POPULATION PK AND EXPOSURE-RESPONSE MODELING TO SUPPORT THE DESIGN OF TRIALS WITH DEBIO 0123, A WEE1 INHIBITOR, IN CANCER PATIENTS

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BACKGROUND

- Debio 0123 (D0123) is a brain-penetrant, orally available, highly selective inhibitor of the WEE1 kinase
- By phosphorylating cyclin-dependent kinase 1 (CDK1, also known as CDC2), WEE1, a DNA damage-activated kinase, induces cell cycle arrest and permits DNA repair before cell cycle progression[1]
- WEE1 is therefore an attractive therapeutic target, as its inhibition induces mitotic catastrophe and apoptosis in cancer cells[2]

OBJECTIVES

- A population PK (popPK) model was built to characterize the pharmacokinetics (PK) of D0123 and its main active metabolite (M1) when administered as monotherapy or in combination with carboplatin (CBDCA)[3,4] and to quantify sources of PK variability in patients (pts) from two D0123 trials
- The popPK model results were combined in an exposure-response analysis to support the dosing regimen of further D0123 trials

DESIGN OF THE TRIALS

- D0123-101 and D0123-102 are two phase 1 trials evaluating the safety, tolerability, PK and preliminary antitumor activity of D0123 in patients with advanced solid tumors
- In D0123-101 Arm A, D0123 was administered as monotherapy in cycle 1 and in combination with CBDCA from cycle 2 on D1. In Arm B, D0123 was administered in combination with CBDCA (Table 1)
- In D0123-102, D0123 was administered daily as monotherapy (Table 1)

Table 1. Design of D0123-101 and D0123-102 trials

Trial / Phase	Dosing Regimen	Cycle Duration	Number of Subjects	Drug Dose Level
D0123-101 / Phase I	Phase 1 / Dose-escalation • Arm A: cycle 1: D0123 on D-3 and D1-D3 ; cycle 2 onwards: D0123 on D1-D3, CBDCA on D1 • Arm B: D0123 on D1-D3 and D8-10, CBDCA on D1	21 days	N=38 in arm A N=17 in arm B	Arm A: 30 / 60 / 100 / 150 / 200 / 300 / 400 / 520 mg Arm B: 300 / 400 / 520 / 720 mg
D0123-102 / Phase I	Phase 1 / Dose-escalation D0123 daily administration	21 days	N=27	30 / 60 / 90 / 150 / 200 / 260 / 350 mg

METHODS

Pharmacokinetic and pharmacodynamic analysis

- Serial blood samples were collected after single and repeated doses (steady-state) of D0123
- D0123 and M1 plasma concentrations were measured by LC-MS/MS. Data were reported in molar units accounting for the free fraction
- Pharmacodynamic analyses were performed on paired skin biopsies, taken at baseline and after D0123 treatment (D3 or steady-state based on the trial). Phospho-CDC2 (pCDC2) levels, assessed in the epidermis by immunohistochemistry, were quantified using H-score. Changes from baseline were calculated in evaluable paired skin biopsies

Population Pharmacokinetics Modeling

- Data from 82 pts with advanced solid tumors, 9 dose levels from 30 mg to 720 mg, and 5232 observations were included in the popPK model
- The analysis was performed using a nonlinear mixed-effects modeling approach with NONMEM® (Versions 7.4.4; ICON plc, Dublin, Ireland), and Perl speaks NONMEM (Uppsala University, Sweden)
- First-order conditional estimation method with interaction and user-defined subroutine ADVAN6 were used to estimate the population typical values of the PK parameters, interindividual variability, and residual variability for D0123 and M1
- Gender, age, body weight, body mass index (BMI), renal function, co-administration of CBDCA, and cancer type were tested as potential covariates which were selected using a forward addition process followed by backward elimination, applying significance levels of 0.01 and 0.001, respectively
- Visual predictive checks confirmed adequate predictive performance and stability of the final model

RESULTS

Figure 1. Structure of the base model**.** Ka = absorption constant; RAC= formation rate of the metabolite through hepatic first pass; Fm= metabolite fraction; M1= main active metabolite; Kx = micro constants

