# A Semi-physiological Population Pharmacokinetic Model Developed Using Clinical Dose Escalation and Dose Confirmation Data for an Oral Fixed-Dose Combination of CDA Inhibitor Cedazuridine with Decitabine (ASTX727) in Subjects with Myelodysplastic Syndromes

Abstract #W-043

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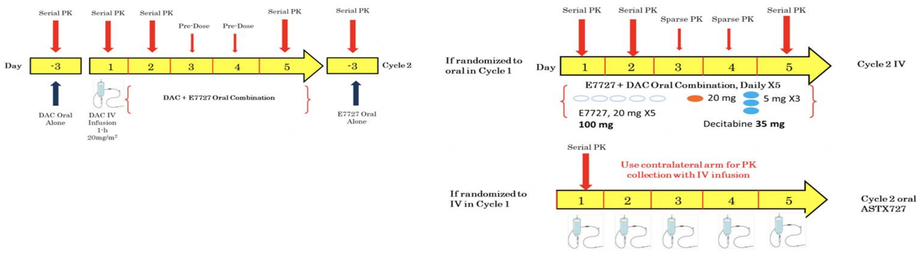
## BACKGROUND AND INTRODUCTION

- Cytidine deaminase (CDA) rapidly degrades decitabine (DEC), an approved treatment for myelodysplastic syndromes, resulting in poor and variable bioavailability
- Low doses of oral DEC co-administered with a novel and potent CDA inhibitor, cedazuridine (C), have been shown in clinic to produce exposures similar to IV DEC with acceptable inter-patient variability
- Modeling Objectives:
  - Further develop a semi-physiological population pharmacokinetic (PK) model ([1]) to characterize the PK enhancement of oral DEC when co-administered with cedazuridine
  - Identify potential covariates that impact the PK of C and/or DEC
- Analysis Data:
  - A Phase 1-2 Clinical Study, ASTX727-01, was used for the PK analysis
  - The Study consisted of Dose Escalation (DE) and Dose Confirmation (DC) Phases
  - 40 subjects contributed data in the DE Phase which consisted of a single arm, PK guided 3+3 design to establish the target dose combination resulting in exposures similar to 20 mg/m$^2$ DEC 1 hour infusion
  - Subjects in DE were divided into five cohorts: 40:20, 60:20, 100:20, 100:40, and 100:30 mg C:DEC
  - 70 subjects contributed data in the phase-2 stage that consisted of a standard 2x2 crossover design to confirm that the chosen dose of 100:35 mg C:DEC does indeed achieve exposures similar to IV DEC

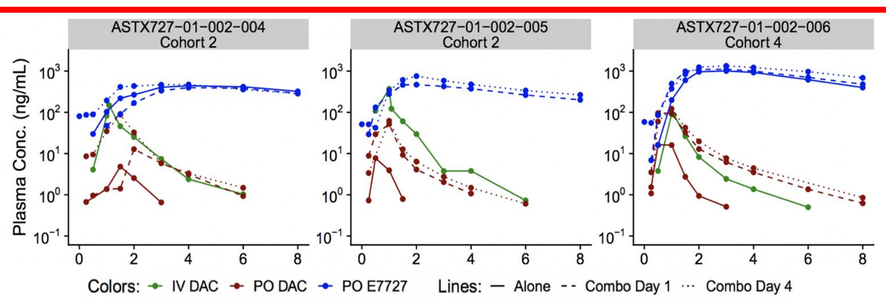
### Figure 1. ASTX727-01 Dose Escalation (left) and Dose Confirmation (right) Dosing and PK Sampling Schedules



