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P-2143: PORTICO – Double-blind, randomized placebo-controlled, adaptive phase IIb trial with vafidemstat in borderline personality disorder – aggregated baseline characteristics, demographics and safety

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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% of psychiatric outpatients and 20% of psychiatric inpatients. Despite the burden of this disease, no pharmacological treatment has been approved to-date and psychotherapy is the first-line treatment for these patients.

Vafidemstat is an oral, brain penetrant, irreversible inhibitor of the histone lysine demethylase LSD1, which is being developed for the treatment of CNS conditions. Vafidemstat increases sociability and decreases agitation and aggression across different animal models and has shown promise in reducing agitation and aggression in several clinical trials (e.g., REIMAGINE -EUDRA CT# 2018-002140-88).

The primary aims of the PORTICO trial are to investigate the efficacy of vafidemstat in the treatment of agitation and aggression on the Clinical Global Impression (CGI), as well as overall disease severity on the Borderline Personality Disorder Checklist (BPDCL) in adult BPD patients. The purpose of this presentation is to review the aggregated baseline characteristics, demographics, and safety data from the fully enrolled sample.

Methods: PORTICO is a global randomized, double-blind placebo-controlled, adaptive 14-week Phase IIb trial (EUDRA CT# 2020-003469-20) that enrolled 210 participants in a 1:1 ratio of active treatment with vafidemstat (1.2 mg) or placebo. PORTICO has two primary independent endpoints, the CGI–Severity focused on agitation and aggression and the Borderline Personal Disorder Checklist. Secondary endpoints include both safety, and treatment of psychiatric comorbidities such as depression and anxiety (e.g., BDI-II, STAI).

Results: PORTICO enrolled the last patient in July 2023. As of September 2023, PORTICO randomized 210 participants, and 131 of the originally planned participants (N = 150) completed the trial. Analyses of aggregated blinded data cut as of August 23, 2023, are found in Tables 1-5. Although a concomitant medications are not shown due to space limitations, PORTICO participants' most common concomitant medications with ≥3.0 usage included antidepressants (21.7%), over-the-counter analgesics such as paracetamol (19.7%), birth control (18.2%), psycholeptics (16.2%) (mostly anxiolytics (8.1%) and antipsychotics (7.1%)), anti-inflammatory and antirheumatic drugs (12.6%), asthma medications (7.6%), antibacterials (7.6%) (mostly penicillin (3.5%) and amoxicillin (2.5%)), antihistamines (5.1%) proton pump inhibitors (4.0%), as well as antiepileptics, cold and cough suppressants, and vitamins (each 3.0%).

Table 1. Baseline Demographics

Demographic Characteristic	Statistic	Overall (N=198)
Psychotherapy at Baseline	N	156 (78.8%)
	Y	42 (21.2%)
Age (n=198)	Mean (SD)	32.0 (10.60)
	Median	30.0
	(Q1, Q3)	(23.0, 37.0)
	Min, Max	18.0, 63.0
	Min, Max	18.0, 63.0
Race	Black/African American	14 (7.1%)
	White	165 (83.3%)
	Other	19 (9.6%)
Sex	Female	149 (75.3%)
	Male	49 (24.7%)
BMI (kg/m2) (n=198)	Mean (SD)	26.2 (4.63)
	Median	25.8
	(Q1, Q3)	(22.5, 29.5)
	Min, Max	18.7, 46.3
Height (cm) (n=198)	Mean (SD)	167.9 (9.86)
	Median	167.0
	(Q1, Q3)	(161.0, 173.0)
	Min, Max	144.8, 192.0
Weight (kg) (n=198)	Mean (SD)	74.2 (15.90)
	Median	73.0
	(Q1, Q3)	(62.5, 84.0)
	Min, Max	40.8, 122.5

Table 2. Medical History (>2% occurrence)

Body System Derived Term	Overall (N=198) n (%)
Any Medical History	193 (97.5%)
Psychiatric disorders	185 (93.4%)
Borderline personality disorder	174 (87.9%)
Major depression	56 (28.3%)
Depression	36 (18.2%)
Generalized anxiety disorder	20 (10.1%)
Insomnia	19 (9.6%)
Attention deficit hyperactivity disorder	18 (9.1%)
Anxiety	15 (7.6%)
Alcohol use disorder	9 (4.5%)
Post-traumatic stress disorder	7 (3.5%)
Drug abuse	6 (3.0%)
Initial insomnia	6 (3.0%)
Social anxiety disorder	6 (3.0%)
Suicide attempt	6 (3.0%)
Nervous system disorders	38 (19.2%)
Migraine	13 (6.6%)
Headache	9 (4.5%)
Tension headache	5 (2.5%)
Respiratory, thoracic and mediastinal disorders	30 (15.2%)
Asthma	25 (12.6%)
Surgical and medical procedures	28 (14.1%)
Musculoskeletal and connective tissue disorders	25 (12.6%)
Immune system disorders	22 (11.1%)
Seasonal allergy	13 (6.6%)
Drug hypersensitivity	6 (3.0%)
Gastrointestinal disorders	21 (10.6%)
Gastrooesophageal reflux disease	6 (3.0%)
Metabolism and nutrition disorders	20 (10.1%)
Obesity	11 (5.6%)
Infections and infestations	16 (8.1%)
Skin and subcutaneous tissue disorders	15 (7.6%)
Injury, poisoning and procedural complications	14 (7.1%)
Blood and lymphatic system disorders	10 (5.1%)
Anaemia	6 (3.0%)
Reproductive system and breast disorders	10 (5.1%)
Vascular disorders	9 (4.5%)
Hypertension	7 (3.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (3.5%)
Endocrine disorders	6 (3.0%)