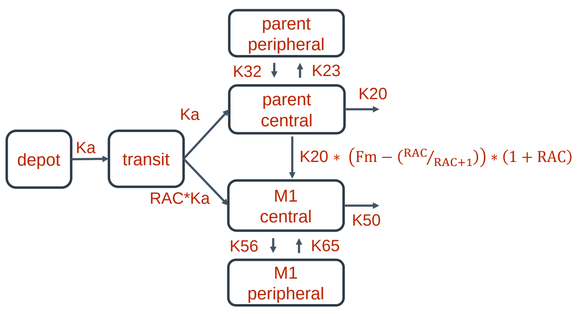


Figure 2. Prediction-corrected visual predictive checks (pcVPCs) of the final popPK model for (A) D0123-101 and (B) D0123-102 trials. Gray circles show observed data

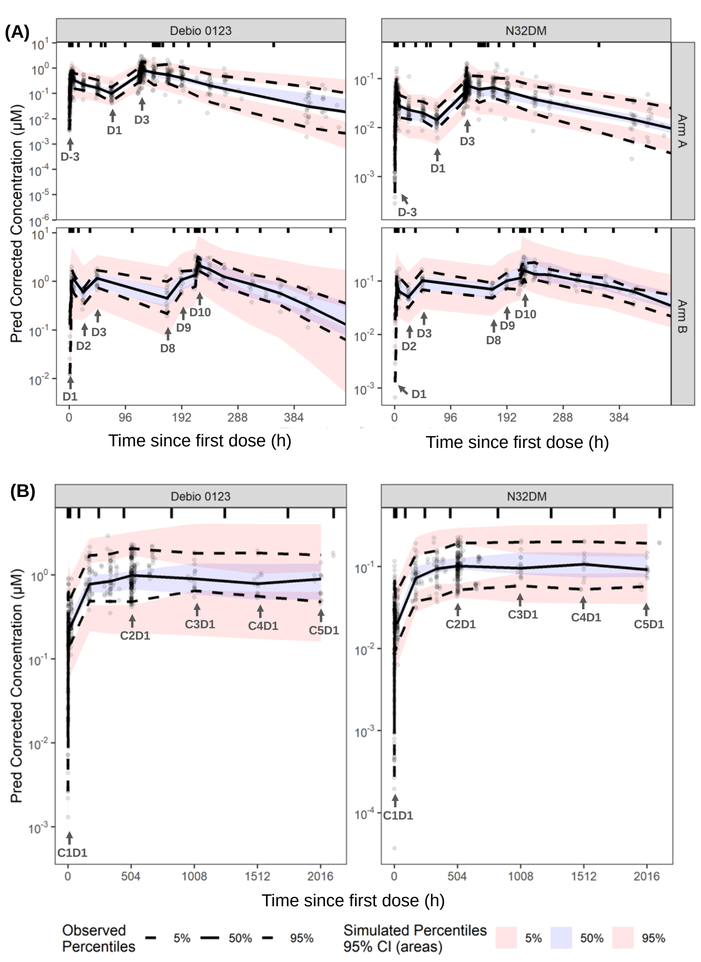


Figure 3. Effect of carboplatin and gender on D0123 exposure (M1 not shown)

