# vivoryon therapeutics

Tackling AD at the roots: early intervention to address multiple hallmarks of AD

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# VIVORYON THERAPEUTICS

# Investment Highlights

- Enzyme inhibition for targeted intervention: Modulating the activity of proteins altered in disease settings
- Lead product candidate varoglutamstat in AD: Phase 2a evidence of disease-modifying activity and FDA Fast Track designation:
  - ◆ Statistically significant (p = 0.05, d = 0.23¹) change from baseline in working memory after 3-months treatment
  - Upstream intervention with dual MoA: Targeting Abeta and CCL2 modulation
  - Addresses all three major hallmarks of AD: Abeta aggregation, neuroinflammation and tau pathology, as well as synaptic function
  - Preclinical evidence provides strong therapeutic rationale for combining varoglutamstat with monoclonal Abeta antibodies to treat AD<sup>2</sup>; future opportunity to explore varoglutamstat in combinations with own and external assets
- Ongoing Phase 2b program in AD designed towards clear path to potential regulatory approval<sup>3</sup>
- Oral small molecule: Good blood-brain-barrier penetration, intracellular activity, attractive COGS
- ◆ Large pharma partnership deals: Simcere (QPCT/L in AD; Greater China regional partnership potentially worth up to US\$ 565 M), OSI/Astellas (DPP4), AstraZeneca (CDK9)
- Follow-up programs in oncology, inflammatory diseases/NASH and AKI/fibrosis
- ◆ Strong IP including composition of matter coverage beyond 2035



# EXPERIENCED LEADERSHIP

Seasoned Biopharma Experts Covering All Relevant Aspects of Drug Development

## MANAGEMENT



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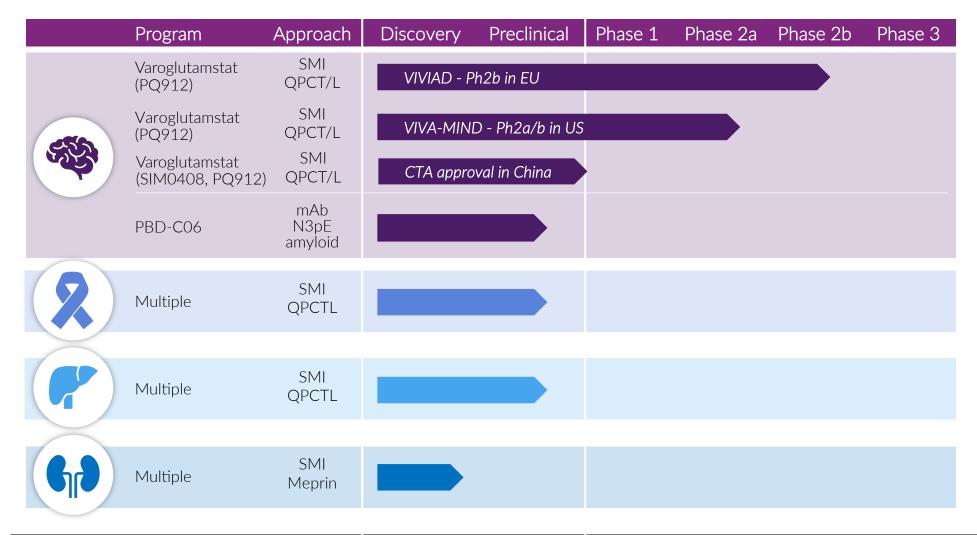
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# DIVERSE PIPELINE ADDRESSING SEVERE INDICATIONS





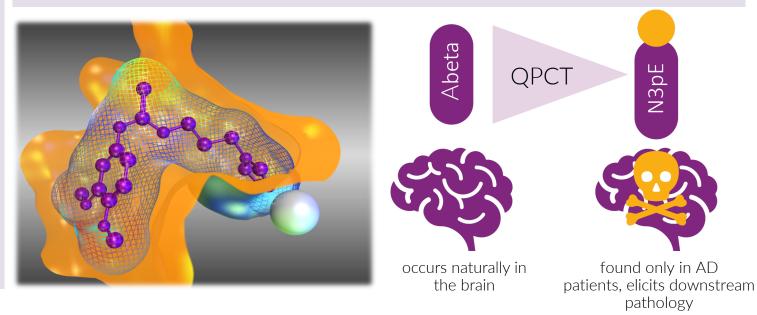
# ALZHEIMER'S DISEASE

## THE BURDEN

- ~30 million people suffering from AD worldwide, number expected to double by 2050, with ~12.7 million in the US alone
- Heavy burden on patients, families, caregivers and the public healthcare system
- No cure available, five established drugs on the market address symptoms only
- Aducanumab recently approved amid controversial discussion on reduced Abeta plaque load as surrogate marker for cognitive improvement

