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Final Results: PORTICO a double-blind, randomized placebo-controlled, adaptive phase IIb trial to assess vafidemstat's efficacy in treating borderline personality disorder

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Background: Borderline personality disorder (BPD) is a common mental health disorder with an estimated prevalence in the general adult population between 0.5% and 5.9% and higher in clinical settings (up to 10% in psychiatric outpatients and 20% of psychiatric inpatients). Despite the disease burden, there are no approved pharmacologic treatments, and psychotherapy is the only treatment. Vafidemstat is an oral, brain penetrant, irreversible inhibitor of the histone lysine demethylase LSD1, in development for CNS conditions. Vafidemstat increased sociability and memory, and decreased aggression across different animal models, and reduced agitation and aggression in several clinical trials (e.g., REIMAGINE-EUDRA CT# 2018-002140-88).

The primary aims of the PORTICO Phase IIb BPD trial were to investigate the efficacy of vafidemstat in the treatment of agitation and aggression, as well as overall disease in adult BPD patients.

Table 1. Baseline Demographics*

Demographic Characteristic	Statistic	Placebo (N=104)	Vafidemstat (N=106)	Overall (N=210)
Psychotherapy at Baseline	N	82 (78.8%)	84 (79.2%)	166 (79.0%)
	Y	22 (21.2%)	22 (20.8%)	44 (21.0%)
	P-value Chi-Square Test		0.9434	
Age	Mean (SD)	31.8 (10.89)	32.4 (10.68)	32.1 (10.76)
	Median	29.0	31.0	30.0
	(Q1, Q3)	(23.0, 37.5)	(23.0, 40.0)	(23.0, 38.0)
	Min, Max	18.0, 63.0	18.0, 64.0	18.0, 64.0
	Mean Difference (SE) vs. Placebo		0.6 (1.49)	
	95% CI: Difference vs. Placebo		(-2.3, 3.5)	
	P-value T-Test vs. Placebo		0.6926	
Race	Asian	7 (6.7%)	4 (3.8%)	11 (5.2%)
	Black Or African American	7 (6.7%)	9 (8.5%)	16 (7.6%)
	White	86 (82.7%)	87 (82.1%)	173 (82.4%)
	Other	4 (3.8%)	6 (5.7%)	10 (4.8%)
	P-value Chi-Square Test		0.6927	
Sex	Female	79 (76.0%)	78 (73.6%)	157 (74.8%)
	Male	25 (24.0%)	28 (26.4%)	53 (25.2%)
	P-value Chi-Square Test		0.6918	
BMI (Kg/m^2)	Mean (SD)	26.6 (4.48)	26.0 (4.89)	26.3 (4.69)
	Median	26.2	25.3	25.8
	(Q1, Q3)	(23.1, 29.9)	(21.8, 29.4)	(22.5, 29.7)
	Min, Max	18.8, 35.3	18.7, 46.3	18.7, 46.3
	Mean Difference (SE) vs. Placebo		-0.6 (0.65)	
	95% CI: Difference vs. Placebo		(-1.9, 0.7)	
	P-value T-Test vs. Placebo		0.3478	
Height (cm)	Mean (SD)	168.4 (10.36)	167.4 (9.09)	167.9 (9.73)
	Median	167.0	167.0	167.0
	(Q1, Q3)	(160.0, 175.6)	(162.0, 172.7)	(161.0, 173.0)
	Min, Max	147.3, 192.0	144.8, 190.5	144.8, 192.0
	Mean Difference (SE) vs. Placebo		-0.9 (1.34)	
	95% CI: Difference vs. Placebo		(-3.6, 1.7)	
	P-value T-Test vs. Placebo		0.4861	
Weight (kg)	Mean (SD)	75.8 (16.05)	73.0 (15.91)	74.4 (16.00)
	Median	74.6	71.3	73.0
	(Q1, Q3)	(64.7, 88.3)	(61.8, 82.6)	(62.5, 85.2)
	Min, Max	40.8, 114.8	45.8, 122.5	40.8, 122.5
	Mean Difference (SE) vs. Placebo		-2.8 (2.21)	
	95% CI: Difference vs. Placebo		(-7.1, 1.6)	
	P-value T-Test vs. Placebo		0.2138	

