A Population Pharmacokinetic Model of Tolinapant in Subjects with Advanced Solid Tumors and Lymphomas

Abstract #PMX513

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BACKGROUND AND INTRODUCTION

ASTX660 is a synthetic small molecule dual antagonist of cellular inhibitor of apoptosis protein (cIAP) 1 and X-linked inhibitor of apoptosis protein (XIAP). ASTX660 exhibits potent proapoptotic and tumor growth inhibitory activity in non-clinical models.

Study ASTX660-01 consists of 2 phases: Phase 1 to identify maximum tolerated dose (MTD) for Phase 2, and Phase 2 to evaluate anti-tumor activity of ASTX660 in patients with specific tumor types.

The objective of this analysis is to develop a population PK (PopPK) model to describe ASTX660 PK in subjects with advanced solid tumors or lymphoma.

METHODS

The dataset for population PK model development included 3825 ASTX660 concentration measurements from 208 subjects enrolled in study ASTX660-01.

The demographic characteristics (age, weight, height and body surface area [BSA]) as well as laboratory data were tested as covariates on PK parameters.

The covariate analysis was performed using a forward inclusion and backward elimination process. During the forward inclusion, the significant level was p<0.05 with 1df (4OBJ value of 3.84) and during the backward elimination, p<0.001 with 1df (4OBJ value of 10.8).

The analysis was performed using NONMEM version 7.4.4 [1] using FOCE-I method aided by PsN version 5.0.0. Graphical diagnostics were generated using R version 3.3.3.

RESULTS

- The analysis dataset included a total of 208 subjects (110 males and 98 females) with the majority of subjects receiving ASTX660 180 mg capsule formulation (176; 84.6%).
- The majority of available ASTX660 concentration data were <1000 ng/mL (range 1.01 ng/mL – 3550.68 ng/mL).
- The PK data were collected up to 8.6 weeks, with the majority of the data obtained within 2500 hours (3.5 months) since first dose.
- The analysis dataset included 110 males (52.9%) and 98 females. The mean weight (WT) for male and female subjects were 83.5 kg and 66.1 kg, respectively (range 34.5 kg – 172.3 kg). The mean age was 60.4 years (range 24 years – 84 years). Age was comparable between males and females (mean of 60.8 years and 60 years for males and females, respectively).
- A two-compartmental model with non-linear elimination adequately described ASTX660 PK.
- ASTX660 absorption was described using a transit compartment model, with the number of transit compartments (NN) fixed to 2.
- Formulation was found to be a significant covariate on the transit rate constant (K_{tr}). The relative bioavailability was found to be dose-dependent and described using the power model as follows:

  $F = 1 \cdot (\text{ASTX660 dose [mg]}/180)^{0.31}$

  where F = relative bioavailability.
- Between subject variability (BSV) terms were included on maximum elimination rate (V_{max}), central volume of distribution (V_c), F, K_{tr}, and residual unexplained variability (RUV).
- A proportional error model was used to describe RUV.

Figure 1. Final Model

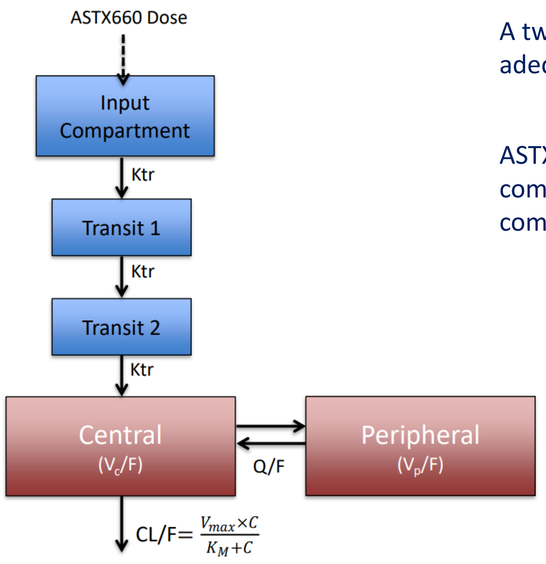

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Table 1. Final PK Model for ASTX660: Parameter Estimates

