Upstream intervention to address multiple hallmarks of AD

Tackling AD at the roots

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Vivoryon is Uniquely Positioned to Improve Health Outcome in Patients with Early Alzheimer's Disease

Unique First-in-Class Approach

Stops production of neurotoxic N3pE-amyloid

- **Validated MOA:** targeting all key hallmarks of AD (amyloid, tau, neuroinflammation)
- **Avoids mAb constraints:** ARIA, imaging, infusions, costs
- **Large addressable market:** worldwide ~55m people living with dementia, of which estimated 60-70% is AD

Robust Development Program

Phase 2 studies progressing well

- **VIVIAD (EU):** Fully recruited (259 pts), ~82 weeks of treatment, final topline data readout: during end of Q1/2024
- **VIVA-MIND (US):** recent DSMB decision for 600 mg BID – same dose as VIVIAD with faster titration

Proven Team of Innovators

Strong discovery and development

- **Management:** track record of bringing multiple innovative drugs to market
- **Healthy runway:** cash through key value generating milestones into H2/2024
- **Leader** in oral QPCT/L inhibitor small molecule development

AD: Alzheimer's disease

Seasoned Executive Team Equipped with Expertise in Drug Development

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[1] *until March 1, 2024;* [2] *CFO effective March 1, 2024*

Multiple Inflection Points for Lead Asset Varoglutamstat, Research Activities Provide Further Opportunities for Future Growth

Program		Approach	Discovery / Preclinical / Phase 1 / Phase 2a / Phase 2b / Phase 3	Status
AD	Varoglutamstat (PQ912)	SMI QPCT/L	*VIVIAD: Ph2b in EU*; *VIVA-MIND: Ph2a/b in US*	**VIVIAD**: Fully recruited; **Final readout during end Q1/24** **VIVA-MIND**: Treatment duration of 72 weeks
	Varoglutamstat (SIM0408, PQ912)	SMI QPCT/L	*CTA approval in China*	Partnered with Simcere in Greater China; Clinical development in preparation
RESEARCH ACTIVITIES: increased activity with positive VIVIAD results				
AD	NCE	SMI QPCT/L		Pre-IND; Exploring second generation programs in AD
	PBD-C06	mAb N3pE amyloid		Pre-IND; Partnered with Simcere in Greater China
Multiple disease areas	NCE	SMI QPCTL		Pre-IND
Fibrosis	NCE	SMI Meprin		Pre-IND

mAb: monoclonal antibody; NCE: novel chemical entity; SMI: small molecule inhibitor; CTA: Clinical Trial Application

AD Landscape: Growing Incidence Rate and High Disease Burden on Patient Care Ecosystem

~55 Million Worldwide Living with Dementia[1]

AD is the most common form of dementia and may contribute to 60–70% of cases[1]

An estimated 6.7 million Americans are living with AD[2]

~$1.3 Trillion Economic Burden from Dementia[3]

50% attributable to care by informal carer who provides on average, 5 hours of care per day[4]

More than 11 million Americans provide unpaid care for a family member or friend with dementia, a contribution to the nation valued at nearly $340B[2]

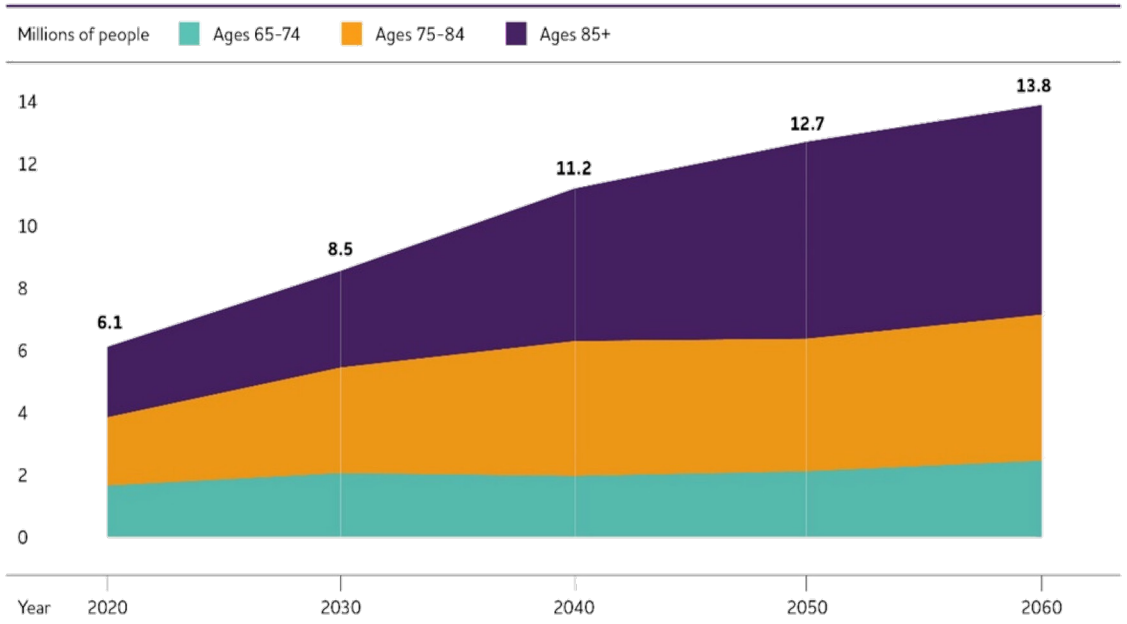
Early AD Represents Significant Unmet Need

