

TITLE: A Seamless Two-Stage Phase I/II Trial Design with Backfill and Joint Monitoring for Dose Optimization

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ABSTRACT: The FDA's Project Optimus initiative emphasizes dose optimization through randomized cohorts and comprehensive evaluation across dose levels. Additionally, early-phase oncology trials must efficiently evaluate antitumor activity while maintaining patient safety, requiring robust statistical frameworks for futility monitoring. We propose a seamless two-stage Phase I/II trial design integrating dose optimization with efficacy evaluation. Stage 1 employs a dose-finding approach with patient backfilling, utilizing Bayesian optimal boundaries for efficacy and toxicity to select two promising doses for further evaluation. The backfill strategy enables sequential enrollment while previous patients continue their evaluation periods, thereby accelerating the trial. Stage 2 simultaneously identifies the optimal dose and evaluates treatment effectiveness through joint monitoring of efficacy and toxicity outcomes. Stage 2 incorporates Bayesian optimal boundaries for both futility and efficacy stopping, enabling early decision-making while explicitly controlling Type I error rates. Simulation studies across realistic scenarios demonstrate superior operating characteristics of the proposed design compared to existing designs, making this approach particularly valuable for modern oncology drug development where efficiency, accuracy, and patient safety are paramount.

PRESENTING AUTHOR BIO: Belay Birlie Yimer (PhD) is an Associate Director of Biostatistics at Astellas Pharma Europe Ltd., with 10+ years of experience across academia and the pharmaceutical industry. His current work focuses on innovative statistical methods for early-phase clinical trial design.