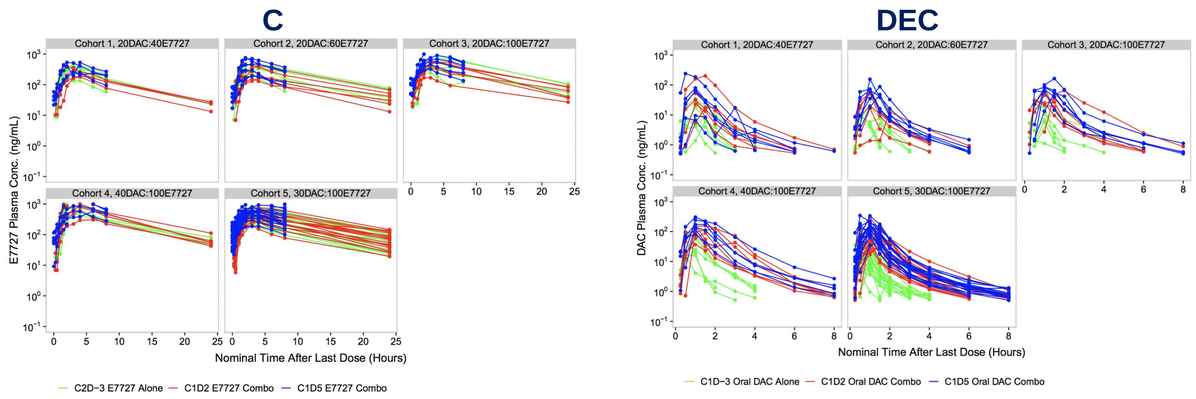

## Exploratory Data Analysis

- Typical C and DEC concentration profiles for subjects in the DE stage are shown in Figure 2
- Figures 3 and 4 show all C and DEC profiles from DE stage overlaying dosage forms and days and stratifying by cohort
- The figures highlight the lower apparent exposures for oral DEC given alone as compared to IV DEC exposures. On the other hand, C given in combination with oral DEC show much higher apparent exposures that appear close to IV DEC exposures which demonstrates the potent CDA inhibitory effect of C and its enhancement of oral DEC PK
- C profiles did not show any significant differences when given alone compared to combination with DEC, which suggested that C PK is not being impacted by DEC. As a result, both C alone and in combination data were used simultaneously to estimate C parameters

### Figure 2. Sample of Individual C & DEC Profiles from DE Stage Overlaid Across Days and Dosage Form



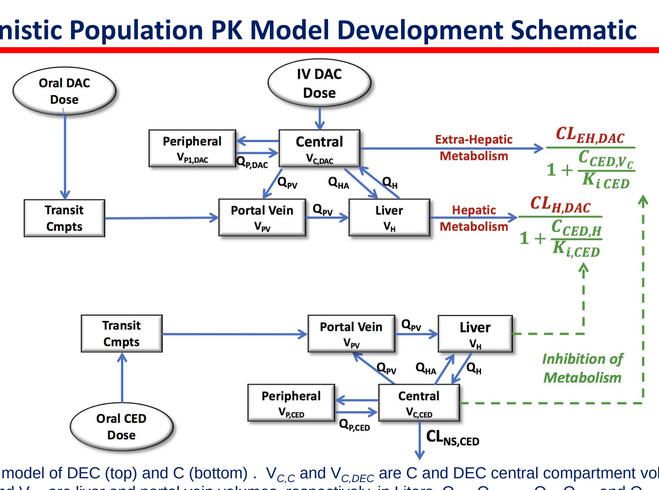

### Figure 3. C and DEC Profiles Overlaid Across Days and Dosage Form and Stratified by Dose




## Semi-Mechanistic Population PK Model Development

- A previously developed semi-mechanistic model describing the inhibition of P450 metabolism when dosed concomitantly with P450 inhibitors [1,2] was adapted and modified. The model describes the following key elements of DEC metabolism and CDA inhibition by C, shown schematically in Figure 4:
  - DEC is primarily cleared through metabolism in the liver by CDA
  - Minimal renal clearance; minimal gut metabolism due to DEC primarily being absorbed in stomach
  - Extra-hepatic CDA metabolism has been reported in clinical DEC IV studies
- Model development and exploration included:
  - PK observations were log-transformed to achieve normal distributions
  - Multi-dose C PK observations from the ASTX727 combination were utilized
  - Sequential and simultaneous fitting techniques
  - Proportional and additive error models
  - Additive and exponential inter-individual variability (IIV)
  - C and Oral DEC transit absorption models [3]
  - Parameter correlations and covariate effects were evaluated
  - Data processing and visualization was performed in R®
  - PK model parameters estimated using NONMEM®
- Model Qualification:
  - Standard diagnostics inspected for evidence of systemic lack of fit and to confirm absence of bias.
  - Visual predictive checks (VPCs) of the observed data compared to simulated results demonstrated the model's ability to adequately project additional scenarios of interest for ASTX727 therapy