## A PATH FORWARD

- VVY discovered QPCT-mediated formation of a neurotoxic Abeta variant,
   N3pE amyloid (pGlu-Abeta), as driver of AD pathology<sup>1,2</sup>
- VVY is developing small molecule inhibitors to prevent N3pE amyloid formation - rather than aiming to clear existing plaques<sup>3</sup>





# DRUG DEVELOPMENT IN ALZHEIMER'S DISEASE

## THE CHALLENGE

- ◆ Low success rate and long development phase delay new treatments and discourage investment in AD drug development
- Studies across drug development programs have identified important strategies for decreasing the risk and increasing the likelihood of success in drug development programs
- ◆ These experiences provide guidance for our approach to AD drug development

# THE "RIGHTS" OF AD DRUG DEVELOPMENT1





Targets appropriate biologic process for AD therapeutic intervention



Right Drug

Has appropriate PK/PD profile, brain distribution, preclinical efficacy and safety in Phase 1



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## Right Biomarkers

Guide participant selection, monitor target engagement, disease modification and side effects



## Right Participants

Are in appropriate phase of AD (preclinical, prodromal, dementia)



Is prudently designed and run as well-powered study with appropriate endpoints and duration

Right Trial



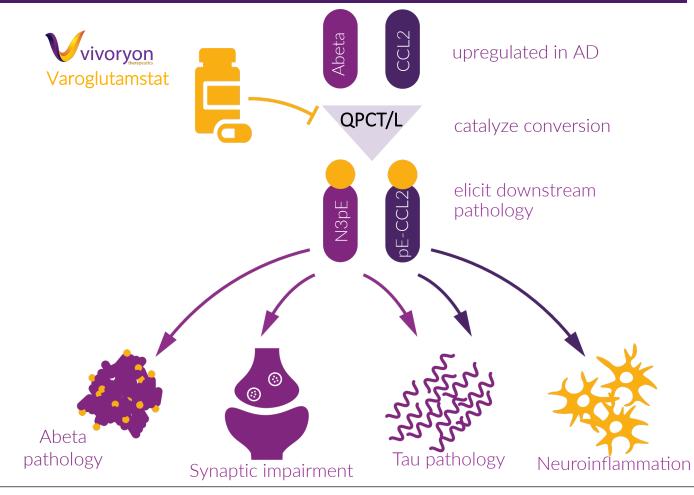
# TARGETING QPCT/L IN AD

Validated Target for Intervention Upstream of Pathological Processes

## ROLE OF QPCT/L IN AD PATHOLOGY

- Increased activity of glutaminyl cyclase (QPCT) is associated with AD pathology in humans<sup>1</sup>
- QPCT catalyzes formation of neurotoxic N3pE amyloid by cyclization of N-terminal glutamate on Abeta<sup>2</sup>
- N3pE amyloid correlates with QPCT expression and MMSE status in AD patients and is not found in healthy individuals<sup>3</sup>
- Varoglutamstat targets all aggregation states of Abeta as N3pE is equally present in soluble and insoluble forms of Abeta<sup>4</sup>
- Targeting QPCTL (isoform of QPCT):
  - ◆ Inhibits neuroinflammation by modulating CCL2 activity
  - ◆ Increased levels of QPCTL and high pE-CCL2 levels correlate strongly with low MMSE scores<sup>5</sup>

## NEUROTOXIC N3PE DRIVES AD PATHOLOGY





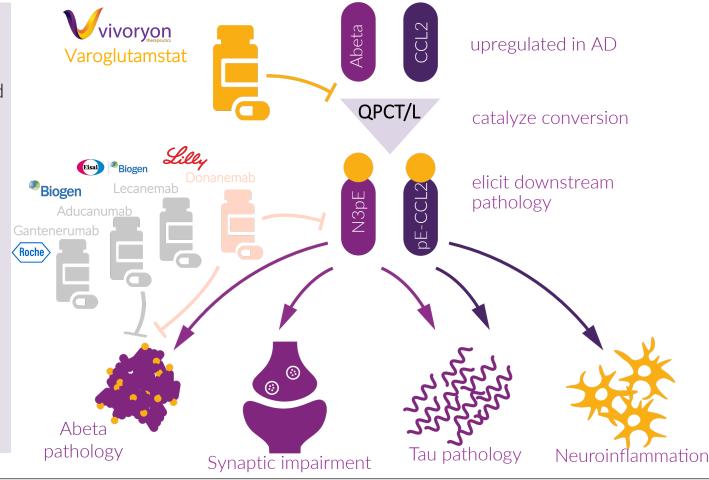
# TARGETING MULTIPLE PATHOGENETIC HALLMARKS OF AD

Varoglutamstat Inhibits Formation of Toxic Abeta Species Upstream of Other Approaches

