Flexible formulation assessments in FIH studies for poorly soluble drugs accelerates dosage form development, manufacturing and supply for patient POC trials

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PURPOSE

Arguably the primary early development goal for a new chemical entity (NCE) is to demonstrate proof-of-concept (POC) in a patient population in the most time and cost-effective way possible. The drug product strategy is crucial to success. The general philosophy over the last decade for first-in-human (FIH) studies has been to “keep it simple”, with the use of rudimentary, pharmacy-prepared, fit-for-purpose formulations such as drugs and powders in bottle and capsules. The intended benefit of this strategy is to minimize upfront development time and CMC expenditure prior to generating clinical safety and pharmacokinetics (PK) data, to warrant further investment in the asset.

Given the prevalence of NCEs with challenging biopharmaceutic properties, this approach presents limitations, especially where enabling formulation technologies are required to ensure adequate bioavailability. Not only does this present risks given the reliance on surrogate tools to predict human exposure, such as nonclinical, *in vitro* or *in silico* data, but also a high probability of needing a bridging study to a suitable (solid) dosage form prior to the patient POC trial.

Here we describe how the integration of formulation development, compounding and GMP manufacturing activities within the FIH to POC program can streamline development and maximize potential for clinical success.

A program design framework is proposed, describing how (i) FIH programs can be rapidly initiated via compounding of simple formulations, such as drug-in-capsule where appropriate, or enabled GMP intermediates such as solid dispersions where necessary, (ii) multiple technologies can be screened within a FIH protocol to identify the simplest formulation type which gives the desired bioavailability/PK, and (iii) switches to solid dosage forms can be bridged during the single (SAD) and multiple (MAD) ascending dose stages of the protocol without affecting the critical path, thereby allowing an immediate supply of GMP clinical trial material into patient-based POC trials. Two case studies are presented.

METHOD(S)

Integrated early drug development programs were designed for two molecules, based on their physicochemical and biopharmaceutic properties. In both programs, drugs products were prepared either by pharmacy compounding of the NCE, compounding of GMP intermediate, or the GMP manufacture of finished drug products. All formulations were prepared in real-time during the FIH clinical study, using arising safety and PK data to inform the drug product choice for the next study period as part of an adaptive protocol.

RESULT(S)

Case Study 1

- Compound 1 (Cmp-1), a predicted DCS Class IIb molecule, was administered in a FIH study using a fit-for-purpose crystalline suspension formulation prepared via pharmacy compounding for a placebo-controlled, double blind, SAD assessment.
- In parallel formulations were developed using solubilization-enhancement technologies, comprising two lipidic capsule formulations and a spray-dried dispersion (SDD) powder-in-bottle (PiB) for bed side reconstitution.
- The formulation compositions selected were based on API:excipient compatibility studies, *in vitro* screening using biorelevant media and short-term stability testing.
- Flexibility in unit dose was achieved via a use of a bracketing strategy (capsule fill weight from a fixed bulk powder concentration, and SDD weight from a common blend).
- Representative batch release data and short-term (7 day and 35 day) stability data were generated and included in the regulatory submission.
- In parallel to the FIH trial, a relative bioavailability study was conducted in 16 healthy volunteers using a 5 period non-randomized sequential design. Dose selection was informed in real-time by data emerging from the ongoing SAD study. The three enabled drug products were manufactured and dosed in the fasted state at weekly intervals.
- An interim decision was taken after period 4 to select the lead prototype for dosing in the fed state in the final study period.
- One of the lipidic capsule formulations demonstrated superior clinical PK performance for Cmp-1, and was used for the MAD assessment (once daily for 10 days) in two cohorts of 8 subjects upon immediate conclusion of the SAD protocol.
- The integrated program design was estimated to have saved over 8 months of R&D time in comparison to performing a separate critical-path solid dose development and bridging study post FIH and prior to POC. In addition to time, this approach also used a significantly less amount of API and resulted in significant cost savings.

