Case Study:

STREAMLINING PSYCHIATRY CLINICAL DEVELOPMENT: SUCCESSFUL PHASE II MAJOR DEPRESSIVE DISORDER TRIAL

Phase II randomized trial investigating a new therapeutic agent as adjunctive therapy in Major Depressive Disorder (MDD) in patients with a history of failure to achieve a satisfactory response to at least 2 treatment courses of a therapeutic dose of an antidepressant medication therapy.

122	32	1
PATIENTS	SITES	COUNTRY (US)

SERVICES PROVIDED

- Full-service (including Medpace Central Labs, Medpace Bioanalytical Labs, and Medpace Core Lab).

CHALLENGES

- Study drug was a controlled substance with potential for dissociative effects. The FDA requested close compliance monitoring to ensure no misuse or abuse of the study drug.
- Placebo response is a serious issue in psychiatry studies, requiring a robust mitigation strategy.
- At the time of study initiation, there was insufficient data available to support that patients could safely drive during the planned dosing period for the study. As such patients were restricted from driving a car for 28 days during the study.
- The recruitment period began during the acute stage of the COVID-19 pandemic, with 50% of patients enrolled in 2020 and 2021, and the remaining 50% enrolled in 2022 (post-acute stage).
- Several broad categories of Adverse Events (AEs) including sedation, dissociation, drug abuse, dependence and withdrawal were identified as AEs of Special Interest (AESIs). As there are many potential signs and symptoms which may be suggestive (but not definitive evidence) of these AESI categories, careful review and assessment by the investigator was required to ensure consistency in reporting.

THE SOLUTIONS

- To address FDA's concerns about potential misuse or abuse of study drug, a 2-pronged approach was implemented.
  - First patients were only dispensed 3 tablets of study drug at a time. The protocol allowed for either a midweek visit where the patient would come to the site to pick up another bottle of study drug, or the site could use Direct-To-Patient (DTP) shipment of study drug using a study designated courier to make just in time shipments of study drug to the patient's home
  - Second, an external medication compliance vendor, Scene Health, was engaged to support robust compliance monitoring to ensure that patients did not misuse or abuse the study drug. Patients were required to take a video of themselves taking their study medication each night before bed, and to display the number of pills remaining in the bottle within the video. Scene Health committed to reviewing each video by 10 am the next morning and sent alerts to sites in all cases where the patient did not follow the dosing instructions exactly as required. This allowed prompt follow-up with patients by site staff to ensure any potential dosing issues were addressed prior to the next planned dosing time.
- Multiple strategies were used to mitigate the impact of placebo response.
  - The Placebo Control Reminder Script© (PCRS) was read to all patients prior to each administration of the Montgomery-Asberg Depression Rater Scale (MADRS). The PCRS has demonstrated success in decreasing placebo response in clinical studies.[1]
  - To confirm patient eligibility, a remote SAFER interview was conducted by appropriately trained staff from the Massachusetts General Hospital (MGH) Clinical Trials Network and Institute (CTNI). "SAFER" is an abbreviation for State versus Trait, Assessability, Face Validity, Ecological Validity, Rule of Three Ps (pervasive, persistent, and pathological). This is a specific, remote semi structured interview that has been developed in the context of depression trials to confirm patient eligibility with a protocol-specified history, diagnosis, and disease severity.[2]
  - All site staff received study specific training regarding staff behaviors which can increase placebo response.
- Inability to drive during the dosing period represented a significant burden on patients and their families. Medpace was able to arrange for patient access to a centrally billed Uber Health account which allowed patients to make all necessary travel arrangements independent from site staff. The study also allowed patients to be reimbursed for actual travel expenses if use of Uber Health was not practical in their geographic area. This included milage reimbursement in cases where a family member would be transporting the patient.
- Ad-hoc subgroup analyses were included in the SAP/TFL/CSR to explore the impact of the COVID-19 pandemic in study endpoints.
- Robust training was provided to investigators regarding proper identification, assessment, and reporting of AESIs to ensure all signs and symptoms were properly categorized. Additionally regular review of all identified AESIs was conducted by the Sponsor and Medpace medical teams, and follow up with investigators to clarify reported terms and support appropriate AESI category mapping.

RESULTS

Overall medication adherence was excellent during the trial with >97% compliance with IP dosing requirements. Additionally, there were no instances of misuse or abuse of IP during the trial, an issue of critical concern for the FDA.

Use of Scene Health resulted in near real-time identification of potential issues related to proper dosing of IP, and prompt management of cases where patients needed a refill of background antidepressant medications.

Availability of centrally bill Uber Health services ensured patients had access to flexible transportation options during the study treatment period, easing the burden of study participation.

A difference in subject response to both active treatment and placebo was observed between those patients enrolled in the COVID-19 acute stage and those enrolled in the post-acute stage. Placebo response during the acute stage was higher than that observed during the post-acute stage, likely due to the additional social stressors created by the pandemic.

The additional Investigator training, and medical review of AESIs ensured the production of clean and timely data to be used in the Tables, Figures, and Listings to accurately characterize the safety profile of the IP.

REFERENCES

1. Cohen EA, Hassman HH, Ereshefsky L, Walling DP, Grindell VM, Keefe RSE, Wyka K, Horan WP. Placebo response mitigation with a participant-focused psychoeducational procedure: a randomized, single-blind, all placebo study in major depressive and psychotic disorders. Neuropsychopharmacology. 2021 Mar;46(4):844-850.
2. Freeman MP, Pooley J, Flynn MJ, Baer L, Mischoulon D, Mou D, Fava M. Guarding the Gate: Remote Structured Assessments to Enhance Enrollment Precision in Depression Trials. J Clin Psychopharmacol. 2017 Apr;37(2):176-181.