Each year, an estimated 10 in every 100,000 individuals develop early onset dementia[5]

Early-onset affects people under the age of 65

Although there is no known cure, early diagnosis and treatment can lead to better quality of life[6]

Projected number of people age 65 and older (total and by age) in the U.S. population with Alzheimer's dementia, 2020 to 2060[2]



Created from data from Rajan et al.[3]

[1,3,4] WHO, 2023, Mar 15, Dementia, www.who.int/*/fact-sheets/detail/dementia; [2] 2023 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2023;19(4); [5] Alzheimer's Association, 2021, Jul 21, Press Release; [6] Johns Hopkins Medicine, 2023, Nov 08, www.(*)/alzheimers-disease/earlyonset-alzheimer-disease

Overcoming Challenges In Alzheimer's Disease – Our Solution

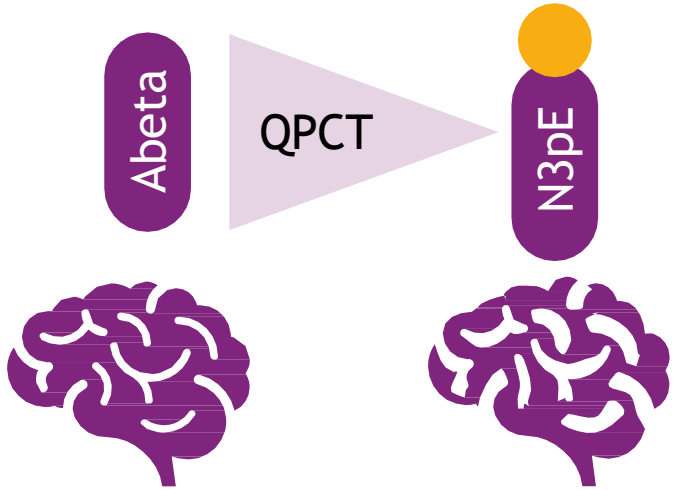
ONGOING CHALLENGES IN AD

- Recent advances with **mAbs** (e.g. lecanemab, donanemab) show promise, but come with **significant limitations**
- **Multitude of clinical studies, but statistical significance** does **not necessarily** imply a **meaningful drug** to individual patients and their caregivers
- **Lack of meaningful endpoints** to enable reliable evaluation of study data for correlation to real-life benefit
- **Meaningful trial design** is needed to leverage existing data to select the right patients/appropriate treatment duration
- **New modalities** are needed to address hallmarks of AD beyond Abeta

VIVORYON'S APPROACH

Discovered QPCT-mediated formation of a neurotoxic Abeta variant, N3pE-Abeta (pGlu-Abeta), as driver of AD pathology[1,2]

Pioneering small molecule-based therapies designed to prevent N3pE-Abeta formation - rather than aiming to clear existing plaques[3]



