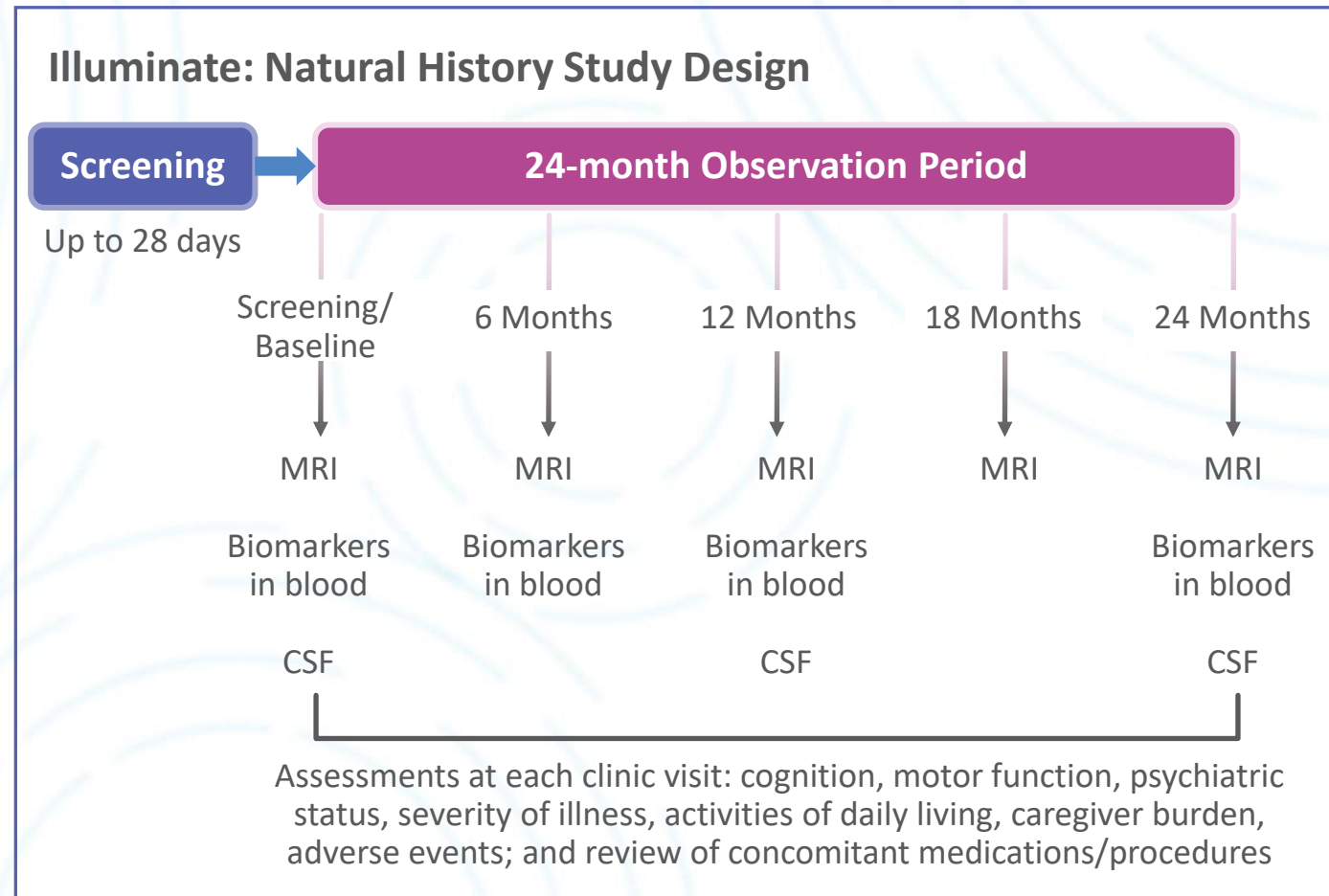
ILLUMINATE Natural History Study
Updated Interim Analysis

ILLUMINATE continues to provide important insights and a rich dataset on biomarkers and clinical measures of disease progression in ALSP over 12 months

- sCSF1R and NfL levels are remarkably altered in ALSP, which are key biomarkers of disease pathology

- Totality of data, including longitudinal progression observed on selected MRI measures and clinical endpoints, support engagement with regulatory authorities

- Quality and consistency of data in this interim analysis support chosen biomarkers for pharmacological activity

- MRI measurements on ventricular volume and gray matter volume are emerging as key indicators of disease progression
  - White matter lesion volume and corpus callosum MRI measurements are variable and less sensitive over 6 months

- Interim MoCA and CBFS data support their use as clinical endpoints in ALSP at 12 months

sCSF1R: soluble Colony Stimulating Factor 1 Receptor; NfL: neurofilament light chain; MRI: magnetic resonance imaging; MoCA: Montreal Cognitive Assessment, CBFS: Cortical Basal Ganglia Functional Scale

First ALSP Natural History Study: Design

ILLUMINATE – setting up for clinical success in ALSP

- **First ever multicenter[†], natural history study of ALSP patients with confirmed *CSF1R* gene mutation**

- **Sample size:** ~50 subjects (globally)

- **Objectives:**
  - Characterize biomarkers & clinical measures of disease progression in ALSP
  - Possibility for external comparator arm for interventional studies
  - Observation period: 24 months

- **Key assessments:**
  - MRI: Baseline & every 6 months
  - CSF biomarkers: Baseline, 12- & 24-months
  - Clinical assessments: Baseline, every 6 months

Illuminate: Natural History Study Design

Screening	24-month Observation Period

Up to 28 days

Screening/Baseline — 6 Months — 12 Months — 18 Months — 24 Months

MRI | MRI | MRI | MRI | MRI

Biomarkers in blood | Biomarkers in blood | Biomarkers in blood | | Biomarkers in blood

CSF | | CSF | | CSF

Assessments at each clinic visit: cognition, motor function, psychiatric status, severity of illness, activities of daily living, caregiver burden, adverse events; and review of concomitant medications/procedures

Key Eligibility Criteria

- ≥18 years of age with evidence of *CSF1R* gene mutation

- Symptomatic (Definitive) ALSP
  - Subjects who fulfill both of the following criteria:
    - More than two findings of clinical signs or symptoms in any of the following categories:
      - Cognitive impairment or psychiatric problem
      - Pyramidal signs on neurological examination
      - Extrapyramidal signs, such as rigidity, tremor, abnormal gait, or bradykinesia
      - Epilepsy
    - MRI findings consistent with ALSP: specifically, bilateral cerebral white matter lesions

- Prodromal ALSP
  - MRI findings consistent with ALSP (bilateral cerebral white matter lesions)
  - Prodromal subjects may have none or up to 2 ALSP-related clinical signs or symptoms

Natural History Study Baseline Demography

	Prodromal (N=18)	Symptomatic (N=14)
Age at Screening (yrs.)		
number	18	14
Mean (SE)	45.7 (4.0)	44.1 (2.8)
Median	40.5	44
Sex		
Female: number (%)	11 (61.1%)	8 (57.1%)
Male: number (%)	7 (38.9%)	6 (42.9%)
Race		
White: number (%)	17 (94.4%)	14 (100.0%)
Black: number (%)	1 (5.6%)	0
Ethnicity		
Hispanic or Latino: number (%)	2 (11.1%)	1 (7.1%)
Not Hispanic or Latino: number (%)	16 (88.9%)	12 (85.7%)
Not Stated: number (%)	0	1 (7.1%)
Time from Diagnosis (yrs.)		
number	9	14
Mean (SE)	0.86 (0.39)	0.76 (0.33)
Median	0.17	0.38

Fluid Biomarker Baseline Levels Altered in ALSP

Baseline Soluble CSF1R Levels in CSF

Baseline NfL Levels in CSF (Left) & Serum (Right)

sCSF1R levels in CSF: Healthy (51), Prodromal (4), Symptomatic (7)

NfL in CSF (pg/ml): Healthy (25), Prodromal (4), Symptomatic (7)

NfL in serum (pg/ml): Healthy (67), Prodromal (17), Symptomatic (14)
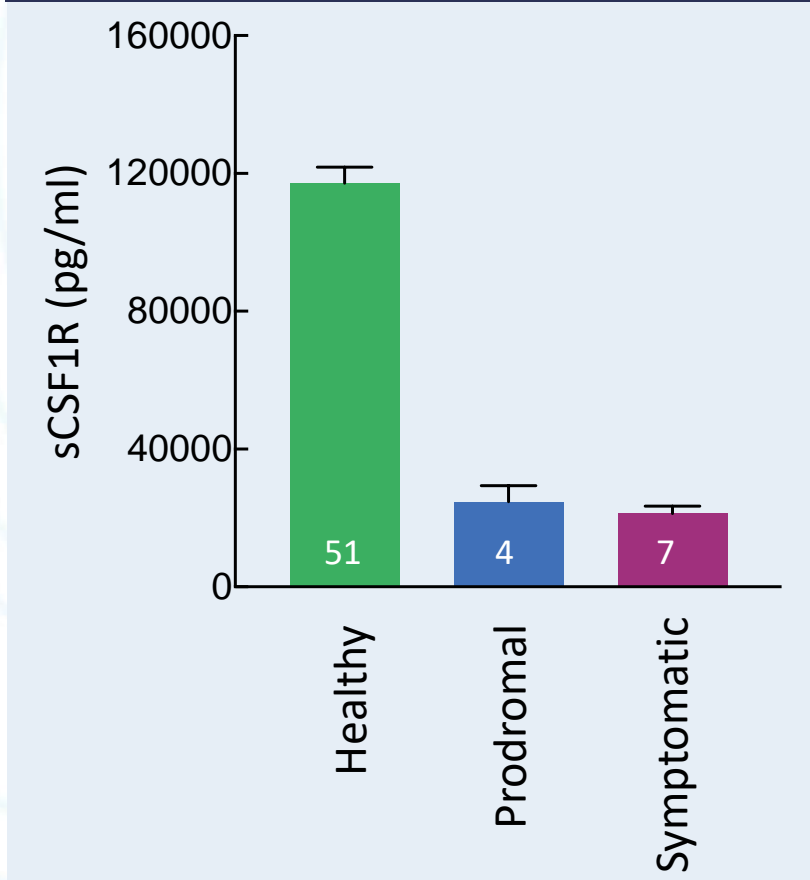
sCSF1R levels reduced in prodromal and symptomatic vs healthy
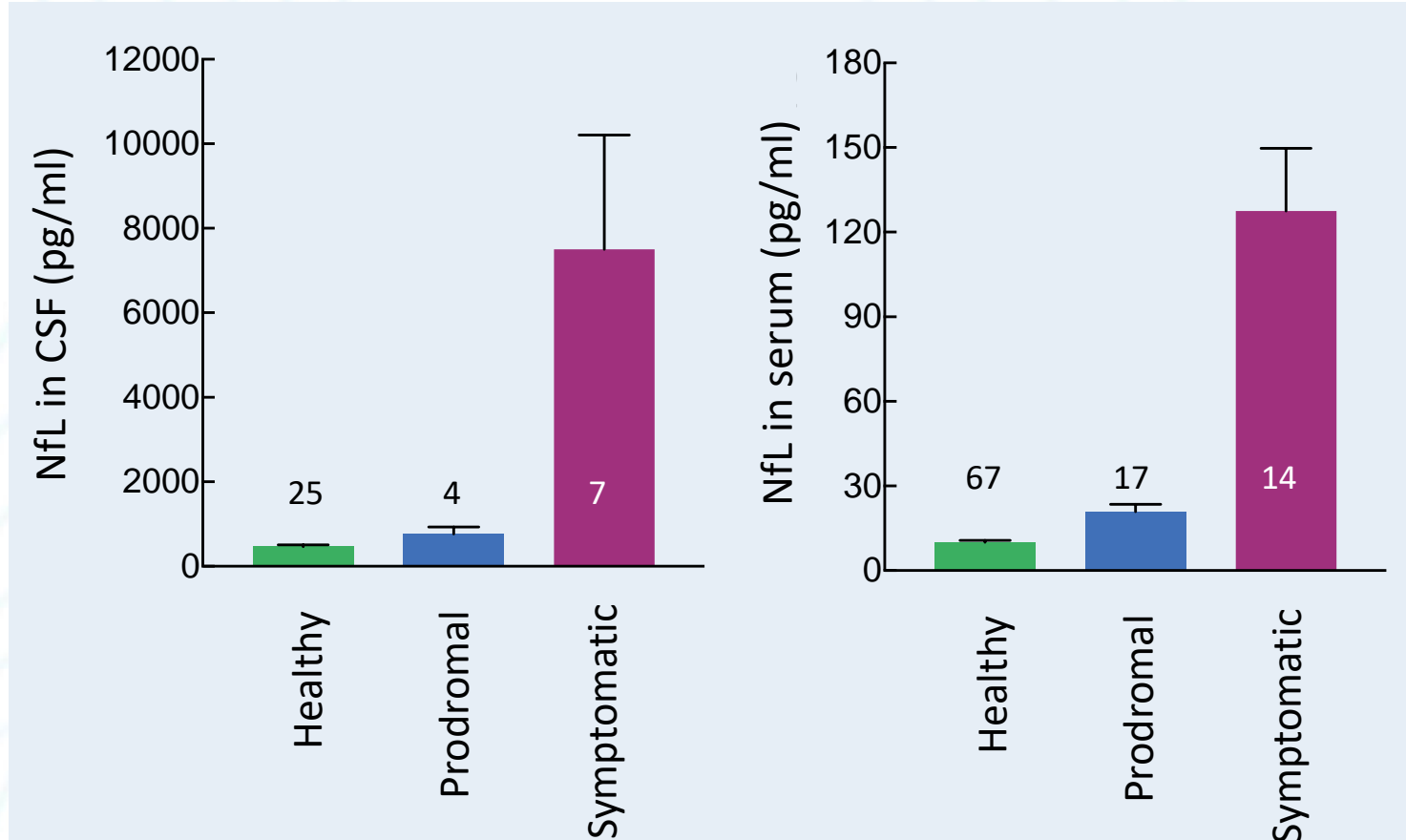
NfL levels increased in symptomatic reflecting active neurodegeneration

Healthy: healthy volunteers from VGL101 Phase 1 trial; CSF1R: Colony Stimulating Factor 1 Receptor; CSF: cerebrospinal fluid; NfL: neurofilament light chain

ILLUMINATE MRI Markers of Disease Progression: Ventricular Volume

Symptomatic participants demonstrated greater ventricular expansion at baseline and progression over 6 months relative to prodromal participants

