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 (PD) 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 to adjust the study design and conduct within a day from the interim safety review meeting. As all changes were within the authorised adaptive scope, we were able to make changes to dosing regimens and assessments and we introduced a meal prior to dosing without the need for Regulatory or Ethics Committee submissions.

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 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 30 minutes pre-dose for dosing in the fed state or approximately 1 hour post-dose in the fasted state), lunch (approximately 4 hours post-dose), snack (approximately 7 hours post-dose) and dinner (approximately 13 hours post-dose qd and approximately 11 hours post-dose bid).

Pharmacokinetic sampling was adjusted for Cohorts 2 and 3, adding a serial PK sampling day to assess the effects of food and adjusting sampling time points on all serial PK sampling days 1, 6 and 7.

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

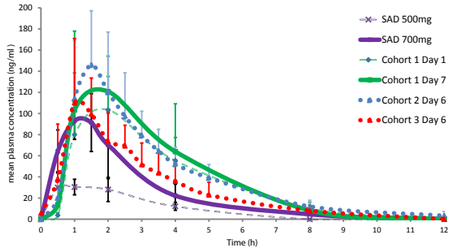
Following a single ascending dose (SAD) study, the main objectives of this study were to determine a therapeutic, well tolerated multiple dosing regimen of Sulforadex®. A daily dose of 600 mg was expected to be therapeutic and well within the exposure limits set by pre-clinical and the SAD studies.

The PK profile in fasted condition resembled the profile of the SAD study (Figure A). However, in Cohort 1, the mean C_{max} exceeded the exposure limit of 135 ng/mL (Figure C) on Day 7. It was thought that C_{max} 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 C_{max} exceeded that measure.

This was accompanied by gastrointestinal (GI) side effects (Figure D). To lower C_{max} and to improve tolerability, food was introduced before dosing in Cohorts 2 and 3. At 600 mg qd dosing with food (Cohort 2) C_{max} the still exceed the exposure limit. Therefore in Cohort 3 the daily dose was split into 2 x 300 mg. With food, T_{max} was delayed around 2 hours. 300 mg bid Sulforadex® in fed condition (Cohort 3) produced a C_{max} between 81.63 ng/mL to 123.24 ng/mL. AUC_{0-24} ranged from 244.06 ng·hr/mL to 306.09 ng·hr/mL. This is considered a therapeutic -and within limit- exposure.

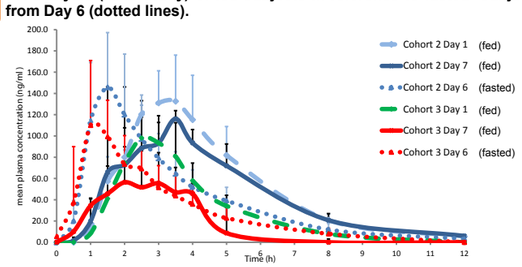
GI tolerability improved with food and further by splitting the daily dose: Fasted dosing of 600 mg qd resulted in 8 AEs per 7 doses and 4 AEs per 6 doses in fed state (Figure D); whereas 300 mg bid Sulforadex® demonstrated a significant decrease in occurrence of GI AEs (2 AEs per 12 doses in fed state and 1 AE per 2 doses in fasted state; Figure D).

A **PK analysis comparing fasted groups from SAD and MAD studies.**



Mean plasma concentration of sulforaphane is plotted with standard deviation bars.

B **PK analysis (MAD study) of fed subjects in reference to fasted subjects from Day 6 (dotted lines).**



Mean plasma concentration of sulforaphane is plotted with standard deviation bars.

C Summary of plasma PK parameters for sulforaphane following oral administration of 600 mg qd (Cohort 1 and 2) and 300 mg bid (Cohort 3) Sulforadex®.