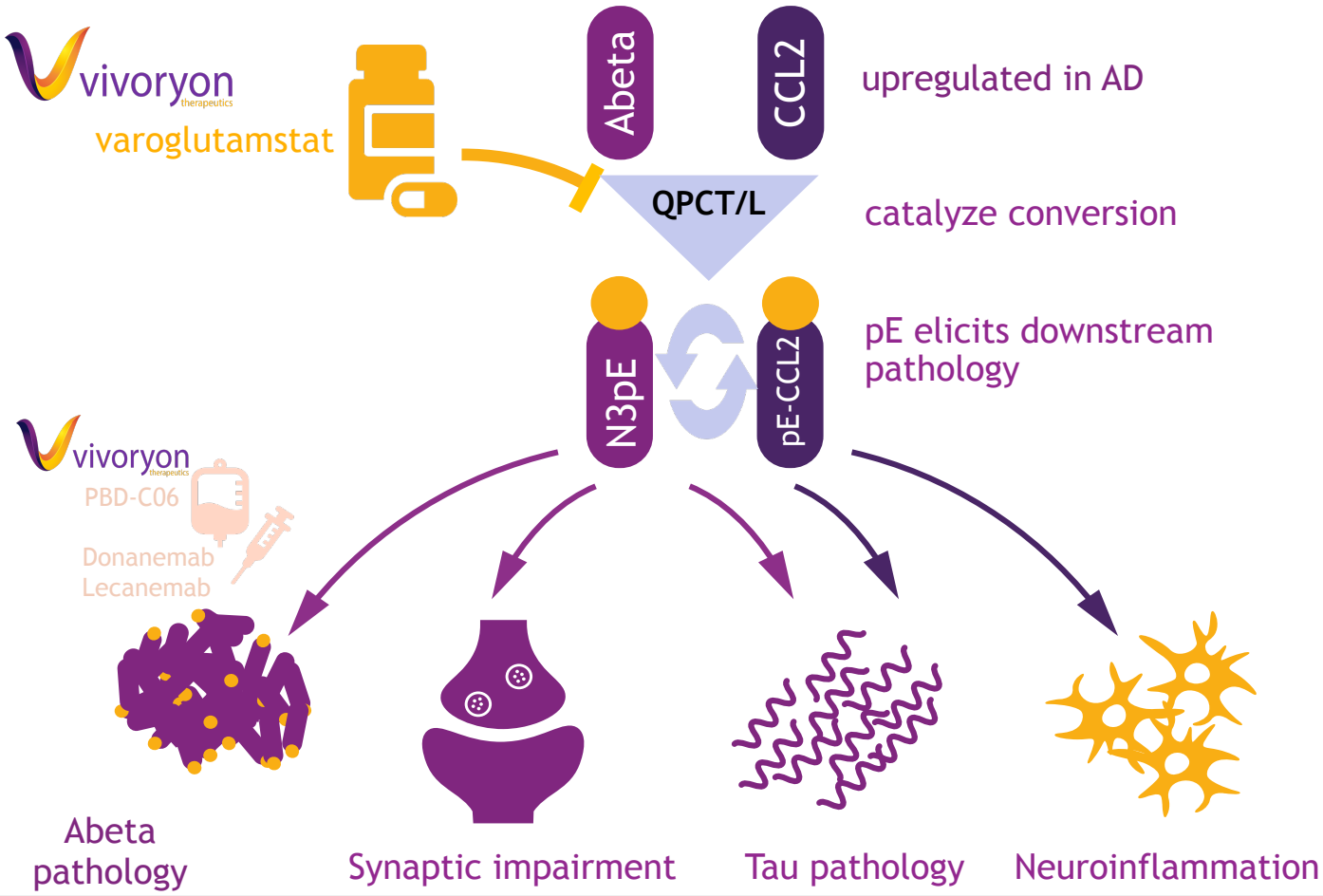
[1] Schilling et al., Nat. Med. 2008; [2]Grochowska et al., EMBO 2017; [3]Buchholz et al., J. Med. Chem 2006, Nussbaum et al., Nature 2012

Our Lead Product Candidate, Varoglutamstat, Targets Multiple Key Hallmarks of Alzheimer's Disease Early in Pathological Process

ROLE OF QPCT/L IN AD PATHOLOGY

- Increased activity of glutaminyl cyclase (QPCT) is associated with AD pathology in humans[1]
- QPCT catalyzes formation of neurotoxic N3pE-Abeta- which is not found in healthy individuals. [2,3]
- Varoglutamstat efficiently inhibits QPCT, thus targeting N3pE-Abeta monomer formation and all of its aggregation states[4]
- Varoglutamstat also efficiently inhibits QPCTL (isoform of QPCT) leading to decreased neuro-inflammation by attenuating CCL2 activity[5]
- Low MMSE scores correlate with high N3pE-Abeta, high QPCT levels, high pE-CCL2 and high QPCTL levels in AD patients[3,5]
- QPCT/L activity is the key driver of a pathologic cycle involving neuroinflammation, pE-CCL2 and N3pE-Abeta[5]

VAROGLUTAMSTAT TARGETS AD PATHOGENESIS EARLY-ON



[1] Gunn et al., J.Neurochem 2021; [2] Schilling et al., Nat. Med. 2008; [3] Morawski et al., JAD 2014; [4] Upadhaya et al., Brain 2014; [5] Hartlage-Rübsamen et al., Acta Neuropathol, 2015;

