Population pharmacokinetic analysis of the IAPs antagonist Debio 1143 and its major metabolite in oncologic patients

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Introduction

- Debio 1143 (D-1143) is an antagonist of Inhibitors of Apoptosis Proteins (IAPs) under clinical development for cancer therapy.
- D-1143 and its major metabolite (D-1143-M) are both P-gp substrate and inhibitor as well as CYP3A4 inhibitors.
- D-1143 and D-1143-M pharmacokinetics (PK) was investigated in three Phase I clinical study as a single agent and in combination with cytarabine/daunorubicin (Cyt/Daun) and with carboplatin/paclitaxel (Carbo/Pac).

Objectives

- To characterize D-1143 and D-1143-M concentration-time profiles.
- To investigate D-1143/D-1143-M interaction and potential covariates influencing the disposition of D-1143 and D-1143-M.

Methods

Data

Study	Patients	Dosage Regimen	PK Data
D-1143-101 MTD as a single agent	48 Advanced solid tumors and lymphomas	Daily x 5 (with or without single lead-in dose one week earlier) or x14 every 21 days Dose range: (5-900) mg	• rich profile at two occasions • several trough concentrations
D-1143-102[1] MTD with Cyt/Daun	29 Poor-risk AML	Daily x 5 days Dose range: (100-400) mg	• rich profile at two occasions • several trough concentrations
D-1143-103 MTD with Carbo/Pac	17 squamous NSCLC, platinum-resistant ovarian cancer or TNBC	Daily x 5 every 21 days Dose range: (100-400) mg	• rich profile at one occasion • several trough concentrations

AML: acute myelogenous leukemia; MTD: maximum tolerated dose; NSCLC: non-small cell carcinoma; PK: Pharmacokinetics; TNBC: triple negative breast cancer
[1]Only D-1143 plasma concentrations were assessed.

Analytical methods

- D-1143 and D-1143-M plasma concentrations were assessed using a validated LC/MS/MS method with a lower limit of quantification of 2.5 ng/mL.

Covariates

- Demographics: age, sex, body surface area and cancer type.
- Coadministered chemotherapy agents: Cat/Dar and Carb/Pac.
- Biochemical parameters: aspartate and alanine aminotransferase, alkaline phosphatase, albumin and unconjucated bilirubin.

Data Analysis

- Comparison of multi-compartment models with linear elimination and a variety of absorption models (including mechanistic model to capture the observed D-1143 enterohepatic recycling) to describe D-1143 PK.
- Assumption of linear metabolism from D-1143 to D-1143-M and equal volumes of distribution and comparison of multi-compartment models to depict D-1143-M PK.

D-1143/D-1143-M interaction model

- Competitive and non-competitive inhibition models:

$$\mathbf{CL=CL_0*f(C)} \qquad \mathbf{CL=CL_0*f(AUC)}$$

where CL D-1143 or D1143-M clearance, CL_0 mean population CL, C time-dependent D1143-M or D-1143 predicted concentration and AUC D1143-M or D-1143 $AUC_{0\text{-}24}$.

f(C): linear, exponential or E_{max} equations

f(AUC): linear, exponential or power equations.

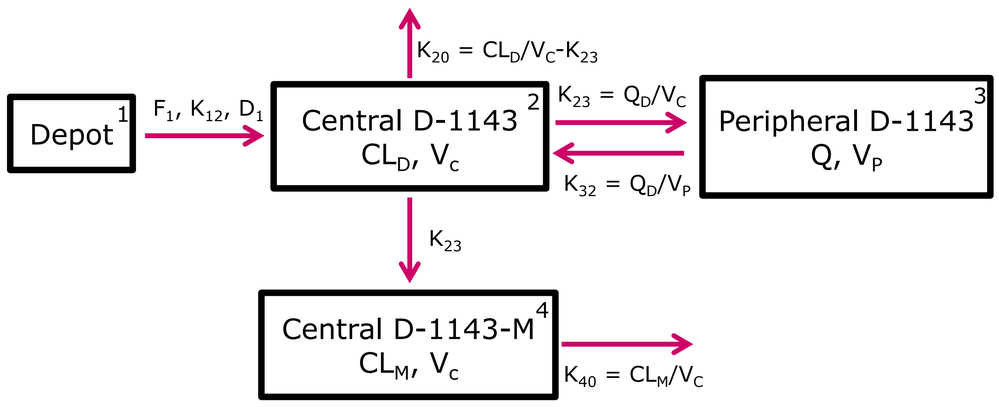
Covariate Analysis

- Linear models were used for demographics and biochemical covariates as well as on Carb/Pac and Cyt/Daun or appropriate categorized biochemical parameters (coded as 0/1).

Results

- 94 oncologic patients provided 1717 D-1143 and 888 D-1143-M concentrations.

Simultaneous D-1143 and D-1143-M structural pharmacokinetic model



F_1, relative bioavailability; K_{12} and D_1, first- and zero-order absorption rate constants; K_{23}, metabolic conversion rate constant; CL_D and CL_M, D-1143 and D-1143-M clearances; Q_D, D-1143 intercompartmental clearance; V_c and V_p volume of distribution of D-1143 central and peripheral compartments.