** Safety Population*

Methods: PORTICO was a randomized, double-blind placebo-controlled, adaptive 14-week Phase IIb trial (NCT04932291) with two primary independent endpoints, the Borderline Personality Disorder Checklist (BPDCL) and CGI–Severity focused on agitation and aggression (CGI-S A/A). Secondary efficacy endpoints included the Borderline Evaluation of Severity over Time (BEST) and State-Trait Anger Expression Inventory-2 (STAXI-2). Additional secondary endpoints included the Beck Depression Inventory-II (BDI-II) and State-Trait Anxiety Inventory (STAI) as covariates, as well as safety. Exploratory efficacy endpoints included the Agitation-Aggression Psychiatric Inventory-Clinician Report (AAPI-CR), Brief Assessment of Cognition (BAC), and Columbia-Suicide Severity Rating Scale (C-SSRS).

Figure 1. PORTICO Study Design

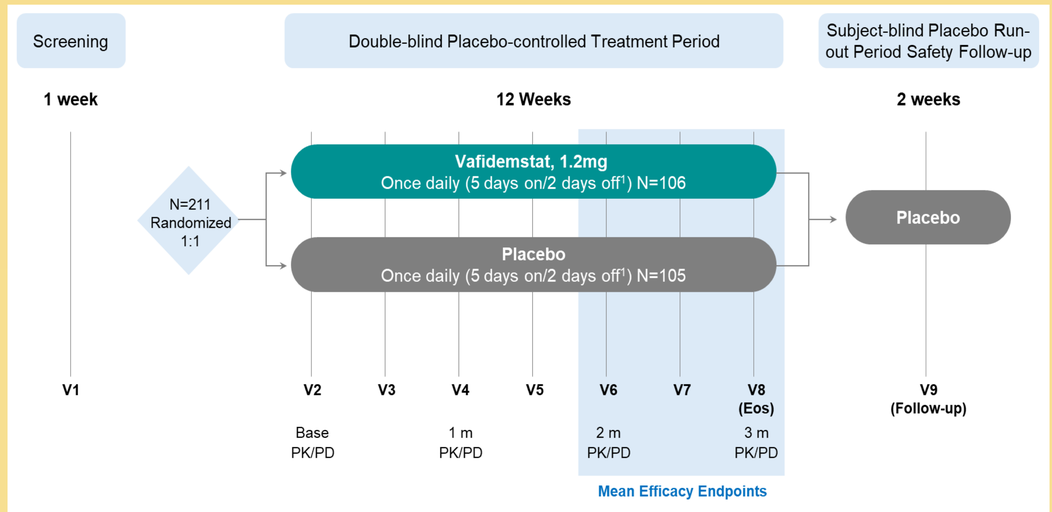


Table 2. Treatment-Emergent Adverse Events (TEAEs)*

Category	Placebo (N=104) n (%), e	Vafidemstat (N=106) n (%), e	Overall (N=210) n (%), e
Treatment-Emergent AEs (TEAEs)	68 (65.4%), 214	61 (57.5%), 192	129 (61.4%), 406
Treatment-Related TEAEs	33 (31.7%), 68	36 (34.0%), 91	69 (32.9%), 159
TEAEs Leading to			
Study Discontinuation	1 (1.0%), 1	5 (4.7%), 8	6 (2.9%), 9
Study Drug Withdrawal	1 (1.0%), 1	5 (4.7%), 8	6 (2.9%), 9
Study Drug Interruption	3 (2.9%), 4	5 (4.7%), 7	8 (3.8%), 11
TEAEs by Severity	68 (65.4%), 214	61 (57.5%), 192	129 (61.4%), 406
Mild	60 (57.7%), 157	51 (48.1%), 128	111 (52.9%), 285
Moderate	35 (33.7%), 52	29 (27.4%), 57	64 (30.5%), 109
Severe	4 (3.8%), 5	5 (4.7%), 7	9 (4.3%), 12
TEAEs by Outcome	68 (65.4%), 214	61 (57.5%), 192	129 (61.4%), 406
Recovered/Resolved	66 (63.5%), 174	56 (52.8%), 165	122 (58.1%), 339
Not Recovered/Not Resolved	17 (16.3%), 29	14 (13.2%), 18	31 (14.8%), 47
Recovering/Resolving	9 (8.7%), 10	8 (7.5%), 9	17 (8.1%), 19
Recovered/Resolved With Sequelae	1 (1.0%), 1	0 (0.0%), 0	1 (0.5%), 1
Death	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0
Unknown	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0