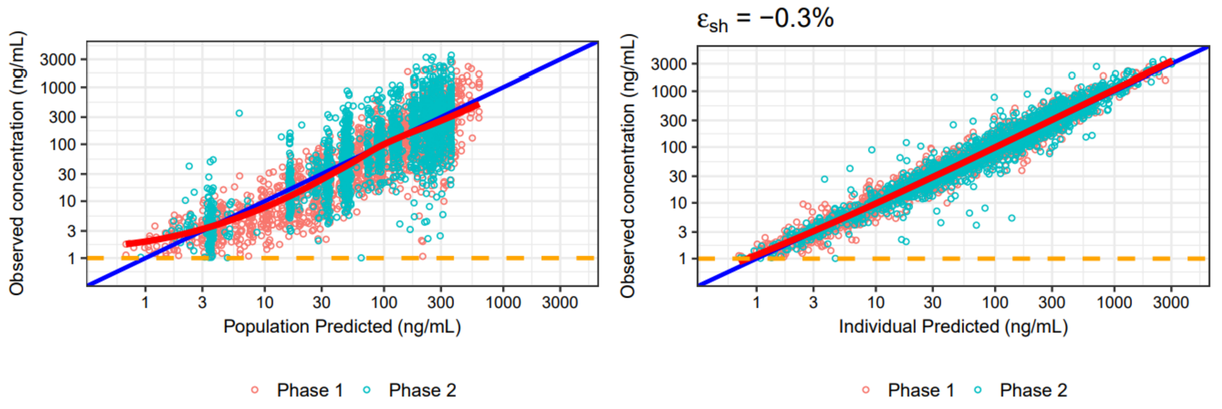
Parameters	Typical Value (%RSE)	BSV (%RSE)	BOV (%RSE)
Michaelis-Menten Constant (K_m, ng/mL)	2100 (34.7)	-	-
Maximum Elimination Rate (V_{max}, ng/h)	155 (30.7)	22.5 (16.6)	-
Apparent Central Volume of Distribution (V_c/F, L)	442 (6.5)	33.3 (15.5)	-
Apparent Peripheral Volume of Distribution (V_p, L)	2390 (5.9)	-	-
Apparent Inter-compartmental Clearance (Q/F, L/h)	84.5 (6.0)	-	-
Transit Rate Constant for Powder Formulation ($K_{tr,powder}$, h^{-1})	100 Fixed	-	-
Transit Rate Constant for Capsule Formulation ($K_{tr,capsule}$, h^{-1})	5.8 (7.6)	41.9 (57.7)	135 (10.7)
Relative Bioavailability (F, unitless)	1 Fixed	69.2 (11.3)	28.0 (15.7)
Exponent on Relative Bioavailability (unitless)	0.31 (23.6)	-	-
Proportional RUV for Phase 1 Subjects (%)	37.1 (5.0)	12.3 (41.9)	-
Proportional RUV for Phase 2 Subjects (%)	35.3 (7.3)	33.5 (13.2)	-

RSE = relative standard error, RUV = residual unexplained variability, BSV = between-subject variability, BOV = between-occasion variability. Note: RSE were derived from sampling importance resampling. * F = 1·(ASTX660 dose [mg]/180)$^{0.31}$.

Figure 2. Goodness-of-Fit Plots

The PK model adequately described the observed data.

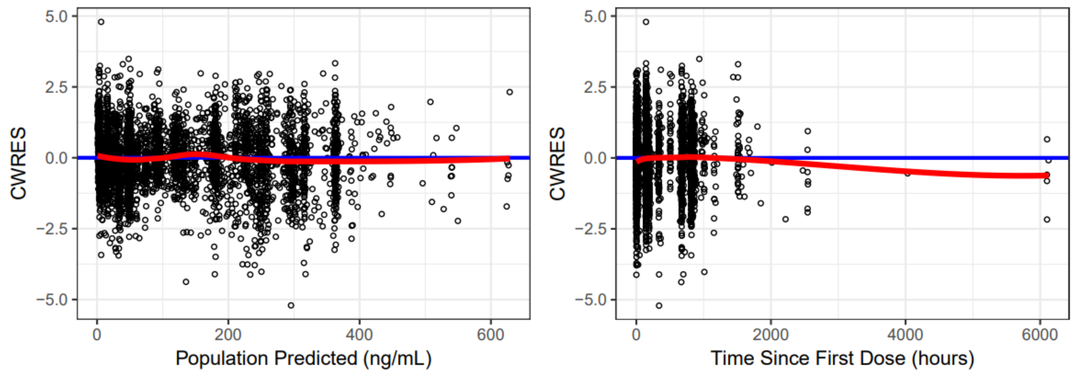
No clear bias was observed for both population (left figure) and individual (right figure) predictions.



