Population Pharmacokinetics Analysis for Guadecitabine (SGI-110) and Decitabine after Subcutaneous Dosing with SGI-110 in Patients with Relapsed/Refractory AML and MDS

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INTRODUCTION

Guadecitabine is next-generation HMA formulated as a dinucleotide of decitabine and deoxyguanosine delivered as a low volume and pharmaceutically stable subcutaneous (SC) injection. In vivo conversion to active metabolite decitabine results in longer effective half-life and more extended decitabine exposure window than decitabine IV infusion. The differentiated PK profile may lead to improved biological and clinical activity and safety over currently available HMAs (Issa *et al.* Lancet Oncology 2015).

SGI-110-01 (NCT01261312) was a phase 1-2, dose escalation, multicenter study of subcutaneous regimens of SGI-110 in subjects with intermediate or high-risk myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML). Several dosing regimens were tested. In regimen 1 and its phase 2 expansion, guadecitabine was administered daily for 5 days of a 28-day cycle. In regimens 2a and 2b, it was administered weekly or twice-weekly, respectively, for 3 weeks of a 28-day cycle. In another part of the phase 2 expansion, it was administered daily for 10 days (1-5 and 8-12) of a 28-day cycle.

The PK data included full concentration-time profiles of parent SGI-110 and its active metabolite, decitabine obtained after the first dose and after dose on day 5 (for regimen 1 and expansion), day 8 (for regimen 2a) or day 12 (for expansion 10-day regimen) of cycle 1.

The abstract reported results of the population PK analysis of data from 98 patients. Since the time the abstract was submitted, more data became available, and the model was updated. This poster describes the population PK modeling of data using an updated dataset from 124 patients.

Objectives of Analysis

- To establish and evaluate a predictive population PK model that describes the SGI-110 and decitabine concentrations in subjects with MDS or AML, including estimation of the population parameters, inter-individual variability of model parameters, and intra-individual variability;
- To evaluate the effect of body size, gender, disease type, and other predictive factors on the PK model parameters.

DATA

The dataset contained 1579 SGI-110 and 1603 decitabine PK samples from 124 patients. Figures 1-2 display the observed data, stratified by nominal dose. Lines show medians of observed values for each dose and time point (values below quantification limit were removed from the plots). Mean age was 67.9 (range 29.1-86.1). Mean body weight was 80.6 kg (48.4-177). The dataset included 87 male and 37 female patients.

Figure 1. Pharmacokinetic data for SGI-110

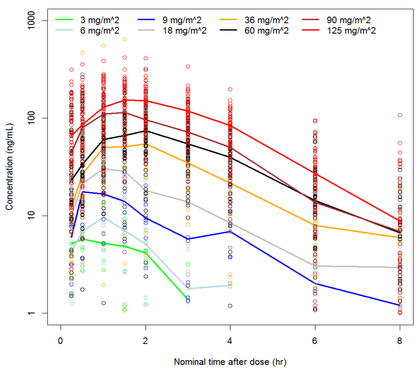
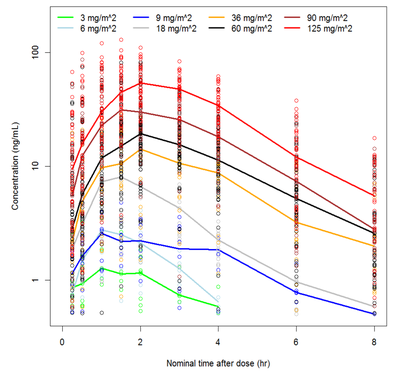


Figure 2. Pharmacokinetic data for Decitabine



METHODS

- The population PK analysis was conducted via nonlinear mixed-effects modeling with the NONMEM 7.3.0 (FOCEI method).
- SGI-110 PK was described by one-compartment model with first order absorption; absorption rate changed at estimated time post-dose; random effects on all parameters; inter-occasion variability of absorption rate and bioavailability parameters.
- Decitabine kinetics was described by two-compartment model. Complete SGI-110 to decitabine metabolism was assumed. The model accounted for the differences in the molar weights of SGI-110 (580 Da) and decitabine (228 Da).
- The combined additive and proportional residual error model was assumed for both SGI-110 and decitabine data, with the same inter-subject variability of the magnitude of the proportional error.
- Effects of weight, age, renal impairment, white blood cell counts, CDA (cytidine deaminase) activity, other lab factors, and nominal dose on SGI-110 and decitabine clearance parameters were investigated.
- Analysis used significance level of 0.05 (objective function change of 6.64 points) for model selection.
- The model was evaluated using extensive set of diagnostic plots and visual predictive check techniques. The estimates of precision (asymptotic standard errors) were provided for all model parameters.

