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Topline Results from The Phase 2 VIVA-MIND Study Varoglutamstat (PQ912) in Early AD

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Background

- PQ912 (varoglutamstat) is an oral small molecule inhibitor of glutaminy cyclases (QC) and isoglutaminy cyclases (IsoQC) which reduce the pyroglutamate formation of A β and CCL2 respectively.
- Inhibiting formation of these post-translationally modified proteins is associated with benefits in preclinical AD models.
- In Ph1, a wide range of doses with good safety and tolerability was established with threshold levels of QC inhibition achieved.
- In early Ph2A (SAPHIR), encouraging preliminary biomarker and clinical results were reported¹ that support further Ph2 development.

Design and Methods

- A seamless Ph2A-B double-blind placebo-controlled RCT evaluating efficacy and safety of PQ912 in Early AD (NCT03919162)²
- Ph2A tests 3 descending doses (600mg, 300mg, 150mg BID) using a continuous Pocock safety boundary
- Decision of advancing to Ph2B is guided by a Stage Gate futility analysis of the first 180 subjects at Week 24

Objectives

- Selecting the highest safe and well-tolerated dose of PQ912
- Evaluating the longer-term safety and efficacy of this dose

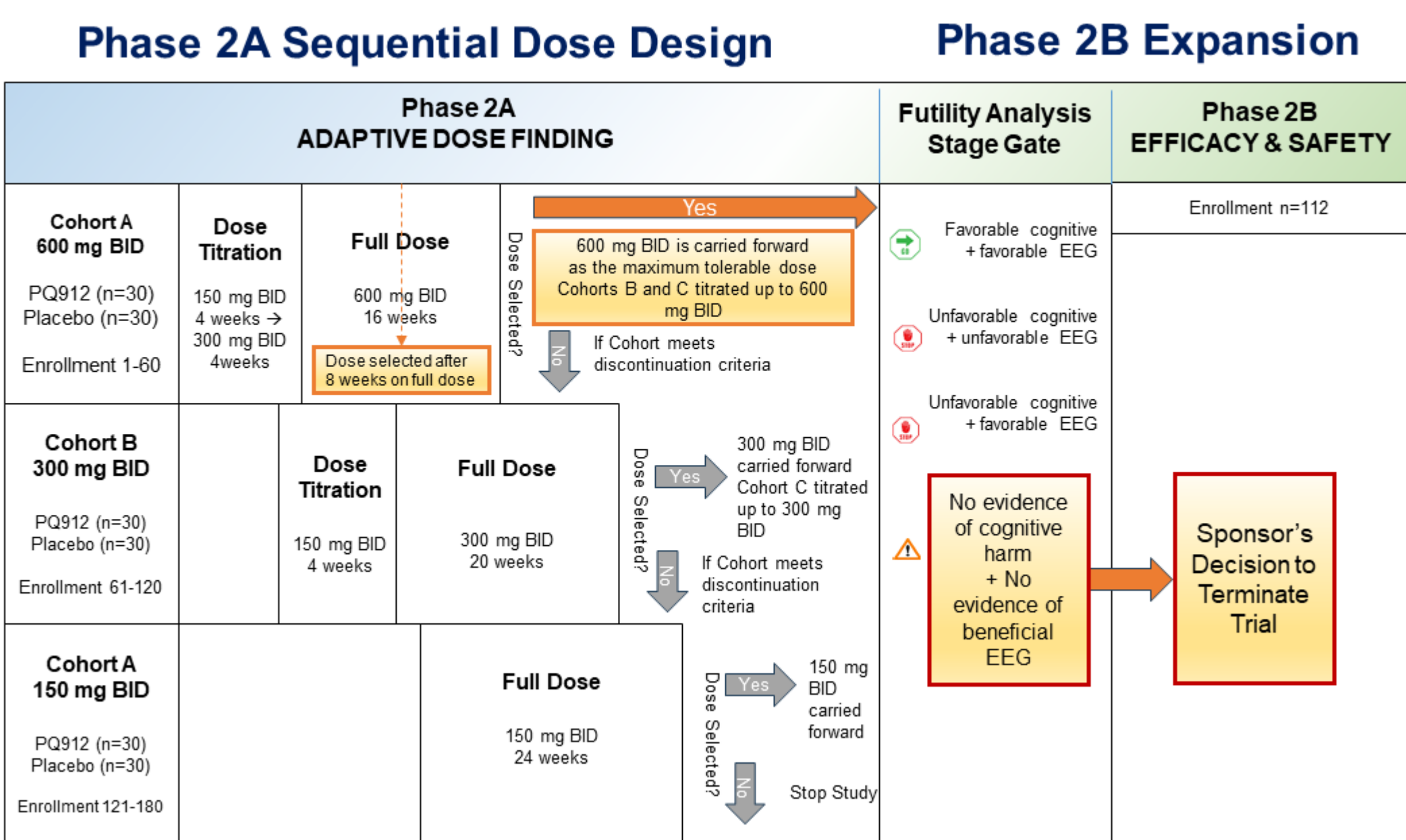
Key Inclusion Criteria

- Ages 50-89
- Diagnosis of MCI due to AD or mild probable AD dementia
- Mini-Mental State Examination (MMSE) 20-30
- Montreal Cognitive Assessment (MoCA) < 26
- Clinical Dementia Rating global 0.5 or 1 with memory > 0.5
- Positive CSF AD biomarker signature
- MRI consistent with AD diagnosis
- Study partner with frequent participant interaction

Key Exclusion Criteria

- Non-AD neurodegenerative diseases
- Meeting diagnostic criteria for Possible AD