### Figure 4. Semi-Mechanistic Population PK Model Development Schematic




Schematic pharmacokinetic interaction model of DEC (top) and C (bottom) . $V_{C,C}$ and $V_{C,DEC}$ are C and DEC central compartment volumes, $V_{P,C}$ and $V_{P,DEC}$ are C and DEC peripheral compartment volumes, $V_H$ and $V_{PV}$ are liver and portal vein volumes, respectively, in Liters. $Q_{P,C}$, $Q_{P,DEC}$,, $Q_H$, $Q_{HA}$, and $Q_{PV}$ are C and DEC peripheral compartment, liver, hepatic artery, and portal vein flow rates, respectively, in L/hr. $CL_{NS,\,C}$, $CL_{H,DEC}$ and $CL_{EH,DEC}$ are C clearance, DEC hepatic and extra-hepatic clearance due to CDA metabolism, respectively. $C_{C,VC}$ and $C_{C,H}$ are C concentrations (ng/mL) in the central and liver compartments, respectively. $K_{i,C}$ is the inhibition constant of C for CDA inhibition. Fraction unbound and blood to plasma ratio were fixed based on studies to 0.99/0.65 and 1/1 DEC/C, respectively

## Final Semi-Mechanistic Population PK Model

A systematic search found that optimal model structure and parameter estimates (Table 1) were achieved with:

- Transit compartment oral DEC and C absorption models
- Gut DEC metabolism was evaluated and excluded due to lack of significance
- Exponential IIV and proportional plus additive error models
- Sequential fits for IV DEC followed by oral DEC (alone and combination). Observed C concentrations were used to drive inhibition of DEC metabolism
- Simultaneous fits for oral C alone and in combination
- Extra-hepatic DEC clearance was expressed as a fraction of hepatic clearance to avoid overparameterization and nonidentifiability
- Significant covariates that were included in the model were:
  - Height as a body size measurement for scaling physiologic parameters
  - Gender and CrCL on C clearance (CLNS,C) and transit rate constant (ktr), respectively
  - Gender on DEC hepatic clearance (CLH,DEC) and central volume (VC,DEC)
- Apparent correlations between CLH,DEC and VC,DEC , and between CLNS,C and VP,C random effects were handled by adding ETA correlation scaling parameters
- Standard diagnostic plots of observed vs. predicted log-transformed C and DEC final models, Figures 6 and 7, demonstrate that the model is capable of predicting concentrations comparable to the observed data
- Figure 8 shows VPCs of the observed data compared to simulated results and demonstrates the model's ability to adequately project additional desired ASTX727 therapy scenarios

### Table 1: Final Oral C and Oral DEC Models Parameter Estimates

**ORAL C**

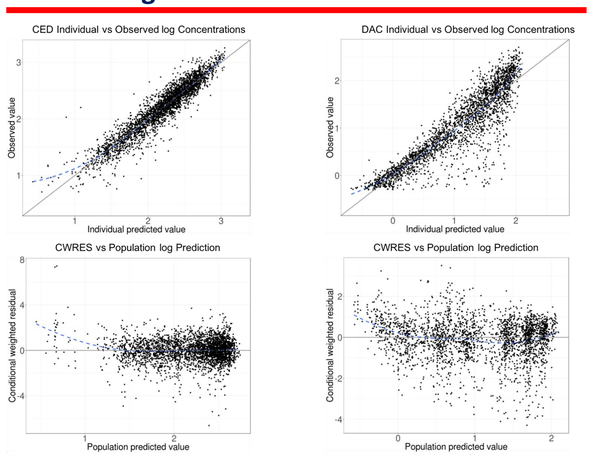
| Parameter | Estimate | Mean | Median | CI (95%) | Units |
|---|---|---|---|---|---|
| $k_{tr,C}$ | 0.730 | 0.728 | 0.722 | (0.643, 0.851) | /h |
| $V_{c,C}$ | 6.23 | 6.29 | 5.53 | (0.858, 15.9) | L |
| $CL_{NS,C}$ | 24.3 | 24.4 | 24.4 | (22.5, 26.3) | L/h |
| $Q_{p,C}$ | 49.5 | 48.9 | 47.2 | (34.1, 69.3) | L/h |
| $V_{p,C}$ | 177 | 179 | 179 | (158, 200) | L |
| Effect of CrCL on $CL_{NS,C}$ | 0.712 | 0.735 | 0.726 | (.590, 0.913) | - |
| Effect of Sex on $k_{tr,C}$ | 1.15 | 1.15 | 1.14 | (1.02, 1.29) | - |
| Scale-ETA$_{CL_{NS,C}\text{-}V_{p,C}}$ | 1.12 | 1.14 | 1.14 | (1.04, 1.25) | - |
| **Interindividual variability** | | | | | |
| $\omega k_{tr,C}$ | 28.6 | 27.9 | 27.6 | (20.8, 36.4) | CV % |
| $\omega CL_{NS,C}$ | 54.2 | 53.7 | 53.6 | (47.4, 60.2) | CV % |
| **Residual error** | | | | | |
| σadd | 0.161 | 0.159 | 0.159 | (0.147, 0.173) | SD |

