Pharmacokinetics and Exposure–Response Analyses of Revumenib Support Dosing in a Broad Population of Patients with Relapsed/Refractory Acute Leukemias

Poster Number 157

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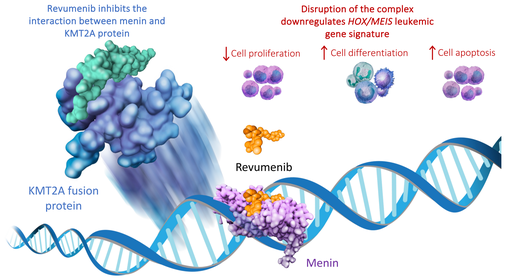
PURPOSE

- Revumenib is a selective, orally bioavailable small-molecule inhibitor of the menin-lysine methyltransferase 2A (KMT2A) interaction (**Figure 1**)
- Revumenib is being investigated for treatment of *KMT2A*-rearranged (*KMT2Ar*) or nucleophosmin-mutated (*NPM1m*) relapsed/refractory (R/R) acute leukemias in the Phase 1/2 AUGMENT-101 trial (NCT04065399)[1]
- Traditionally, there remains, on average, a 9-year delay in the drug approval for pediatric labeling after initial approval of a drug for use in adults[2]; however, the AUGMENT-101 study took the approach of studying pediatrics and adults concurrently to assess the pharmacokinetics (PK) of multiple formulations, safety, and efficacy in this vulnerable population

Figure 1. Revumenib mechanism of action

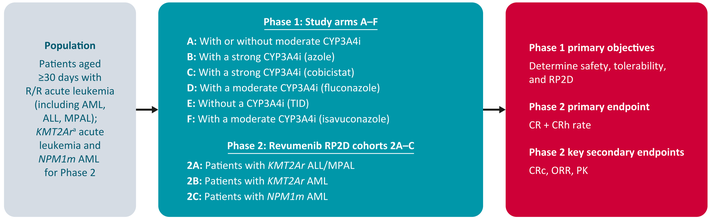


- This analysis sought to determine the PK and exposure–response (E-R) relationship of revumenib for the treatment of patients with R/R acute leukemias

METHODS

- The Phase 1/2 AUGMENT-101 trial evaluated revumenib, administered orally in 28-day cycles as a capsule, tablet, or oral-solution ± cytochrome P450 3A4 inhibitor (CYP3A4i), in adult and pediatric participants with R/R *KMT2Ar* or *NPM1m* acute leukemias (**Figure 2**)
  - The Phase 1 dose-escalation portion included multiple arms (A to F) to enable evaluation of different dosing regimens and dosing with a strong, moderate, or no CYP3A4i to identify the recommended Phase 2 dose (RP2D)
  - Phase 2 evaluated the RP2D of 163 mg every 12 hours (q12h) with a strong CYP3A4i
- Additional patients from the Phase 1/2 trial of revumenib in patients with colorectal cancer and other solid tumors (NCT05731947) were included to evaluate the effect of formulation (tablet vs. capsule) on PK parameters
- As of July 2023, 251 patients who had evaluable PK profiles were included in this analysis
  - Additional data through July 2024 were included in the formulation assessment of tablets vs. capsules
- Models were developed for physiologically based PK (PBPK), population PK (PopPK), E-R for efficacy and E-R for safety to guide doses of revumenib and assess drug–drug interactions
  - The PBPK model was developed and qualified using a combination of in vitro, nonclinical, and clinical data
  - PopPK analysis based on a 2-compartment model was conducted
  - E-R for safety was conducted in 251 patients for key continuous and binary safety biomarkers, while E-R for efficacy was assessed in 125 patients for the gene-related, efficacy binary, and time-to-event endpoints
- Monte Carlo simulations (N=1000) were conducted to support the selection of proposed registrational doses

Figure 2. Overview of the Phase 1/2 study design



[a]Centrally confirmed by FISH.

