**HOW ADAPTIVE STUDY DESIGN CAN ENRICH AN EARLY PHASE MULTIPLE ASCENDING DOSE STUDY**

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**Introduction**

The use of adaptive design in clinical research is attractive due to its flexibility, efficiency and safety. Adaptive design is valuable during the early stages of drug development as it helps maximising the collection of relevant data towards Proof of Concept whilst minimising participant exposure, safety risks and time and cost of the development [1].

Recently we have published an article with a step by step guide on how to write adaptive protocols in the early phase development of new medicines [2]. To illustrate the benefits of this concept we present results from a randomised, double-blind, placebo-controlled, multiple ascending dose study to evaluate the safety, tolerance, pharmacokinetics (PK) and pharmacodynamics, of Sulforadex® in healthy male subjects following daily dosing for 7 days. Sulforadex® is a chemically stable, synthetic sulforaphane (naturally occurring in brassica vegetables such as broccoli) which is being developed as a potential treatment to prevent the progression of early-stage prostate cancer.

The adaptive design allowed us to immediately react to emerging PK and tolerability data and by adding a pre-dose meal for consecutive days, we were able to provide daily PK assessments and adjust the daily dose in accordance with evolving data and dosing schedule.

**Aim**

This randomised, double-blind, placebo-controlled study aimed to determine the safety, tolerability and PK of multiple doses of Sulforadex® over 7 days.

**Methods**

**Study Design**

Eighteen (18) subjects (12 active: 6 placebo) entered the study. All subjects completed the study and were included in the safety and PK analyses. All cohorts (6 volunteers each) were dosed for 7 days: Cohorts 1 and 2 received 600 mg Sulforadex® once daily, Cohort 3 received 300 mg bid twice daily.

For Cohorts 2 and 3 the protocol was amended to include a meal prior to dosing on all days, except on Day 6 (fasted). Standardized meals were served at the following times: breakfast (approximately 7 hours post-dose) and dinner (approximately 13 hours post-dose) and approximately 11 hours post-dose bid.

**Statistical Analysis**

The results of Adverse Event (AE) recording, vital signs, 12-lead ECG and standard clinical laboratory safety tests were listed by subject and analysed by descriptive statistics. PK data was listed for each subject, along with univariate statistics including arithmetic and geometric means, standard deviations (SD), minimum, maximum and median values, and inter-subject coefficients of variation (CV). PD data was listed by univariate statistics including arithmetic and geometric means, SD, minimum, maximum, median values and CV.

**Results**

Following a single ascending dose (SAD) study, the main objectives of this study were to determine a therapeutic, well tolerated multiple dose regimen of Sulforadex®. A daily dose of 600 mg was expected to be therapeutic and well within the exposure limits set by pre-clinical and the SAD studies.

The PK profile in fasted condition resembled the profile of the SAD study (Figure A). However, in Cohort 1, the mean Cmax exceeded the exposure limit of 135 ng/mL (Figure C) on Day 7. It was thought that Cmax was reached at around 1.5 hours post-dose, at which time no PK sample had been scheduled for Cohort 1, i.e. the actual Cmax exceeded that measure. This was accompanied by gastrointestinal (GI) side effects (Figure D).

To lower Cmax and to improve tolerability, food was introduced before dosing in Cohorts 2 and 3. At 600 mg qd dosing with food (Cohort 2) Cmax the still exceed the exposure limit. Therefore in Cohort 3 the daily dose was split into 2 x 300 mg. With food, Tmax was delayed around 2 hours. 300 mg bid Sulforadex® in fed condition (Cohort 3) produced a Cmax between 81.63 ng/mL to 124.24 ng/mL. AUC0-24 ranged from 244.06 ng·hr/mL to 306.09 ng·hr/mL.

**Discussion**

Using a well designed early phase adaptive protocol, pre-defined adaptive specifications can be implemented within a day following interim blinded data review.

In this study evolving PK and tolerability data demonstrated that Cmax exceeded pre-defined limits with concomitant GI tolerability issues. We were able to respond to that data by rapidly adjusting dosing regimen and PK assessments and by adding a pre-dose meal for consecutive days.

**E Adaptive protocol features applied in the conduct of the study**

The anticipated dosing regimen for the mandatory and optional cohorts can be adjusted without changing the study protocol, enabling the statistician to take into account evolving PK and tolerability data and to adjust the dosing regimen in real-time (Figure E). Adaptive specifications can be implemented within a day following interim blinded data review.

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**Acknowledgements & conflicts of interest**

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**References**