RESULTS

- Final PK model (Table 1) included effects of weight on all clearance and volume parameters, the effect of nominal dose on SGI-decitabine conversion fraction, the effect of age on k_a, and effects of white blood cell count on SGI100 and decitabine clearance parameters.
- Goodness-of-fit plots (Figure 5 - Figure 6) indicated good fit of observed data.
- Dependencies of the random effects on covariates (not shown) do not reveal any trends not accounted for by the model.
- Various visual predictive check plot (Figure 7) indicated that the model captured both the central tendency and the inter-subject variability of SGI-110 and decitabine PK.
- Effect of CDA was evaluated for 69 patients who had CDA data. Trend of increase in decitabine clearance and decrease of SGI-110 clearance with increase of CDA was noticeable.

Covariate effects on model parameters are illustrated in Figure 3. Similar plots for the model that includes CDA effect are presented in Figure 4. This model utilized data from fewer patients (as CDA data were not available in Phase 2 of the study), and therefore parameter estimates were less precise (had wider confidence intervals).

Table 1. Parameter Estimates for the Final PK Model

Structural model parameters and covariate effects		Estimate	%RSE
CL/F (L/hr)	SGI-110 clearance	371	5.42
V/F (L)	SGI-110 volume	511	7.84
$k_{a,early}$ (1/h)	SGI-110 absorption rate when time after dose < MTIME	0.766	12.3
MTIME (hr)	Time of change of absorption rate constant	0.869	1.39
$k_{a,late}$ (1/h)	SGI-110 absorption rate when time after dose > MTIME	2.27	12.5
CL_D/F (L/hr)	Decitabine clearance	398	4.25
V_D/F (L)	Decitabine central volume	11.4	132
Q_D/F (L/hr)	Decitabine inter-compartment clearance	626	17.8
$V_{D,2}$/F (L)	Decitabine peripheral volume	228	7.92
$k_{a,age}$	Effect of age on k_a	-1.01	45.4
$Fconv_{NDOSE}$	Effect of dose on conversion fractions	0.136	18.7
CL_{WBC}, $CL_{D,WBC}$	Effect of white blood cells on SGI-110 and decitabine clearance	0.621	18.7

Inter-Individual Variability Parameters		Estimate	%RSE	Variability	Shrinkage
ω^2_{CL}	SGI-110 clearance	0.0903	19.3	CV=30.0%	7.9%
ω^2_{V}	SGI-110 volume	0.318	17.3	CV=56.4%	11.2%
ω^2_{ka}	SGI-110 absorption rate	0.5	34.3	CV=70.7%	29.3%
ω^2_{CLD}	Decitabine clearance	0.0282	32.6	CV=16.8%	27.2%
ω^2_{F1}	SGI-110 bioavailability	0.0451	36.1	CV=21.2%	31.6%
ω^2_{ε}	Residual error	0.116	20.3	CV=34.0%	0.0%
Inter-Occasion Variability Parameters		**Estimate**	**%RSE**	**Variability**	**Shrinkage**
$\omega^2_{IOV,F}$	SGI-110 bioavailability	0.0587	13.5	CV=24.2%	28.9%
$\omega^2_{IOV,F}$	SGI-110 bioavailability	0.0587	same	same	18.1%
$\omega^2_{IOV,ka}$	SGI-110 absorption rate	0.637	17.4	CV=79.8%	20.0%
$\omega^2_{IOV,ka}$	SGI-110 absorption rate	0.637	same	same	25.3%
Residual Variability Parameters		**Estimate**	**%RSE**	**Variability**	**Shrinkage**
σ^2_{prop}	SGI-110 proportional	0.0847	10	CV=29.4%	2.0%
σ^2_{add}	SGI-110 additive	1.11	31.2	SD=0.976	2.0%
$\sigma^2_{D,prop}$	Decitabine proportional	0.0498	9.24	CV=22.2%	3.2%
$\sigma^2_{D,add}$	Decitabine additive	0.0574	19.2	SD=0.223	3.2%

Figure 3. Covariate Effects for the Final Model

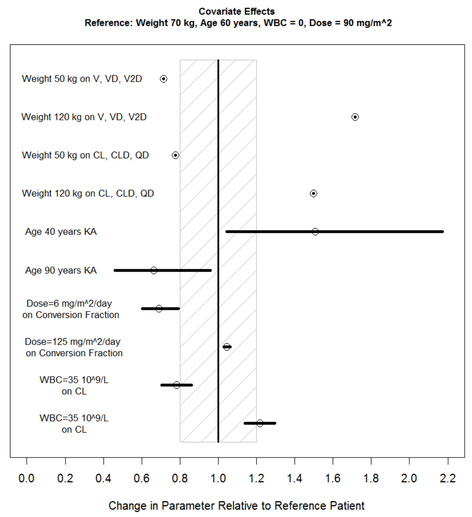


Figure 4. Covariate Effects for the Model with CDA Effects

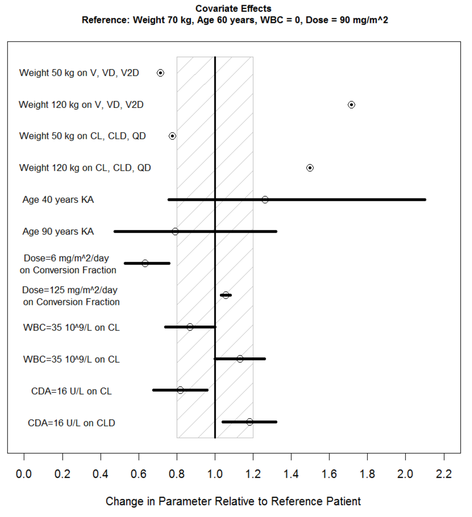


Figure 5. Goodness of Fit for the final model: SGI-110
DV: Observed concentrations; PRED: population predictions of the model; IPRED: individual predictions of the model; CWRES: conditional weighted residuals; TIME: time after dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines.