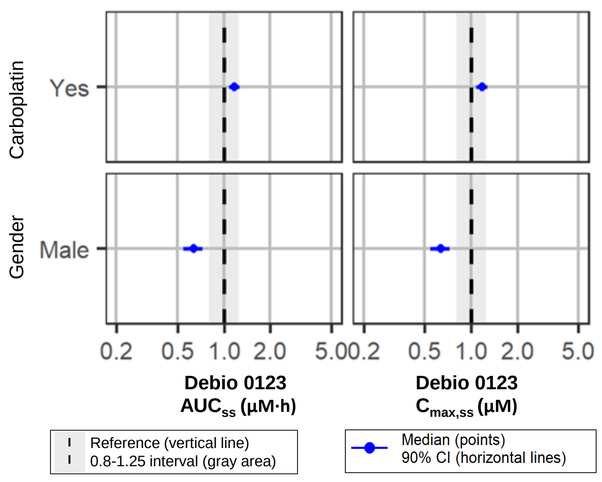
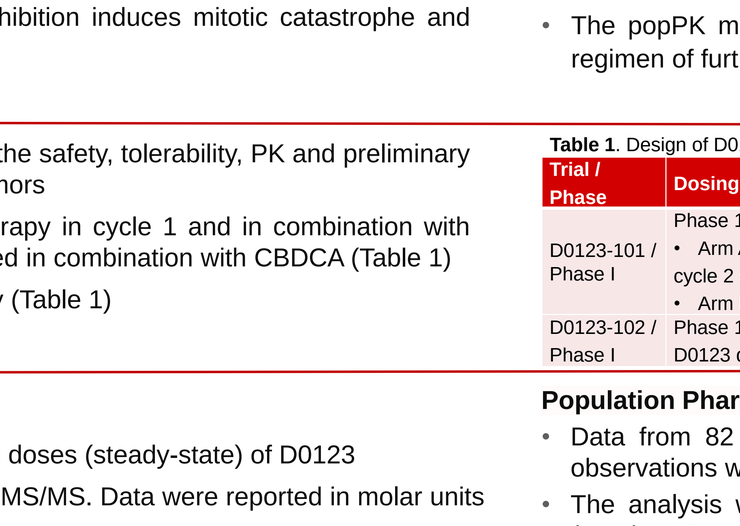


Figure 4. Goodness of Fit Plots of the final popPK model for D0123 (M1 not shown). (A) CWRES vs time, (B) CWRES vs PRED. Gray lines show the 0 line. Blue lines show locally weighted scatterplot smoothing fits whereas blue area is the 95% confidence interval



popPK model

- A two-compartment model with additive residual error on log scale was shown to best characterize D0123 and M1 plasma concentrations, one-transit compartment model was used to describe D0123 absorption process while a first-pass effect was necessary to model M1 formation. The fraction of metabolism (Fm) was set to 19% and the central volume of distribution of M1 was fixed to the value of the parent. The bioavailability was set to 1 (Figure 1)
- pcVPCs show that the final popPK model adequately predicts D0123 and M1 concentrations from the schedules of both trials (Figure 2). The model provided good overall description of the data and their variability with no major bias or trends. Conditional weighted residuals (CWRES) were evenly distributed around 0 and showed no trends over time or by concentration and a low number of outliers (|CWRES|>5) was observed (Figure 4)
- While body weight, age, BMI and renal function were not relevant factors impacting the PK, the covariate analysis suggests a lower D0123 bioavailability (by 36%) in males compared to females (Figure 3). However, the model was constructed primarily with data from female patients (80%) and additional data will be needed for further evaluation of the gender effect
- Concomitant carboplatin appeared as a statistically significant covariate (increase of 18% in bioavailability) but most likely without any clinical relevance (<20% difference in D0123 exposure compared to monotherapy) (Figure 3)

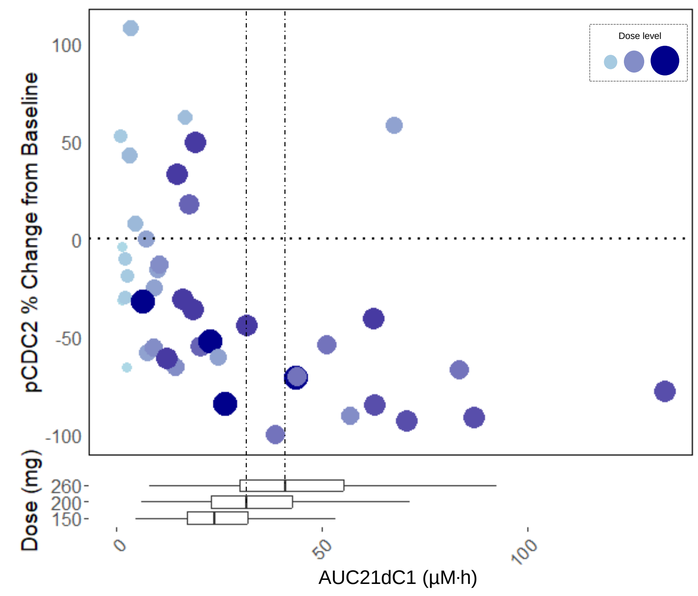
Table 2. Parameter estimates of the final popPK model. RSE=relative standard error. CI= Confidence Interval