	Cohort/Day of analysis	Dose	AUC_{0-24h}[1] (ng.hr/ml)	C_{max}[1] (ng/ml)	T_{max}[2] (h)
Fasted	1/Day1	600 mg	369.45 (56.52)	126.00 (29.28)	2.00 (1.00, 2.00)
	1/Day7	600 mg	414.93 (84.14)	152.50 (41.94)	2.00 (1.00, 4.00)
	2/Day6	600 mg	467.78 (96.41)	150.25 (47.20)	1.25 (1.00, 2.00)
	3/Day6	300 mg bid	306.09 (28.58)	123.23 (37.67)	1.00 (1.00, 3.00)
Fed	2/Day1	600 mg	573.25 (116.85)	145.00 (28.40)	3.00 (2.50, 3.50)
	2/Day7	600 mg	504.67 (98.76)	131.50 (35.58)	3.50 (1.50, 3.50)
	3/Day1	300 mg bid	294.47 (33.24)	106.28 (16.89)	2.75 (2.50, 3.50)
	3/Day7	300 mg bid	244.06 (22.23)	81.63 (8.89)	3.00 (2.50, 5.00)

[1]Mean (±SD)
[2]Median (Minimum, Maximum)

D Summary of drug-related AEs reported in MAD study in comparison to SAD study, excluding placebo groups.

	SAD study		MAD study				
	500 mg (n=6)	700 mg (n=6)	Cohort 1 600 mg (n=4)	Cohort 2 600 mg (n=4)		Cohort 3 2 x 300 mg (n=4)	
AE drug-related (number of events):	Fasted 1 dose	Fasted 1 dose	Fasted 7 doses	Fed 6 doses	Fasted 1 dose	Fed 12 doses	Fasted 2 doses
Gastrointestinal disorders	2	4	8	4	2	2	1
General disorders and administration site conditions	1		1				
Nervous system disorders	1			1		1	
Respiratory, thoracic and mediastinal disorders			2				
Vascular disorders		1					
Eye disorders						2	
Total no. of AE (drug-related and unrelated)	6	8	12	5	2	5	1

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 C_{max} exceeded pre-defined limits with concomitant GI tolerability issues. We were able to respond to that data by rapidly adjusting dosing regimens and PK assessments and by adding a pre-dose meal for consecutive cohorts.

Figure E shows how relevant pre-defined adaptive design features were applied during this study.

E Adaptive protocol features applied in the conduct of the study

ADAPTIVE FEATURES IN THE APPROVED PROTOCOL	HOW WE USED THEM
The anticipated dosing regimens for the mandatory and optional Cohorts can be adjusted in accordance with PK, safety and tolerability data collected up to the decision making time-point. The term dosing regimen includes (1) the dose level administered, (2) the frequency of dosing and (3) the duration of dosing, i.e. the number of doses administered. Accordingly these can be adjusted individually or in combination.	Cohort 3: The daily 600 mg dose was divided into 2 x 300 mg doses.
Sulforadex® may be administered with food.	Cohorts 2 and 3: Sulforadex ® was administered with food on Days 1-5 and 7. To intra-individually evaluate the effect of food , Sulforadex ® was administered fasted on Day 6.
Additional or less PK/PD (blood and/or urine) samples may be taken in accordance with evolving data and dosing schedule.	Cohorts 2 and 3: An additional serial PK sampling day was introduced on Day 6 (fasted). Additional time points for PK sample collection (1.5, 2.5, 3, 3.5 and 5 h) were introduced on all days to ensure capture of T_{max} and full PK profile with and without food.
Timing of PK/PD samples may be adjusted in accordance with evolving data and dosing schedule/regimen.	

The practical application of relevant adaptive features led to the determination of a suitable dosing regime with good tolerability at therapeutic sulphoraphane plasma concentrations.

As all adjustments were within the adaptive scope of the protocol, no regulatory or Ethics Committee submissions were required and the study could proceed and complete as scheduled.

References

1. Lorch U, Berelowitz K, Ozen C, Naseem A, Akuffo E, Taubel J. The practical application of adaptive study design in early phase clinical trials: a retrospective analysis of time savings. *Eur J Clin Pharmacol 2012,* 68: 543-551.
2. Lorch U, O'Kane M, Taubel J. Three steps to writing adaptive study protocols in the early phase clinical development of new medicines. *BMC Medical Research Methodology* 2014 14:84.

Abbreviation List

AE	Adverse Event
AUC	Area Under Curve
bid	twice a day
GI	Gastrointestinal
MAD	Multiple Ascending Dose
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
qd	one a day
SAD	Single Ascending Dose

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