

Making Adaptive Trials Work

Attaining Orphan Drug Exclusivity Protection

Trial design: “Seamless” phase 2/3 integrated trial design

Disease area: Rare, HIV-associated neurological disease

Challenge

The FDA granted “orphan drug” status to a proposed treatment for a rare but serious neurological disease associated with HIV. Facing a short window of time to prove the effectiveness of the treatment in order to benefit from the exclusivity protection that orphan status provides, the sponsor decided to pursue an innovative, adaptive trial design combining the traditionally separate phase 2 learning and phase 3 confirmatory studies in one continuous trial.



With such “seamless” combined phase 2/3 studies, FDA/EMA regulatory review board statisticians closely scrutinize the ability of the trial design to maintain rigid control over the type 1 error. It is the responsibility of the sponsor company to build sufficient error control into their design and defend the integrity and statistical validity of the study in the regulatory review. In this case, the FDA summarily rejected the sponsor’s seamless design attempt. With the clock ticking, the sponsor engaged Cytel to redesign an acceptable, well-controlled adaptive trial.

“We want to acknowledge Cytel’s pivotal role. Without Cytel we would not have got this far. You have been very service-oriented and responsive”

- Scott Harris, Chief Medical Officer, Napo Pharmaceuticals”

Balancing Speed with Control to Attain Orphan Drug Exclusivity Protection

Response

- Cytel biostatisticians first analyzed the sponsor's submitted seamless design to determine why the FDA rejected the study
- Cytel then developed three distinct designs as valid trial alternatives:
 - Single Four-Arm Trial: A single, phase 3 four-arm design with three dose groups and placebo
 - Two Separate Trials: Stage a four-arm phase 2 trial to select the best dose; then run a phase 3 two-arm trial
 - Seamless Phase 2/3 Trial: Start with four arms; select the best dose at the interim look; continue the study as a two-arm confirmatory trial

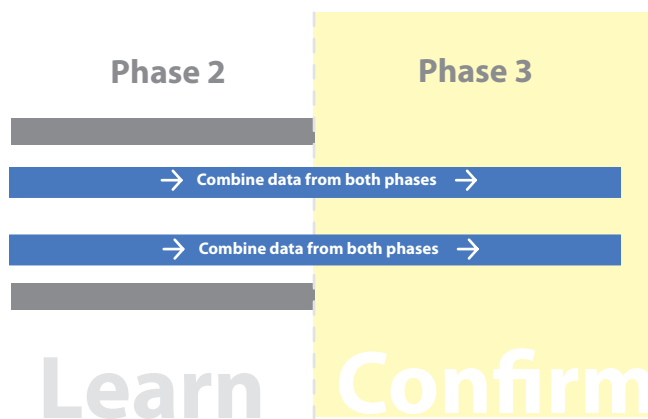
Adaptation

- Using Cytel's trial simulation techniques, the operating characteristics of the three proposed alternatives were compared.
- Cytel recommended an implementation of the seamless phase 2/3 design based on implementation of recently published statistical techniques (Posch et al, 2005).

Outcome

- The resulting integrated phase 2/3 "redesign" by Cytel was presented to and accepted by the FDA review board.
- With an approved seamless design, the sponsor began patient recruitment planning and expects to complete the trial well within the prescribed orphan status time frame.

Phase 2/3 Combined



- The latest statistical methods permit the option, upon interim analyses, to drop doses and/or optimize sample size while moving from the phase 2 to the phase 3 stage
- Starting with four arms, select best dose(s) at interim; continue with two-arms in the confirmatory (phase 3) stage
- More than one dose can be carried into the confirmatory stage, along with a placebo

The Cytel Advantage

Experience and statistical expertise provide the difference between an innovative trial concept and a validated, regulatory-accepted clinical trial. With all that's riding on today's development programs, you can't afford to experiment.

Now sponsor organizations can turn to the biostatistical and implementation expertise of Cytel, whose leaders pioneered the science and technology of adaptive trial design and who have trained thousands of health sciences biostatisticians and clinicians, including regulatory staff.

Cytel Pharmaceutical Research Services puts Cytel's trial design innovation and implementation experience on your side. From trial simulation and process development to independent data assessment and regulatory review, Cytel stands with you every step of the way.