Translating *In Vivo* Evidence for Relevance of QPCT/L Inhibition into Human AD

Abeta Pathology	QPCT is essential for N3pE amyloid formation *in vivo*[1] 5XFAD mice, QPCT ko and tg	QPCT/ N3pE	Dose-dependent reduction of QPCT activity in CSF & serum (Ph1 + Ph2a)
Neuroinflammation Tau Pathology	CCL2 activity promotes neuroinflammation and accelerates tau pathology[2] rTg45105 mice, CCL2 AAV	CCL2/ Tau	Dose-dependent decrease of pE-CCL2 in serum (Ph1)
Cognition	QPCT inhibition improves cognitive parameters in AD mouse models[3] hAPPSLxhQPCT mice, MWM	Cognition/ Memory	Statistically significant changes from baseline in working memory as measured by CogState (Ph2a)

[1]*Jawhar et al., 2011;* [2]*Joly-Amado et al. 2020; Hartlage-Rübsamen et al., 2015;* [3]*Hoffmann et al., 2017*

Building Comprehensive Robust Clinical Evidence Including Well-designed and Well-powered Placebo-controlled Phase 2b Program

Phase 1
205 volunteers

- Dose range: 10-1800 mg single dose; 20-800 mg BID
- CSF based PK/PD model
- Fed / fasted and 3 formulations

Phase 2a
120 patients

- 12w of treatment
- Evidence of positive effect on synaptic recovery
- MTD reached at 800mg BID
- Discontinuation rates show room for improvement

Phase 2b: VIVIAD
259 patients

Q1 2024

- Average of >80w of treatment anticipated
- Slower up-titration to 600mg BID improves tolerability while maintaining high target occupancy
- Results during end of Q1/2024

Phase 2a/b: VIVA-MIND
180/414 patients

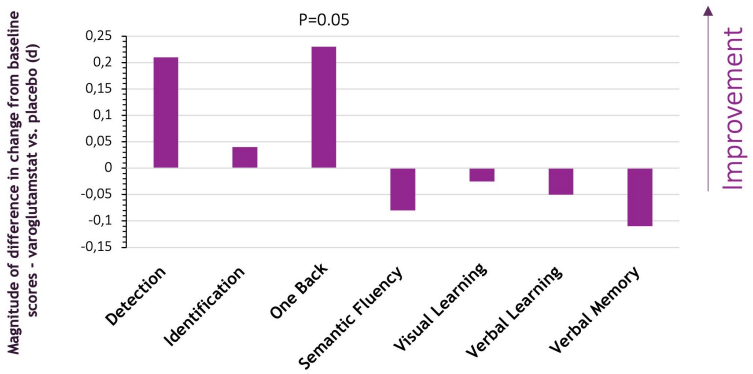
- Treatment duration of 72w in Phase 2a portion
- Complementary to VIVIAD with adaptive design and approvable regulatory endpoints (CDR-SB)
- Potential to expand into Phase 3

Results-dependent regulatory strategy

- **Option for accelerated/conditional approval if Phase 2b VIVIAD results are supportive**
- **Option for amendment of VIVA-MIND to full confirmatory Phase 3 study**

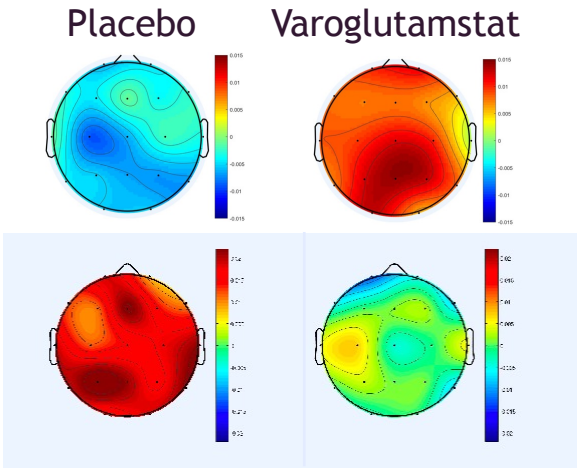
Completed Phase 2a SAPHIR Study Provides Evidence of Significant Changes in Working Memory and Synaptic Recovery after only 12 Weeks of Treatment

Significant Changes in Working Memory[1]



- Statistically significant changes from baseline in working memory (One Back Test, p = 0.05, d = 0.23, ITT) in AD patients after 12 weeks of treatment

Recovery EEG Synaptic Activity[1,2]