Plots are Mean ± SE
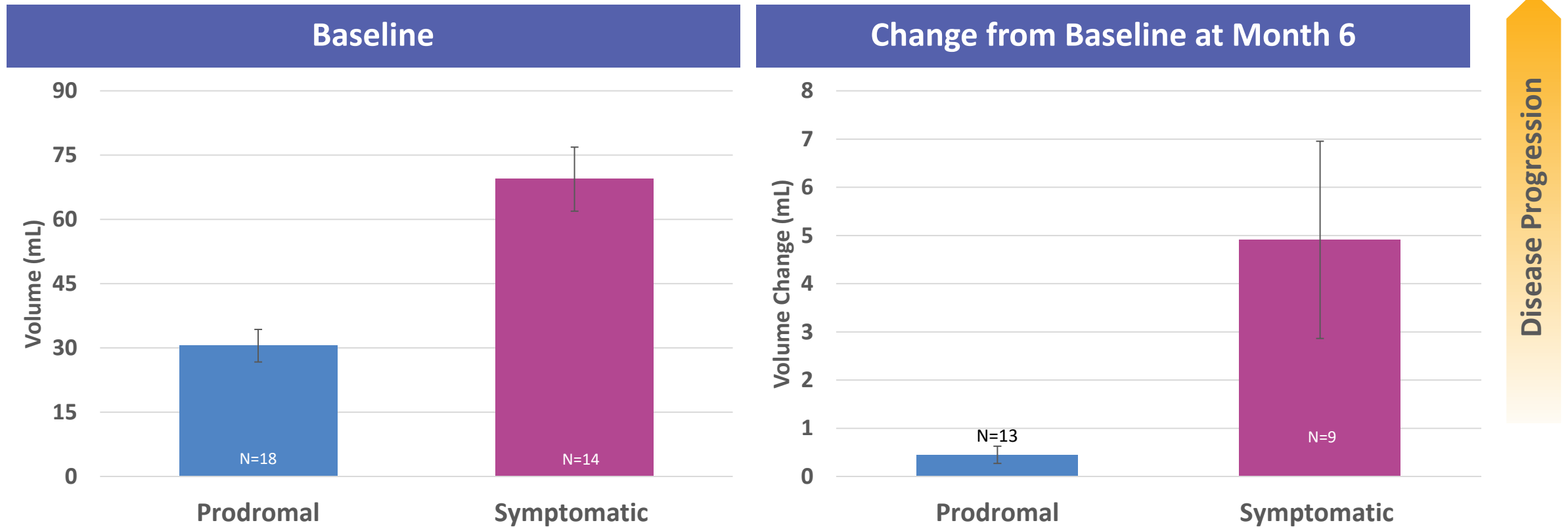
ILLUMINATE MRI Markers of Disease Progression: Gray Matter Volume

Symptomatic participants demonstrated greater gray matter atrophy at baseline and progression over 6 months relative to prodromal participants
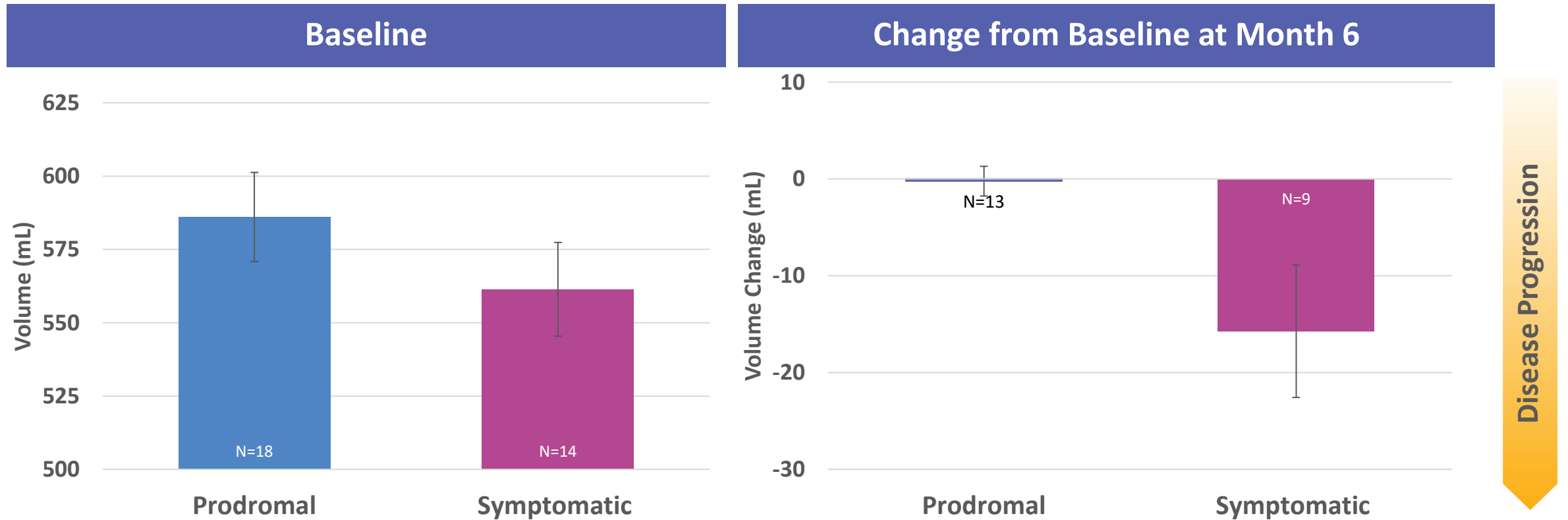
Plots are Mean ± SE

ILLUMINATE Clinical Endpoint:
Montreal Cognitive Assessment (MoCA)

Symptomatic participants demonstrated greater impairment at baseline and progression at 12 months

Plots are Mean ± SE
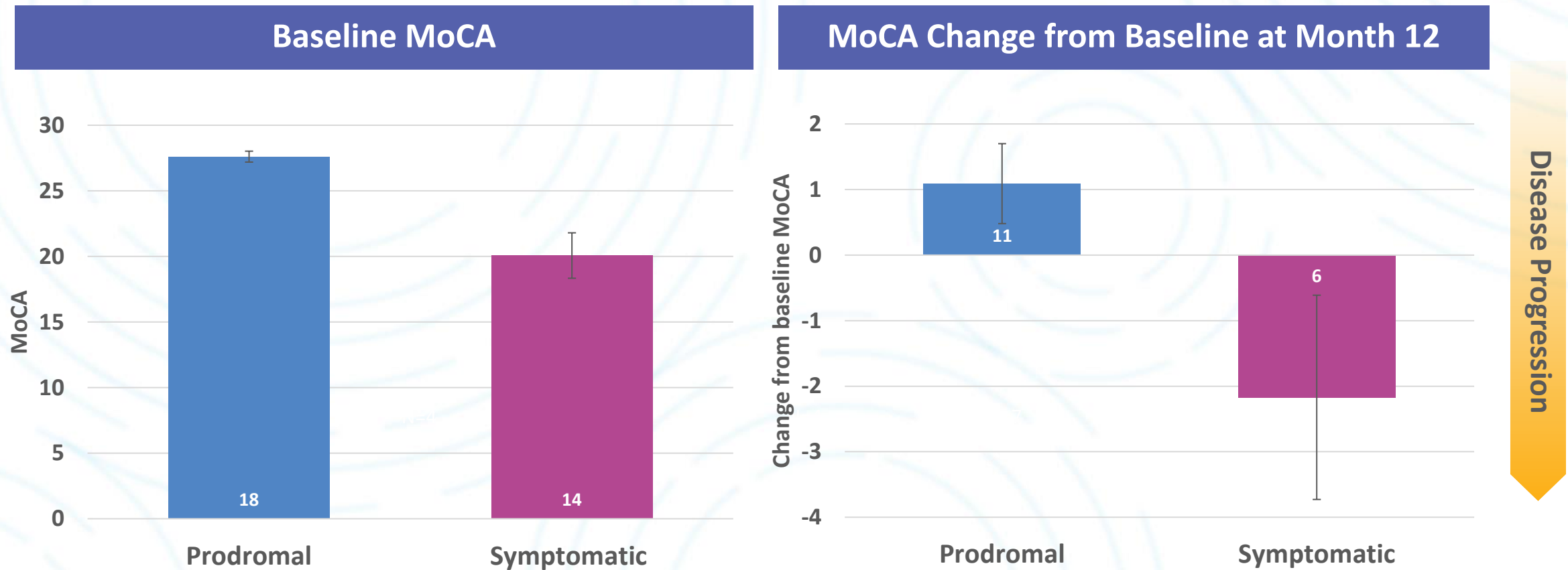
ILLUMINATE Clinical Endpoint:
Cortical Basal Ganglia Functional Scale (CBFS)

Symptomatic participants demonstrated greater impairment at baseline and progression at 12 months

Baseline CBFS

CBFS Change from Baseline at Month 12

Disease Progression

Plots are Mean ± SE
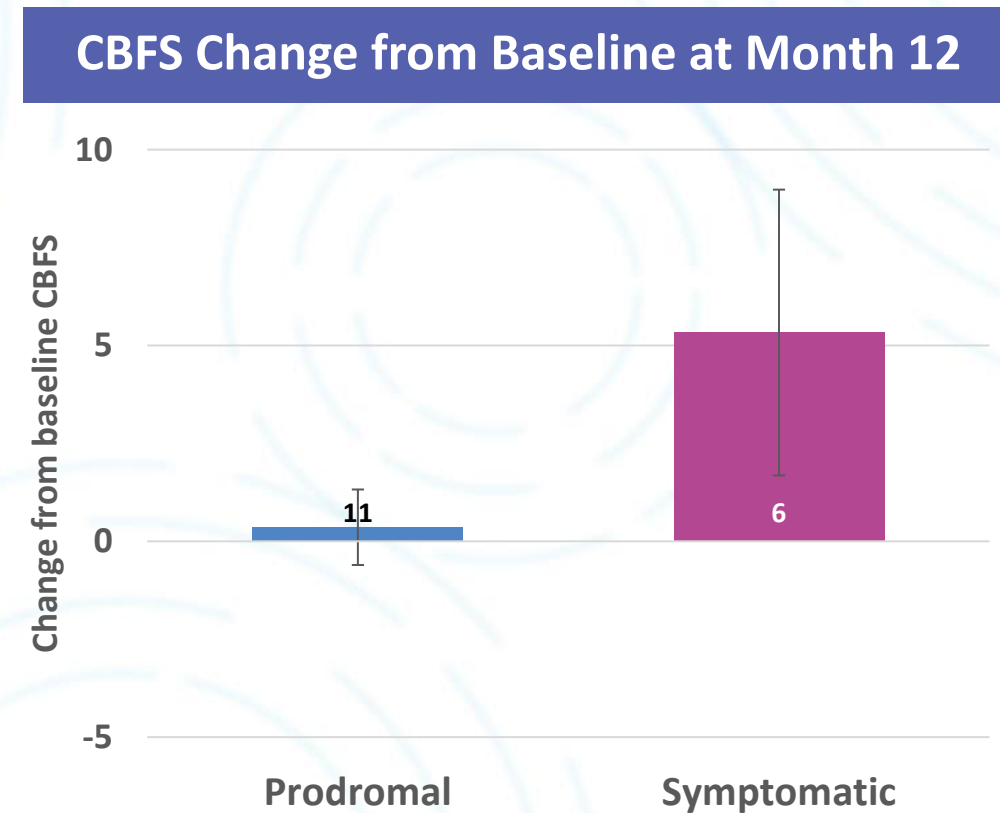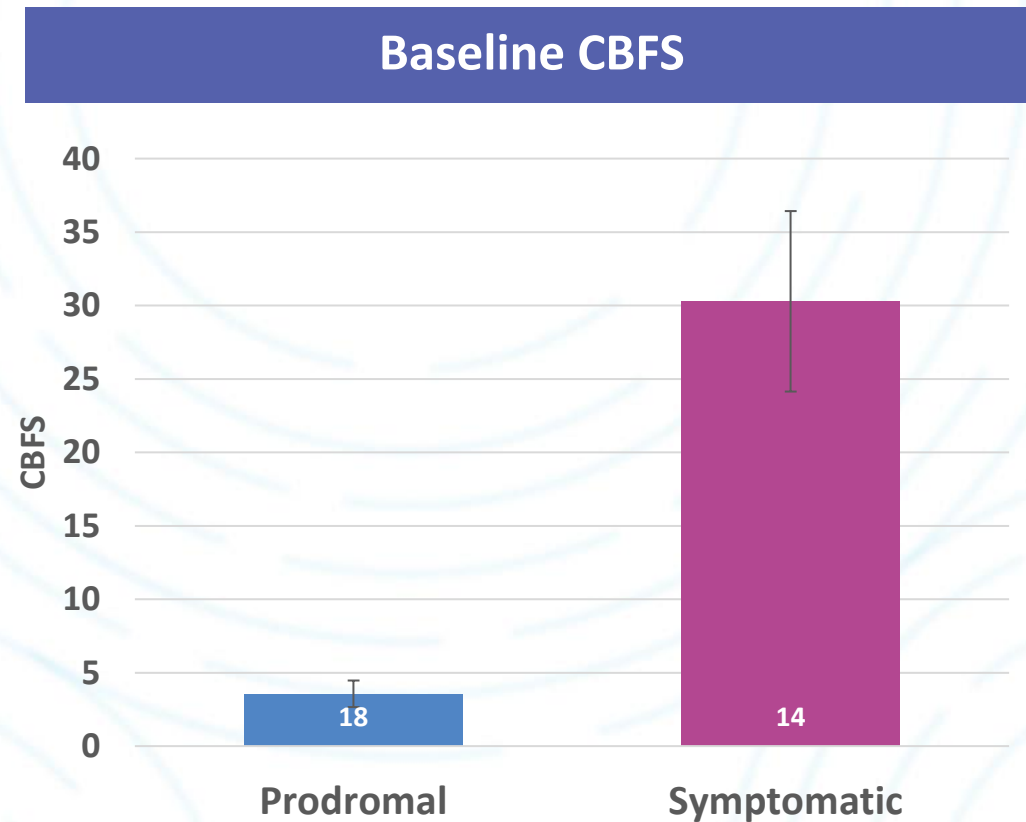
IGNITE Phase 2 Proof-of-Concept Trial of Iluzanebart (VGL101) in ALSP
1st Interim Analysis

vigilant for you®

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

IGNITE Phase 2 Trial 1st Interim Analysis: Executive Summary

IGNITE interim analysis on 6 patients at 6 months (20 mg/kg) further supports iluzanebart (VGL101) safety and PK/PD profiles, and clinical strategy

- Favorable safety and tolerability data
  - Most patients did not report treatment-related adverse events (AEs)
  - No treatment-related severe or serious AEs
  - No discontinuations due to AEs

- Predictable PK and brain penetration profile consistent with VGL101 Phase 1 data in healthy volunteers

- CNS target engagement and downstream pharmacological activity consistent with VGL101 Phase 1 data in healthy volunteers for 20 mg/kg
  - Reduction in sTREM2 CSF levels and increase in osteopontin CSF levels, indicating CNS target engagement
  - Increases in sCSF1R CSF levels, a key biomarker of ALSP disease pathology

- Directionally supportive changes at 6 months for individual subjects on MRI and NfL biomarkers of disease progression

- Quality and consistency of data on 6 subjects after 6 months support continuation of IGNITE and ILLUMINATE without modification

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Iluzanebart (VGL101) ALSP Phase 2 Open-Label Proof-of-Concept Trial Design

