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 once weekly, every other week for 10 days 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).

The abstract reported the 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 quantile limit were removed from the plots). Mean conversion was 67.9% (range 25.1-86.1). Mean body weight was 80.6 kg (48.4-177). The dataset included 87 male and 37 female patients.

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 g/mol) and decitabine (282 g/mol) and for differences in molar activities due to differences in molar weights.
- Dosing with SGI-110 in Patients with Relapsed/Refractory AML and MDS
- 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.

Results
- Final PK model (Table 1) included effects of weight on clearance and volume parameters, the effect of nominal dose on SGI-decitabine conversion fraction, the effect of age on ka, and effects of white blood cell count on SGI100 and decitabine clearance parameters.
- Goodness-of-fit plots (Figure 1-6) 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 plots (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 effects 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).
- Parameters of the model changed with increasing disease severity (Table 2).
- Goodness of fit for the final model with three covariates: weight, age, and white blood count, was shown in Figure 6. The solid red line and the two solid black lines represent the 80% and 90% confidence intervals.

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 twocompartment 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 covariance dependences 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.
- Age, sex, and 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.