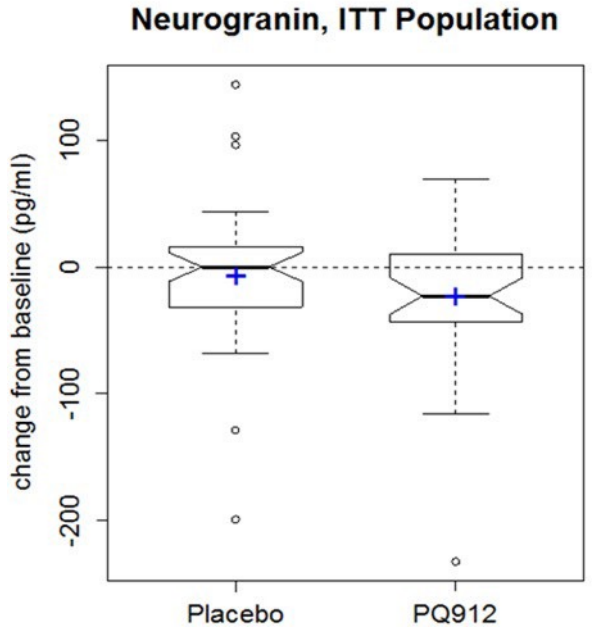


Alpha wave neuronal connectivity

Theta wave synaptic dysfunction

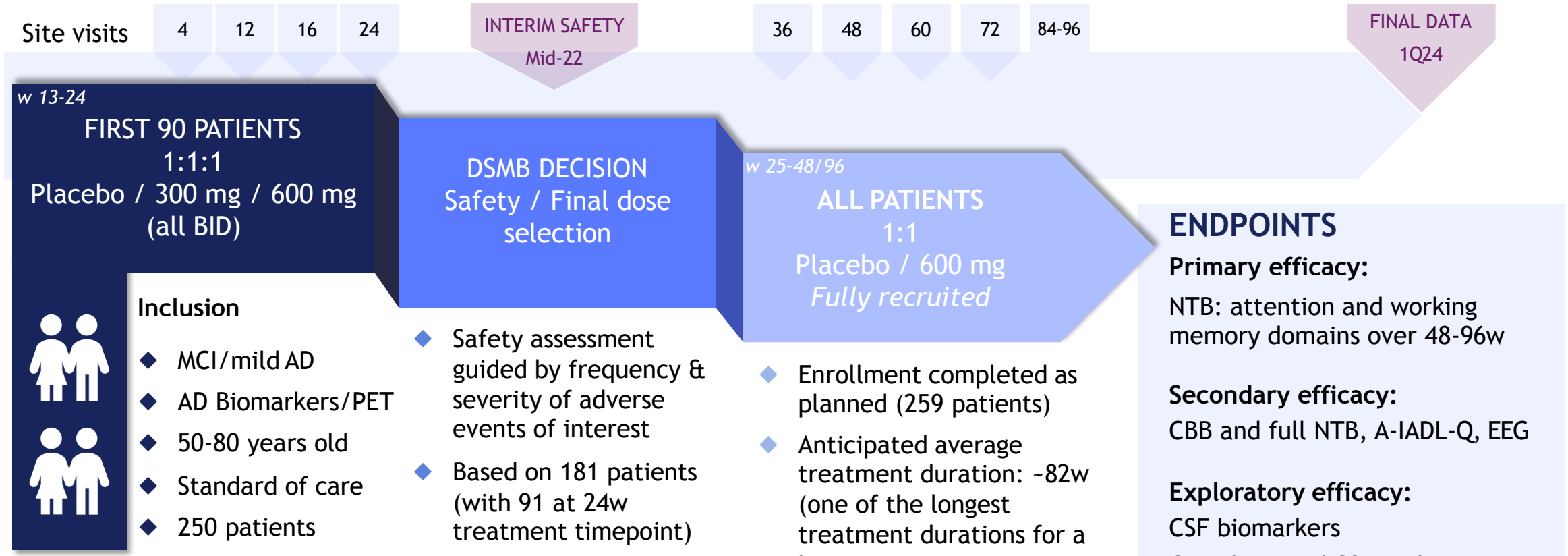
- Significant (p=0.002, ITT and PP) decrease in theta power
- Post hoc analysis of alpha wave: significant increase on connectivity - amplitude envelope correlation (AEC) p=0.025

Reduction of Neuronal Injury Biomarker[1]



[1]Scheltens et al., Alzheimer's Research & Therapy, 2018; [2]Briels et.al., Clinical Neurophysiol. 2020

VIVIAD Phase 2b European Study Assesses Safety, Tolerability and Efficacy of Varoglutamstat in Patients with MCI and Mild AD[1,2]



ENDPOINTS

Primary efficacy:

NTB: attention and working memory domains over 48-96w

Secondary efficacy:

CBB and full NTB, A-IADL-Q, EEG

Exploratory efficacy:

CSF biomarkers

Correlation of CSF with serum biomarkers

Winterlight Speech Assessment

A-IADL-Q: Amsterdam IADL Questionnaire; *BID: twice daily; CBB: Cogstate Brief Battery; DSMB: data safety monitoring board; PET: positron emission tomography;* [1]*https://clinicaltrials.gov/ct2/show/NCT04498650,* [1]*Vijverberg et al.; Alzheimer's Research & Therapy 2021,* [2]*Weber et al., AAIC 2022, poster P1-403, abstract 69290*

VIVIAD Phase 2b: Inclusion Criteria Enabled Precision Recruitment

Recruiting the right patients with early AD is a critical success factor for VIVIAD

BASIC REQUIREMENT:

- Mandatory for inclusion: all patients had low Abeta and high p-tau CSF values (Elecsys/Roche)

RETHINKING MCI ASSESSMENT:

- Precision recruitment of individuals with at least minimal cognitive impairment by using the WAIS IV inclusion criterion (at least half a standard deviation worse than age and education matched healthy population)

➢ **Study population exactly represents early AD population**

	N	Mean	Median	SD	Value
Age	259	68,44	70	7,40	63 to 74
MMSE total score - V1	259	24,51	25	2,73	22 to 27
WAIS-IV total score - V1	259	27,75	28	12,36	19 to 37

VIVIAD Update: Discontinuation Rates are Favorable and Comparably Low

Metric	Varoglutamstat VIVIAD (blinded)	Lecanemab CLARITY AD (placebo/active)	Donanemab TRAILBLAZER ALZ 2 combined tau (placebo/active)
# of patients	259	1,734	1,736
Duration	~78 weeks*	72 weeks	76 weeks
Total Discontinuations	12.7%*	15.6% / 18.8%	19.7% / 26.9%
Discontinuations due to AE	3.5%*	2.9% / 6.9%	2.4% / 5.8%

Observations:

- Total number of discontinuations remains low in VIVIAD throughout the study at <13%* (blinded data)
- Safety update at recent data cut-off confirms low number of discontinuations due to AEs in VIVIAD throughout the study at <4%* (blinded data)
- Studies are of comparable treatment duration

*Cut-off November 20, 2023

Delivering Comprehensive Dataset Through Well-Designed VIVIAD Study in Q1/24

Positioning varoglutamstat as a first-line, single-agent therapy for patients with early AD

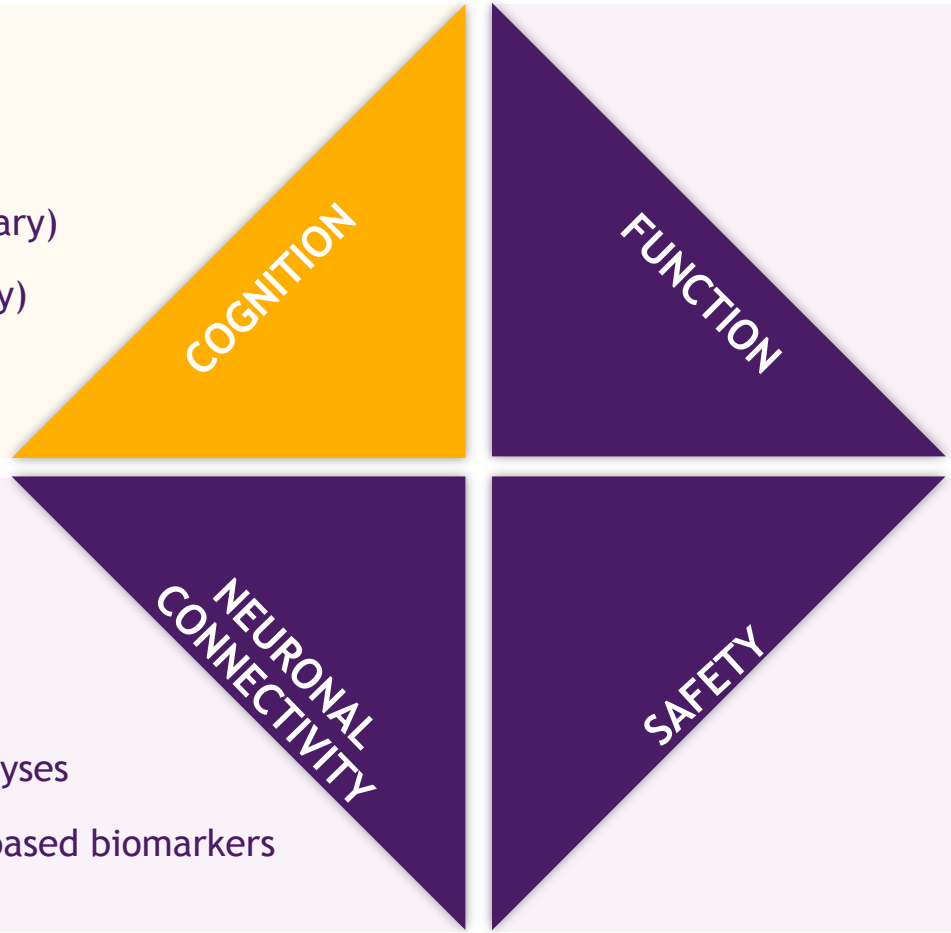
Can varoglutamstat improve cognition?

