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Real-Time Drug Product Manufacturing to Enable Accelerated Early Clinical Development of Spray Dried Dispersion Based Formulations

Nikki Whitfield[1], John McDermott[1], Derek Law[2], Graham Sibley[2], Mike Birch[2], Anthony Kennedy[2], Richard Johnson[3], Karen Commbes[3]

1. Quotient Sciences, Mere Way Ruddington Fields, Nottingham NG11 6JS, UK
2. F2G Limited, Lankro Way, Eccles, Manchester, M30 0LX, UK
3. Upperton Limited, BioCity Nottingham, Pennyfoot Street, Nottingham NG1 1GF, UK

Quotient Sciences, Mere Way, Nottingham, NG11 6JS, UK - info@QuotientSciences.com - www.QuotientSciences.com

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PURPOSE

F901318 is a first in class antifungal treatment. The drug has low water solubility properties and therefore utilization of an enabled formulation technology was essential to ensure sufficient oral bioavailability in early clinical studies.

The use of such formulations to support first-in-human (FIH) and proof-of-concept (POC) studies can be time and cost consuming due to the extended effort required to develop the formulation, generate the regulatory data package and manufacture the clinical material ahead of initiating the FIH trial. These challenges can be overcome however if fit-for-purpose GMP drug products are manufactured in real time during clinical dosing. Benefits include rapid initiation of the study and an ability to customize formulations based on emerging clinical data. Development of a drug product format for longer-term treatment can be performed in parallel.

In this case study, an early development program was designed to rapidly initiate first-in-human (FIH) evaluation (Stage 1), transition to the solid oral dosage form and confirm tablet performance in healthy volunteers (Stage 2) prior to manufacturing process scale-up to support a Phase II clinical study in patients (Stage 3)

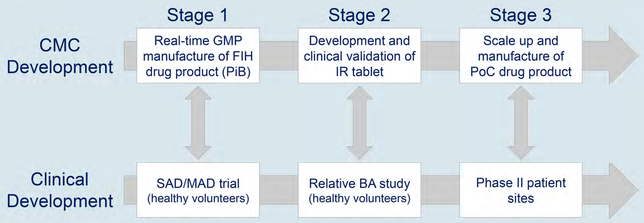

Figure 1: Overview of F901318 SDD development program

METHOD(S)

A spray-dried dispersion (SDD) for delivery as a suspension was developed to support Stage 1. The bulk SDD GMP formulation composition and associated manufacturing process was established using spray-drying process parameter scouting batches and a development dissolution methodology (Figure 1.)

A confirmation batch was manufactured to provide batch analysis and stability data (7 day) to support a clinical trial application (CTA) for the FIH study. The drug product dossier was written flexibly to allow extension of the bulk SDD shelf life to 4 months based upon emerging data. Following approval, clinical drug product manufacture was conducted in real time in accordance with the ongoing demands of the clinical study.

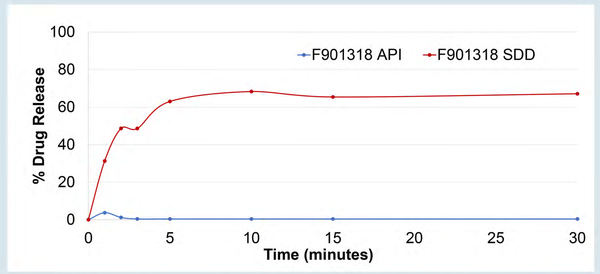

Figure 2: Dissolution comparison: F901318 drug substance vs formulated spray dried dispersion

Stage 2 was initiated in parallel with ongoing conduct of the FIH trial. An immediate release (IR) tablet formulation incorporating the SDD was developed using discriminatory (non-sink) dissolution test methodology to characterize formulation performance before selecting the tablet composition to advance to clinical assessment.

Batch analysis and short term (7 days) stability data were collected to support the clinical trial application for a 4-period, sequential clinical study in 10 healthy volunteers. Initially, the clinical study determined relative bioavailability of the tablet formulation relative to the suspension before adjusting the tablet dose required to achieve equivalent drug exposure to the suspension and assessing food effect to confirm the treatment to be dosed in Phase II.

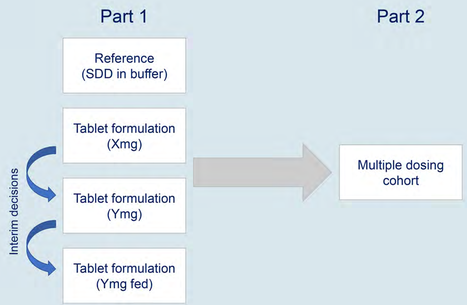

Figure 3: Clinical study design – evaluation of SDD and SDD tablet

Due to the real time manufacturing approach, a relatively small batch size was used throughout the FIH and tablet confirmation clinical evaluation to minimize drug substance consumption. However the Phase II patient study required greater tablet numbers to support the clinical design. The SDD tablet scale up (Stage 3) was initiated on receipt of the initial positive emerging data during the Stage 2 clinical evaluation and the manufacturing process was scaled to approximately ten times that used for the Phase I clinical study.

RESULT(S)

Adopting a real time drug product manufacturing approach allowed initiation of the FIH study within 12 weeks of initiating SDD process transfer.

The IR tablet composition was identified in parallel and data generated for the regulatory submission within 12 weeks of commencement of formulation development, and was dosed to healthy volunteers in 26 weeks.

The tablet formulation demonstrated 101% relative bioavailability versus the SDD suspension formulation (figure 4).

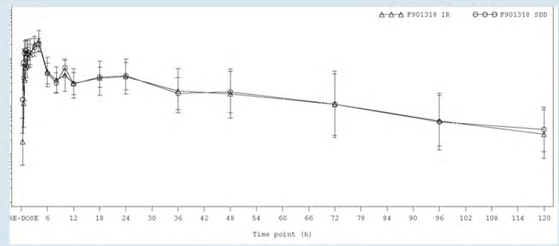

Figure 4: Geometric mean (±geometric SD) plasma concentrations of F901318 from SDD suspension and tablet after single dose administration

The scale up of the SDD tablet process and generation of data for inclusion in the regulatory filing to support the Phase II clinical program was completed within 9 weeks

CONCLUSION(S)

Real time adaptive GMP manufacturing strategies allowed rapid implementation of an early development program for F901318. Potential time and cost challenges around utilization of an SDD formulation strategy to overcome bioavailability risks were successfully mitigated. The accelerated initiation of FIH studies using an SDD based suspension, and rapid transition to a clinically validated tablet formulation to support Phase II studies was achieved in less than 13 months

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