Parameter	Estimate	RSE (%)	95% CI
Typical values			
Absorption rate constant Ka (1/h)	0.37	9.61	[0.308;0.447]
Formation rate of the metabolite RAC	0.18	8.66	[0.148 ; 0.208]
D0123 central volume Vc / F1 (L)	419	2.84	[299;584]
D0123 clearance CL / F1 (L/h)	11.4	2.39	[10.2;12.8]
D0123 intercompartmental clearance Q / F1 (L/h)	34.8	4.51	[25.5;47.5]
D0123 peripheral volume Vp / F1 (L)	685	1.27	[584;812]
M1 central volume VcM / F1 (L)	420	2.84	[299;584]
M1 clearance CLM / F1 (L/h)	20.9	1.67	[18.9;23.1]
M1 intercompartmental clearance QM / F1 (L/h)	178	2.51	[138;230]
M1 peripheral volume VpM / F1 (L)	2441	1.09	[2079;2893]
Bioavailability F1	1	fixed	fixed
Covariate Effects			
Carboplatin on F1 (reference: no carboplatin)	0.179	32.2	[0.0663 ; 0.293]
Gender on F1 (reference: female)	-0.364	15.1	[-0.472 ; -0.256]
Between Subject Variability			
On Ka	0.26	19.7	[0.160 ; 0.360]
On Vc / F1	0.558	47.4	[0.0392 ; 1.08]
On CL / F1	0.137	18.2	[0.0879 ; 0.185]
On F1	0.0964	20.2	[0.0583 ; 0.135]
Residual Error			
Additive Error of D0123 (log(µM))	0.392	5.25	[0.351 ; 0.432]
Additive Error of M1 (log(µM))	0.35	5.25	[0.314 ; 0.385]

Exposure-response analysis

- A relationship between plasma exposure (AUC over the first cycle) and decrease in pCDC2 levels was observed in both D0123-101 arm A and D0123-102 trials (Figure 5)
- Consistent target engagement, evidenced by pCDC2 reduction, is achieved with regimens of ≥ 200 mg daily (Figure 5)

Figure 5. Change of pCDC2 after D0123 monotherapy (D0123-101 arm A cycle 1, D0123-102 cycle 1) vs 21-day cycle 1 AUC (AUC21dC1; D0123 and M1 combined). Boxplots show the simulated exposures for virtual pts (n=1000) at three dose levels with daily administration. Dash-dotted line represent median exposure for 200 and 260 mg virtual cohorts



CONCLUSIONS & PERSPECTIVES

- The PK of D0123 and its main metabolite M1 was adequately described by a parent-metabolite model with 1 transit compartment and a first-order rate of absorption. The disposition of D0123 and M1 consisted of a 2-compartment model with first-order rate of elimination including IIV on Ka, F1, CL, Vc
- The covariate analysis indicated a slight increase in D0123 exposure when co-administered with carboplatin compared to monotherapy. Gender and carboplatin covariates will be further assessed in a model refined with additional data from ongoing and future trials
- Exposure-response analysis revealed a relationship between D0123 exposure and pCDC2 reduction. Combined with popPK model simulations, these data were used to support dose selection for further development

Abbreviations: AUC=area under the curve; AUC21dC1= AUC over the first cycle; CL= clearance; CBDCA= carboplatin; CDC2=cell division cycle 2; CDK1 = cyclin-dependent kinase 1, CI= Confidence interval; CWRES=conditional weighted residuals; D0123= Debio 0123; F1=bioavailability; Fm= metabolite fraction, Ka = absorption constant; p-CDC2=phospho-CDC2; M1= D0123 main metabolite; pcVPC=Prediction-corrected visual predictive check; RAC=formation rate of the metabolite through hepatic first pass; RSE=relative standard error; Vc = central volume of distribution

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