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

Screening

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

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

Follow up

Primary Analysis:
6 months (all subjects)
20 mg/kg + 40 mg/kg

Final Analysis:
12 months (all subjects)
20 mg/kg + 40 mg/kg
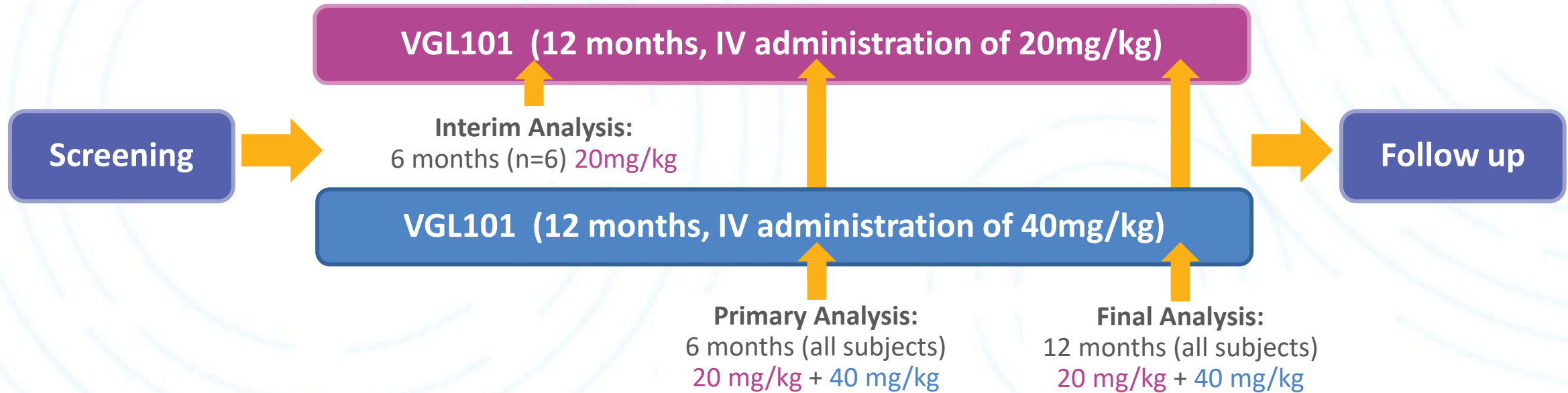
Study Population	▪ Patients with symptomatic ALSP related to *CSF1R* gene mutation
Study Design	▪ Open-label, ~15 patients
Treatment Duration	▪ 12 months (with opportunity for further extension), monthly IV administration
Outcome Assessments	▪ Safety and tolerability of VGL101 ▪ MRI-based assessment of brain volume and white matter lesions ▪ CSF biomarkers for neurodegeneration and target engagement ▪ Clinical outcome measures and PK

Iluzanebart (VGL101) ALSP Phase 2 Patient Population

Key Clinical Inclusion Criteria

- Documentation of a *CSF1R* gene mutation

- Clinical symptoms consistent with ALSP

- MRI findings consistent with ALSP

- Mild and early-moderate stages defined by cognitive and ambulation status

Key Clinical Exclusion Criteria

- Any neurological disease that poses a risk to the participant or produces symptoms like ALSP

- Patients unable to complete study procedures

- Comorbidities not permitting safe study participation

Phase 2 Baseline Demographics

	Phase 2 Baseline (N=6)
Age at Screening (yrs.)	
n	6
Mean (SE)	40.3 (3.3)
Median	41
Sex	
Female: n (%)	2 (33.3%)
Male: n (%)	4 (66.7%)
Race	
White: n (%)	5 (83.3%)
Black: n (%)	1 (16.7%)
Ethnicity	
Hispanic or Latino: n (%)	0
Not Hispanic or Latino: n (%)	5 (83.3%)
Not Stated: n (%)	1 (16.7%)
Time from Diagnosis (yrs.)	
Mean (SE)	0.94 (0.33)
Median	0.71

Target Engagement (6 months)	Microglia State (6 months)	Disease Pathophysiology (6 -9 months)	Clinical Progression (12 months)
Fluid: • sTREM2 (CSF)	**Fluid:** • sCSF1R (CSF) • Osteopontin (CSF)	**Fluid:** • NfL (serum & CSF) **Imaging:** • MRI measures ventricle and gray matter volumes	**Cognition & function:** • MoCA • CBFS • CDR+NACC-FTD

Proximal to target ←→ Proximal to disease
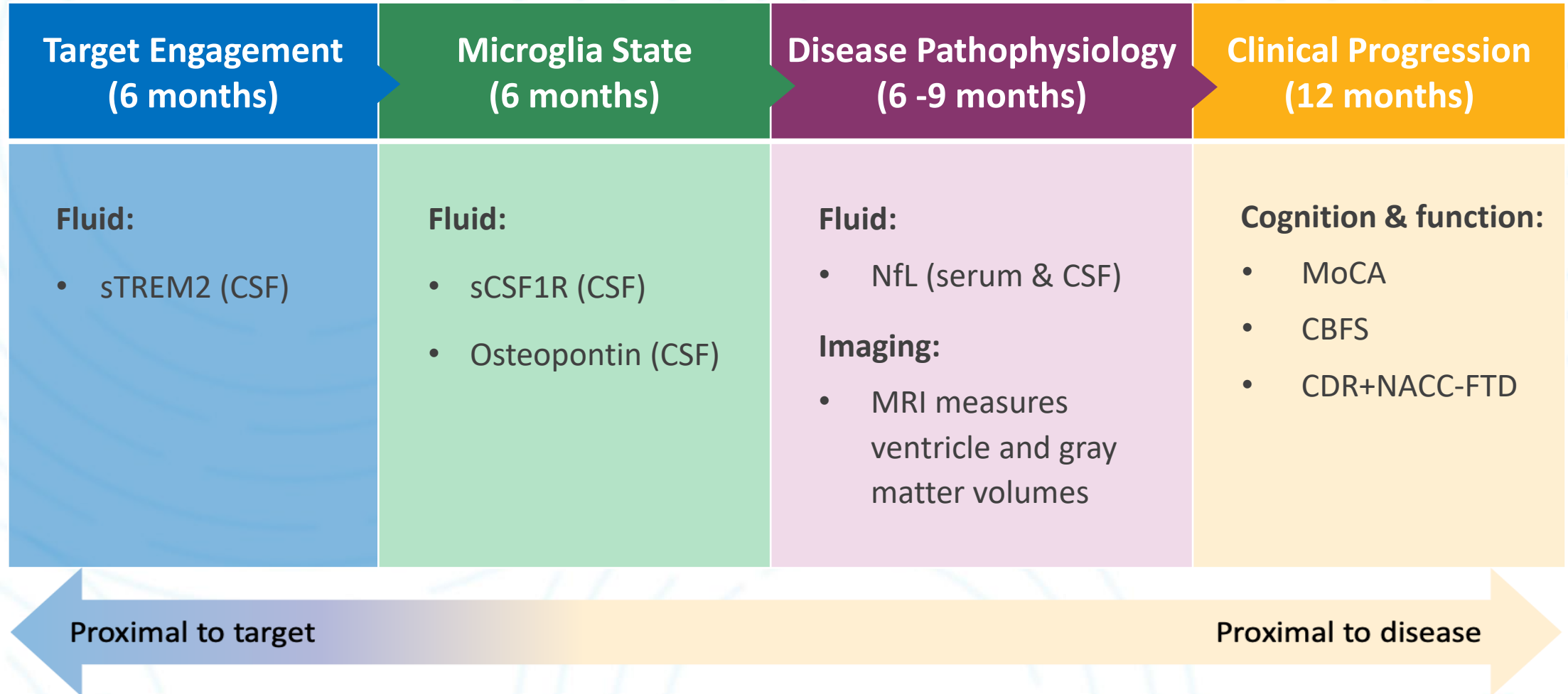
IGNITE Interim Safety Data Summary

Favorable safety & tolerability profile

Summary of Safety Outcomes (N=6)[a]	Patients with TEAEs
Any AE, n (%)	4 (66.7)
Treatment-related AEs, n (%)	2 (33.3)
Mild[c]	2 (33.3)
Moderate[c]	1 (16.7)
Severe	0
Treatment-related AEs occurring in ≥2 participants, n (%)	0
SAEs, n (%)	1 (16.7)
Treatment-related serious AEs, n (%)	0
Discontinuation of study drug due to AEs, n (%)	0

[a]IGNITE Ph2 interim data cut as of 22 September 2023

[b]Events determined by investigator to be "related" to study drug.

[c]Mild to moderate AEs include 1 patient with mild hepatic enzyme increase and; 1 patient with both mild irritability, tremor and lethargy, and moderate pruritus, lethargy and amnestic disorder (memory loss)

AE: adverse event; SAE: serious adverse event; TEAE: treatment emergent adverse event

Overview of Safety & Tolerability:

- VGL101 was generally well tolerated

- Majority of patients did not report treatment-related AEs

- No treatment-related severe AE or SAE

- No discontinuations due to AE

- One patient was briefly hospitalized for non-treatment related SAEs of abdominal pain, asthenia, vomiting, and diarrhea

- No hematological AEs

- No imaging-related abnormalities

Iluzanebart (VGL101) PK in IGNITE:
Predictable and Consistent with Phase 1
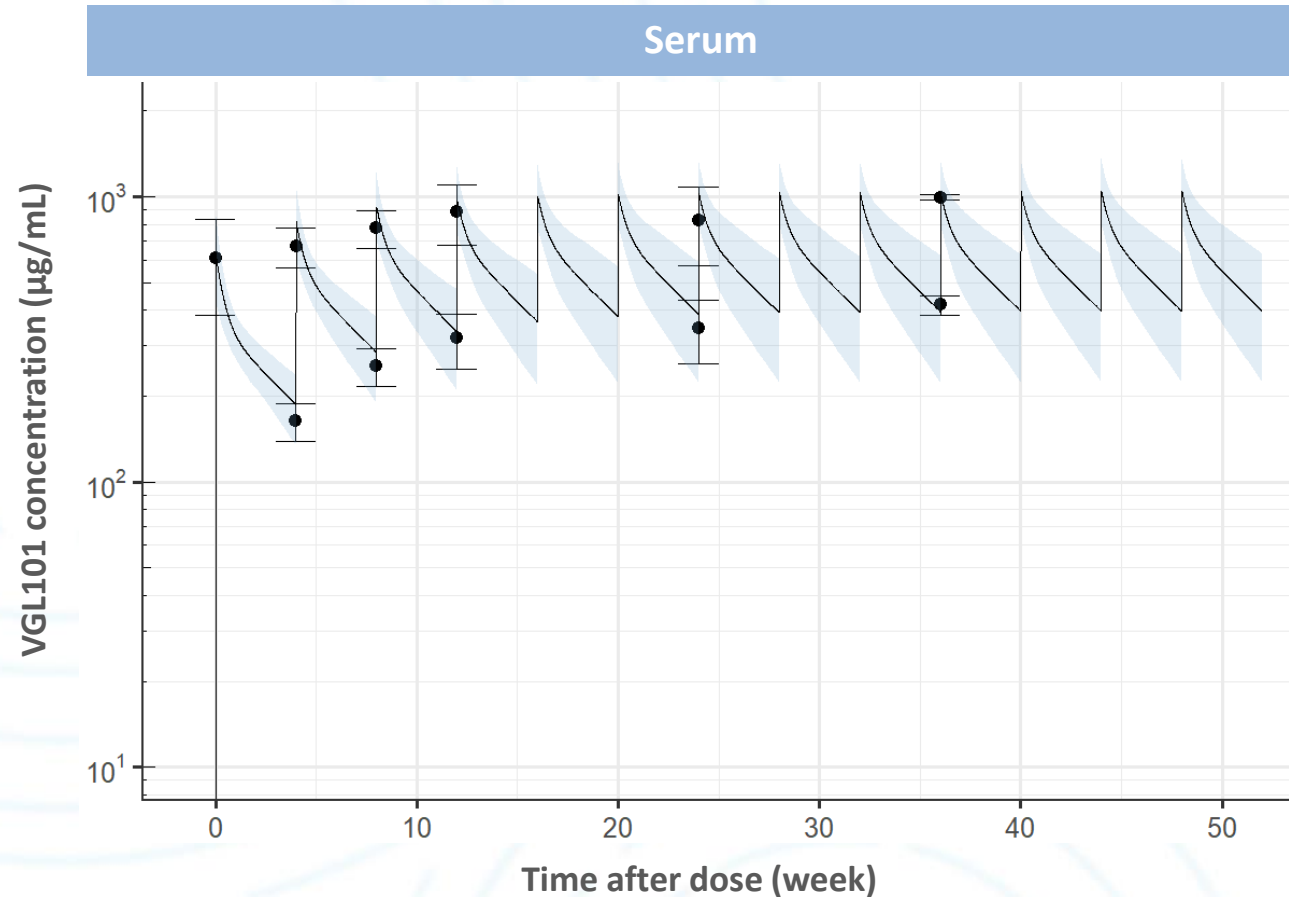
Brain penetration and achieving projected CSF therapeutic exposures:
~0.5% CSF-to-serum ratio for ALSP patients (vs 0.1 – 0.2% for healthy subjects in Phase 1)

Simulated median (line) PK and 95 % prediction interval (shaded) based on HVs at 20 mg/kg monthly. Dots are mean (+/- SD) of observed PK in ALSP patients

NfL levels in CSF and Serum were Highly Correlated
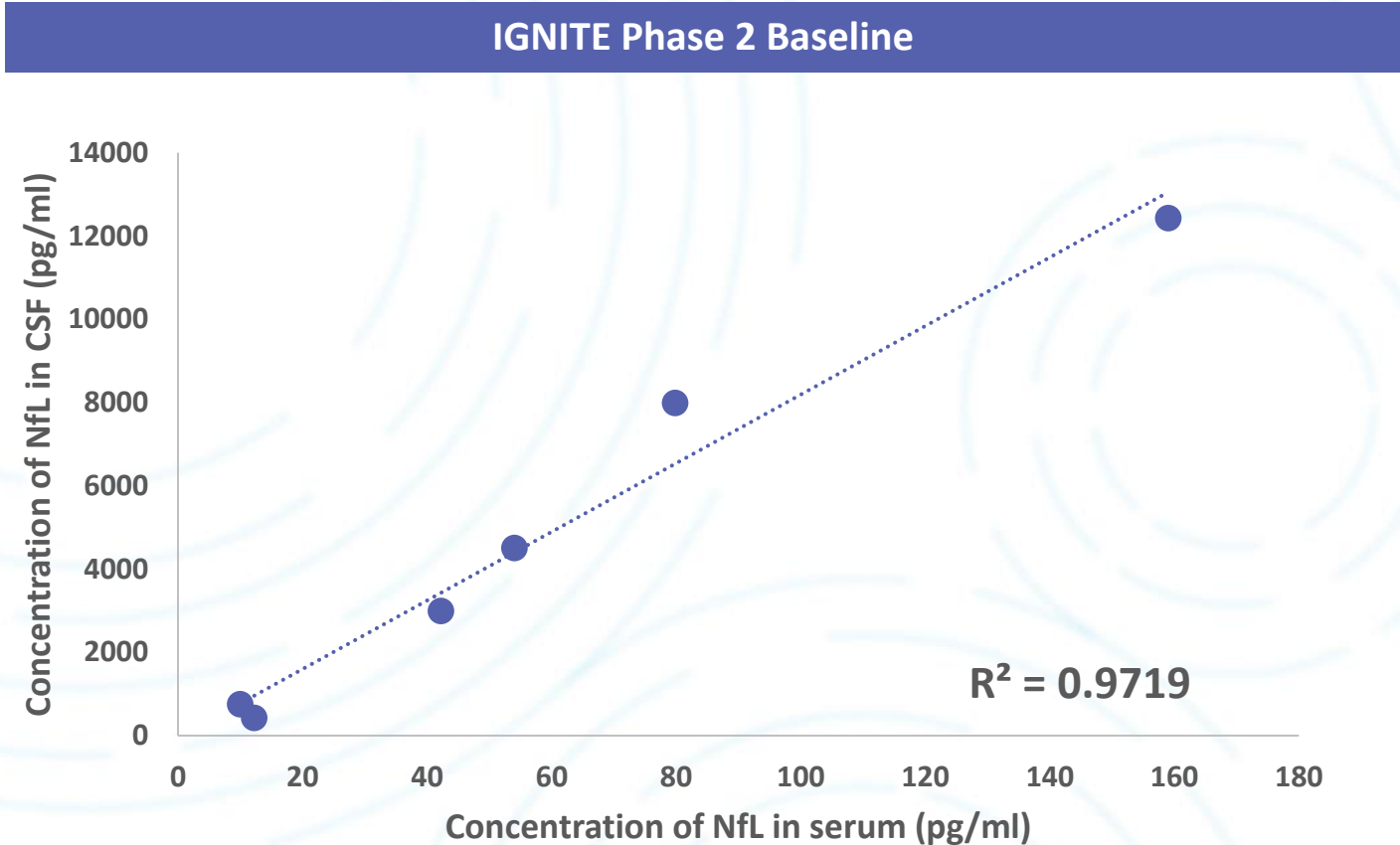
IGNITE Phase 2 Baseline