- Sequential mixed zero and first order absorption (no improvement with mechanistic model).
- Distinct F1 associated with rich profile at occasion 1 and rich profile at occasion 2/trough concentrations.
- Interindividual variability (IIV) assigned to: F_1, CL_D, V_C, V_P, D_1, K_{23} and CL_M.

Final Pharmacokinetic model

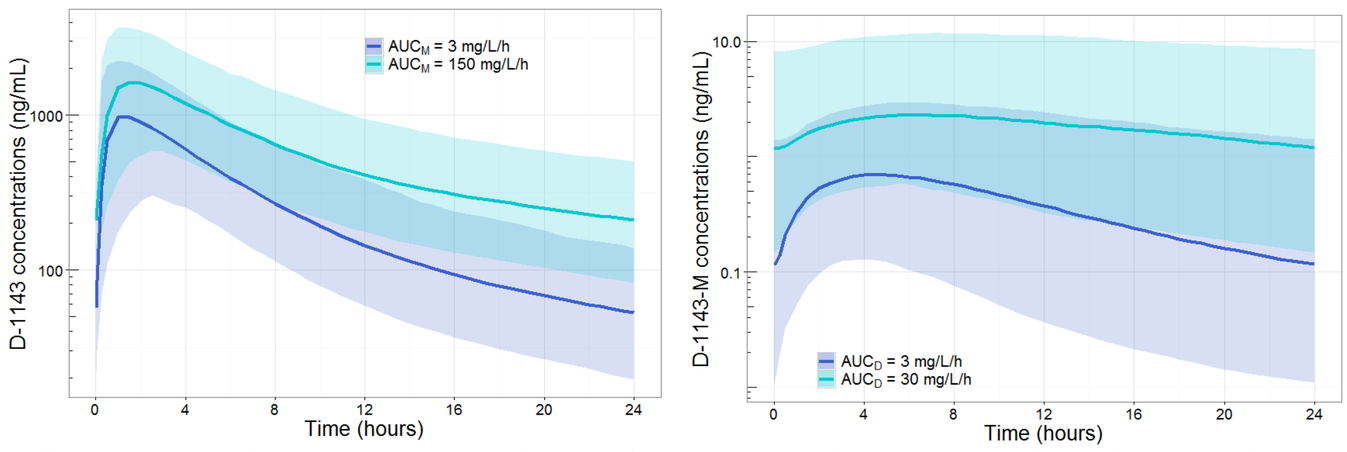
Parameter	Population mean			
	Estimate	RSE(%)	IIV(%) IOV(%)	RSE(%)
F_1			37 25	12 10
Rich profile at occasion 1	0.46	21		
Rich profile at occasion 2 /Trough concentrations	0.36	20		
CL_D (L/h)	7.0	23	21	15
θ_{AUC_M}	0.19	11		
$\theta_{Carb/Pac}$	-0.35	4		
V_C(L)	3.1	13	80	15
Q (L/h)	4.1	21		
V_P(L)	62	24	28	22
$K_{12}(h^{-1})$	0.30	3		
D_1(h)	0.43	30	169	17
$K_{23}(h^{-1})$	0.34	14	55	12
CL_M (L/h)	0.38	17		
θ_{AUC_D}	0.36	20		

IOV, interoccasion variability; θ_X, effect of the X covariate on the typical value (TV) of CL_D and CL_M as follows:

$$\mathbf{TVCL_D = CL_D * (1 + \theta_{Carb/Pac} * I_{carb/Pac}) * (AUC_M/MAUC_M)^{-\theta_{AUC_M}}}$$
$$\mathbf{TVCL_M = CL_M * (AUC_D/MAUC_D)^{-\theta_{AUC_D}}}$$

with AUC_M and AUC_D, D-1143-M and D-1143 AUC; $MAUC_M$ and $MAUC_D$ median AUC_M and AUC_D population values; $I_{Carb/Pac}$= 1 when patients received Carb/Pac, 0 otherwise.

- D-1143 and D-1143-M mutual interaction was described using power non-competitive inhibition models.



Simulated median concentration-time profiles (solid line) with $PI_{90\%}$ (shaded areas) of D-1143 (left panel) and D-1143-M (right panel) obtained with minimal and maximal inhibition conditions, *i.e.* AUC_M=3 and 150 mg/L/h for D-1143 and AUC_D=3 and 30 mg/L/h for D-1143-M.

Conclusions

- D-1143 PK is characterized by non-linear kinetics, evidenced, at least in part, by the modeling of metabolism inhibition loops between D-1143 and D-1143-M.
- Including the Carbo/Pac coadministration as covariate improved the model and demonstrated interaction by decreasing D-1143 CL. This effect is under investigation since it could not be discriminated from other D-1143-103 study specificities.
- If some variability remains to be figured out, this model is already a robust support for further D-1143 Exposure/Response evaluation as chemo/radio-sensitizer.