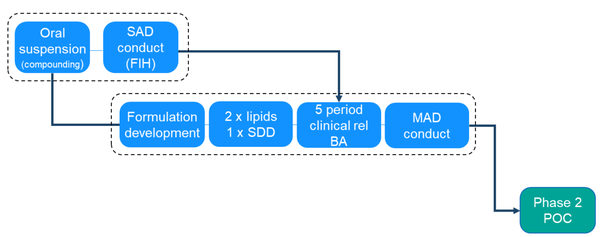

***Figure 1**: Integrated compounding and GMP manufacturing for FIH-POC program design for a DCS Class IIb molecule*

Case Study 2

- Compound 2 (Cmp-2), a predicted DCS Class IIb/IV drug, required the use of enabled solid dose formulation technologies for oncology patient trials.
- Preclinical safety data supported the administration of Cmp-2 in an FIH healthy volunteer study to assess safety, tolerability and PK. Each subject was administered two doses of Cmp-2 as part of dose escalation.
- *In silico* physiologically-based PK modelling and simulation (M&S) and *in vitro* biorelevant characterization studies were used to select a micronized API in capsule and a lipidic suspension capsule for the FIH study.
- Flexibility in unit dose was achieved via a use of a bracketing strategy (capsule fill weight from fixed bulk formulations).
- Representative batch release data and short-term (7 day and 30 day) stability data were generated and included in the regulatory submission.
- Selected drug products were manufactured in real-time under GMP for each dosing period based on safety and PK data from the previous dose.
- Part 1 of the protocol consisted of 5 groups of 6 subjects, each of whom was dosed twice in the fasted state. Dose escalation was performed with the micronized API capsule formulation in periods 1-3, 5 and 6, the lipidic formulation was assessed in period 4. Optimized versions of the lead formulation (micronized API capsule) were developed in parallel to increase unit dose per capsule, and refine excipient levels for rapid scale-up. These were tested in periods 7-10 via a regulatory amendment.
- Part 2 of the protocol consisted of 8 subjects who were dosed fed and fasted with the lead formulation.
- Based on human PK data an optimized formulation (micronized API capsule) was identified within a flexible SAD protocol prior to immediate manufacture for the patient POC study. Overall program duration was 12 months.

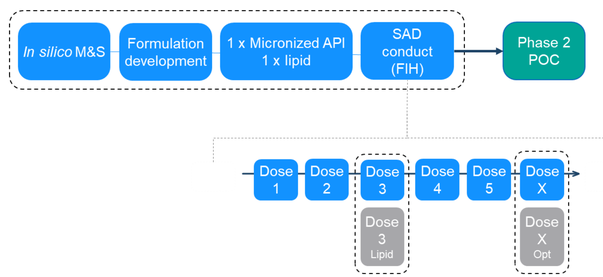

***Figure 2**: Formulation screening within an integrated FIH-POC program for DCS a Class IIb/IV molecule*

CONCLUSION(S)

The majority of NCEs entering development have sub-optimal solubility, presenting challenges to development teams as they try to control CMC investments whilst shortening time to POC. Integration of flexible compounding and GMP manufacturing within the FIH-to-POC program has been shown to offer significant benefits in achieving these objectives. The ability to manufacture and dose multiple formulations in “real-time”, using human data to make informed decisions, coupled with the ability to use smaller batch sizes and abbreviated data packages ensures CMC spend can be appropriately managed. Based on the Developability Classification System (DCS)[2], a road-map has been proposed to inform formulation transitions within FIH studies that enable a seamless progression into patient POC trials (Figure 3). Drug development programs using this approach have been shown to save, on average, 15 months of time when compared to traditional practices[3].

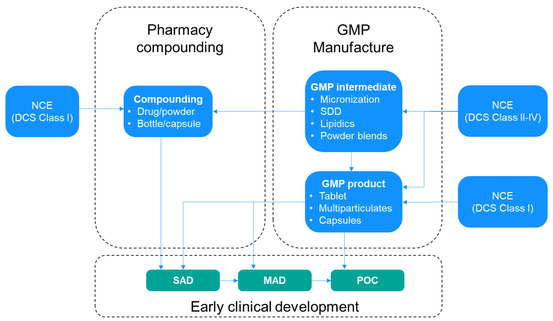

***Figure 3:** Integration of pharmacy compounding and GMP manufacturing in FIH to accelerate drug products for POC studies*

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