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Population pharmacokinetic modeling of orally administered fostroxacitabine bralpamide (fostrox, MIV-818) and its metabolite troxacitabine in a phase I/IIa liver cancer study

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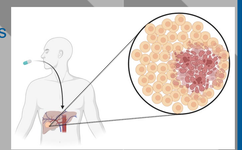
Introduction

Fostrox is a type of new smart chemotherapy, that targets tumor cells while sparing normal cells. Being an orally administered prodrug, based on the nucleoside analog troxacitabine, fostrox is designed to direct high levels of the active metabolite to the liver through first pass metabolism, while minimizing systemic exposure.

Fostrox is in clinical development in combination with lenvatinib in patients with advanced hepatocellular carcinoma (HCC) who progressed on prior treatment (NCT03781934). The combination has shown an acceptable safety and tolerability profile with encouraging efficacy outcome.



Aim

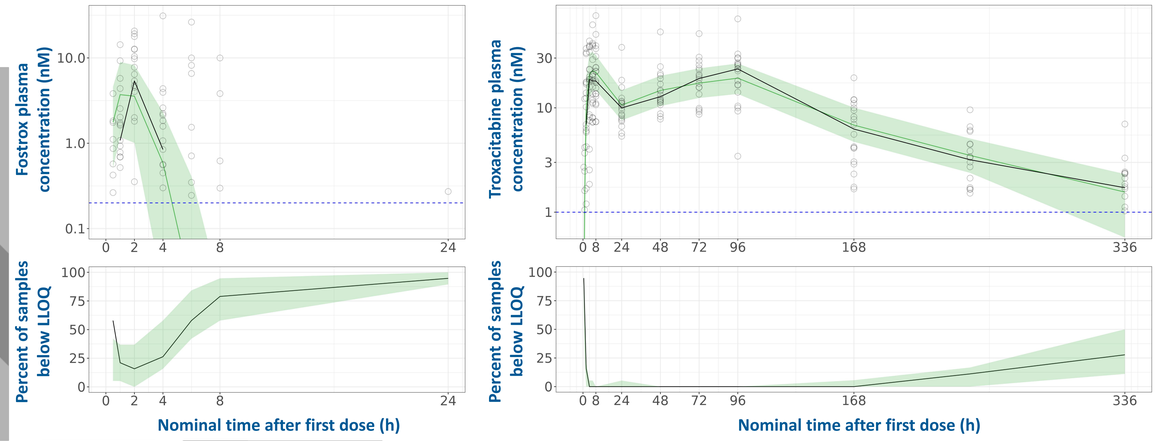
- To develop population pharmacokinetic (PK) models for fostrox and its main metabolite troxacitabine independently, as functions of fostrox dose, time, and potential covariates in patients with HCC, intrahepatic cholangiocarcinoma and liver metastases from solid tumors enrolled in a phase I/IIa study.
- To perform population simulations based on the final models to assess the expected area under the concentration-time curve ($AUC_{0\text{-}inf}$) and maximal plasma concentration (Cmax) during a cycle with 5 daily doses.

Method

- Fostrox and troxacitabine plasma concentration-time data from 42 patients treated with fostrox (3-70 mg QD for up to 5 days in 21-day cycles) monotherapy or in combination with lenvatinib (standard dose for HCC) were analyzed using nonlinear mixed effects modeling (NONMEM version 7.4.3).
- Plasma samples were collected up to 4 or 8h post dose in Cycle 1 Day 1, pre-dose the remaining days in Cycle 1 and up to 2-4h post dose on Day 4 or 5 in Cycle 1 and/or in Cycle 2.
- One-, two-, and three-compartment distribution models were evaluated, as well as linear and concentration-dependent elimination.
- Potential absorption models included zero and first-order processes, with and without an initial lag-time.
- The M3 method was applied to handle the high proportions of observations below the lower limits of quantification (LLOQ) (Beal, 2002).
- The final base models were evaluated for potential effects of lenvatinib coadministration on fostrox and troxacitabine clearance (CL), dose on bioavailability, creatinine clearance (CRCL) on troxacitabine CL, and weight-dependence for both analytes' CL and volume of distribution (V).
- P-values of 0.01 and 0.001 were used for model acceptance in forward inclusion and backward elimination steps, respectively.
- Preliminary individual estimates of $AUC_{0\text{-}inf}$ were assessed for each individual and cycle.
- Simulations of PK profiles for 100,000 hypothetical individuals were generated and Cmax and $AUC_{0\text{-}inf}$ were assessed on a population level.

Results

Observed and predicted plasma concentrations of fostrox (single dose) and troxacitabine (5 doses) after oral administration of 30 mg fostrox.



59% of the PK observations for fostrox and 13% for troxacitabine were below the LLOQ. The fostrox data supported a one-compartment model with rapid elimination (left figure). The troxacitabine data supported a two-compartment model with relatively long half-life (right figure).

Nonlinear components in absorption or elimination were not supported by the data.

The absorption processes were described by sequential zero-order (constant rate) and first-order (concentration-dependent) processes, with an initial lag for troxacitabine. The absorption model for troxacitabine includes fostrox absorption and metabolism to troxacitabine.

The absorption profiles were variable and between-subject variability (BSV) was supported by the data for absorption lag time (troxacitabine only), zero-order absorption duration, and first-order absorption rate. BSV was also supported on fostrox CL and troxacitabine V.

Considerable variability between cycles was noticed, and between-cycle variability was supported on the zero-order absorption duration (both analytes) and relative bioavailability (troxacitabine).

None of the evaluated parameter covariate relations were supported by data.

Visual predictive check (VPC) graphs for the dose level with most data are shown above. The final models accurately describe the median trends for both analytes. Prediction-corrected VPCs showed good agreement between observed and predicted upper and lower percentiles (not shown).

Population predicted exposures to fostrox and troxacitabine after 5 daily doses of fostrox 30 mg

Analyte	Cmax median prediction (nM)	Cmax 90% prediction interval (nM)	$AUC_{0\text{-}inf}$ median prediction (nM*h)	$AUC_{0\text{-}inf}$ 90% prediction interval (nM*h)
Fostrox	7.4	1.2 - 33	88	17 - 470
Troxacitabine	46	20 - 110	4600	2200 – 9400

$AUC_{0\text{-}inf}$: Area under the concentration-time curve for a cycle with 5 daily doses of fostrox. Cmax: Maximal plasma concentration during a cycle with 5 daily doses of fostrox. Median: Predictions for the median individual in the population. 90% Prediction interval: 90% of the individuals in the population will have values within these limits

Conclusion

- Fostrox was quickly absorbed and eliminated, and the systemic exposure to fostrox was low, as expected from a prodrug
- The PK models described the fostrox and troxacitabine data well with dose linear increase in exposure and linear elimination
- The exposure to fostrox and troxacitabine was not affected by lenvatinib coadministration
- The predicted exposure at the recommended phase 2 dose of fostrox (30 mg QD for 5 days in 21-day cycles) in combination with lenvatinib standard dose supports tolerability[1,2]

Acknowledgements

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References

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