Accelerating Development with Combined SAD/MAD Approach

Single ascending dose (SAD) and multiple ascending dose (MAD) studies are typically the first in human studies. They seek to gain information on safety and tolerability, general pharmacokinetic (PK) and pharmacodynamic (PD) characteristics, and of course identify the maximum tolerated dose (MTD).

Conventionally, SAD and MAD studies were conducted separately, but increasingly are combined into an 'umbrella' protocol which addresses both SAD and MAD objectives.

This approach can result in both time and cost savings, and allow additional valuable information to be gained earlier and inform subsequent development. When the studies are designed as a combined approach, adaptive principles are used as decisions will be made mid-study to adjust dose, change the number of subjects receiving a certain dose, or stop a treatment entirely.

In one recent project, we provided early phase trial design and biostatistics operational support for our client, an emerging biopharma with an early phase pipeline of products in neurological indications.

Challenge

With a constrained budget, and minimal infrastructure our client wanted an operationally efficient solution for a first-in-human study and day to day support from an expert team who would require minimal oversight.

Solution

Cytel statistical consultants devised an adaptive maximizing SAD/ MAD design combining multiple PK, PD, safety and tolerability objectives.

To create the study design, the Cytel consultant used Cytel's specialist Compass software which is dedicated to the design, simulation, and execution of early phase clinical trials. It provides a systematic and efficient way to investigate and compare conventional versus adaptive dose-finding designs.

The below figure describes the structure of an example combined SAD/ MAD approach.

Single Ascending Dose (SAD) → Multiple Ascending Dose (MAD)
Phase 1 Design: 1 protocol, 2 parts (SAD & MAD)

	N	Day1	Day4	Day8	Day11	Day15	Day18	Day22	Day25	Day29	Day36	Day43	Day50
Panel 1a	2	Dose1		Dose3		Dose5		placebo					
Panel 1b	2	Dose1		Dose3		placebo		Dose7					
Panel 1c	2	Dose1		placebo		Dose5		Dose7					
Panel 1d	2	placebo		Dose3		Dose5		Dose7					
Panel 2a	2		Dose2		Dose4		Dose6		placebo				
Panel 2b	2		Dose2		Dose4		placebo		Dose8				
Panel 2c	2		Dose2		placebo		Dose6		Dose8				
Panel 2d	2		placebo		Dose4		Dose6		Dose8				
Panel 3a	8					Dose2	-->	Dose2					
Panel 3b	2					placebo	-->	placebo					
Panel 4a	8							Dose4	-->	Dose4			
panel 4b	2							placebo	-->	placebo			
Panel 5a	8									Dose6	-->	Dose6	
Panel 5b	2									placebo	-->	placebo	
Panel 6a	8										Dose8	-->	Dose8
Panel 6b	2										placebo	-->	placebo

Day 1 usually Monday; Day 4 usually Thursday; all safety data reviewed before next higher dose
Dose levels subject to change based on review of previous dose('s') safety data
Subjects randomized to Panels; Panels 1 & 2 single dose; Panels 3-6 multiple dose
Analysis of PK / PD results separately for SAD and MAD portions

Value Added

The trial has been designed to provide a solid understanding of dose tolerability and PK/ PD measurements at doses with target levels of response. This enabled the client to move forward with a good regulatory package which provides the FDA and EMA the best evidence of early phase drug effect.