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A Rapid Formulation Development and Clinical Testing program to evaluate the pharmacokinetics of a novel enabled formulation of Abiraterone acetate

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PURPOSE

Abiraterone acetate is a marketed drug (Zytiga®) used to treat prostate cancer. The drug has low oral bioavailability with high variability and a significant positive food effect (> 10 fold increase in Cmax and AUC). The extent of the food effect is dependent upon the composition (fat content) of the meal. Therefore, in order to control pharmacokinetic (PK) variability and exposure, the product label for Zytiga® requires patients to avoid consumption of food for at least two hours either side of drug administration.

A new 'Super-API' formulation of Abiraterone acetate has been developed using a novel process applying continuous flow precipitation of the API in the presence of selected pharmaceutical excipients to generate a formulation having supramolecular structure with the goal of increasing availability of the API for absorption, and thus increase bioavailability and reduce variability.

A clinical study in healthy volunteers was designed to evaluate the PK of Abiraterone acetate in Super-API form. To accelerate timelines, drug product was manufactured immediately prior to dosing at a co-located GMP production and clinical testing facility which enabled both rapid clinical assessment of prototype performance and the ability to adjust formulation parameters in real-time based on emerging clinical data.

RapidFACT

RapidFACT uses a Translational Pharmaceutics® delivery platform which utilises an integrated GMP production and clinical testing facility (1). Using this platform drug product can be manufactured within 7 days of dosing at reduced scale, removing scale-up and stability data package generation from the critical path to obtaining clinical data on product performance (2-4).

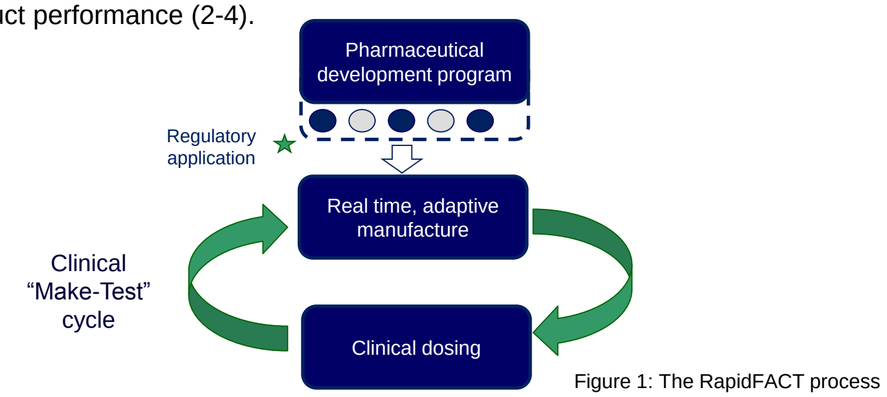

Figure 1: The RapidFACT process

Following initial dosing, the Translational Pharmaceutics platform also allows GMP drug products to be made in real-time in response to interim analysis of clinical data, typically on a 7-14 day cycle. Drug products can be selected from a panel of pre-approved fixed formulation compositions. Alternatively, building upon ICH Q8 Development Pharmaceutics and Quality-by-Design principles(3), products can be selected from any point within a continuous formulation design space (Figure 1). In this scenario, a range of product performance attributes are obtained by varying the quantitative composition of one or more formulation components(4).

CONCLUSION

- The Translational Pharmaceutics delivery platform allowed the second dose of Super-API to be selected based on clinical PK and safety data generated from the first dosing period.
- Rapid formulation and clinical testing strategies allowed the accelerated evaluation of the Super-API formulation at two dose levels, and in the fasted and fed states in less than 18 months.
- The data showed a significant increase in bioavailability with reduced variability, which can potentially lead to a 3-fold reduction in dose compared to the marketed Zytiga® products.
- The Super-API formulation eliminated the significant positive food effect observed for marketed Zytiga® products. As a result administration of the Super-API formulation with food does not risk side effects as a consequence of greatly increased exposure.
- The results from the study support the potential avoidance of restrictive food labelling in future prescribing instructions for Super-API drug products of Abiraterone acetate.

METHODS

Super-API formulation of Abiraterone acetate was prepared as a powder in a bottle (PiB) containing abiraterone acetate and pharmaceutical excipients. Super-API of Abiraterone acetate was prepared using a proprietary technology to support the continuous flow precipitation step of the formulation preparation, prior to freeze drying to recover the Super-API powder.

Super-API PiB formulations were evaluated in a 3-period, 3-treatment sequential crossover study in 12 healthy male volunteers to evaluate two dose levels of Super-API in the fasted state, and to assess exposure in the presence of food. PK samples were collected to 72 hours post dose. The performance of the Super-API was compared to literature data on Zytiga®.

RESULTS

- Super-API formulation had rapid absorption with T_{max} at 0.5 to 0.75 hours post dosing.
- The Super-API formulation had an estimated 3-fold increase in fasted state exposure relative to literature data on Zytiga®.
- Half-life was essentially unchanged by the change in formulation, or by administration with food.
- Variability was reduced to 30 to 40%.
- When Super-API was administered in the fed state, the food effect was eliminated (Figure 2).
- There were no serious or severe AEs.

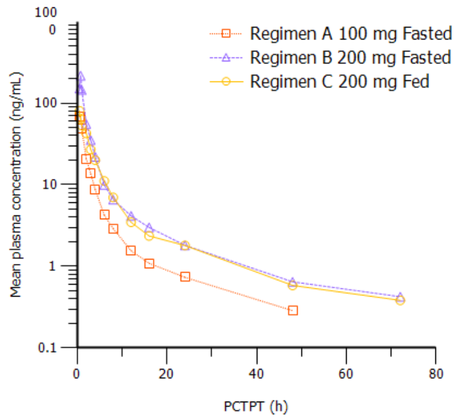

Figure 2: Mean plasma PK profiles for Super-API formulation of Abiraterone acetate in healthy volunteers

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