- Liver impairment Child-Pugh class A or more severe
- History of moderate or severe skin reactions to medications
- Current moderate/severe skin or subcutaneous disease
- Major depressive episode $\leq$ 6 months of screening
- History of diagnosis of schizophrenia
- Uncontrolled bipolar disorder $\leq$ 5 years of screening
- Seizures disorder $\leq$ 2 years of screening
- Contraindication to lumbar puncture and MRI

Figure 1. Study Design



Results

- Baseline demographics were similar across treatment arms (Table 1).
- The first dose cohort of PQ912 (Figure 1) either 600mg or placebo BID did not cross the safety boundary in Ph2A, supporting this dose selection for all participants thereafter.
- The trial was terminated prematurely (Sponsor's decision) prior to the Ph2A stage gate.
- An abbreviated futility analysis was conducted, with the provisional result of 'halt enrollment.'
- There were no significant differences between PQ912 and placebo in LS mean change from baseline to week 72 in primary or secondary outcomes (Figure 3 and Table 2).

Table 1. Baseline Characteristics

Baseline Characteristics of mITT Subjects				
Variable		PQ912 (n = 52)	Placebo (n = 57)	P-value
Age		72.9 $\pm$ 8.3	70.8 $\pm$ 7.4	
Sex - no. (%)	Female	24 (46.2)	30 (52.6)	
APOE genotype - no. (%)	E-4 carrier	34 (65.4)	44 (80.0) ^a	0.14 ^b
	Non-carrier	18 (34.6)	11 (20.0) ^a	
Initial diagnosis - no. (%)	MCI due to AD	30 (57.7)	38 (66.7)	0.44 ^b
	Mild probable AD	22 (42.3)	19 (33.3)	
MoCA total score		18.8 $\pm$ 3.5	19.3 $\pm$ 3.7	
MMSE total score		24.3 $\pm$ 2.8	24.9 $\pm$ 2.7	
CDR-SB score		3.35 $\pm$ 1.53	2.99 $\pm$ 1.70	

Percentages shown are column percentages; Plus-minus values are means $\pm$ standard deviations

^an = 55 placebo is the denominator in the calculation of percentages for APOE genotype

