

# Adaptive Trial Accelerates FDA Approval

Company Secures Orphan Exclusivity to Market Fulyzaq™

**Trial design: Confirmatory Two-Stage Adaptive Dose Selection**  
**Disease area: HIV/AIDS therapy-related gastrointestinal distress**

## Challenge

The FDA had granted Napo Pharmaceuticals orphan drug status for its proposed drug Fulyzaq™ (crofelemer) to treat non-infectious diarrhea in HIV/AIDS patients undergoing antiretroviral therapy. Facing a short timeframe to prove treatment efficacy and achieve the exclusivity protection of orphan status, Napo chose to pursue an innovative, adaptive trial design combining the traditionally separate Phase 2 and Phase 3 studies into one continuous trial.



In such two-stage confirmatory adaptive trials, FDA/EMA regulatory statisticians closely scrutinize the trial design's ability to maintain strong control of the familywise type-1 error rate. It is the sponsor's responsibility to build sufficient error control into their design, defending the integrity and statistical validity of the study to the regulators.

The FDA rejected Napo's first two-stage trial design attempt. With the clock ticking, Napo engaged Cytel to design a well-controlled adaptive trial that would withstand regulatory scrutiny and significantly shorten the development path compared with traditional approaches.

**“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**”

# Optimizing Adaptive Speed and Control to Achieve Orphan Drug Exclusivity Protection

## Response

- Cytel biostatisticians first analyzed Napo's two-stage trial design to determine the reasons for the FDA's initial rejection
- Three distinct designs emerged as valid 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
  - Two Stage Adaptive Confirmatory Trial: Start with four arms; select the two "best" doses at the interim look; continue as a two-arm confirmatory trial

## Adaptation

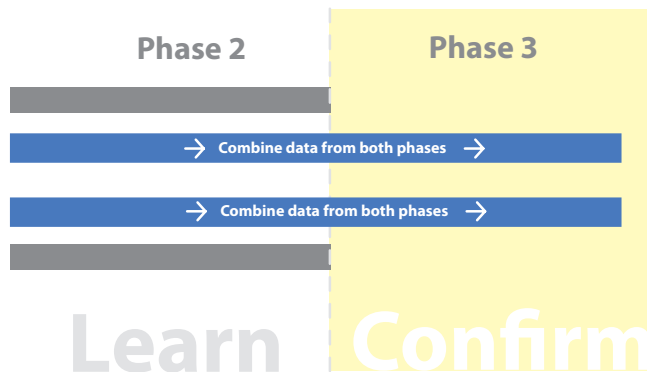
- Trial simulations helped compare the operating characteristics of the three alternatives
- Cytel recommended an implementation of the Two-Stage Adaptive Confirmatory design, further supported by published statistical techniques (Posch, et al, 2005)

## Outcome

- Cytel's resulting two-stage adaptive dose selection redesign was accepted by the FDA
- Shortly after design acceptance, recruitment began and sites opened
- Two doses were selected at the interim analysis for the Phase 3 stage
- Following study conclusion, the NDA submission was filed well within the prescribed orphan drug status timeframe
- The FDA approved Fulyzaq™ early 2013, following the confirmatory two-stage adaptive trial

## Two Stage Adaptive Trial

- The FDA's Guidance for Adaptive Trials recognizes the option, upon interim analyses, to drop doses and move from Phase 2 dose selection directly 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



## Cytel Clinical Research Services

At Cytel we believe the clinical development of drugs, biologics and devices is crucial for human welfare. Our mission is to improve success rates in this endeavor. We do this by improving the design and implementation of clinical trials, often employing adaptive approaches. Every Cytel-designed adaptive trial examined by FDA reviewers has been found acceptable.

All the major pharmaceutical, biotech and medical device companies are our customers. We also count among our customers and research partners leading academic, medical research institutions, and regulatory agencies worldwide.