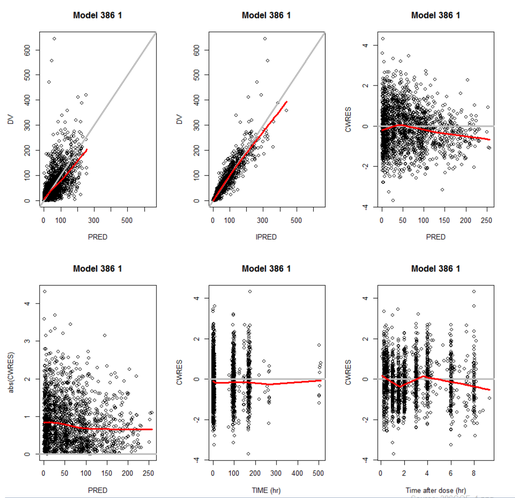


Figure 6. Goodness of Fit for the final model: Decitabine
DV: Observed concentrations; PRED: population predictions of the model; IPRED: individual predictions of the model; CWRES: conditional weighted residuals; RES: residuals; TIME: time after dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines.

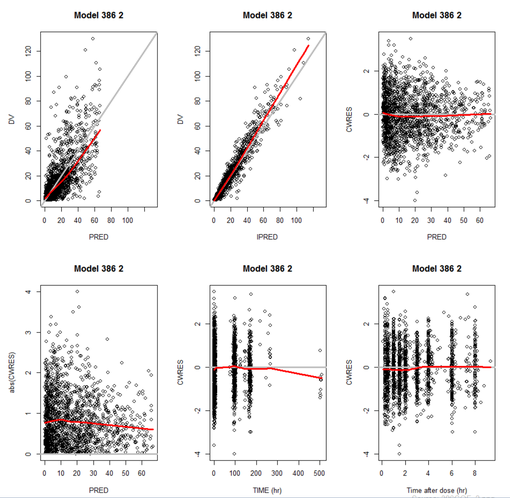
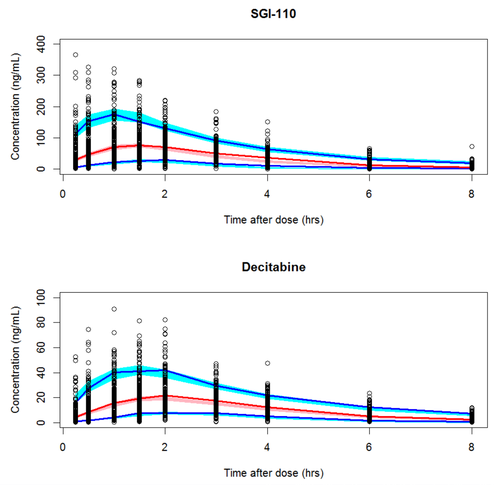


Figure 7. Visual Predictive Check for the final model: Dose-Normalized Concentration versus Time after Dose, Original Scale
The lines show median (red), and the 10th and 90th percentiles (blue) of the observed concentrations scaled by the factor 60/NDOSE. The shaded regions show the 80% confidence intervals on these quantities obtained by simulations. The circles show observed data. The simulated values were computed from 1000 trials simulated using dosing, sampling, and the covariate values of the analysis dataset.



SUMMARY/CONCLUSIONS

- The plasma concentration-time course for guadecitabine (SGI-110) and active metabolite decitabine following multiple SC administration was accurately described by a combination of one-compartment pharmacokinetic model with the first-order absorption for guadecitabine and two-compartment pharmacokinetic model for decitabine.
- Goodness-of-fit variability diagnostics and predictive check evaluation indicated that the model correctly captured both central tendency, inter-subject, and covariate dependencies of SGI-110 and decitabine pharmacokinetics.
- Guadecitabine and decitabine clearance and volume parameters increased with body weight according to allometric scaling with fixed power coefficients of 0.75 and 1, respectively, justifying dosing selection based on BSA.
- Apart from the effect of body-size on clearance and volume parameters of guadecitabine and decitabine, no other covariates (such as gender, disease type, laboratory values) had clinically relevant effects on guadecitabine and decitabine PK.

Poster presented at: 2017 ACCP Annual Meeting, San Diego, CA September 17 – 19, 2017
Poster can be downloaded from www.astx.com
17SGI-110-PB17(705)