**ORAL DEC**

| Parameter | Estimate | Mean | Median | CI (95%) | Units |
|---|---|---|---|---|---|
| $V_{C,DEC}$ | 84.8 | 85.9 | 85.8 | (75.6, 97.7) | L |
| $CL_{H,DEC}$ | 251 | 339 | 310 | (181, 627) | L/h |
| $f_{EHCL,DEC}$ | 0.743 | 0.607 | 0.598 | (0.265, 1.05) | - |
| $Q_{p,DEC}$ | 17.9 | 18.0 | 17.9 | (15.4, 20.6) | L/h |
| $V_{p,DEC}$ | 38.6 | 38.8 | 38.6 | (32.7, 45.1) | L |
| $K_{a,DEC}$ | 3.28 | 3.47 | 3.41 | (2.79, 4.32) | /h |
| $MTT_{DEC}$ | 0.323 | 0.327 | 0.327 | (0.301, 0.353) | h |
| $K_{i,C}$ | 46.8 | 47.1 | 45.7 | (33.9, 66.7) | ng/mL |
| Effect of sex on $CL_{H,DEC}$ | 0.851 | 0.850 | 0.850 | (0.761, 0.937) | - |
| Effect of sex on $V_{C,DEC}$ | 0.831 | 0.836 | 0.833 | (0.720, 0.963) | - |
| Scale-ETA$_{CL_{H,DEC}\text{:}V_{C,DEC}}$ | -0.519 | -0.475 | -0.474 | (-0.985, 0.00562) | - |
| **Interindividual variability** | | | | | |
| $\omega CL_{H,DEC}$ | 20.7 | 21.2 | 21.0 | (15.2, 27.6) | CV % |
| $\omega k_{a,DEC}$ | 95.8 | 96.4 | 96.4 | (74.0, 118) | CV % |
| $\omega MTT_{DEC}$ | 34.4 | 32.0 | 32.1 | (25.2, 38.3) | CV % |
| **Residual error** | | | | | |
| σprop,DECIV | 17.2 | 17.4 | 17.4 | (14.4, 20.4) | CV % |
| σadd,DECIV | 0.119 | 0.109 | 0.115 | (0.0581, 0.163) | SD |
| σprop,DECPO | 25.6 | 26.0 | 26.2 | (22.1, 29.4) | CV % |
| σadd,DECPO | 0.165 | 0.162 | 0.160 | (0.136, 0.195) | SD |

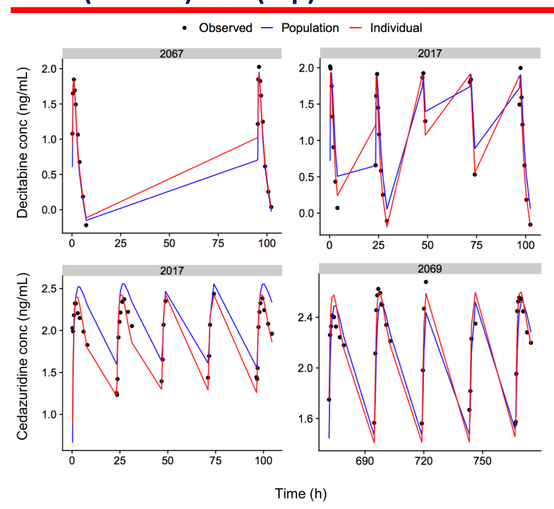
$\omega_{parameter}$ = variability of the given parameter; $\sigma_{prop}$ = proportional error; $\sigma_{add}$ = additive error; $V_{C,DEC}$ = volume of central compartment for decitabine; $CL_{H,DEC}$ = hepatic clearance for decitabine; $f_{EHCL,DEC}$ = fraction of extrahepatic clearance for decitabine; $Q_{p,DEC}$ = inter-compartmental clearance for decitabine; $V_{p,DEC}$ = peripheral volume for decitabine; $K_{a,DEC}$ = absorption rate constant for decitabine; $MTT_{DEC}$ = mean transit time for decitabine; $K_{i,C}$ = Cazuridine inhibition constant; Sex-parameter = sex effect on given parameter; Scale-ETA $_{CL_{H,DEC}:V_{C,DEC}}$ = scaling factor for shared ETA between decitabine clearance and central volume; DECIV = IV decitabine model; DECPO = oral decitabine model; $k_{tr,C}$ = transit rate constant for cedazuridine; $V_{c,C}$ = volume of central compartment for cedazuridine; $CL_{NS,C}$ = non-specific clearance for cedazuridine; $Q_{p,C}$ = inter-compartmental clearance for cedazuridine; $V_{p,C}$ = volume of peripheral compartment for cedazuridine; CrCL-parameter = creatinine clearance effect on given parameter; Scale-ETA $_{CL_{NS,C}\text{-}V_{p,C}}$ = scaling factor for shared ETA between cedazuridine non-specific clearance and peripheral volume; CV = coefficient of variation; SD = standard deviation; CI = confidence interval