Endpoints:

Cogstate NTB (primary/secondary)

Winterlight Speech (exploratory)

WAIS-IV coding test/DSST (exploratory)



Can varoglutamstat improve activities of daily living?

Endpoint:

A-IADL-Q (key secondary)

Can varoglutamstat restore neuronal networks?

Endpoints:

EEG theta power (secondary)

Selected EEG connectivity analyses

Large panel of CSF and blood-based biomarkers (exploratory)

Does varoglutamstat have the right risk/benefit ratio?

Endpoints:

Discontinuation due to adverse events

TEAE (serious, severe)

ARIA / MRI

VIVA-MIND Update: Recent DSMB Decision Leads to Progress and Enables Further Study Design Flexibility

- Ongoing Phase 2 study running in parallel to VIVIAD to provide clear picture of cognitive changes and support Vivoryon's regulatory strategy
- Adaptive study design involving titration, futility and expanded efficacy evaluation following VIVIAD

600 mg 2x daily | Treatment duration = 72 weeks | 1:1 Randomization

Phase 2a
- Adaptive dose-finding portion of study: DSMB recommended 600 mg BID
- n=180 patients

→

Phase 2b
- Seeks to enroll an additional 234 patients at 600 mg BID

→

Option to Amend to Phase 3
- Based on adaptive design of study
- Contingent on VIVIAD study results and regulatory discussions

Primary Endpoint:
- Clinical dementia rating scale – sum of boxes (CDR-SB)

Key Secondary Endpoints:
- ABC score
- Quantitative EEG-relative theta wave power
- FAQ (Functional Activities Questionnaire)
- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog-13)
- Neuropsychiatric Inventory

ADNI ABC: neuropathologic assessment; BID: twice daily; DSMB: data safety monitoring board; https://clinicaltrials.gov/ct2/show/NCT03919162

Leveraging Core Expertise in QPCT/L Oral Small Molecule Inhibitors to Generate Multiple Avenues of Addressing Unmet Need

ALZHEIMER'S DISEASE

- Established program in Early AD with varoglutamstat including product life cycle management
- New small molecule oral second generation QPCT/L inhibitors with improved profile
- Building AD franchise with potential NCE oral QPCT/L
- Discovery efforts underway

CHRONIC KIDNEY DISEASE

- VIVIAD provides unique opportunity to assess long-term effect of varoglutamstat on kidney function measured by biomarkers in elderly subjects
- QPCT/L inhibitors have shown strong pharmacological evidence to reduce inflammatory and fibrotic processes in kidney

QPCT/L Small Molecule Inhibitor Platform & Related Pathways

CANCER/NASH/CNS/other

- Researching novel second generation QPCT/L NCE lead molecules with improved profile for disorders not requiring blood brain barrier penetration

AKI/FIBROSIS

- Novel meprin alpha/beta single and dual selective small molecule inhibitors
- *In vivo* proof of concept in AKI animal model
- Unique recognition pattern allows design of selective and specific meprin protease inhibitors

AKI: acute kidney injury; NASH: nonalcoholic steatohepatitis; CNS: central nervous system; QPCT: glutaminyl cyclase; QPCTL glutaminyl cyclase-like protein; QPCT/L glutaminyl cyclase and glutaminyl cyclase-like protein

Core Asset Varoglutamstat Well-Positioned to be a Leader in QPCT/L for Early AD, Future Opportunities Build on AD and Go Beyond

Aiming for first line single agent treatment of patients with early AD

- Only product in late-stage development addressing neurotoxic N3pE-Abeta formation[1]
- Not limited to clearing existing plaques
- Well-tolerated
- No signs of product related ARIA in clinical setting
- Convenient oral administration
- Maintaining synaptic and neuronal functionality