** Safety Population*

Results: A total of 211 participants were randomized 1:1 to vafidemstat 1.2 mg or placebo and followed for 14 weeks. There were no meaningful differences in baseline demographics or characteristics between treatment groups (Table 1). Statistical significance was not achieved on the primary endpoints (BPDCL, p=0.3839 & CGI-S A/A, p=0.2266) – Figure 2. Nominal statistical significance was obtained on the BEST Total Score (p=0.0260) and STAXI-2 Trait Anger (p=0.0071), reflecting a 30.9% decrease in overall BPD disease and 58.6% decrease in agitation/aggression compared to placebo (Figure 2). A forest plot of all primary and secondary efficacy endpoints favored vafidemstat over placebo, and a multivariate global statistical test (GST) was statistically significant (p=0.0362) – Figure 3.

Treatment-Emergent Adverse Events (TEAEs) were slightly lower in those receiving vafidemstat, though Treatment-Related TEAEs were similar between groups (Table 2). The majority of TEAEs recovered or resolved (Table 2). There were no deaths in PORTICO, suicidal ideation was low, and intentional self-injury was lower in the vafidemstat-treated group (0.9%) versus placebo (5.8%) – data not shown.

Figure 2. Evolution over time of CGI-S A/A, BPDCL, STAXI-2 Trait Anger, and BEST scales in patients treated with vafidemstat or placebo

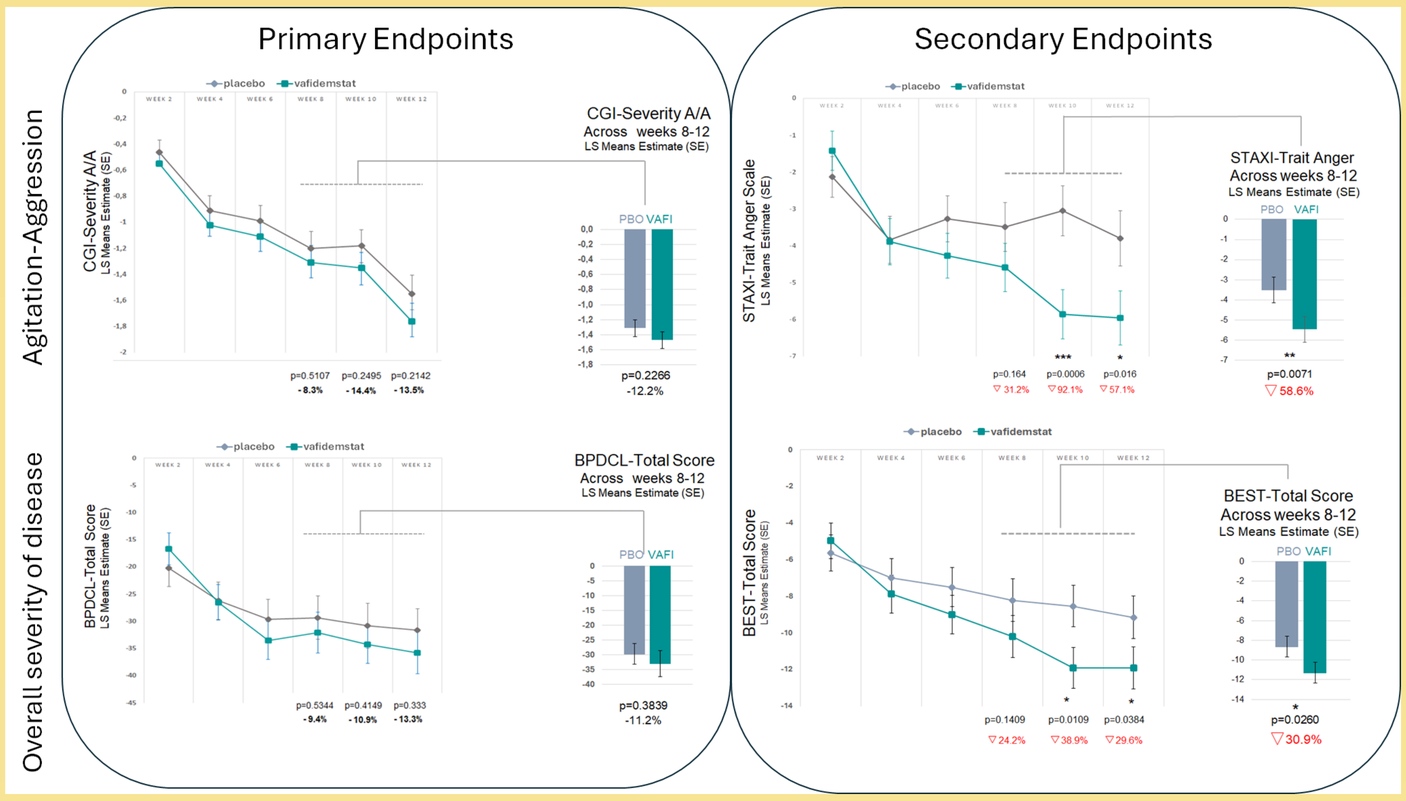
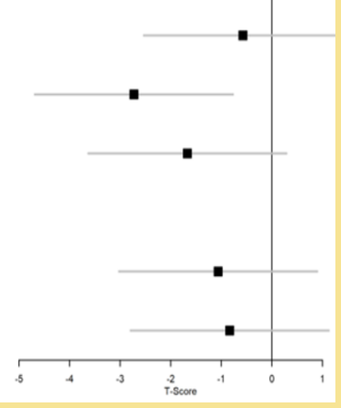