Concentration of NfL in CSF (pg/ml) vs Concentration of NfL in serum (pg/ml)

$R^2 = 0.9719$

Fluid Biomarker Data: Patient A

Demonstrated directionally supportive changes in all fluid biomarkers

CSF Biomarker	Treatment effect	
	Hypothesized*	Observed**
sTREM2	⬇	-26%
sCSF1R	⬆	+34%
Osteopontin	⬆	+32%

*Arrows denote directional change hypothesized to be consistent with target engagement and increased microglial activity
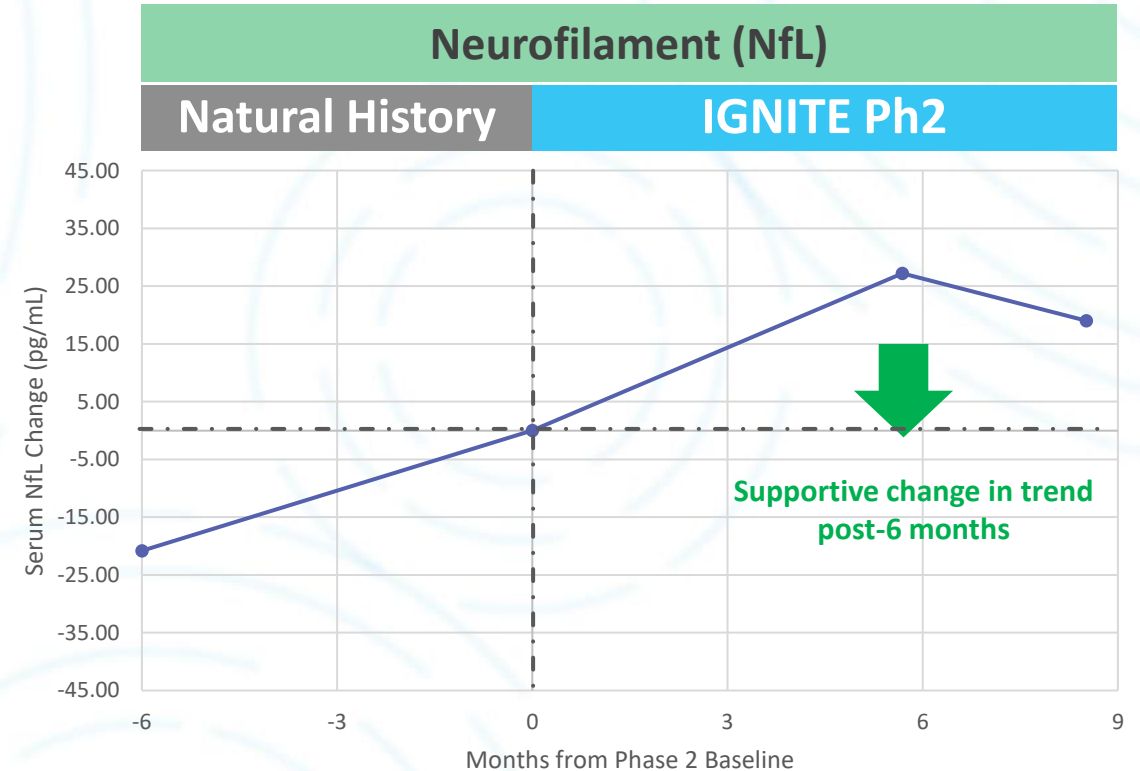**Change from baseline at 6-month visit

Neurofilament (NfL)

Natural History	IGNITE Ph2

Supportive change in trend post-6 months
(NfL reduction in CSF at 6 month)
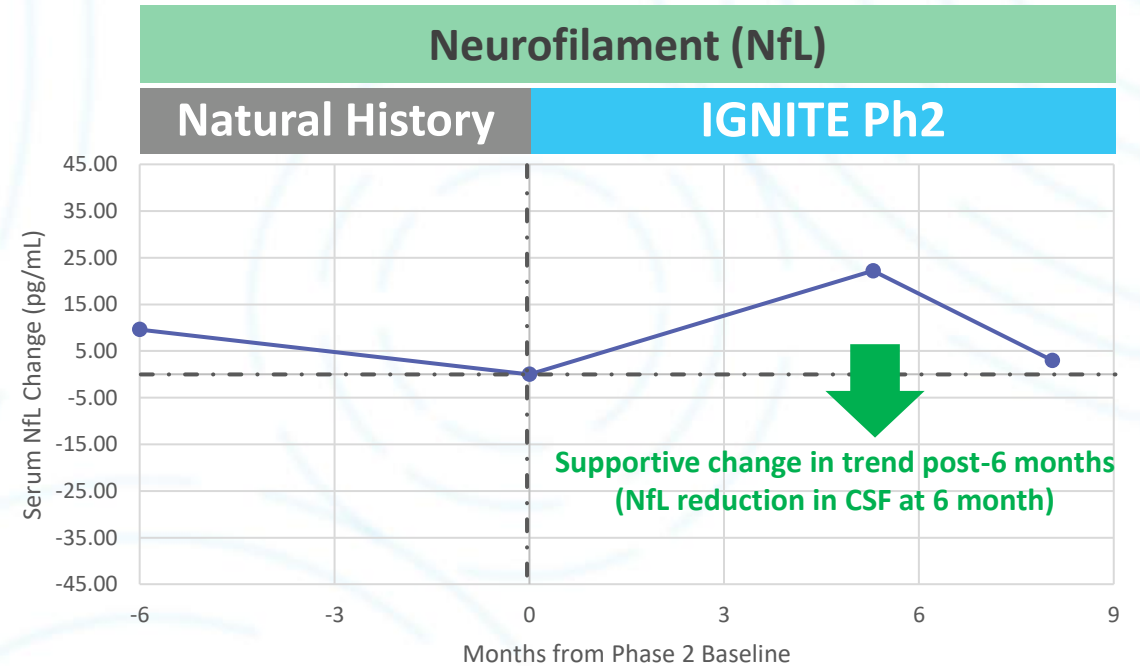
Serum NfL at Phase 2 baseline: 80 pg/mL
Serum NfL change in Natural History is estimated using patient's own subject-level regression of ILLUMINATE and IGNITE baseline data

MRI Biomarker Data: Patient A

Demonstrated directionally supportive changes in both MRI measures

Gray Matter Volume

Natural History | IGNITE Ph2

+ 10.0 mL

Ventricular Volume

Natural History | IGNITE Ph2

- 3.8 mL
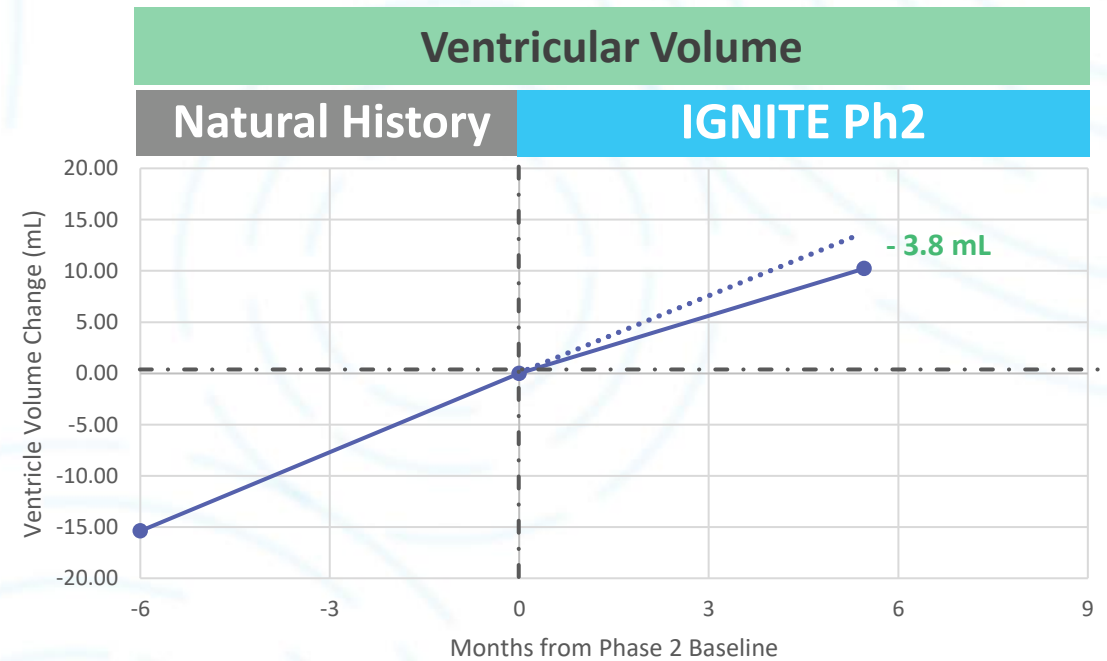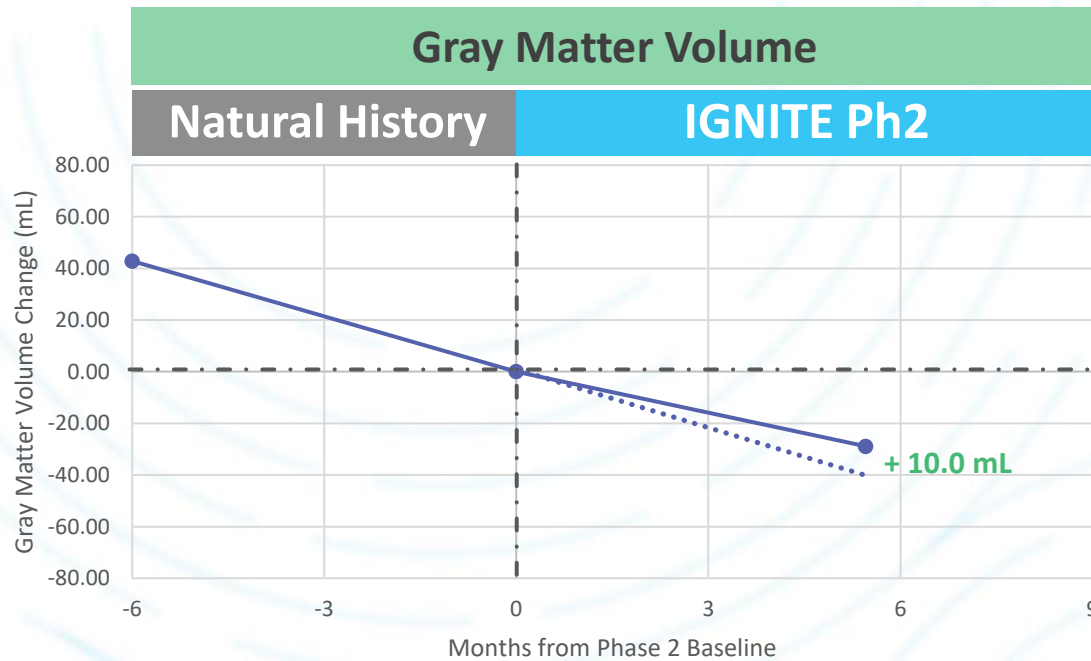
······· MRI change in Natural History estimated using patient own's subject-level regression of ILLUMINATE data

Fluid Biomarker Data: Patient B

Demonstrated directionally supportive changes in most fluid biomarkers

CSF Biomarker	Treatment effect	
	Hypothesized*	Observed**
sTREM2	⬇	+60%
sCSF1R	⬆	+32%
Osteopontin	⬆	+7%

*Arrows denote directional change hypothesized to be consistent with target engagement and increased microglial activity
**Change from baseline at 6-month visit

Neurofilament (NfL)

Natural History | IGNITE Ph2

NfL reduction below baseline
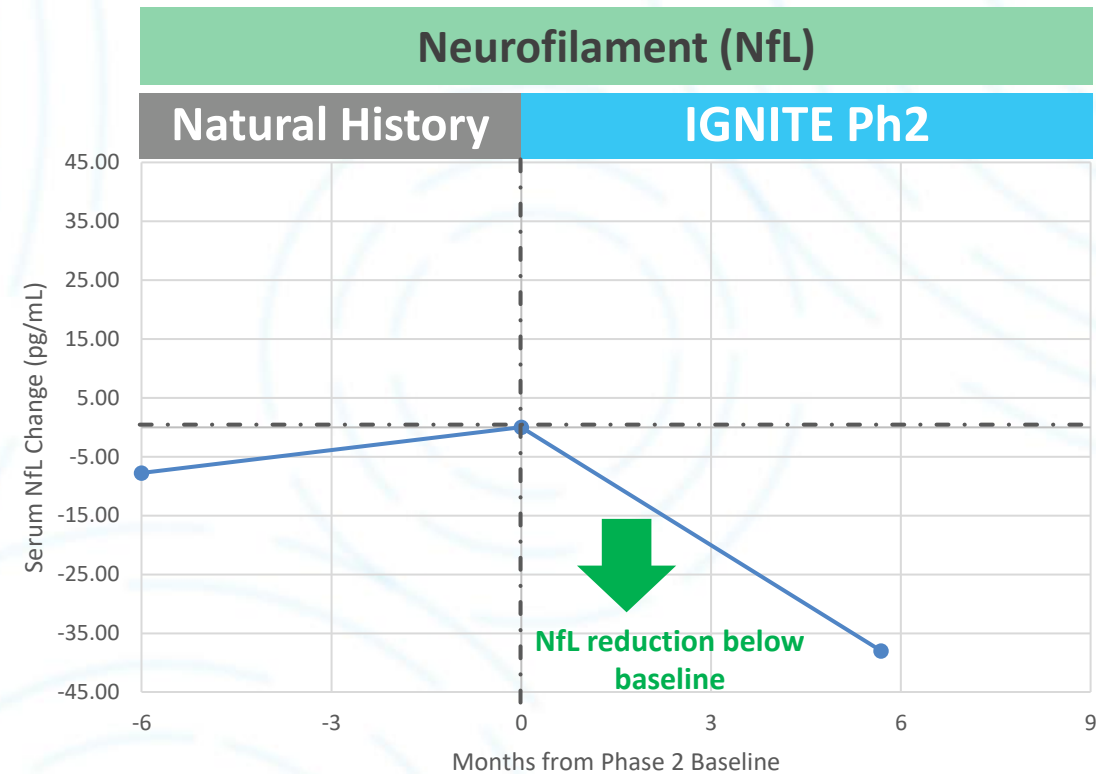
Serum NfL at Phase 2 baseline: 159 pg/mL
Serum NfL change in Natural History is estimated using patient's own subject-level regression of ILLUMINATE and IGNITE baseline data

