PORTICO – A Case Study in Overcoming Methodological Challenges in Borderline Personality Disorder Clinical Development

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Methodological Issue: Previously ISCTM panel presentations (Ropacki, 2020) highlighted the methodological challenges in conducting BPD clinical trials including: lack of a 'gold standard' measure, uncertain but high placebo rate, large sample sizes, difficult and non-adherent patient population, endpoint timing challenges, and the fact that a large percentage of BPD patients are receiving psychotherapy.

Introduction: As of July 2021, there now have been 18 failed industry-sponsored clinical trials in Borderline Personality Disorder (BPD) and no approved pharmacological interventions to-date. The purpose of this presentation is to provide an overview of the methodology and design of PORTICO, a double-blind, randomized, placebo-controlled, adaptive 14-week Phase IIb trial to evaluate the efficacy and safety of vafidemstat in an adult BPD population. PORTICO is the first clinical trial specifically designed to address many of the methodological challenges in BPD clinical development.

The question is whether novel methodological approaches employed in PORTICO will facilitate enrollment and help enroll a more representative BPD population, as well as increase treatment adherence, decrease dropout rate and result in cleaner data that will hopefully lead to a treatment option in a population with high unmet need and no approved drug therapy. The novel approaches include an adaptive design that employs multiple primary, secondary and exploratory endpoints, selection of a small number of specialized BPD sites with established clinician-patient relationships, blinding the primary endpoint timing, implementing less restrictive inclusion/exclusion criteria but only in stable and/or treated participants, and allowing flexibility around alcohol and marijuana use, but removal of non-adherent substance abusing subjects.

Methods: Up to 156 participants will be enrolled and randomized in a 1:1 ratio (78 subjects per arm) to active treatment with vafidemstat (1.2 mg) or placebo to yield an expected 124 completed study subjects, since it is anticipated that 20% of subjects will drop out of the trial. PORTICO will involve 9 study visits, a blinded protocol where some information related to the study design has been blinded to reduce the risk of bias in the assessment of the study endpoints. Inclusion and exclusion criteria designed to address BPD clinical development challenges are described below.

Study design includes a one-week screening period to ensure study eligibility criteria, followed by 14 weeks where subjects receive vafidemstat or placebo. The multiple primary endpoints include the Clinician's Global Impression – Severity focused on agitation and aggression (CGI-S A/A), as well as the Borderline Personality Disorder Checklist (BPDCL). Participants and Investigators are blinded to treatment allocation, as well as to the timing of the primary efficacy endpoints.

BPD Clinical Development Challenges	BPD Clinical Development Potential Solutions
1. No 'Gold Standard' Measures	1. Include multiple primary, and additional secondary and exploratory endpoints
2. Unknown placebo rate	2. Implement an adaptive trial design
3. Difficult and non-adherent population 'Revolving Door' patients; Poor adherence; High Dropout Rate; Affectively unstable	3. Select small number of specialized BPD sites with longstanding clinician-patient relationships
4. Patient dropout and decreased compliance near end of trial	4. Blind timing of the primary endpoint
5. Multiple comorbidities & concomitant medications	5. Implement less restrictive Inclusion & Exclusion criteria, in stable and/or treated patients
6. Substance Abuse	6. Flexibility on ETOH and marijuana, but removal of non-adherent substance abusing subjects

Key Real-World Inclusion/exclusion criteria:

Inclusion Criteria

- Men and women 18-65 years of age with DSM-5 diagnostic criteria for BPD at least 3 months before the Screening visit.
- Outpatient known to the site or investigator and has been treated by the site or investigator for at least the last 3 months prior to the Screening visit.
- Agitation-Aggression Psychiatric Inventory-Clinician Report (AAPI-CR) Agitation & Aggression (A/A) subscale score of $\geq$ 16 (severity x frequency) summed across the four (4) items comprising the A/A subscale, and the sum of the A/A subscale severity scores $\geq$ 6.
- Stable living environment for >6 months before the Screening visit.
- BMI of at least 18.5 kg/m^2, but no more than 35 kg/m^2
- Stable in their permitted regimen of background therapy (including psychotherapy) and they must maintain treatment throughout the study and not initiate any prohibited medications during the trial. Subjects not receiving psychotherapy should not initiate psychotherapy during the trial.

Exclusion Criteria

- DSM-5 diagnosis of intellectual disability, autism spectrum disorder, schizophrenia, schizoaffective disorder, bipolar disorder (or related disorders) or MDD w/psychosis.
- Current DSM-5 diagnosis of panic disorder or post-traumatic stress disorder (PTSD). However, subjects with PTSD, generalized anxiety disorder (GAD), social anxiety disorder (SAD), MDD without psychosis, attention deficit hyperactivity disorder (ADHD) are eligible if symptoms have been stable for at least 90 days prior to the Screening visit, these disorders are not the primary focus of treatment, changes in any treatment for these disorders would not likely be required for the duration of the study, and in the investigator´s opinion these disorders will not interfere with the assessment and/or accuracy of the study endpoints.
- Use of illicit drugs (including medically indicated illicit drugs) for at least one week before Screening and subjects unwilling to abstain from use of these substances during the study. Use of alcohol or cannabinoids is not allowed within 24 hours prior to of a study visit.
- History of moderate or severe substance or alcohol use disorder according to DSM-5 or use of illicit drugs, and subjects unwilling to abstain from use of these substances during the study.
- The concomitant use of MAO inhibitors is forbidden 14 days before Screening visit and throughout the study. The concomitant use of other antidepressants in stable dose for at least 2 months before the Screening visit is allowed for the treatment of psychiatric comorbidities (as per full inclusion/exclusion criteria).
- The concomitant use of mood stabilizers and nootropics in stable dose for at least 2 months before Screening visit are allowed for the treatment of psychiatric comorbidities (as per full inclusion/exclusion criteria).

Results: As a methodological poster, the results will be forthcoming. The primary efficacy analysis compares active treatment to placebo. Both primary endpoints (CGI S A/A and BPDCL) will be analyzed for significance as the difference between active treatment and placebo from baseline to specific week. The post-baseline results for both primary endpoints will be analyzed using a mixed model repeated measures (MMRM), including as fixed factors: visit, treatment arm, psychotherapy at baseline, the interaction between treatment and visit as well as the baseline value (last measurement prior to treatment initiation) for the endpoint.

Conclusion: PORTICO is BPD clinical trial that encourages enrollment of a real-world BPD population allowing common comorbidities and concomitant medications that are typically exclusionary, as well subjects to receive psychotherapy.

CONFLICT OF INTERESTS: *Michael Ropacki and Sonia Gutiérrez are employees of ORYZON GENOMICS S.A. This study was sponsored by ORYZON GENOMICS S.A.*