Flexible strategies for the conduct of human metabolism studies with oncology molecules

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INTRODUCTION

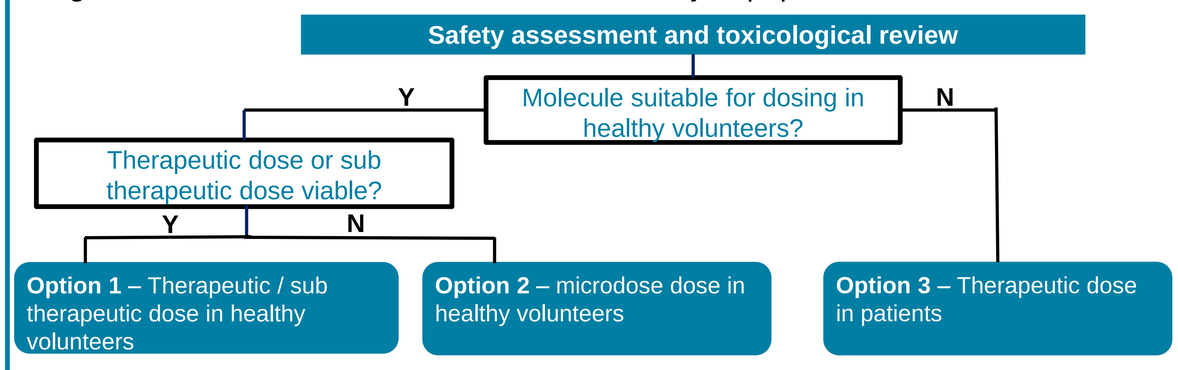
The key objectives of human ADME studies are to evaluate mass balance, determine the routes and rates of elimination and gain an understanding of the metabolic fate of the drug. Conventionally, this is assessed in healthy volunteers following the administration of a single dose of the radiolabelled drug. A successful study outcome requires a significant amount of bespoke expertise in areas including ^{14}C drug substance and drug product development, clinical dosing and sample collections, and also mass balance and metabolism analysis and reporting.

ADME studies with oncology molecules can present additional logistical challenges given that patient dosing can often be desired or required (e.g. for non-molecular targeted drugs). Here we present three different options for the conduct of such studies, to deliver robust scientific data in the most time and cost effective route.

A key consideration in all cases to ensure efficient and effective study conduct, is the close co-ordination of drug product manufacturing and clinical testing activities due the inherent radiolytic instability of ^{14}C formulations. For healthy volunteer studies we describe an approach using the concept of Translational Pharmaceutics™ and how integrated GMP and clinical facilities can enable the rapid production, release and dosing of oral and IV ^{14}C drug products within as little as 48 hours [1]. For patient-based studies these principles can also be applied for the “on demand” per-patient manufacture and supply of drug products for dosing at specialist oncology clinics in line with individual subject recruitment.

MATERIALS AND METHODS

Three alternative approaches to supporting human ADME studies for oncology molecules are described using an integrated approach to drug product development, GMP manufacturing and clinical testing. All of these options provide tailored solutions to gain the critical data needed, in the desired subject population.



Option 1: Study in healthy volunteers with clinical or sub-clinical ^{14}C doses

- Single dosing period
- Standard sample collection and analysis
- Efficient use of ^{14}C API
- Real time mass balance data generation
- Metabolite profiling and identification from pooled study samples

Case Study: Molecule X, a molecular targeting drug, was in Phase II development. Based on a full and successful safety and toxicological review the molecule was deemed suitable to be dosed in healthy volunteers at the therapeutic dose. The drug was formulated into a simple ^{14}C labelled suspension with 7 days shelf life and this data was submitted to the UK regulatory authorities. The suspension was then manufactured and QC/QP released 2 days prior to dosing in n=6 volunteers in the clinic. All sample collections performed and analysed for mass balance in real time to show >90% recovery. [2]

Option 2

Option 2: Study in healthy volunteers with ^{14}C microdose

- Single dosing period
- Standard sample collection
- AMS analysis
- Efficient use of ^{14}C API
- Delayed but consolidated mass balance data generation
- Metabolite profiling from pooled study samples
- Metabolite identification from correlation with unlabelled samples from other studies

Case Study: Elacytarabine, a Cytotoxic drug, required mass balance data to support a market application. After a thorough review of the molecule information is was decided that normal approaches could not be taken due to the toxicity of the drug and logistical challenges of recruiting patients.