MRI Biomarker Data: Patient B

Demonstrated directionally supportive changes in both MRI measures
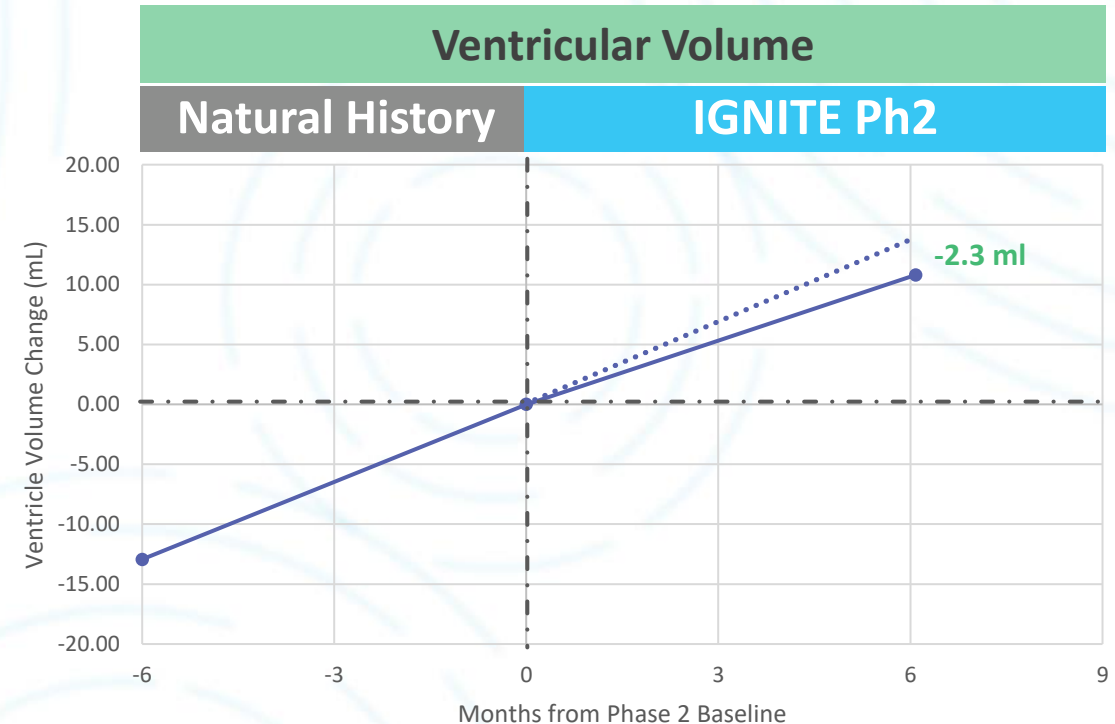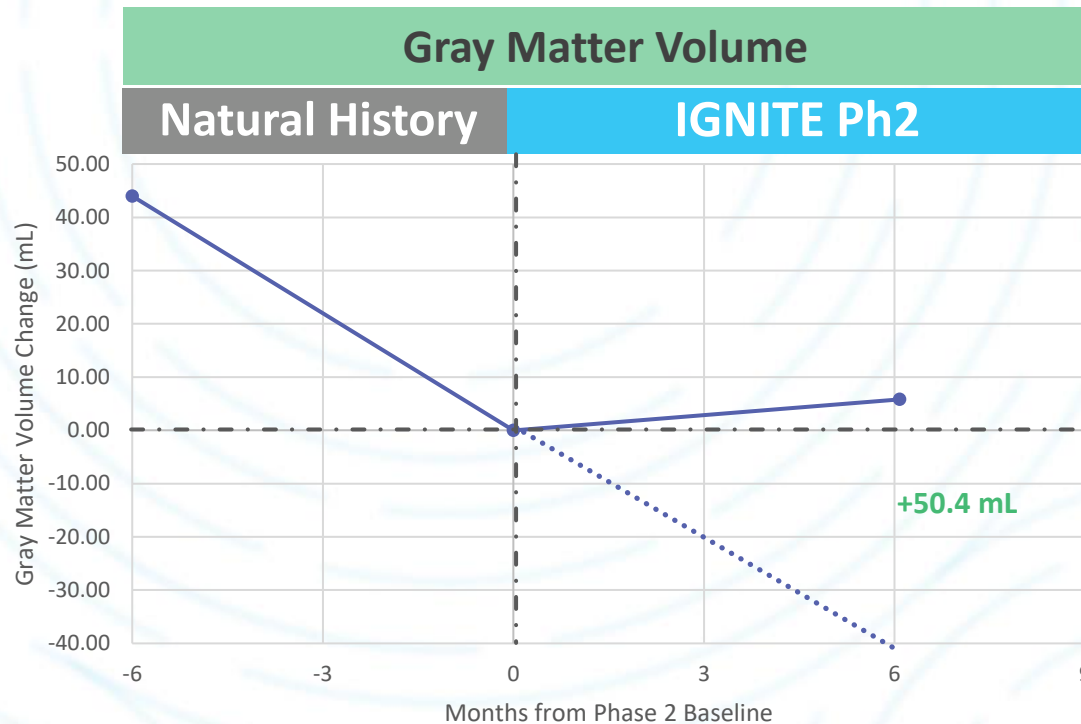
..... MRI change in Natural History estimated using patient own's subject-level regression of ILLUMINATE data
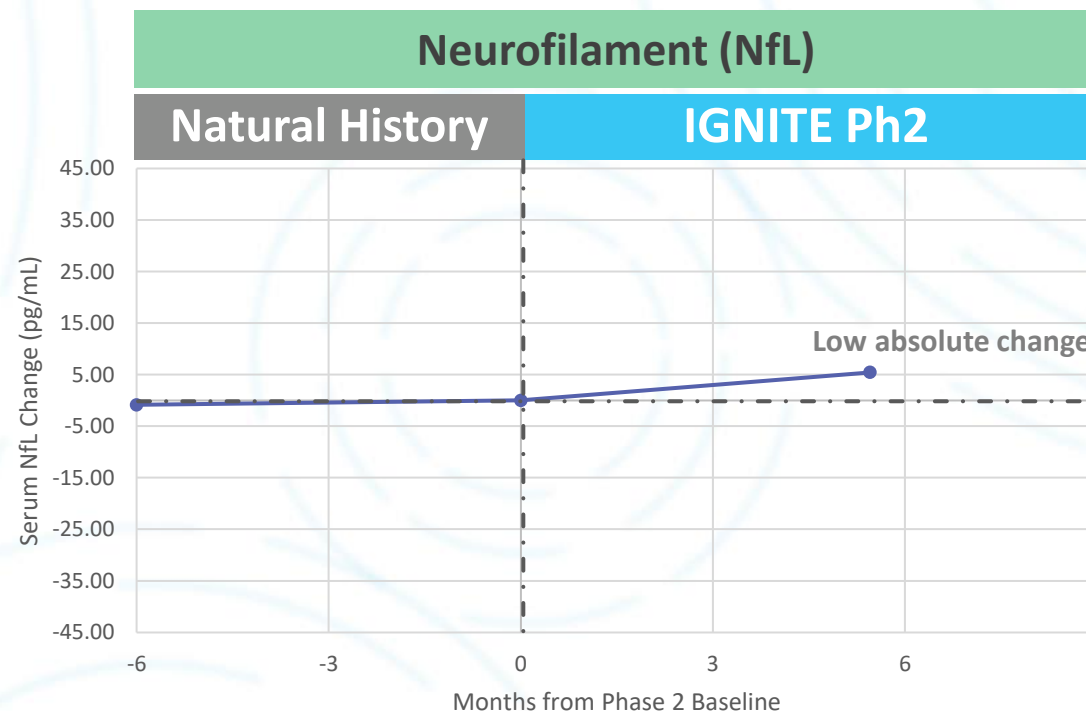
Fluid Biomarker Data: Patient C

Demonstrated directionally supportive changes in most fluid biomarkers

CSF Biomarker	Treatment effect	
	Hypothesized*	Observed**
sTREM2	⬇	-5%
sCSF1R	⬆	-5%
Osteopontin	⬆	+20%

*Arrows denote directional change hypothesized to be consistent with target engagement and increased microglial activity
**Change from baseline at 6-month visit

Neurofilament (NfL)

Natural History	IGNITE Ph2

Serum NfL Change (pg/mL) vs Months from Phase 2 Baseline

Supportive change in trend post-6 months

Serum NfL at Phase 2 baseline: 42 pg/mL
Serum NfL change in Natural History is estimated using patient's own subject-level regression of ILLUMINATE and IGNITE baseline data

(vigil)

MRI Biomarker Data: Patient C

Did not demonstrate supportive changes in MRI measures
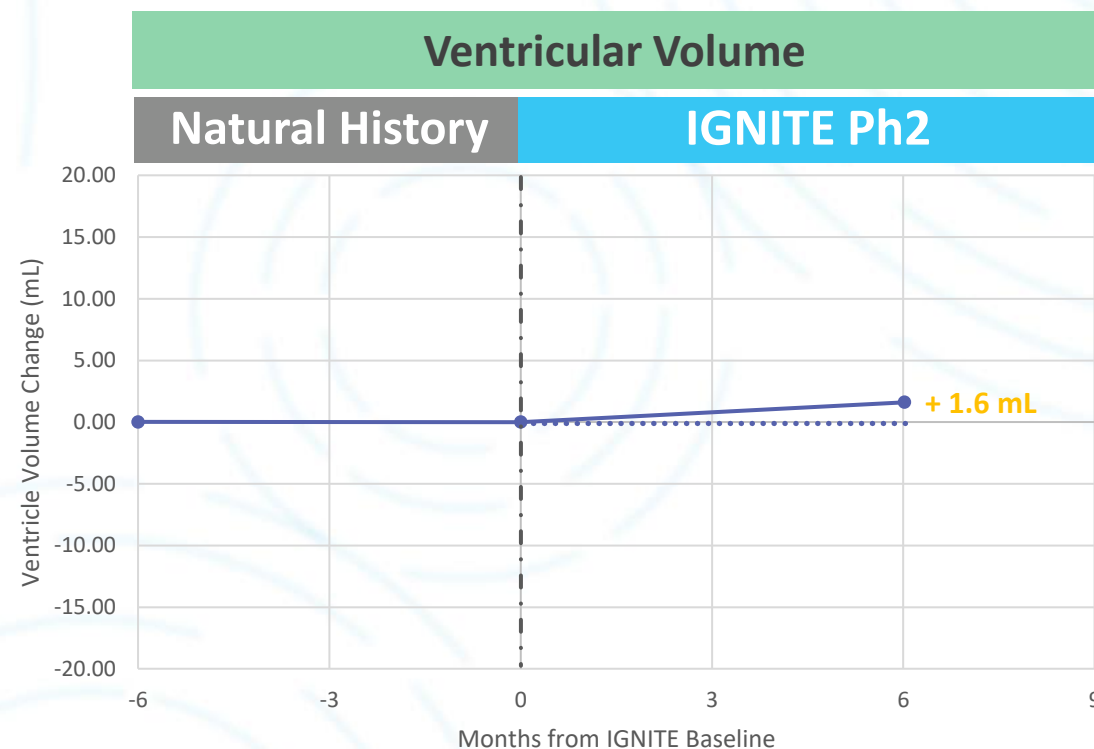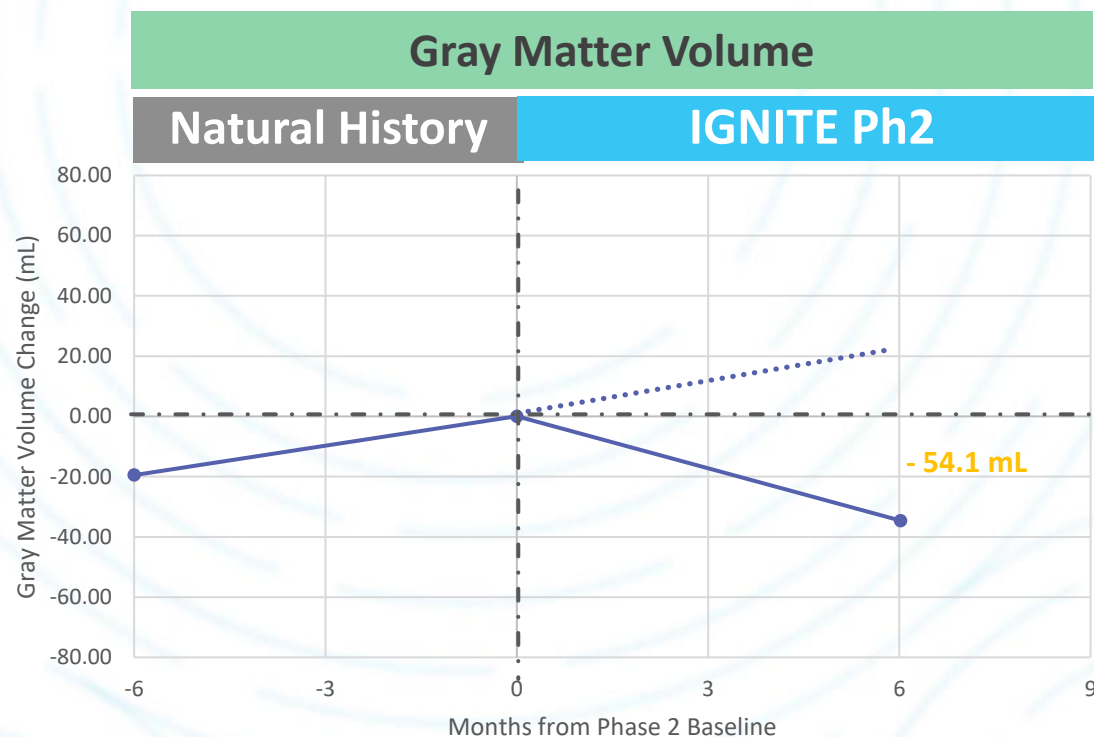
...... MRI change in Natural History estimated using patient own's subject-level regression of ILLUMINATE data
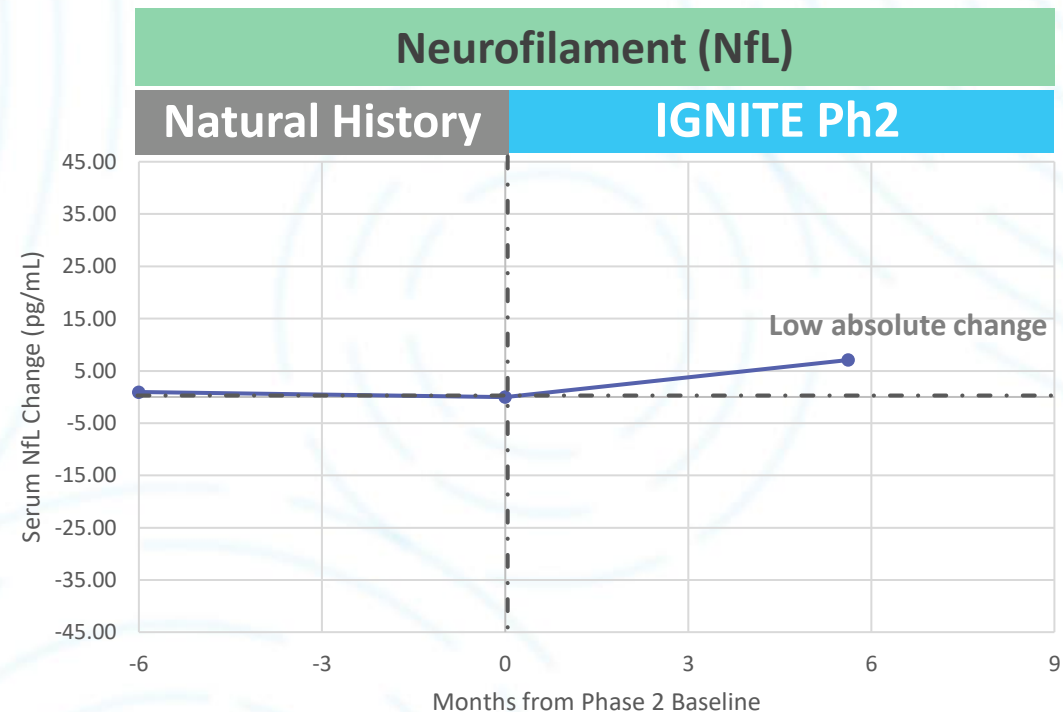
Fluid Biomarker Data: Patient D

