# Conduct of Clinical ADME Study for Vosaroxin in Oncology Patients via Real-Time Adaptive Manufacture of Intravenous Drug Product

QUOTIENT CLINICAL
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## INTRODUCTION

Vosaroxin is a cytotoxic molecule currently in Phase III development for treatment of acute myeloid leukaemia (AML). Conduct of a clinical ADME study was required to evaluate the mass balance, determine routes and rates of elimination and gain an understanding of the metabolic fate of vosaroxin. Due to the genotoxicity of vosaroxin, dosing in healthy volunteers was not possible and therefore administration was in oncology patients with solid tumors. Patient recruitment for these types of studies is often unpredictable and prolonged over a period of 6-18 months which in turn leads to challenges with the drug substance and drug product shelf-life requirements. The radiolabelled drug substance and drug product can be inherently unstable due to radiolysis risk. This poster describes a new approach for conduct of these studies via on-demand GMP manufacture of the drug product on a per-patient basis.

## METHODS

A small scale GMP manufacturing process for $^{14}C$ intravenous vosaroxin solution was established via the development program described below.


Diagram 1 – schematic of process

Stage 1 – Technical transfer

Vosaroxin was formulated as a sterile product for clinical development. Sterility was achieved by heat sterilization. However, for the purposes of the ADME trial, the manufacturing method was adapted to an aseptic double filtration process and the batch size reduced to ensure on-demand per patient manufacturing could be performed. A laboratory based experiment was conducted to test the new process and confirm that the radiolabelled vosaroxin injection was comparable to the existing formulation.

Stage 2 – CMC (regulatory) batches

The vosaroxin solution (using unlabelled API) was manufactured in triplicate under GMP conditions to replicate the final clinical manufacturing process and provide representative regulatory data. The process was assessed via the use of in-process controls, microbial testing and analytical testing. In-process controls included visual appearance, weight/volume controls and equipment testing such as isolator and filter integrity. The vosaroxin solution was analysed for bioburden, endotoxin, HPLC assay and related substances. Short term chemical and physical stability was assessed at T=0, T=2 and T=7 days at 2-8ºC.

A radiolabelled trial using $^{14}C$ vosaroxin API was performed off the critical path to confirm radioactivity content could be achieved within the defined specification. A single batch was prepared to replicate the CMC trial and final manufacturing processes and specifications.

Stage 3 – Aseptic Process Validation (APV)

To fully validate the sterile manufacturing process, a study specific aseptic process validation was conducted using 3 separate operators. The APV process utilised "worst-case" principles substituting API and microbiological/endotoxin controlled excipients with non-sterile / non-bioburden controlled materials alongside nutrient growth media to 'challenge' the proposed aseptic process. The APV process included critical process parameters of the production preparation such as manipulations, preparation conditions and all known interventions. Microbial testing was conducted throughout this trial to evaluate the process and the operators.

Stage 4 – IMPD Regulatory Submissions

The IMPD for the $^{14}C$ vosaroxin drug product was prepared and incorporated into the final Clinical Trial Application. The CTA was submitted to the Dutch Authorities (CCMO) along with the clinical protocol.

Stage 5 – Real time clinical manufacturing, distribution and dosing

Clinical $^{14}C$ vosaroxin injection was manufactured once a patient was identified. The drug product was manufactured, QC/QP released, shipped directly to the clinic and then dosed all within 7 days. Six patients were dosed with ≤100 µCi radioactivity at 60 mg/m$^2$ vosaroxin. The product was labelled at 0.9 µCi/mg. The pharmacokinetics and total radioactivity (TRA) in plasma and urine were analysed over 7 days post dose and the blood:plasma ratio measured. Faeces are collected over 7 days post dose and analysed for TRA to confirm mass balance recovery.

