A semi-physiological population pharmacokinetic model was developed using clinical data from a Phase 3 study of ASTX727 in subjects with myelodysplastic syndromes.

Abstract

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A semi-physiological Population Pharmacokinetic Model Developed Using Clinical Data from a Phase 3 Study of ASTX727 in Subjects with Myelodysplastic Syndromes

BACKGROUND AND INTRODUCTION

- Cytidine deaminase (CD) 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 CDI/CD inhibitor, cedazuridine (C), have been shown in clinical trials to produce exposures to DEC in the 100 mg L. An integrated population pharmacokinetic model (PK model) was developed to characterize the PK enhancement of oral DEC when co-administered with cedazuridine.
- Identify potential covariates that impact the PK of DEC and/or CDI.

Analysis Data:
- A Phase 2-3 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 3x3 design to establish the target dose combination resulting in exposures similar to 20 mg/m² DEC 1 hour infusion. Subjects in DE were divided into five cohorts: 5/10, 20/50, 100/100, 100/40, and 100/30 mg CDI/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 CDI/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

Table 1: Final C and Oral DEC Models Parameters Estimates

| Parameter                | Oral DEC | C | CDI | DECPO | DEC | CDA | DEC2
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<tr>
<td>Median (95% CI)</td>
<td>0.730 (0.65, 0.82)</td>
<td>0.71 (0.60, 0.81)</td>
<td>0.475 (0.40, 0.54)</td>
<td>0.395 (0.34, 0.45)</td>
<td>0.33 (0.29, 0.37)</td>
<td>0.63 (0.57, 0.69)</td>
<td>0.31 (0.27, 0.35)</td>
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<td>CV (%)</td>
<td>0.70 (0.62, 0.77)</td>
<td>0.69 (0.60, 0.77)</td>
<td>0.47 (0.40, 0.55)</td>
<td>0.39 (0.34, 0.45)</td>
<td>0.33 (0.29, 0.37)</td>
<td>0.63 (0.57, 0.69)</td>
<td>0.31 (0.27, 0.35)</td>
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| 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 and CDI and CDA inhibition by C:
  - 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 inclusion:
  - PK observations were log-transformed to achieve normal distributions.
  - Multi-dose PK observations from the ASTX727 combination were utilized.
  - Sequential and simultaneous fitting techniques were performed.
  - Additive and exponential inter-individual variability (IVV)
  - C and Oral DEC transit absorption models [3]
  - Covariate and parameter correlation evaluation was performed in R using normal models estimated using NLMEMRII.

- Model Qualification:
  - Standard diagnostics inspected for evidence of systematic 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

Final Semi-Mechanistic Population PK Model

- A systematic search found that optimal model structure and parameter estimates (Table 1) were achieved with:
  - Transient compartment oral DEC and CDI absorption models.
  - Gut DEC metabolism was evaluated and excluded due to lack of significance.
  - Sequential fitting for oral 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 CDA on C clearence (CL/C), and transit rate constant (RR), respectively.
  - Gender on DEC hepatic clearance (CL/H, DEC), and central volume (V, DEC)
  - Apparent correlations between CDA and DEC, and between CL/C and VPC 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, demonstrated that the model is capable of predicting 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.

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

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

Figure 7. VPCs for C and DEC

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 demonstrated that the model was capable of predicting to the observed data across a range of dose regimens of cedazuridine-40 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 (FDA 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 OCC.
- Simulations will further guide clinical development and interpretation of clinical results.

REFERENCES

1. Burroughs E. et al. ACP/Annual Meeting 2017