Demonstrated directionally supportive changes in all fluid biomarkers

CSF Biomarker	Treatment effect	
	Hypothesized*	Observed**
sTREM2	⬇	-20%
sCSF1R	⬆	+16%
Osteopontin	⬆	+18%

*Arrows denote directional change hypothesized to be consistent with target engagement and increased microglial activity
**Change from baseline at 6-month visit

Neurofilament (NfL)

Natural History | **IGNITE Ph2**

Low absolute change

Serum NfL Change (pg/mL)

Months from Phase 2 Baseline

Serum NfL at Phase 2 baseline: 10 pg/mL
Serum NfL change in Natural History is estimated using patient's own subject-level regression of ILLUMINATE and IGNITE baseline data

MRI Biomarker Data: Patient D

Demonstrated directionally supportive change in ventricular volume

Gray Matter Volume		
Natural History	IGNITE Ph2	

-6.8 mL

Ventricular Volume		
Natural History	IGNITE Ph2	

- 0.2 mL
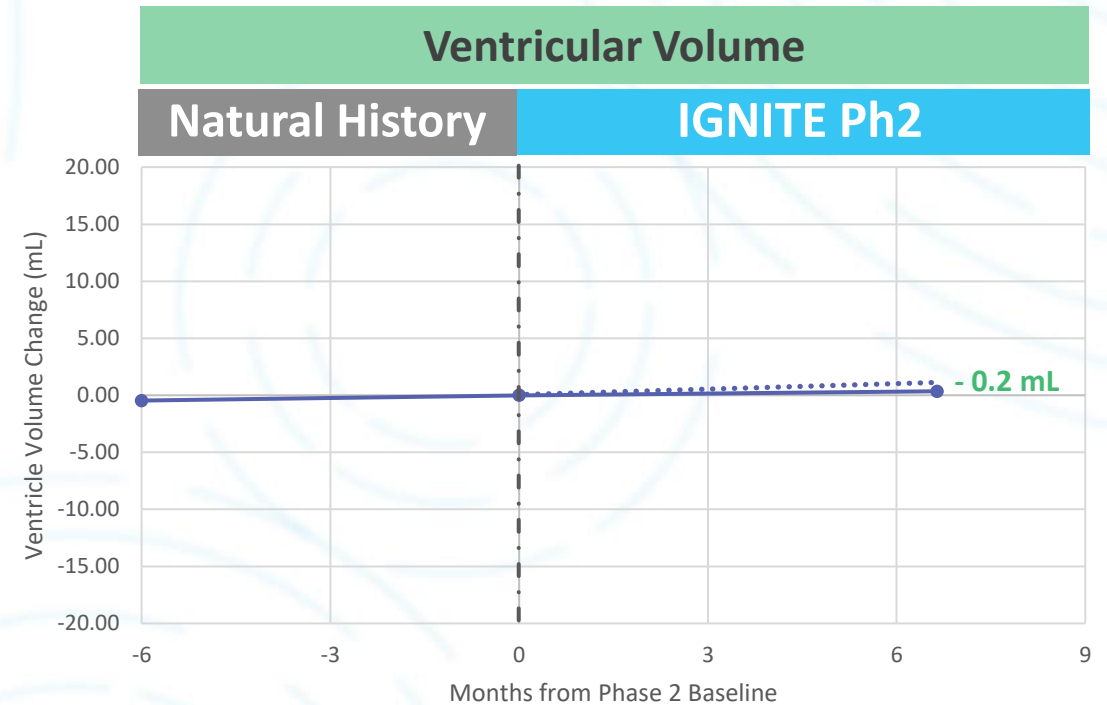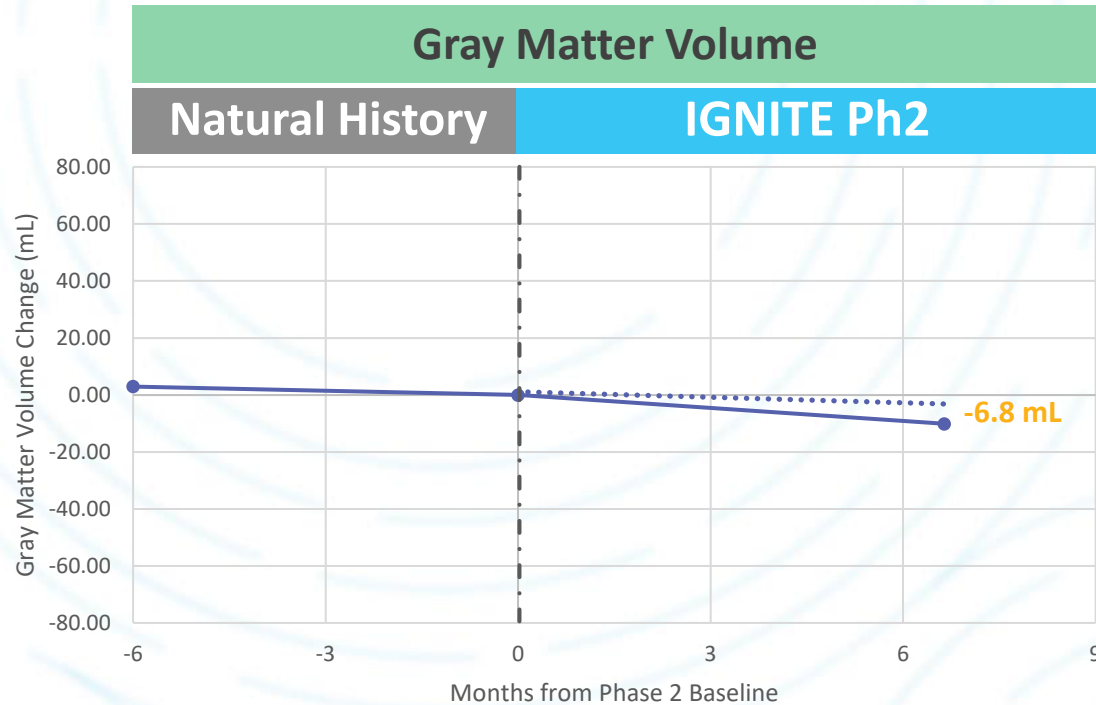
····· MRI change in Natural History estimated using patient own's subject-level regression of ILLUMINATE data
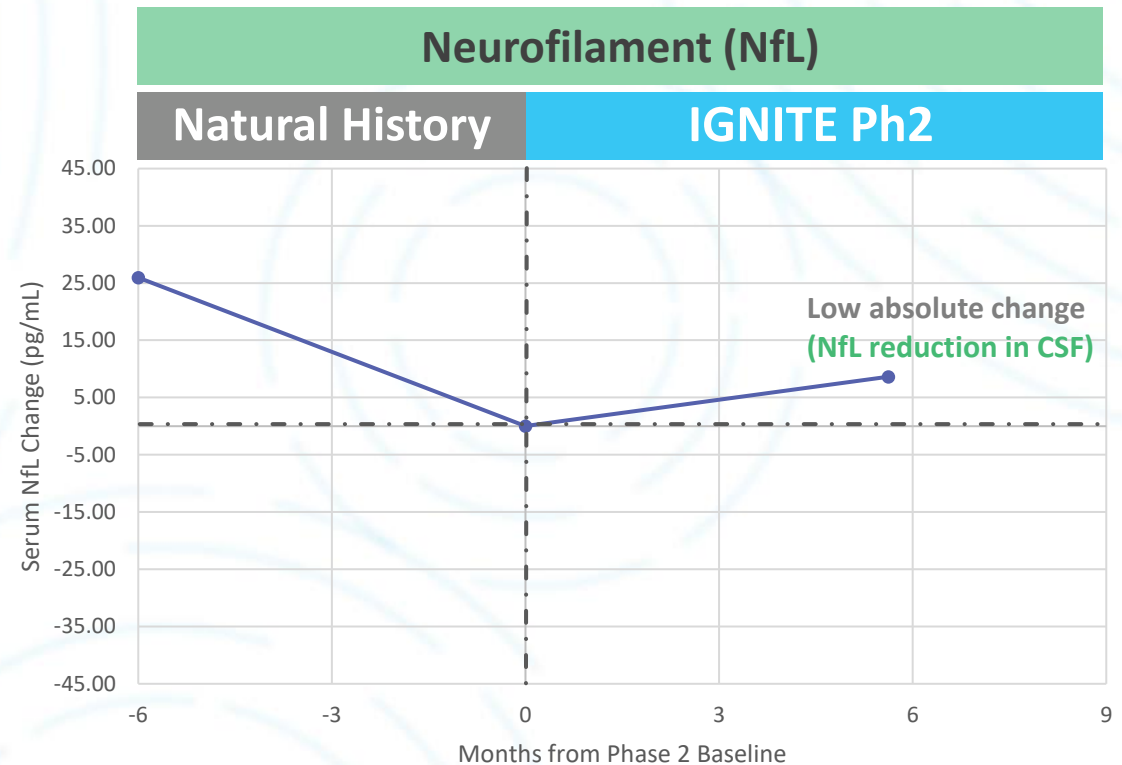
Fluid Biomarker Data: Patient E

Demonstrated directionally supportive changes in most fluid biomarkers

CSF Biomarker	Treatment effect	
	Hypothesized*	Observed**
sTREM2	⬇	-26%
sCSF1R	⬆	+0%
Osteopontin	⬆	+9%

*Arrows denote directional change hypothesized to be consistent with target engagement and increased microglial activity
**Change from baseline at 6-month visit

Neurofilament (NfL)

Natural History	IGNITE Ph2

Low absolute change

Serum NfL Change (pg/mL)

Months from Phase 2 Baseline

Serum NfL at Phase 2 baseline: 12 pg/mL
Serum NfL change in Natural History is estimated using patient's own subject-level regression of ILLUMINATE and IGNITE baseline data

MRI Biomarker Data: Patient E

Demonstrated directionally supportive change in ventricular volume
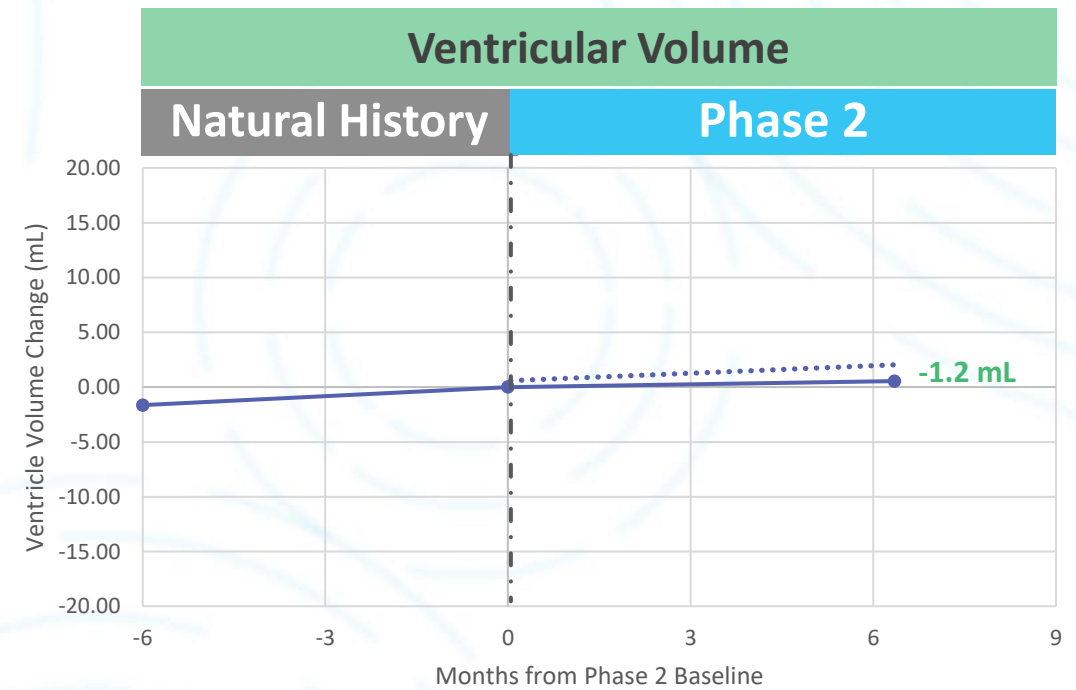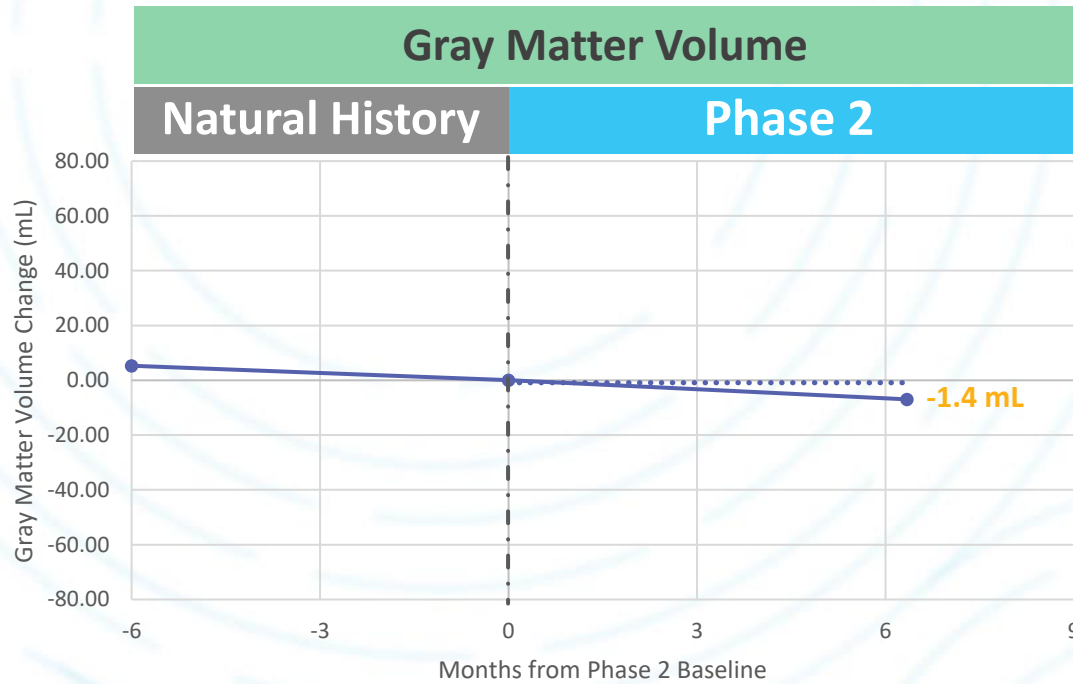
····· MRI change in Natural History estimated using patient own's subject-level regression of ILLUMINATE data