### Figure 5. Final FDC C (left) and DEC (right) Model Diagnostic Plots

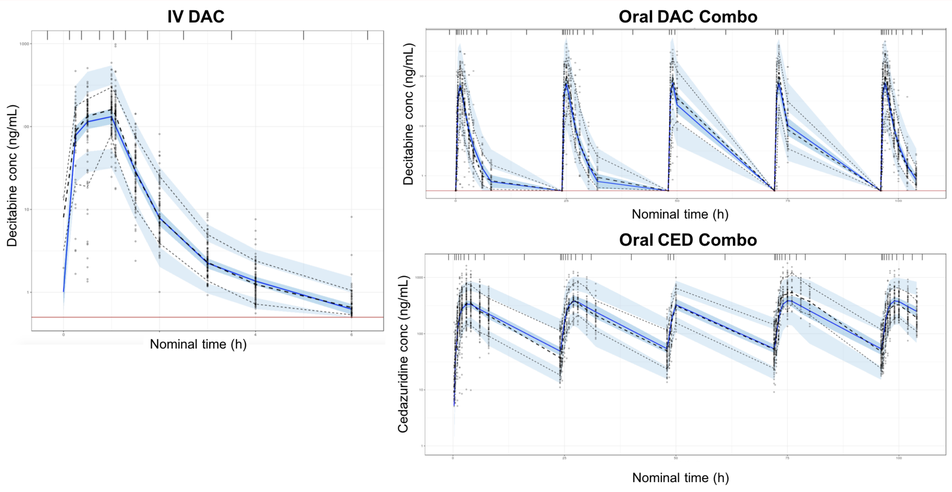



Observations/predictions shown as dots; blue dashed line represents loess smooth trend line

### Figure 6. Final Model Sample Individual Fits for C (bottom) DEC (top)




### Figure 7. VPCs for C and DEC




Black circles are observed data. Black dashed lines represent median (thick) and 10 and 90th percentiles of observed data. Blue line is prediction median and blue bands represent 95% confidence intervals around simulated median, 10, and 90th percentiles of predictions. Red line represents LLOQ

## CONCLUSIONS & FUTURE DEVELOPMENT

- A semi-physiological population PK model was sequentially developed from mono- and combination therapy observations of plasma concentrations from the ASTX727-01 dose escalation and confirmation study
- The analysis characterized the PK enhancement of oral DEC when co-administered with cedazuridine across a range of dose regimens of cedazuridine 40-100 mg and decitabine 20-40 mg
- Covariate and parameter correlation exploration identified influential parameters and lead to better model fits
- The resulting model will be used to interpret outcomes from an ongoing Phase 3 study (FDC ASTX727 of 35 mg DEC / 100 mg cedazuridine), while simulations will quantitatively inform future clinical development of ASTX727
- The model was developed using integrated DE and DC data and qualified through standard diagnostics and a VPC of the ASTX727 dose combination
- Simulations will further guide clinical development and interpretation of clinical results

## REFERENCES

1. Burroughs E, et al. ACoP Annual Meeting 2017
2. Frechen S, et al. Clin. Pharmacokinet. 2013; 52:763–781
3. Savic R, et al. JPKPD. 2007; 34(5): 711-726



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