## RESULTS

Stage 1 – Technical transfer

A small scale manufacturing process was successfully established utilising a double filtration technique to achieve sterility assurance. All specifications were met to ensure product was comparable to the terminally sterilized product.

| Test | Specification | Result |
|---|---|---|
| Appearance | Clear, colourless to light yellow solution | Complies |
| Visible particulates | Absence of visible particulates | Complies |
| HPLC assay and related substances | 90.0 – 110.0% nominal<br>≤0.2% individual<br>≤1.0% total | 102.8%<br>None detected |
| Fill volume | Not less than 11 mL | Complies |

Table 1 – Results of technical transfer batch

Stage 2 – CMC (regulatory) batches

The triplicate CMC batches (and radiolabelled batch) were successfully manufactured and a 7 day shelf-life obtained. Results are shown in Table 2, 3 and 4.

| Test | Specification | Result |
|---|---|---|
| Appearance | Clear, colourless to light yellow solution | Complies |
| Visible particulates | Absence of visible particulates | Complies |
| HPLC assay and related substances | 90.0 – 110.0% nominal<br>≤0.2% individual<br>≤1.0% total | 100.4%<br>None detected |
| Fill volume | Not less than 11 mL | Complies |
| Microbiological assessment | Post filtration samples must have less than 1 CFU/mL | Complies |
| Endotoxin | Not more than 16.6 EU/mL | <10 EU/mL |
| Filter compatibility | HPLC assay of filtered bulk is 90.0 – 110.0% of unfiltered bulk | 100.5% |
| Filter integrity | Bubble point not less than 50 psi | 60 psi |

Table 2 – Results of CMC batches (average of 3 batches)

| Test | T=0 | T=2 days | | T=7 days | |
|---|---|---|---|---|---|
| | | 2-8ºC | 15-25ºC | 2-8ºC | 15-25ºC |
| Appearance | Complies | | | | |
| Visible particulates | Complies | | | | |
| HPLC assay | 100.4% | 99.3% | 98.2% | 97.6% | 97.3% |
| HPLC related substances | None detected ≥0.05% | Individual 0.03%<br>0.03%<br>Total 0.1% | Individual 0.03%<br>0.03%<br>Total 0.1% | Individual 0.09%<br>Total 0.1% | Individual 0.08%<br>Total 0.1% |

Table 3 – Results of stability testing

| Test | Specification | Result |
|---|---|---|
| Appearance | Clear, colourless to light yellow solution | Complies |
| Visible particulates | Absence of visible particulates | Complies |
| HPLC assay and related substances | 90.0 – 110.0% nominal<br>≤0.2% individual<br>≤1.0% total | 100.4%<br>None detected |
| Endotoxin | Not more than 16.6 EU/mL | <10 EU/mL |
| Radioactivity content | Not more than 0.37 MBq/mL | 0.33 MBq/mL |

Table 4 – Results of radiolabelled batch

Stage 3 – Aseptic Process Validation

All three operators were successfully validated following incubation and 100% inspection of all filled final container closures. Furthermore, environmental monitoring was undertaken throughout all activities which successfully demonstrated that a Grade A was maintained at all times.

Stage 4 – IMPD Regulatory Submissions

The regulatory application was submitted to the local authorities and approval was gained within standard timelines.

Stage 5 – Real time clinical manufacturing, and dosing

Six patients with advanced solid tumors were successfully dosed with $^{14}C$ vosaroxin. Once a patient was enrolled an instruction to manufacture notification was sent to Quotient Clinical and drug product was manufactured, QC/QP released, shipped and dosed within 7 days.

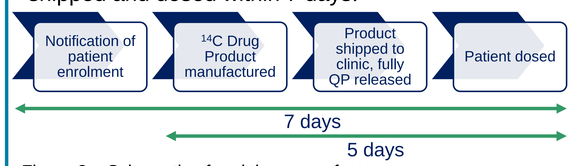


Figure 2 – Schematic of real time manufacture process

## CONCLUSION

Real time adaptive manufacturing provides customised GMP drug products for early development studies in oncology patients. This approach was successfully used for the manufacture and supply of $^{14}C$ vosaroxin injection to support a clinical ADME. Manufacture on per-patient basis ensures product shelf-life can be minimized and stability assured. The $^{14}C$ drug substance can also be used efficiently in line with subject recruitment.