Therefore a ^{14}C labelled microdose of the drug was proposed. The study synopsis was pre-approved with FDA.

A specific intravenous microdose formulation (100µg) was developed in-house and data was collected to support the regulatory submission which involved 48 hours shelf life and reduced QC testing requirements.

The IV solution was manufactured under GMP the day prior to dosing and administered to n=6 healthy volunteers to gain the mass balance data needed. All sample collections performed and analysed for mass balance in real time to show >90% recovery. [3]

Option 3

Option 3: Study in patient population with clinical ^{14}C dose

- Intermittent dosing periods
- Data in defined target patient population
- ‘Per patient’ ^{14}C drug product supply
- Efficient use of ^{14}C API given repeat synthesis/repurification may be required
- Real time but sporadic mass balance data generation
- Metabolite profiling and identification for individual subjects

Case Study: Molecule Z, a Cytotoxic drug, is currently in late Phase II trials and required mass balance and metabolism data to be collected. Due to the toxicity of the drug the only viable option was to dose within patients.

A CMC, manufacture and supply program was developed to support a personalised ‘per patient’ manufacturing process for the IV product.

The IV product was manufactured in real time upon each patient recruitment. The IV product was manufactured, QP released and shipped to a specialist European clinic for dosing within 5 days based on a 7 day shelf life.

RESULTS AND DISCUSSION

Option 1	Option 2	Option 3
Molecule safety profile acceptable	Safety profile does not support therapeutic / sub-therapeutic dose but a microdose is feasible in healthy volunteers	Safety profile does not support healthy volunteer dosing at all OR data is desired / required in target population
Advantages and disadvantages of each option		
Simplest, quickest, cheapest	Still fast route to dose More time, cost and complexity on sample analysis and reporting	Data is achieved in target population ‘per patient’ real time manufacture required Slowest route due to patient recruitment, additional time, cost and complexity regarding ^{14}C API synthesis and sample collection analysis and reporting

In all three case studies detailed above, the ^{14}C drug products were made ‘on demand' under full GMP controls with a ‘fit for purpose' CMC data package and shelf life. Translational Pharmaceutics allowed the most efficient and cost effective route for each option and was able to overcome the challenges in particular relating to option 3.

CONCLUSION

The conduct of clinical ADME studies with oncology molecules can present unique challenges for the development team. Depending upon molecule type and study objectives a range of flexible strategies are available to ensure generation of pivotal, regulatory-compliant datasets, involving dosing at therapeutic or microdose levels in either healthy volunteer or patient subjects. Integral to all these options is the ability to synchronise the ‘real-time’ GMP manufacture of the ^{14}C drug product with clinical dosing. This capability ensures studies can be performed with formulations when stability is limited and/or where study conduct can be protracted due to the patient recruitments rates, necessitating personalized, ‘on-demand’ manufacture.

REFERENCES

1) Scholes et al ‘Translational Pharmaceutics - Interactive Drug Development to Enable Rapid Optimisation of Drug Products in Early Development’, AAPS 2009
2) Shaw, Stevens, ‘Integrated ^{14}C Study Designs to Provide Intravenous Pharmacokinetics and Human Mass Balance and Metabolism from a single Protocol and a Single Regulatory Submission’, EACPT, 2013
3) Shaw et al, ‘Clinical Microdose Study with 14C-Elacytarabine in Healthy Male Subjects to Generate Mass Balance Data To Support Regulatory Submission: An Innovative Microtracer Application’, ISSX 2013