INSIGHT BRIEF

Advancing CNS Development Programs with Complex Early Phase Clinical Trials

Innovative approaches to drive success

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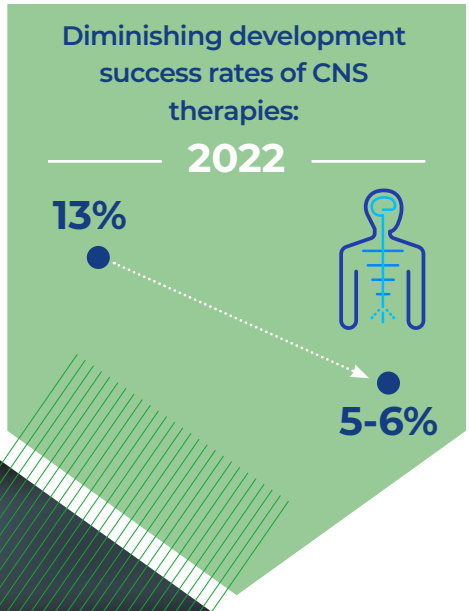
Introduction

In an effort to address the major unmet medical needs of central nervous system (CNS) disorders, novel approaches are being used in Phase I trials. These include innovative study designs, early addition of patient cohorts, incorporating biomarkers, and use of innovative sampling procedures.

This Insight Brief will outline learnings from complex early phase trials, focusing on these key areas, as well as special considerations for rare CNS disease studies.

Challenges and trends in CNS drug development

Overall, neurological disorders have one of the highest rates of morbidity, disability, and mortality globally, with an estimated economic burden of $800 billion/year in the US alone. As prevalence of age-related disorders increases in aging populations, this burden will continue to rise. Yet, development success rates for CNS therapies are diminishing. For example, since 2017, composite success rates for CNS assets spanning Phase I through regulatory submission declined from 13% to 5-6% in 2022, according to IQVIA. In addition, high and growing placebo response rates in CNS studies remain a major obstacle.



Approaches with potential to advance early phase CNS development programs include:

Use of innovative Phase I study designs, *including adaptive designs*

Traditionally, Phase I clinical trials have been conducted mainly in healthy normal volunteers, focusing on collection of safety, tolerability and pharmacokinetic data, and dose escalation. Other Phase I designs—to date used mostly in oncology, but with potential for CNS applications—include grouped crossover dose escalation, alternating cross-over, algorithm-based "3+3" design, and model-based continuous reassessment using a Bayesian approach to model dose escalations.

Early addition of patient cohorts

In addition to healthy volunteers, sponsors are increasingly adding small cohorts of patients with the disease targeted by the investigational product to Phase I studies. Positive efficacy signals in these bridging or Phase Ib patient cohorts can inform 'go/no-go' decisions, potentially enabling sponsors to move into Phase II more rapidly and accelerating development of promising new therapies.

Innovative sampling procedures

These may also be helpful in Phase I studies, such as site-level use of a peristaltic pump for continuous cerebrospinal fluid collection, an approach that has mostly been used only at academic medical centers to date.

Incorporating biomarkers

Use of biomarkers should also be considered in early phase studies. Event-related potentials (ERPs) and quantitative EEG (QEEG) have promise as translational biomarkers in CNS drug development based on their relatively low cost, lack of invasiveness, and potential as quantitative endpoints. For example, recent work has successfully validated a suite of ERPs and QEEG biomarkers in a clinical study on healthy volunteers and patients with schizophrenia. The study found that certain ERP and QEEG measures correlated with functional assessments administered to the schizophrenia patients. These efforts indicate that with standardized methods, it is possible for complex ERP/EEG testing sessions to be reliably performed at trial sites, yielding high-quality data in near real-time.

Special considerations for rare disease studies

In early phase studies of rare diseases such as Friedreich's ataxias and Huntingdon's disease, referral sources are critically important. Partnerships with advocacy organization can help identify potential study participants. These patients need particularly extensive support throughout the study, including for travel to any on-site visits.

Conclusion

There is potential to improve success rates in CNS development programs through novel approaches to Phase I studies, including addition of early patient cohorts and inclusion of biomarkers.

An expert partner can help sponsors implement these innovative steps consistently across multiple clinical sites, optimizing data quality and avoiding potential bias—while providing timely, detailed feedback and learnings to advance the CNS asset as rapidly as possible.

About the Authors

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Dr. Botros is Chief Operating Officer for CenExel CNS and leads operations for all CNS's locations, ensuring that clinical research activities are optimized, reviewed, and fully compliant with federal regulations and ICH/GCP guidelines. She joined CNS in 2008, bringing over 10 years' experience in clinical research.

Prior to being elevated to her current role in 2020, Dr. Botros served as Director of Operations for the CNS Long Beach site for 10 years. She led CNS's Clinical Pharmacology Unit expansion to support both healthy normal volunteers and patient populations in early phase trials and developed the associated standard operating procedures.

Previously, Dr. Botros worked in Dermatology Research as a Clinical Research Fellow, completing almost 50 studies for over 20 pharmaceutical companies. Earlier on, she was a General Physician at the Alexandria Medical University Hospital and an Obstetrician/ Gynecologist at the Kafr Dawar Public Hospital in Alexandria, Egypt.

Dr. Botros received her medical degree from the Alexandria University School of Medicine in Egypt. She is fluent in English, French and Arabic.

David Walling, PhD

Chief Clinical Officer and Principal Investigator, CenExel CNS

David Walling, PhD serves as Chief Clinical Officer and Principal Investigator for CenExel CNS. He co-founded CenExel CNS in 2000, which has grown to become one of the largest clinical research providers in the country and the largest in Southern California.

Dr. Walling is a recognized thought leader in schizophrenia and cognition. In his role with CenExel CNS, he advises pharmaceutical companies in the creation of drug development plans, design and analysis of clinical trials in all phases, and preparation for interactions with regulatory agencies. Dr. Walling has overseen the execution of more than 600 clinical trials and has authored many protocols, articles and white papers.

Before founding CenExel CNS, Dr. Walling was VP of Clinical Services at Psychiatric Management Resources & Stadt Solutions Pharmacy Corporation. He has also served as an Assistant Professor and Research Scientist in Psychiatry and Behavioral Sciences at the University of Texas Medical Branch at Galveston.

Dr. Walling received his doctorate in Counseling Psychology from the University of Southern California.

References

Experimental Medicine Approaches in Early Phase CNS Drug Development

Global, regional, and national burden of neurological disorders in 204 countries and territories worldwide

The Economic Burden of Neurologic Disease — $800 Billion Annually in the US

IQVIA Two Steps Forward One Step Back – The Long Road to Success in CNS

Placebo response mitigation with a participant-focused psychoeducational procedure: a randomized, single-blind, all placebo study in major depressive and psychotic disorders.

Validation of a suite of ERP and QEEG biomarkers in a pre-competitive, industry-led study in subjects with schizophrenia and healthy volunteers

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