Figure 3. Global Statistical Test (GST) consistent with a global treatment effect

Full Analysis Set

Parameter	Cohen's D	GST P-value	Difference	CI	T-Score	P-value
CGI - Severity	-0.1672		-0.16	(-0.42,0.10)	-1.21	0.2266
BPDCL - Total Score	-0.1202	0.2134	-3.44	(-11.22,4.34)	-0.87	0.3839
BEST - Total Score	-0.3093	0.0811	-2.67	(-5.02,-0.32)	-2.25	0.0260
BDI - Total Score	-0.2316	0.0661	-2.61	(-5.68,0.45)	-1.68	0.0944
STAXI						
State Anger Scale Raw Score	-0.0787	0.0853	-0.57	(-2.53,1.39)	-0.57	0.5684
Trait Anger Scale Raw Score	-0.3755	0.0397	-2.02	(-3.49,-0.56)	-2.73	0.0071
Anger Expression Index Raw Score	-0.2300	0.0362	-2.62	(-5.72,0.48)	-1.67	0.0966
STAI						
State Anxiety Raw Score	-0.1461	0.0403	-1.54	(-4.41,1.33)	-1.06	0.2901
Trait Anxiety Raw Score**	-0.1148	0.0503	-1.05	(-3.54,1.44)	-0.83	0.4057



Conclusion: Though the primary endpoints measuring overall BPD disease severity and agitation/aggression were not statistically significant, secondary measures of agitation/aggression (i.e., STAXI-2) and overall disease (i.e., BEST) achieved nominal statistical significance and clinically meaningful reductions as defined by BPD KOLs as ≥25% symptom reduction compared to placebo. All primary and secondary efficacy measures statistically favored vafidemstat over placebo, and the GST was also consistent with a global treatment effect favoring vafidemstat. Treatment with vafidemstat was safe and well-tolerated. This poster reflects the final analyses from PORTICO and an oral presentation of the PORTICO data will be presented during the ECNP New Medication Symposium. Finally, Oryzon will continue discussions with the FDA during an EOP2 meeting to discuss plans for the follow-on Phase III registrational BPD trial, PORTICO-2.

CONFLICT OF INTERESTS: *Michael Ropacki and Sonia Gutierrez are employees of ORYZON GENOMICS S.A. This study was sponsored by ORYZON GENOMICS S.A. All other authors served as PIs for the PORTICO trial.*

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