AML, acute myeloid leukemia; **ALL**, acute lymphoblastic leukemia; **CR**, complete remission; **CRc**, CR composite (CR+CRh+CRp+CRi); **CRh**, CR with partial hematologic recovery; **CYP3A4i**, cytochrome P450 3A4 inhibitor; **FISH**, fluorescence in situ hybridization; ***KMT2Ar***, lysine methyltransferase 2A rearrangements; **MPAL**, mixed phenotype acute leukemia; ***NPM1m***, nucleophosmin 1 mutated; **ORR**, overall response rate; **PK**, pharmacokinetics; **q12h**, every 12 hours; **RP2D**, recommended Phase 2 dose; **R/R**, relapsed/refractory; **TID**, 3 times daily.

RESULTS

- In vitro metabolism data indicated revumenib was metabolized primarily by the CYP3A4 pathway (data not shown)
- Exposures of revumenib were dose-proportional across the therapeutic dose-range of 113–276 mg (or BSA equivalent dose) q12h when administered with or without a strong CYP3A4i

PBPK

- PBPK analysis showed that co-administration of moderate and strong CYP3A4i increased revumenib exposures by 2.5-fold and ~5-fold, respectively (**Table 1**)
  - Of note, the PBPK model was designed based on the maximum inhibitory dosage of the inhibitor, taken on with high control over the dosing
- In pediatric patients <6 months of age, up to 2.3-fold increases in revumenib exposures were observed
  - No substantial difference in fold change was observed in pediatric patients >6 months to 16 years when dosed on a mg/m^2 basis, as compared to the adult equivalent flat dose

Table 1. Prediction of fold change in revumenib exposures in the presence of CYP3A4i in adult patients

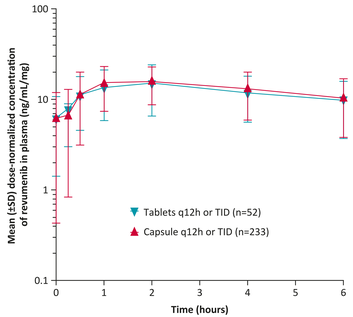
CYP3A4i	Fold change in revumenib AUC	Fold change in revumenib C_{max}
Cimetidine (Weak)	1.16 ↑	1.13 ↑
Fluconazole (Moderate)	2.66 ↑	2.26 ↑
Itraconazole (Strong)	4.14 ↑	3.31 ↑
Cobicistat (Strong)	4.53 ↑	3.58 ↑

AUC, area under the plasma concentration–time curve; **C_{max}**, maximum plasma concentration.

PopPK

- PopPK analysis found no clinically meaningful effect of formulation (tablet vs. capsules vs. oral solution) or food effect (low fat meal vs. fasted) for revumenib (**Figures 3** and **4**)

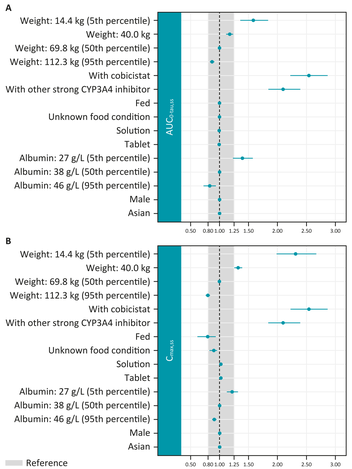
Figure 3. Semi-log mean dose-normalized revumenib concentration–time profiles at steady state between tablets and capsules



q12h, every 12 hours; **SD**, standard deviation; **TID**, 3 times daily.

- PopPK analysis showed no relevant change in revumenib exposures ($AUC_{tau,ss}$ and $C_{max,ss}$) with moderate or weak CYP3A4i
  - These observed data were from patients who took the inhibitor as part of their standard of care (with less clear compliance) and are considered the most relevant for use of revumenib with such inhibitors
- According to the PopPK model, several covariates had statistically significant effects on revumenib exposures (**Figure 4**)
  - For patients <40 kg, ~30% increase in revumenib exposure was observed
  - After univariate analysis, no clinically relevant differences in the PK of revumenib were observed in patients according to body weights between 40–142 kg, race, sex, and mild-to-moderate renal and hepatic impairment
    - Safety and PK of revumenib in patients with severe renal impairment (CL_{cr} 15–29 mL/min), end-stage renal disease (CL_{cr} <15 mL/min), or severe hepatic impairment (total bilirubin >3.0 × ULN and any aspartate aminotransferase (AST) elevation) have not been studied (no recommended dose has been established)

