BUILDING FLEXIBILITY INTO PHASE I PROTOCOLS AND EARLY CLINICAL DEVELOPMENT PROGRAMS
Making drug development decisions within a protocol

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Background and Aims

The transition of a drug candidate into Phase I and other early drug development programs is undergoing considerable examination and change. This has largely been brought about by commercial and scientific drivers to reduce attrition rates coupled with an evolving regulatory environment, all of which encourage the pharmaceutical industry to build both scientific focus and flexibility into the drug development program.

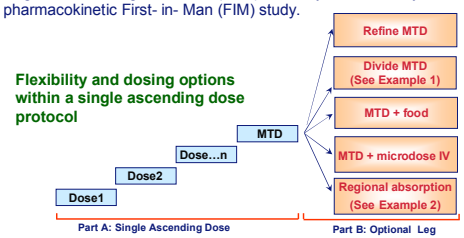
The successful incorporation of flexibility within a single study or a series of protocols depends upon an understanding of the physicochemical properties of the drug, the performance of the formulation and the preclinical safety & pharmacology package. This knowledge is used to preempt possible shortcomings of the lead compound against the target product profile.

One real consequence of this is the opportunity to incorporate multiple options within a study protocol and thereby add value to early clinical studies by addressing "Developability" issues as soon as possible within the drug development program.

"Developability" in this context is used as a collective term describing the physicochemical, pharmacokinetic (ADME) and pharmaceutical characteristics of a lead compound that may have an impact on the clinical development strategy. The purpose in addressing these issues early in development is to optimize drug bioavailability and support key Go/NoGo decision making.

Dose escalation and treatment variations are often restricted by the use of single unit doses; e.g. 1, 10 and 50 mg capsules, to cover a dose range from 1 to 200mg. In such a case a dose of 75mg would require administration of 8 capsules.

The additional ability to manufacture doses within 24-48 hours prior to administration introduces considerable flexibility into the study protocol and enables optional treatments and doses to be incorporated into the study design. Below is a typical schema for a single ascending dose (SAD) safety, tolerability and pharmacokinetic First- in- Man (FIM) study.



A two stage protocol, with appropriate decision algorithms and stopping rules, allows the introduction of treatment options designed to utilize the safety and pharmacokinetic information obtained in the first part of the study.

Flexible options include:

- Minor changes in dose in order to more precisely define the maximum tolerated dose.
- Evaluation of the effect of food on drug bioavailability.
- Administration by a different administration route to assess alternative options to improve or alter the pharmacokinetic profile.
- Administration of a different formulation to assess prototype formulations or delivery options.
- Or: The introduction of a second subject population to evaluate potential effects of gender or age on the pharmacokinetics or safety profile of the candidate drug.

Below are two examples where extemporaneous dose manufacture and flexible design have been accommodated within a single Phase I study protocol.

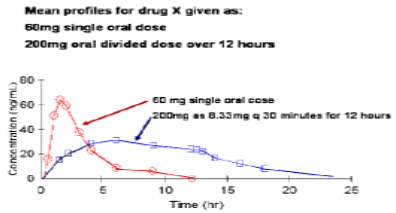
Example 1: Adverse events associated with C_{max}: Simulated controlled-release delivery

Rationale behind the flexible option:
Overt pharmacologically-based adverse events (AEs) were associated with peak plasma concentrations in preclinical studies. Detection of C_{max} associated AEs in Part A of the SAD FIM study would trigger an option to administer the maximum tolerated dose (MTD) as a number of different divided doses in order to establish the potential for formulation driven modified or sustained-release delivery.

Methods:
This was a two-part, single ascending dose, safety, tolerability, pharmacokinetic and pharmacodynamic study with a novel CNS lead compound.
Part A was designed to establish the MTD; Naive cohorts of 8 subjects were used for each dose increment; 6 received active drug and 2 received placebo.
There was a two week period before the start of Part B to allow adequate review of the safety and pharmacokinetic data prior to the start of Part B.
Part B was designed to allow administration of the drug as three divided dose regimens:
1. Six equal aliquots over 2.5 hours
2. Twelve equal aliquots over 5.5 hours, and
3. Twenty-four equal aliquots over 11.5 hours
A single cohort of 8 subjects was used in a three-way crossover design with a week washout between treatments.

Results:
Part A defined the MTD at 60mg. AEs associated with the pharmacological action were observed at doses above 60mg in a dose-related manner.
Pharmacokinetic simulation, based on the ascending dose profiles, indicated that a 200mg dose administered over 3, 6 or 12 hours would reduce the C_{max} and associated AEs.
Part B was successfully completed at all three divided dose regimens. The data for the delivery over 11.5 hours only is given in Figure 1.

Figure 1



Conclusions:

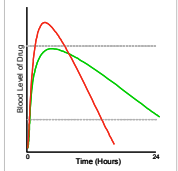
Incorporation of flexibility into this study was only made possible by adopting procedures for the extemporaneous GMP manufacture of the API.

Dividing the MTD has demonstrated to potential for modified release delivery of this drug in order to minimise C_{max} associated AEs.

Example 2: Issues with short half-life : Potential for controlled release delivery if the drug is absorbed from the colon

Rationale behind the flexible option:

Once Daily Dosing



•Good absorption
•Rapid elimination
•SHORT HALF-LIFE

The target product profile was for a once daily oral drug for the treatment of RA/OA.

Once daily dosing usually implies a half-life in excess of 4 hours, depending upon the therapeutic window.

Preclinical data indicated that the half-life in man may be less than 3 hours and therefore may not permit once daily dosing.

There was also solubility and dissolution data to indicate a potential for poor *in vivo* dissolution at therapeutic doses.

Methods:
This was a two part single ascending dose, safety, tolerability, pharmacokinetic and regional absorption study.
Part A was designed to establish the MTD and describe the pharmacokinetic characteristics of the drug.
Part B was designed as a three way crossover to quantify the bioavailability of the drug at the MTD administered directly into the colon as a solution and a particulate form in comparison with the immediate release formulation.

Part B would only take place if the drug half-life determined in Part A was less than 4 hours.
Administration of the drug to the colon as a solution and particulate form was achieved using Enterion™, a telemetric delivery capsule.

Results:
Part A of the study showed the drug to have a half-life of 2-3 hours. This was not considered to be suitable for once daily dosing and therefore Part B of the study was initiated.
Administration of the drug directly into the colon as a particulate form showed a reduced bioavailability of ~8% in comparison with the oral immediate release formulation. However, when the same dose was administered directly into the colon as a solution the relative bioavailability increased to approximately 98%.

Dosing Regimen	Mean AUC (ng.hr/mL)	F_{rel} (%)
IR reference	2.84	-
Colon – particulate	0.22	8
Colon - solution	2.78	98

Conclusions:
Incorporation of a flexible, two part study design, based on existing knowledge of potential bioavailability issues, has provided evidence that this drug could be adequately absorbed form the colon and that a modified release formulation would be possible provided adequate *in vivo* solubilisation is achieved.

Overall Conclusions

From *a priori* knowledge of the physicochemical, preclinical safety, ADME, pharmacology and formulation characteristics of a lead compound it is possible to identify potential "developability" issues and to incorporate these into the early clinical development strategy. This is enabled through the application of certain technologies and the ability to accommodate extemporaneous GMP manufacture. The use of flexible protocols in this way will add considerable value to the early clinical development of new molecules and if used appropriately could help reduce early phase attrition rates.

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