^bP-value following Chi-square tests

Figure 3. Primary Efficacy Measure: CDR-SB Least Square Mean Change

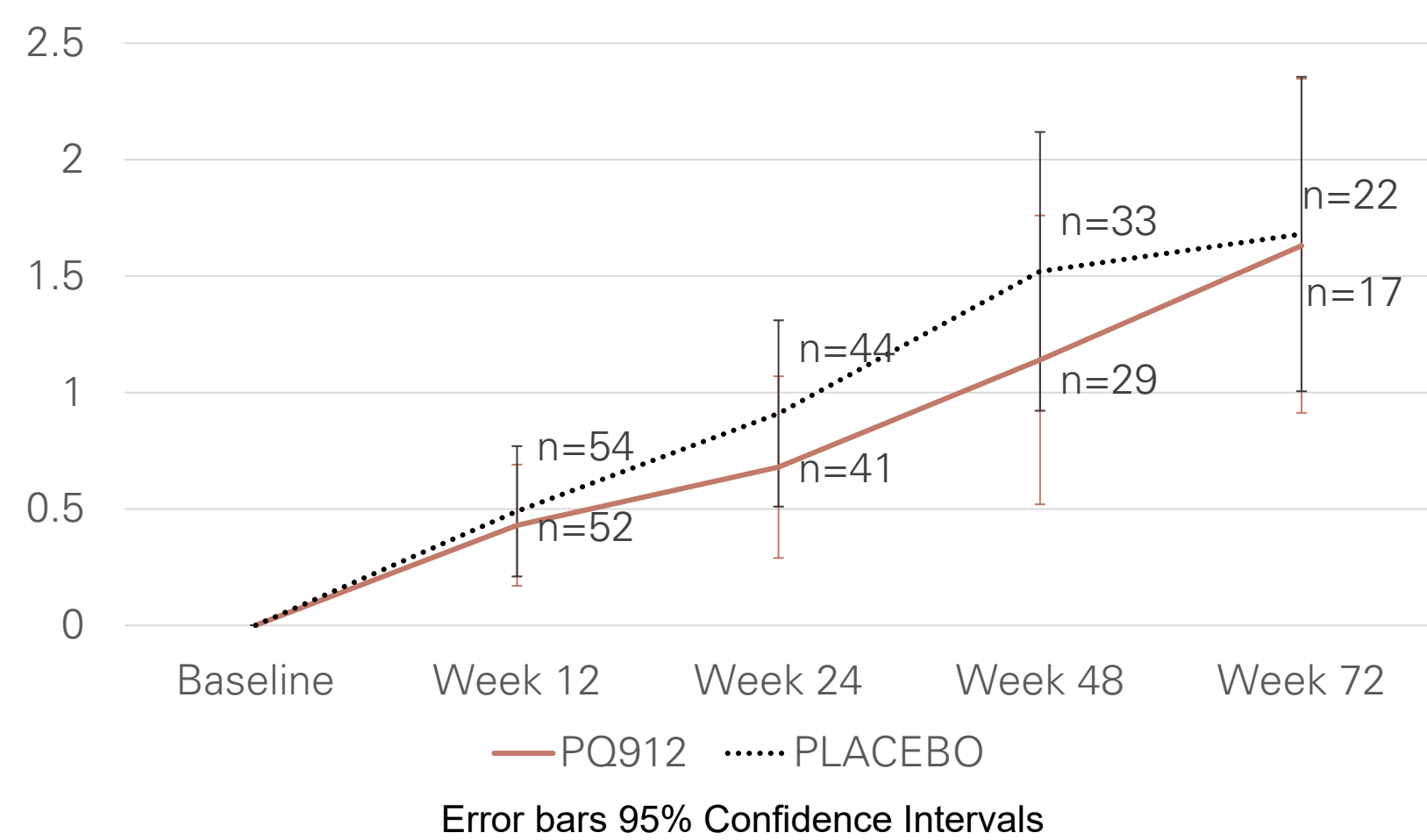


Table 2. Secondary Efficacy Measures

Outcome	Timepoint	PQ912 LS Mean Change	Placebo LS Mean Change	Difference LS Mean Change	95% CI	p-value
CFC2	Week 24	-1.996	-2.875	0.878	-1.220, 2.977	0.4083
	Week 48	-4.847	-5.971	1.124	-1.755, 4.003	0.4385
	Week 72	-6.694	-7.664	0.969	-3.345, 5.283	0.6528
ABC Score	Week 24	-0.156	-0.214	0.058	-0.036, 0.152	0.2261
	Week 48	-0.325	-0.332	0.007	-0.149, 0.164	0.9268
	Week 72	-0.278	-0.378	0.100	-0.103, 0.303	0.3241
qEEG	Week 24	0.01749	0.02275	-0.00526	-0.02017, 0.00964	0.4814
	Week 72	-0.01123	0.01734	-0.02857	-0.06746, 0.01032	0.1398
FAQ	Week 24	1.66	1.99	-0.33	-1.79, 1.13	0.6538
	Week 48	3.37	3.12	0.25	-1.88, 2.38	0.8157
	Week 72	4.36	4.97	-0.60	-4.22, 3.01	0.7377
ADAS-Cog-13	Week 24	0.525	1.625	-1.100	-3.648, 1.448	0.3930
	Week 48	3.167	3.629	-0.461	-3.761, 2.838	0.7808
	Week 72	6.377	4.343	2.034	-2.292, 6.360	0.3496
NPI	Week 24	0.25	0.52	-0.28	-2.42, 1.87	0.7989
	Week 48	1.73	1.66	0.06	-2.95, 3.08	0.9677
	Week 72	-0.14	2.95	-3.09	-7.81, 1.62	0.1933

- CFC2 includes ADAS-Cog-13 Word Recall and Orientation, CDR Cognitive, and FAQ Total Score
- ABC Score includes a composite of 9 measures from the ADNI Neuropsychological Test Battery
- qEEG = "qEEG Global Relative Theta Wave Power"

Safety Results

- Overall rates of TEAEs did not differ significantly between PQ912 and Placebo (Table 3)
- Profiles of TEAEs and attribution to system organ class and preferred terms are shown in Tables 3 and 4.

Table 3. Participants with TEAEs (During Treatment)

Category	PQ912 n=53	Placebo n=56
Any TEAE	45 (84.9)	43 (76.8)