Figure 4. Forest plot of covariate effects on steady-state revumenib exposure for A) $AUC_{0\text{-}tau,ss}$ and B) C_{max}



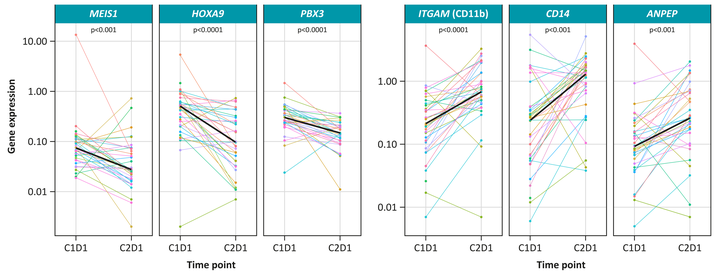
Note: The gray shaded area corresponds to a ratio of 0.8 and 1.25. The dashed vertical line corresponds to a ratio of 1 and represents the typical subject (typical non-Asian female subject with weight = 69.8 kg and albumin = 38 g/L who received capsule formulation under fasted conditions without cobicistat or other strong CYP3A4 inhibitor). The values are the geometric mean and 90% CI fold change in steady-state exposure relative to the typical subject. Steady-state exposures were simulated using a dose of 163 mg q12h.

$AUC_{0\text{-}tau,ss}$, area under the concentration–time curve over the dosing period; **CYP3A4**, cytochrome P450 3A4; **CI**, confidence interval; **$C_{max,ss}$**, maximum concentration at steady state; **q12h**, every 12 hours; **ss**, steady-state; **tau**, dosing interval.

E-R FOR EFFICACY AND SAFETY FROM AUGMENT-101

- All dose levels (113–339 mg q12h) were within an efficacious range, leading to statistically significant downregulation of leukemogenic genes or upregulation of myeloid differentiation genes, with no clear correlations between exposures and expression (**Figure 5**)
- There was no statistically significant relationship between revumenib exposure metrics ($C_{max,ss}$, $C_{min,ss}$, and $C_{avg,ss}$) versus the primary efficacy endpoint (CR+CRh rate) and key efficacy endpoints (response rates or duration of response) within the dose ranges tested
- There was no clear relationship between revumenib exposures and 8 continuous safety biomarkers tested; only 4 of 21 binary safety endpoints tested showed a statistically significant relationship:
  - Neutropenia (grade ≥4)
  - Treatment-emergent adverse events (TEAEs) leading to dose modifications
  - TEAEs leading to dose delay or interruption
  - TEAEs leading to discontinuation

Figure 5. Phase 2 line plots of leukemogenic and of myeloid cell differentiation gene expression-based efficacy endpoints versus time



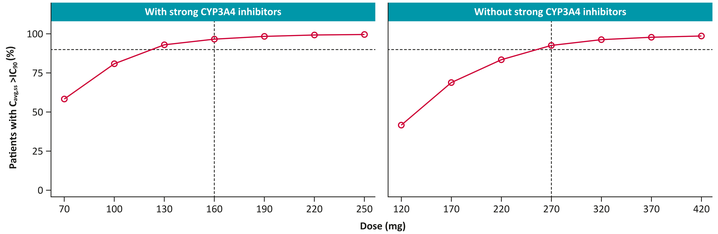
Notes: Colored points and lines are the individual gene expression data; black bold line connects the median gene expression value at each time point. The Wilcoxon test was used to determine the reported p-value. Y axis is on log scale. C1D1 denotes the gene expression levels before the initiation of revumenib treatment, serving as the baseline for comparison. C2D1 refers to the gene expression levels after the commencement of revumenib treatment, allowing for the assessment of treatment impact on gene expression. The genes considered leukemogenic/oncogenic included *MEIS1*, *HOXA9*, and *PBX3*; myeloid differentiation included *ITGAM* (CD11b), *CD14*, and *ANPEP*.