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#### VAROGLUTAMSTAT TARGETS UPSTREAM PATHOGENESIS





# VAROGLUTAMSTAT: POTENTIAL TO ALTER THE COURSE OF AD

Translating in vivo Evidence for Relevance of QPCT Inhibition into Human AD



Neuroinflammation Tau Pathology

Cognition



QPCT is essential for N3pE amyloid formation in vivo<sup>1</sup> 5XFAD mice, QPCT ko and tg

CCL2 activity promotes neuroinflammation and accelerates tau pathology<sup>2</sup> rTg45105 mice, CCL2 AAV

QPCT inhibition improves cognitive parameters in AD mouse models<sup>3</sup>



QPCT/ N3pE

Dose-dependent reduction of QPCT activity in CSF & serum (Ph1 + Ph2a)

CCL2/ Tau

Dose-dependent decrease of pE-CCL2 in serum (Ph1)

Cognition/ Memory

Statistically significant changes from baseline in working memory as measured by CogState (Ph2a)



# CLINICAL DEVELOPMENT STRATEGY

Clear Path To Potential Regulatory Approval Extensive Phase 1 and Phase 2 trials





# Preclinical research In vitro and in vivo studies

#### **COMPLETED**

- QPCT inhibition improves cognitive parameters in AD mouse models
- QPCT is essential for N3pE amyloid and pE-CCL2 formation in vivo



#### Phase 1



#### COMPLETED

 Varoglutamstat is welltolerated – no DLT at 800mg twice daily or up to 3.6g once daily

#### Phase 1

Assessment of safety and tolerability in 60 healthy Chinese volunteers

Planned H1/2022



#### Phase 2a SAPHIR

Assessment of safety and tolerability in 120 patients with early AD

#### COMPLETED

- Statistically significant changes from baseline in working memory after only 3 months of treatment (as measured by CogState)
- High target occupancy detected at doses of 150 mg BID and above



#### Phase 2b VIVIAD

Assessment of safety, tolerability and efficacy in 250 Patients MCI and mild AD

Interim safety readout mid-22; final readout H2/2023

 Endpoints: safety, attention/working memory, NTB, biomarkers

#### Phase 2a/b VIVA-MIND

Assessment of efficacy and safety in 414 patients with early AD

Stage-gate to Ph2b H1/2023

 Endpoints: safety, attention/working memory, CDR-SB, biomarkers

# Pivotal study or accelerated approval

- FDA Fast Track designation granted in 2021
- Two possible scenarios for late-stage development
  - Application for accelerated approval (based on consistent/ positive data of Phase 2b studies)
  - Phase 3 clinical development



# SAPHIR- GUIDING PHASE 2B TRIAL DESIGN

### COGNITION

- ◆ Statistically significant changes from baseline in a working memory parameter within 3 months (One Back Test)
- ◆ Notable changes from baseline in attention (Detection Test, Identification Test)

#### CSF BIOMARKERS

- ◆ Strong QPCT-inhibition (target occupancy >80% at 600 mg BID, >70% at 300 mg BID)
- ◆ Reduction of neuroinflammatory and synaptic markers (pE-CCL2, YKL40, neurogranin)

### SYNAPTIC FUNCTION (EEG)

- ◆ Statistically significant reduction in theta power (marker
- ◆ Notable changes from baseline in functional

## INFORMED TRIAL DESIGN OF EU PHASE 2B

#### **DOSING**

- DLT reached at 800 mg BID; reported AEs mostly mild to moderate, fully reversible (skin and gastrointestinal)
- Varoglutamstat is well-tolerated at doses resulting in high target occupancy (600 mg BID)
- Dose adjustments for Phase 2b to prevent AEs while maintaining high target occupancy

#### **PLANNING**

- Composite Attention/Working Memory Simulation selected as Primary Endpoint
- Robust statistical planning with 3 CogState parameters (one back test, detection, identification)
- Based on available Phase 2a data matched with large historical control data set on longitudinal rate of progression for identical cognitive composite

# MULTIPLE AVENUES TO VALUE GENERATION

Diverse Pipeline of Oral Small Molecule Inhibitors to Address Exceptionally High Medical Need

## ALZHEIMER'S DISEASE

- Small molecule oral QPCT/L inhibitors with good blood-brain barrier penetration
- Inhibits production of N3pE amyloid (pGlu-Abeta): neurotoxic, glutaminylated, soluble Abeta peptides
- Statistically significant effects on CSF biomarkers, synaptic function & working memory after 12w treatment

## CANCER

- Small molecule OPCTL inhibitors to modulate cancer immune checkpoint activity
- Precision intervention to modulate the activity of pro-metastatic chemokines of the CCL family
- Opportunity for combination therapies