Fluid Biomarker Data: Patient F

Demonstrated directionally supportive changes in most fluid biomarkers

CSF Biomarker	Treatment effect	
	Hypothesized*	Observed**
sTREM2	⬇	+14%
sCSF1R	⬆	+24%
Osteopontin	⬆	+118%

*Arrows denote directional change hypothesized to be consistent with target engagement and increased microglial activity
**Change from baseline at 6-month visit

Neurofilament (NfL)

Natural History	IGNITE Ph2

Low absolute change
(NfL reduction in CSF)

Serum NfL Change (pg/mL)

Months from Phase 2 Baseline

Serum NfL at Phase 2 baseline: 54 pg/mL
Serum NfL change in Natural History is estimated using patient's own subject-level regression of ILLUMINATE and IGNITE baseline data

MRI Biomarker Data: Patient F

Demonstrated directionally supportive changes in both MRI measures
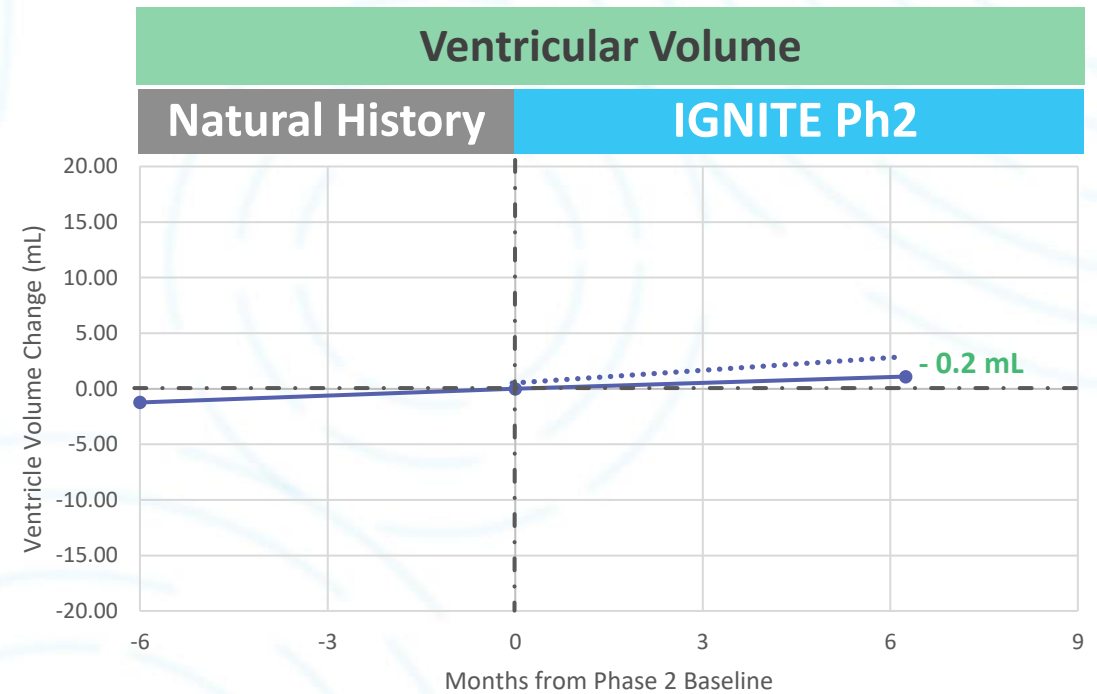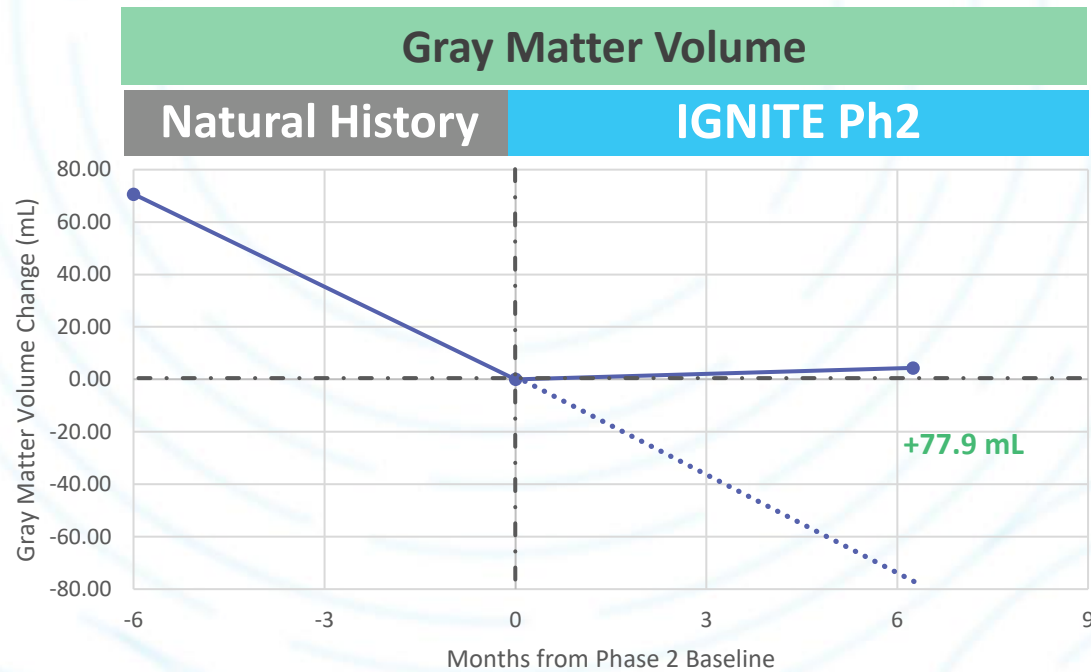
..... MRI change in Natural History estimated using patient own's subject-level regression of ILLUMINATE data

MRI Changes on Gray Matter and Ventricular Volumes

Directional change indicating reduced progression rate in ventricular expansion and gray matter atrophy in certain patients post-iluzanebart (VGL101) treatment vs. pre-treatment

Region	Rate of Progression
Ventricles	5 out of 6 patients had directional change supporting reduced rate of ventricular expansion[1]
Gray Matter Volume	3 out of 6 patients had directional change supporting reduced rate of atrophy[2]

1. Patients A, B, D, E and F; 2. Patients A, B and F

Changes in Biomarker Levels in CSF and Serum

Encouraging directional changes in CSF and serum levels of biomarkers in certain patients post-iluzanebart (VGL101) treatment vs. pre-treatment

Region	Response on Fluid Biomarkers
sCSF1R	4 out of 6 patients showed an increase over baseline (range: 16 – 34 %)[1]
NfL	3 out of 6 patients showed changes in serum NfL trajectory including: ▪ 1 patient showed reduced serum NfL at 6 months from baseline[2] ▪ 2 patients showed reduced serum NfL between 6 and 9 months[3] 2 patients out of 6 patients with low serum NfL baseline (age-normal range) showed low absolute changes in serum NfL at 6 months[4] 2 out of 6 patients showed reduced CSF NfL at 6 months[5]

1. Patients A, B, D and F; 2. Patient B; 3. Patients A & C; 4. Patients D & E; 5. Patients A & F

Overall Summary

IGNITE & ILLUMINATE interim analyses provide further support for continued development of iluzanebart (VGL101) as potential ALSP therapy

- ILLUMINATE NHS continues to provide important insights and a rich dataset on biomarkers and clinical measures of disease progression in ALSP
  - Totality of data, including longitudinal progression observed on selected MRI measures and clinical endpoints, support engagement with regulatory authorities

- IGNITE Phase 2 interim analysis provides further support on safety and PK/PD profiles, and clinical strategy for VGL101 in ALSP
  - Favorable safety and tolerability data
  - CNS target engagement and downstream pharmacological activity consistent with VGL101 Phase 1 data for 20 mg/kg; increases in sCSF1R CSF levels, a key biomarker of ALSP disease pathology
  - Directionally supportive changes at 6 months for individual subjects on MRI and NfL biomarkers of disease progression

- Quality and consistency of interim data support continuation of IGNITE and ILLUMINATE without modification

- Vigil plans to engage with FDA to initiate discussions regarding potential accelerated development pathway for VGL101

- Data on all patients in 20 mg/kg and 40 mg/kg cohorts at 6 months expected in Q3 2024

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

- Rare autosomal dominant neurodegenerative disorder caused by mutation in the CSF1R gene[1-7]

  – Primarily causing degeneration of brain white matter

  – Now recognized as ALSP ICD-10-CM Code G93.44

  – Estimated to affect 10%-25% of known patients with adult-onset leukoencephalopathies

- Adult onset with rapid disease progression[1-2]

  – Incapacitation: 3-4 years from disease onset (average)

  – Death: 6-8 years from disease onset (average)

- No approved therapies

CSF1R, colony stimulating factor-1 receptor.
1. Konno T, et al. *Eur J Neurol.* 2017;24(1):37-45. 2. Papapetropoulos S, et al. *Front Neurol.* 2022;12:788168. 3. Lynch DS, et al. *J Neurol Neurosurg Psychiatry.* 2016;87(5):512-519.
4. Lynch DS, et al. *J Neurol Neurosurg Psychiatry.* 2019;90(5):543-554. 5. Marotti JD, et al. *Acta Neuropathol.* 2004;107(6):481-488. 6. Wider C, et al. *Neurology.* 2009;72(22):1953-1959.
7. NORD. Accessed Oct 14, 2023. https://rarediseases.org/rare-diseases/adult-onset-leukoencephalopathy-with-axonal-spheroids-and-pigmented-glia/.

ALSP Symptoms[1,2]

Cognitive

- Personality change
- New anxiety, depression
- Difficulty in work, decision making
- Inappropriate behavior
- Memory problems
- Word-finding and speech problems

Motor

- Gait and balance problems
- Stiffness, slowness of movement
- Incoordination, tremor
- Swallowing and speech difficulty

As the disease progresses, symptoms multiply and patients become more immobile, to the point of being bedbound and totally dependent for care

1. Sundal C, et al. CSF1R-Related Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia. In: Adam MP MG, et al, ed. *GeneReviews® [Internet]*. Seattle, WA: University of Washington, Seattle; 1993-2023. 2. Konno T, et al. *Eur J Neurol.* 2017;24(1):37-45.

ALSP Progression

Relentlessly Progressive

- 75% survival for approximately 3 years, 50% for 5 years, 25% for 10 years and < 5% for 30 years
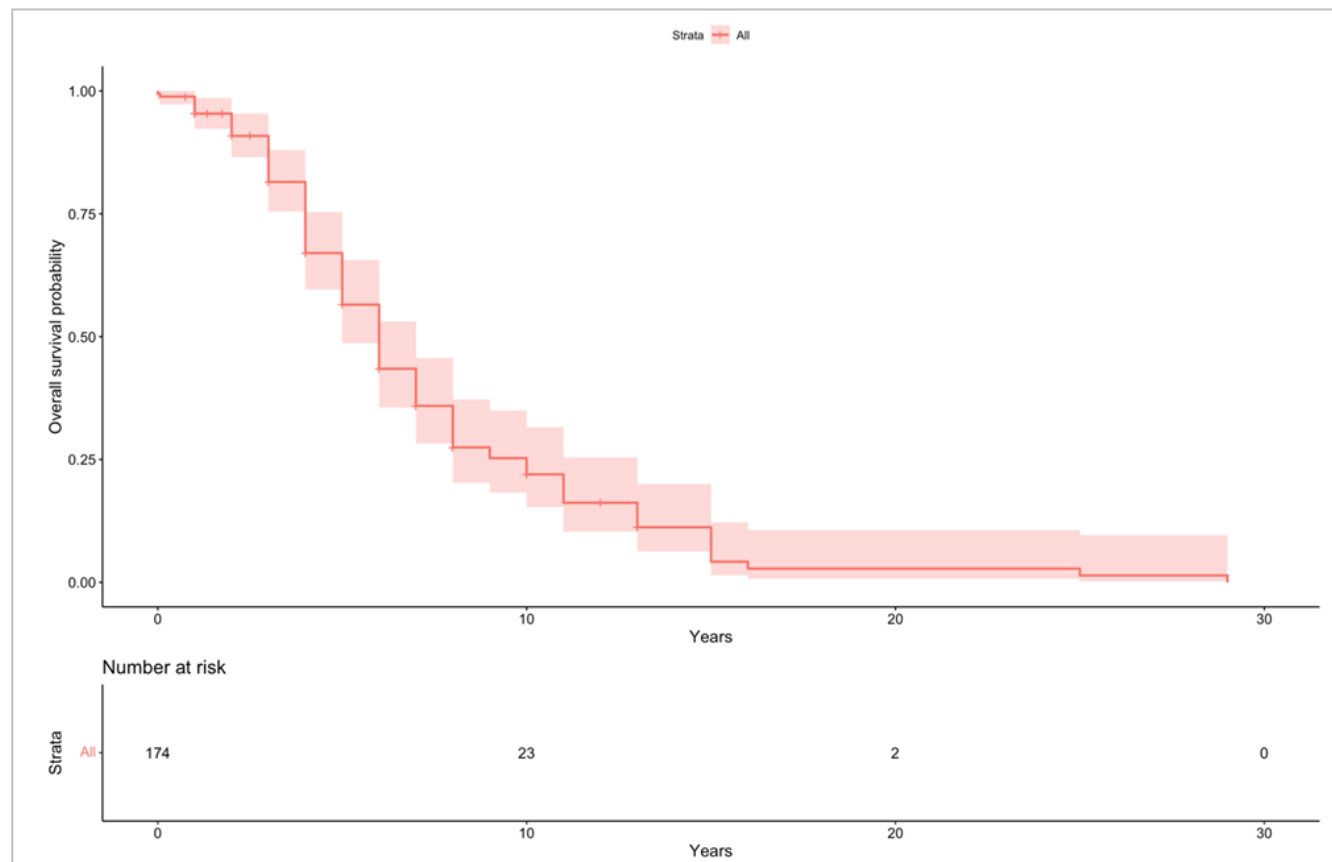
Kaplan-Meier estimates of survival probability (%) and number of patients at risk of death following diagnosis at 10-year intervals were performed with survival time and disease duration related to age of onset of symptoms in patients with ALSP[1]
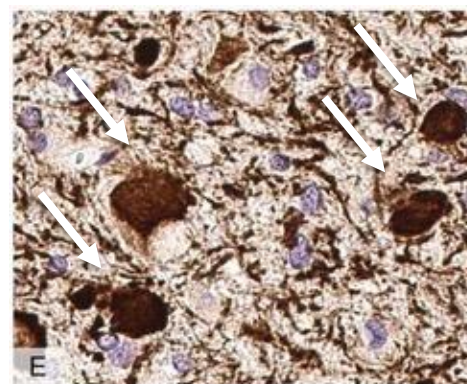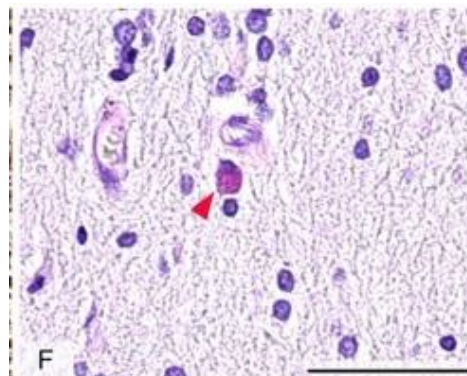
ALSP Pathophysiology – Genetically Caused[1]
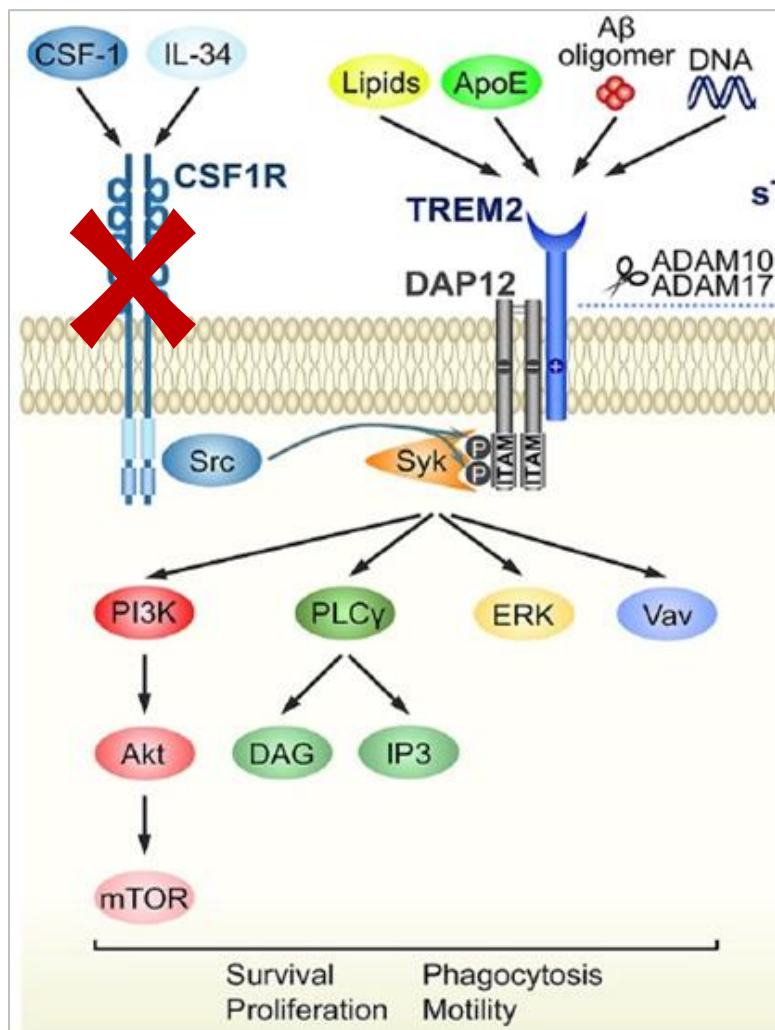
Loss of function mutations in the *CSF1R* gene leading to