The blues lines represent the line of identity, the red lines show the trend in the data (Loess smooth), orange dashed lines represent the LLOQ (1 ng/mL), symbols represent the observed data colored by study phase as indicated in the legend. ε_{sh} = epsilon shrinkage

Figure 3: CWRES Plots

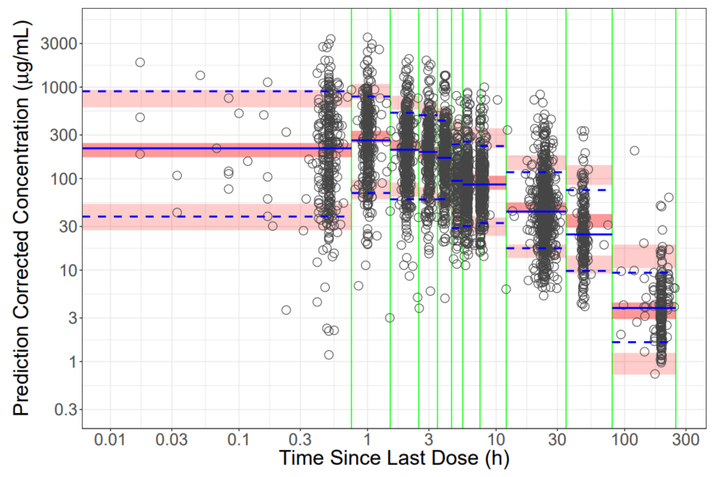
No clear trends were observed with CWRES plots.



CWRES = conditional weighted residuals.

Figure 4. Visual Predictive Check (VPC)

The PK model adequately described observed data



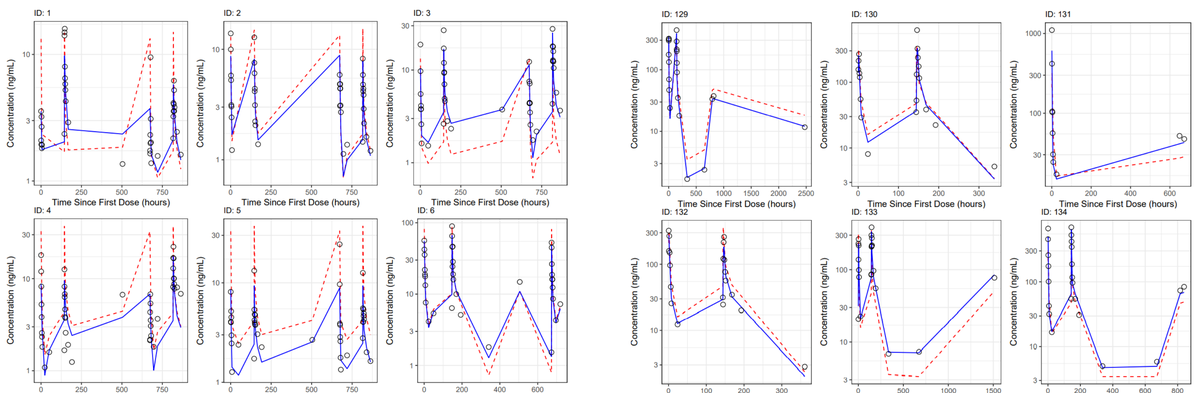
Circles = observed data, dashed blue lines = observed 10th & 90th percentiles, solid blue lines = observed median, red shaded areas = 95% confidence intervals for simulated percentiles, vertical green lines = bin limits.

Figure 5a. Phase 1

Figure 5b. Phase 2

Individual fit plots:

The PK model well described the observed data at an individual level.



Dashed red lines = population model prediction, solid blue lines = individual model prediction, symbols = observed data.

CONCLUSIONS

The population PK model was successfully developed to describe ASTX660 concentration-time data from patients with advanced solid tumors or lymphoma.

Bioavailability of ASTX660 was found to be dose-dependent.

Formulation was identified as a significant covariate on the absorption rate of ASTX660.

None of other covariates were identified as statically significant covariates.

REFERENCES

1. Beal SL, Sheiner LB, Boeckmann AJ, and Bauer RJ (eds) NONMEM 7.4.4 Users Guides. (1989–2018). ICON plc, Gaithersburg, MD, USA.
2. Dosne AG, Berstrand M, Harling K, Karlsson MO. Improving the estimation of parameter uncertainty distributions in nonlinear mixed effects models using sampling importance resampling. JPKPD, 43(6):583-596, 2016.

CONFLICT OF INTEREST

FS & BG accepted consulting fees for this work; DC and AO are employees of Astex Pharmaceuticals, Inc.

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Poster can be downloaded from www.astx.com