C1D1, Cycle 1 Day 1; **C2D1**, Cycle 2 Day 1.

MONTE CARLO SIMULATIONS

- 270 mg BID without strong CYP3A4i or 160 mg BID with strong CYP3A4i represents the dose necessary to maintain target exposures above the preclinical target of ~600 ng/mL in ≥90% of patients (**Figure 6**)

Figure 6. More than 90% of patients achieved the target* revumenib exposure at the 160 mg BID dose with a strong CYP2A4i or 270 mg BID without a strong CYP3A4i



*In preclinical models, revumenib showed significant pharmacodynamic activity, with increased survival in a cell-line xenograft model of *KMT2Ar* leukemia with inhibitory concentration resulting in 90% inhibition (IC_{90}) of ~600 ng/mL (target concentration).

$C_{avg,ss}$, average concentration at steady-state; **CYP3A4i**, cytochrome P450 3A4 inhibitor.

- Based on results of this modeling analysis, the proposed starting dosage and dose modifications based on age (<6 months of age) and weight (BSA-based dosing for patients <40 kg) are shown in **Table 2**

Table 2. Modifications of selected dose

Proposed starting dose*	Co-administered without strong CYP3A4i	Co-administered with strong CYP3A4i
Patients aged ≥6 months weighing ≥40 kg	270 mg BID	160 mg BID
Patients aged ≥6 months weighing <40 kg	160 mg/m^2 BID	95 mg/m^2 BID
Patients aged 2 months to <6 months	100 mg/m^2 BID	60 mg/m^2 BID
Patients aged 1 month to <2 months	70 mg/m^2 BID	40 mg/m^2 BID

*Administered fasted or with a low-fat meal.

BID, twice daily; **CYP3A4i**, cytochrome P450 3A4 inhibitor.

CONCLUSIONS

- Revumenib is a menin inhibitor with acceptable PK for oral twice-daily administration via flat or BSA-based dosing, either with or without a strong CYP3A4i, and as fasted or with a low-fat meal
- Formulation analysis supports the use of tablets or oral solution for equivalent dosing
- Revumenib dosing has been established in a broad age range of patients regardless of race or sex, and with mild-to-moderate renal and/or hepatic impairment
- There were no statistically significant exposure–efficacy relationships for key efficacy endpoints within the dose ranges tested
- Revumenib was well tolerated at the proposed starting doses, with few safety endpoints demonstrating a statistically significant relationship with an increase in revumenib exposure
- The proposed 270 mg BID dose without a strong CYP3A4i and 160 mg BID dose with a strong CYP3A4i, and equivalent BSA-adjusted doses, were predicted to be efficacious for most patients treated with revumenib

REFERENCES

1. Issa GC, et al. *J Clin Oncol.* 2024;JCO2400826. doi: 10.1200/JCO.24.00826.
2. Tanaudommongkon I, et al. *Clin Pharmacol Ther.* 2020;108:1018–1025.

CONFLICTS OF INTEREST

Syndax consultants: **YWL**, **SSm**; Syndax employees: **EC**, **JS**, **RN**, **NM**, **SSu**; former Syndax employee: **HVN**; Syndax Trial investigators: **ATW**, **GCI**. **NM** reports stock, other ownership interests, travel and accommodation expenses from: AstraZeneca, Syndax; and the following patents: Compositions for enhancing targeted gene editing and methods of use thereof (Patent number 11136597, October 2021), Compositions and methods for treatment of cystic fibrosis (US Patent Application No. 15/998,613, filed August 16, 2018). **GCI** reports consulting or advisory role for Novartis, Kura Oncology, Syndax, NuProbe, AbbVie, Sanofi, and research funding from Novartis (Inst), Syndax (Inst), Kura Oncology (Inst), Merck, Cullinan Oncology, Astex Pharmaceuticals (Inst), NuProbe (Inst).

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