## INFLAMMATION/NASH

- Small molecule QPCTL inhibitors to modulate the CCL2-CCR2 axis
- In vivo proof of concept in NAFLD mice
- Investigated as single agent and in combination with meprin inhibitors

## **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



# QPCTL INHIBITION IN CANCER

Opportunity to Develop Oral Small Molecule Inhibitors in Immuno-Oncology

## BACKGROUND

- Large unmet medical need remains to effectively and safely treat cancer patients
- Combination therapies as powerful tool
- Evidence for therapeutic potential of:
  - Interfering with metastasis: modulating potency/stability of CCL chemokines
  - Leveraging the power of innate immunity: target the CD47-SIRPα axis

# OUR APPROACH

- Selective small molecule QPCTL inhibitor prevents:
  - Post-translational modification of CD47 to pE-CD47
  - Full maturation of CCL 2, 7, 8, and 13 to pE-CCL2, 7, 8 and 13 leading to decreased potency and stability

## **OPPORTUNITY**

- Novel orally administered small molecule approach with differentiated mode of action: no antigen sink effect, potential for improved tumor penetration
- Large patent portfolio:
  - Composition of matter and indication coverage with expirations beyond 2035

# IN VITRO PROOF OF CONCEPT

- In vitro/in vivo evidence of synergies with other immunotherapies rituximab, daratumumab, trastuzumab, cetuximab:
  - Combination increases phagocytosis and cytotoxicity over single agent activity



# QPCTL INHIBITION IN INFLAMMATION/NASH

Opportunity to Develop Oral Small Molecule Inhibitors in Inflammatory Kidney and Liver Diseases

## BACKGROUND

- Non-alcoholic fatty liver disease (NAFLD) is a chronic hepatic disorder characterized by steatosis in early stages, leading to non-alcoholic steatohepatitis (NASH) in more advanced stages
- NASH is expected to become the leading cause of liver transplantation in the US in the coming years
- Significant medical need to find effective therapies to manage NASH

## **OPPORTUNITY**

- Novel orally available compounds with a differentiated mode of action targeting a subclass of therapeutically relevant chemokines
- In vitro/in vivo evidence of decreased inflammatory macrophages, and reduced liver fibrosis
- Large patent portfolio:
  - Composition of matter and indication coverage with expirations beyond 2035

# OUR APPROACH

- Treatment of NAFLD by modulating the monocyte/macrophage-related immune response in affected livers using a QPCT/L inhibitor
- CCL2 is upregulated in liver inflammation, our QPCTL inhibitor is used to destabilize CCL 2

# IN VIVO PROOF OF CONCEPT

 In vivo NASH model (STAM<sup>TM</sup>) demonstrated reduction of inflammation score, inflammatory cytokines like CCL2 and TNFalpha



# MEPRIN INHIBITION IN AKI/CKD

Opportunity to Develop Oral Small Molecule Inhibitors In Fibrosis and Kidney Diseases

## BACKGROUND

- The estimated incidence rate of acute kidney injury (AKI) during hospitalization in the US is 2-5%, it arises in more than 50% of intensive care unit patients
- More than 1 in 7, that is 15% of US adults or 37 million people, are estimated to have chronic kidney disease (CKD)
- Significant medical need to find effective therapies to manage AKI/CKD

## **OPPORTUNITY**

- Novel orally available picomolar small molecule inhibitors targeting metalloproteases meprin alpha and/or beta
- In vivo evidence of kidney protection in cisplatin induced AKI model
- Large patent portfolio:
  - Composition of matter and indication coverage with expirations beyond 2037

# **OUR APPROACH**

- Block collagen remodeling in fibrosis by selectively inhibiting the meprin protease
- Provide kidney protection for patients treated with cytostatics by co-medication with meprin inhibitor

- IN VIVO PROOF OF CONCEPT
- Evidence of kidney protection in cisplatin induced AKI model
- Effect on clinical parameters for kidney function demonstrated with with knockout animals and small molecule compound



# VIVORYON THERAPEUTICS

Summary

# PRESENT FOCUS

# **FUTURE OPPORTUNITIES**

# **UPCOMING CATALYSTS**

Differentiated upstream approach targeting all three major hallmarks of AD

Allows intervention very early in disease pathogenesis

Lead candidate varoglutamstat in clinical Phase 2b in AD

> FDA granted Fast Track designation in 2021

Phase 2a data showing statistically significant changes in working memory

Regional partnership with Simcere:

Development opportunities for varoglutamstat and PBD-C06 in AD in Greater China

Investigating potential to develop varoglutamstat in combination with mAbs in AD (own and external assets)

Advancing follow-up programs into the clinic beyond AD