Table 3. Treatment Emergent Adverse Events (TEAEs)

Category	Overall (N=198) n (%), e
Treatment Emergent AEs (TEAEs)	**108 (54.5%), 339**
Treatment-Related TEAEs	**54 (27.3%), 136**
TEAEs Leading to Study Discontinuation	**4 (2.0%), 7**
TEAEs Leading to Study Drug Withdrawal	**6 (3.0%), 9**
TEAEs Leading to Study Drug Interruption	**6 (3.0%), 8**
TEAEs by Severity	**108 (54.5%), 339**
Mild	93 (47.0%), 242
Moderate	50 (25.3%), 85
Severe	9 (4.5%), 12
TEAEs by Outcome	**108 (54.5%), 339**
Recovered/Resolved	96 (48.5%), 276
Not Recovered/Not Resolved	30 (15.2%), 41
Recovering/Resolving	19 (9.6%), 21
Death	0 (0.0%), 0
Any TEAEs of Special Interest (AESI)	**8 (4.0%), 9**
Platelet count decreased	7 (3.5%), 7
Neutrophil count decreased	2 (1.0%), 2
COVID-19 TEAEs	**5 (2.5%), 5**

Table 4. Serious Treatment Emergent Adverse Events (TEAEs)

Category	Overall (N=198) n (%), e
Serious Treatment Emergent AEs (STEAEs)	1 (0.5%), 1
Treatment-Related STEAEs	0 (0.0%), 0
STEAEs Leading to Study Discontinuation	0 (0.0%), 0
STEAEs Leading to Study Drug Withdrawal	0 (0.0%), 0
STEAEs Leading to Study Drug Interruption	0 (0.0%), 0
STEAEs by Severity	1 (0.5%), 1
Severe	1 (0.5%), 1
Moderate	0 (0.0%), 0
Mild	0 (0.0%), 0
STEAEs by Outcome	1 (0.5%), 1
Recovered/Resolved	1 (0.5%), 1
Not Recovered/Not Resolved	0 (0.0%), 0
Death	0 (0.0%), 0
Unknown	0 (0.0%), 0
Recovering/Resolving	0 (0.0%), 0

Table 5. Participant Disposition

Variable	Overall (N=198) n (%)
Completed	117 (59.1%)
Discontinued*	41 (20.7%)
Discontinued Study	41 (20.7%)
Discontinued Treatment	39 (19.7%)
Reason Discontinued Study	
Withdrawal By Subject	13 (6.6%)
Lost To Follow-Up	10 (5.1%)
Protocol Deviation	7 (3.5%)
Adverse Event	3 (1.5%)
Physician Decision	3 (1.5%)
Blood Value During Randomization Visit Was Exclusionary	1 (0.5%)
Failure To Meet Randomization Criteria	1 (0.5%)
Lack Of Efficacy	1 (0.5%)
Non-Compliance With Study Drug	1 (0.5%)
Participant Decision Due To Covid-19	1 (0.5%)
Reason Discontinued Treatment	
Withdrawal By Subject	14 (7.1%)
Lost To Follow-Up	7 (3.5%)
Protocol Deviation	6 (3.0%)
Adverse Event	5 (2.5%)
Non-Compliance With Study Drug	2 (1.0%)
Elevated Gamma-Gt Levels During The Baseline Visit	1 (0.5%)
Lack Of Efficacy	1 (0.5%)
Low Neutrophil Count	1 (0.5%)
Participant Decision Due To Covid-19	1 (0.5%)
Physician Decision	1 (0.5%)

Conclusions:

- PORTICO enrolled a representative real-world BPD population allowing common comorbidities and concomitant medications that are typically exclusionary in other BPD trials, as well as allowed subjects to receive psychotherapy during the trial.
- The screen failure rate was low (36.6%), as compared with the most recent BPD clinical trial (brexpiprazole at 62%)[1], and the dropout rate was likewise lower (20.7% versus 26.3%[1]).
- Aggregated blinded safety data on the fully enrolled sample supports that vafidemstat has been extremely safe and well-tolerated:
  - Only one serious TEAE deemed severe that fully recovered/resolved.
  - Low number of discontinuations (2%) due to TEAEs and 0% due to STEAEs.
  - Low percentage of TEAEs of special interest (4%).

In closing, PORTICO is a global BPD clinical trial evaluating vafidemstat, a novel epigenetic approach for BPD, that enrolled a real-world representative BPD population. It is hoped that the PORTICO efficacy results, expected early next year, together with the excellent safety profile to-date will support vafidemstat as a potential effective new treatment option in a population with high unmet need and no approved drug therapy.

[1]Rothman B, et al. Efficacy and Safety of Brexpiprazole for the Treatment of Borderline Personality Disorder: a 12-Week, Phase 2, Randomized, Double-Blind, Placebo-Controlled, Study. Poster presented at ASCP Annual Meeting; 31 May – 3 June 2022; Scottsdale, Arizona.

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