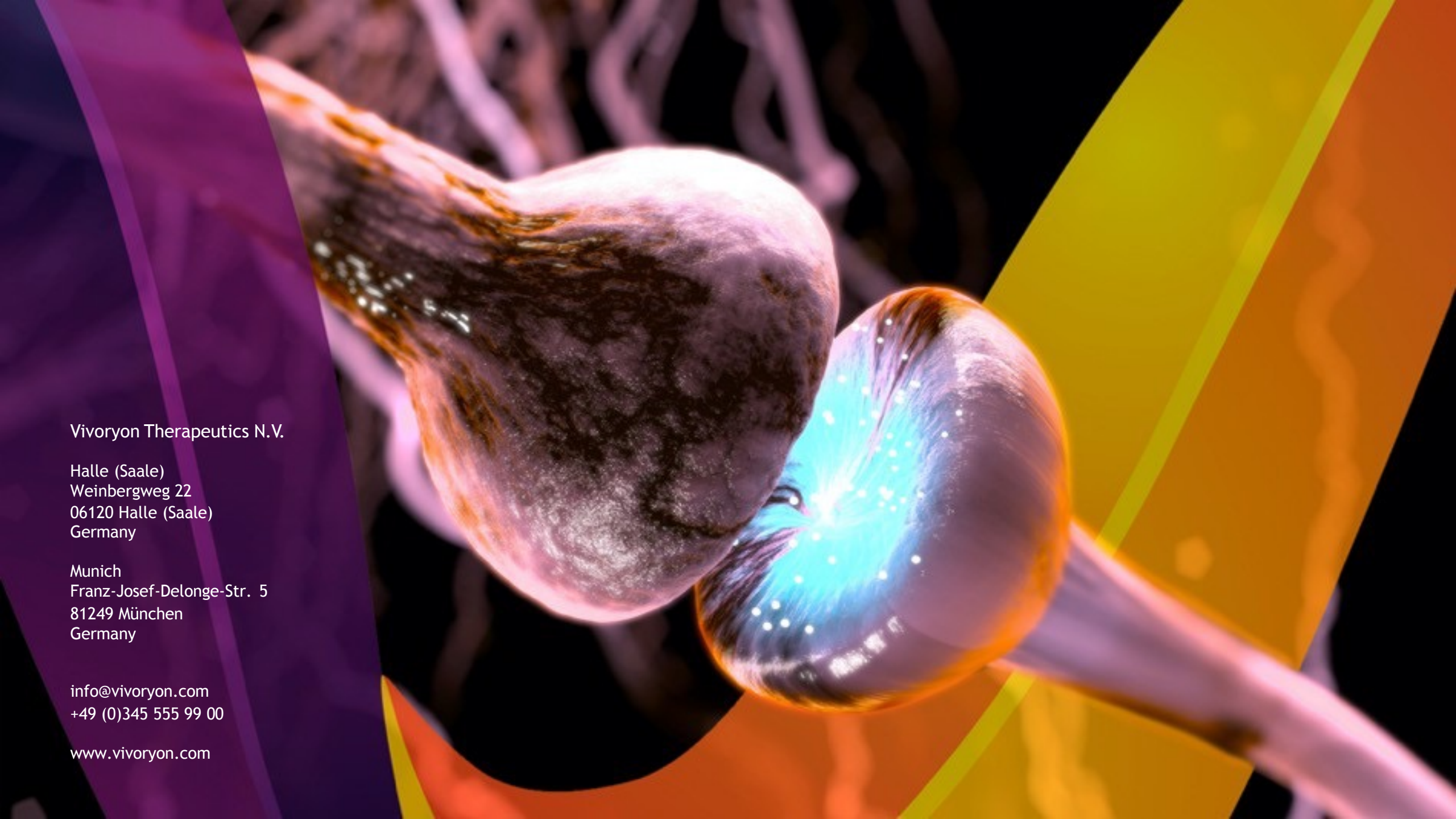
VIVIAD learnings to inform future opportunities in AD and additional indications

- Varoglutamstat future opportunities:
  - Expand target patient population to capture asymptomatic and moderate AD patients
  - Combination with / follow-on to mAbs in AD
  - Development in Greater China with Simcere
- Unveiled growth strategy with activities to further advance broader pipeline of discovery-stage QPCT/L inhibitors and related pathways

Multiple Value-Generating Catalysts Ahead

- VIVIAD European Phase 2b final topline results during end of Q1/2024
- Continue recruitment of VIVA-MIND at 600 mg twice daily post recent DSMB decision
- End of Phase 2 meeting with FDA planned for H2/2024 leveraging VIVIAD data

[1] *Vijverberg et al., 2021*



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