Mild*	18 (34.0)	23 (41.1)
Moderate*	21 (39.6)	16 (28.6)
Severe*	6 (11.3)	4 (7.1)
Any related TEAE	17 (32.1)	18 (32.1)
Serious TEAE	10 (18.9)	5 (8.9)
AESI	1 (1.9)	3 (5.4)
TEAE leading to any study drug dose modification (excluding discontinuation)	4 (7.5)	4 (7.1)
TEAE leading to study drug discontinuation	5 (9.4)	2 (3.6)
TEAE leading to death	2 (3.8)	0
Total number of deaths	2 (3.8)	0

*each is counted only once in the most severe category

Table 4. Safety: System Organ Class (>10% Frequency) & Preferred Terms of Note During Treatment

System Organ Class	PQ912 n=53	Placebo n=56	p-value
Preferred Term			
Infections and infestations	17 (32.1)	17 (30.4)	1.000
Gastrointestinal disorders	15 (28.3)	14 (25.0)	0.829
Diarrhea	9 (17.0)	5 (8.9)	0.259
Injury, poisoning and procedural complications	12 (22.6)	15 (26.8)	0.662
Nervous system disorders	6 (11.3)	13 (23.2)	0.132
Headache	2 (3.8)	4 (7.1)	0.679
Dizziness	1 (1.9)	5 (8.9)	0.207
Skin and subcutaneous tissue disorders	11 (20.8)	6 (10.7)	0.190
Rash maculo-papular	2 (3.8)	1 (1.8)	0.611
Psychiatric disorders	8 (15.1)	9 (16.1)	1.000
Investigations	5 (9.4)	10 (17.9)	0.269
Alanine aminotransferase increased	1 (1.9)	3 (5.4)	0.619
Blood creatine phosphokinase increased	1 (1.9)	2 (3.6)	1.000
Musculoskeletal and connective tissue disorders	11 (20.8)	4 (7.1)	0.052
Back pain	5 (9.4)	1 (1.8)	0.107
General disorders and administration site conditions	6 (11.3)	7 (12.5)	1.000

Conclusions

- PQ912 was safe and well-tolerated in this VIVA-MIND early AD RCT.
- Efficacy assessment did not demonstrate any significant treatment benefits however, the available sample size was limited.
- Biomarker results and PK/PD are pending.

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