- Microglia loss and dysfunction
- Structural and pathophysiological abnormalities of axons
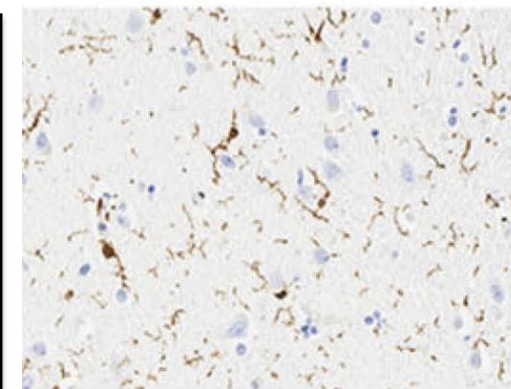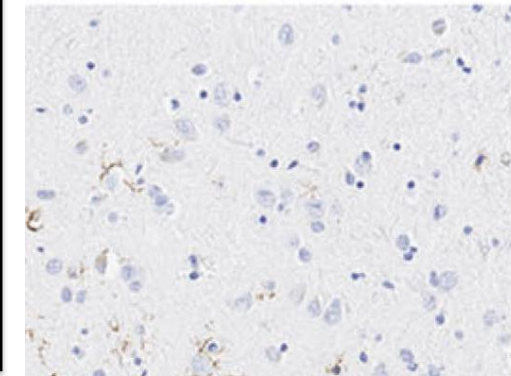- Demyelination of white matter

Axonal spheroids[2]

Pigmented glia[2]

Normal Gray Matter (IBA-1 Staining for Microglia)[3]

ALSP Gray Matter (IBA-1 Staining for Microglia)[3]

Left figure: Konishi & Kiyama Front. Cell. Neurosci. 2018; 1. Papapetropoulos S, et al. Front Neurol. 2022; 2. Lynch DS, et al. J Neurol Neurosurg Psychiatry. 2016; 3. Kempthorne et al. Acta Neuropathologica. 2020
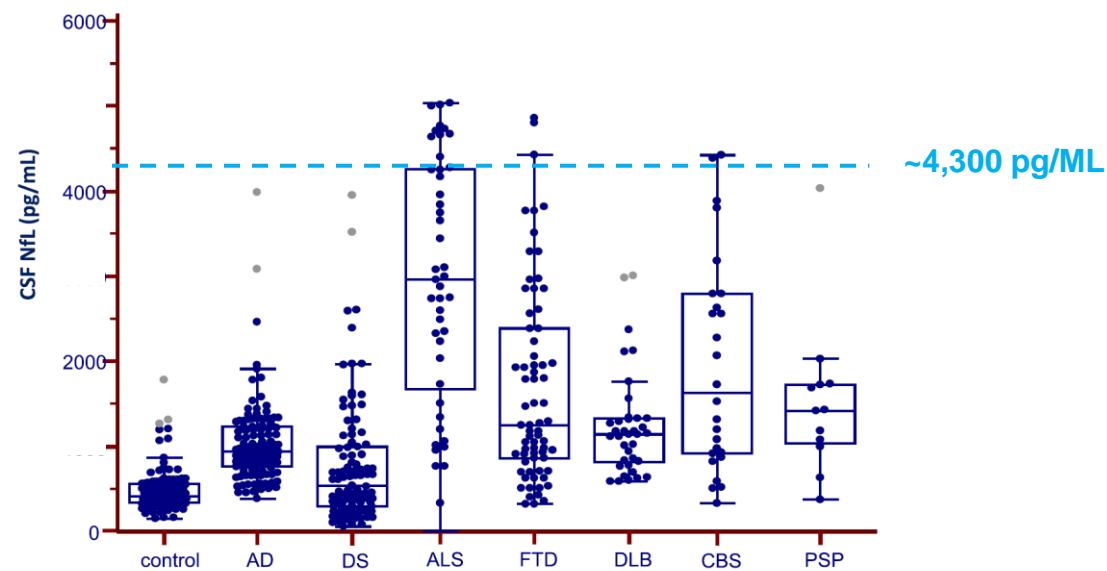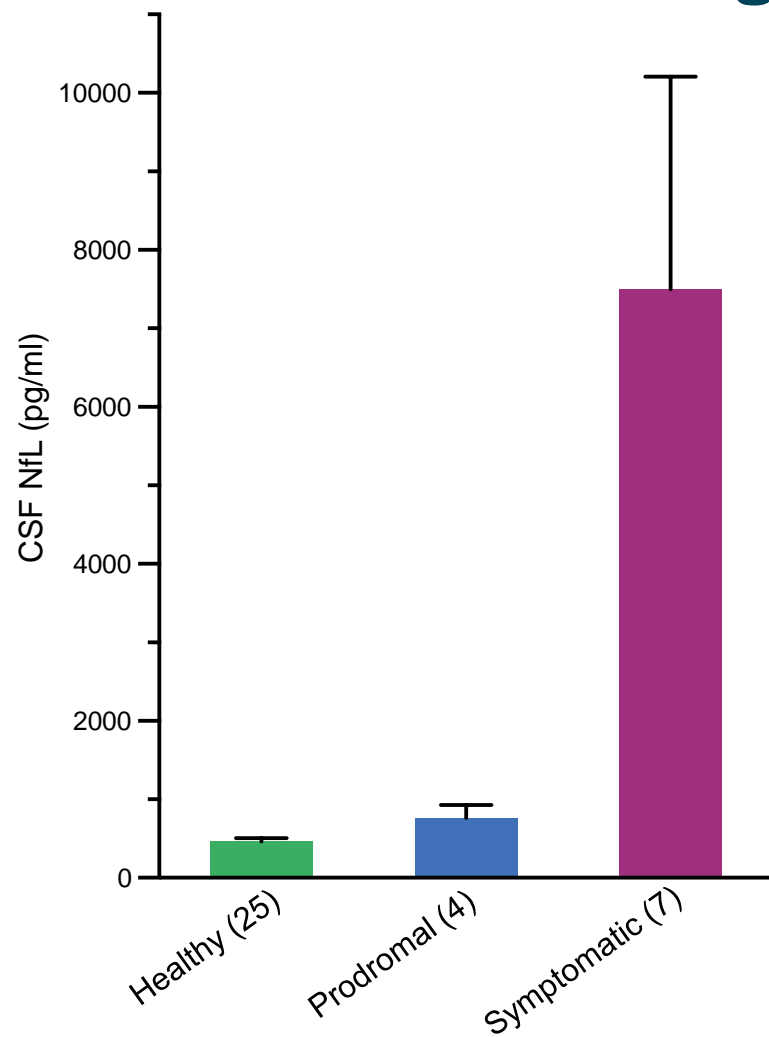
Demonstration of ALSP Progression on MRI

MRI scans of a symptomatic participant in Vigil's ALSP natural history study, ILLUMINATE

| Baseline | 6 Month Scan | 9 Month Scan |
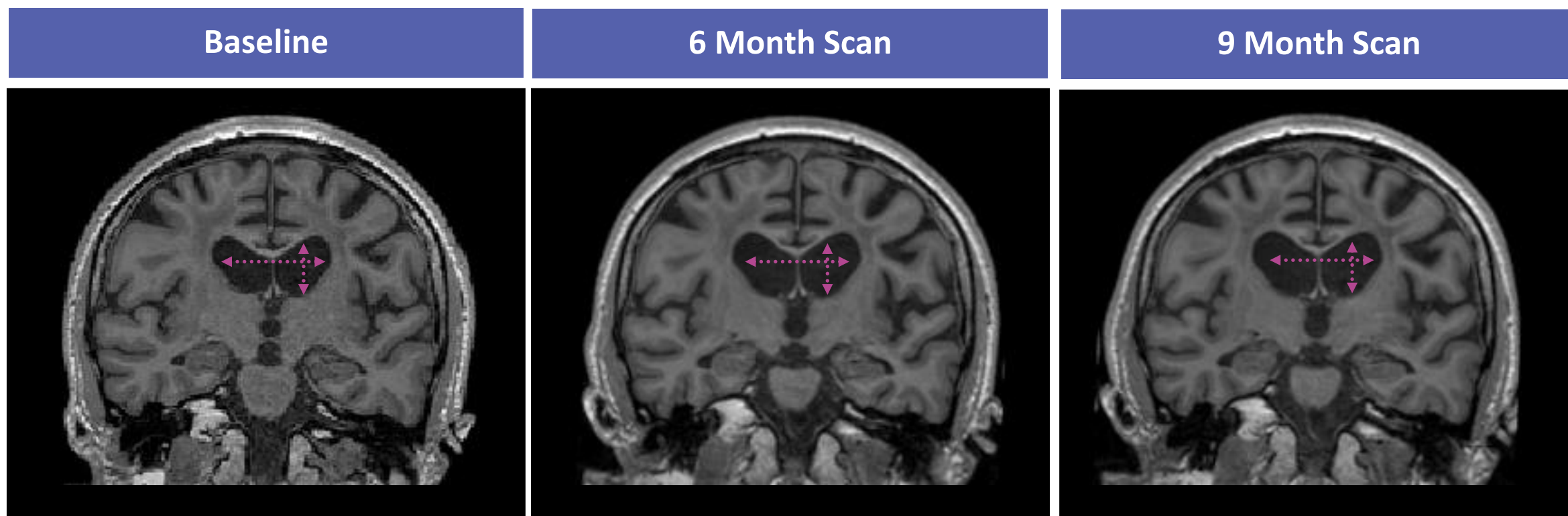
Significantly Elevated Serum NfL Levels in Symptomatic ALSP vs Other Neurodegenerative Diseases

Vigil's ILLUMINATE & IGNITE Interim Data – Key Takeaways

- ILLUMINATE & IGNITE represent 1st ever trials of their kind in ALSP

  - Increasing overall understanding of disease pathophysiology, and biomarkers for disease progression and treatment response

- Positive interim data on VGL101's potential as treatment for ALSP, a devastating disease with no approved therapy

  - Favorable safety and tolerability with an accessible once monthly IV administration

  - Observed differential sCSF1R response in ALSP patients (vs HVs), indicating rescue of microglial activity in ALSP setting

  - Very encouraging changes in MRI and NfL at 6 months compare favorably vs HSCT
    - Indicating impact on disease progression
    - 5 out of 6 patients showed reduction in rate of ventricular expansion
      - Slowing or reduction in ventricular expansion are clinically relevant
      - Even when it works, HSCT needs at least 1 year for observable MRI changes with significant safety/tolerability risks
    - 4 out of 6 patients showed reduction in NfL trajectory in serum or CSF, indicating an impact on neuronal degeneration

  - 1st targeted therapeutic candidate with clinical data in ALSP patients

  - 1st data on TREM2 agonism as a therapeutic approach in a neurodegenerative disease setting

- Excited to continue to participate in IGNITE to generate more data and further evaluate this candidate

Closing Remarks

Ivana Magovčević-Liebisch, PhD, JD
Chief Executive Officer
Vigil Neuroscience, Inc.

Iluzanebart (VGL101): The Only Targeted Therapeutic in Development for ALSP

- ✓ First company to show clinical data on TREM2 agonism as a potential therapeutic approach in patients with a neurodegenerative disease

- ✓ VGL101 demonstrated favorable safety and tolerability, including no hematologic adverse events

- ✓ Clear CNS target engagement and downstream pharmacological activity at 20 mg/kg consistent with Phase 1 data

- ✓ Directionally supportive changes in individual patients at 6 months on MRI and NfL biomarkers

- ✓ Natural History Study continued to provide critical insights on MRI and NfL biomarkers; sCSF1R emerging as key biomarker of ALSP disease pathology

- ✓ Phase 2 IGNITE results from all patients in 20 mg/kg and 40 mg/kg cohorts at 6 months expected in Q3 2024

(vigil)™

Q&A

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