Simultaneous population pharmacokinetic analysis of total and unbound valemetostat in patients with non-Hodgkin lymphoma to quantify the effect of the binding protein, alpha 1-acid glycoprotein

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Objectives

Valemetostat (DS-3201, EZHARMIA®) is an orally administered dual inhibitor of enhancer of zeste homolog (EZH) 1 and EZH2 being investigated for the treatment of various types of cancers, including non-Hodgkin lymphoma (NHL) and solid tumors, and was approved for the treatment of adult T-cell leukemia/lymphoma in Japan in September 2022. The present study was conducted to characterize valemetostat pharmacokinetics (PK) of both total and unbound concentration in patients with NHL, including patients with adult T-cell leukemia/lymphoma and to quantify the effect of covariates, especially binding protein, alpha-1-acid glycoprotein (AAG).

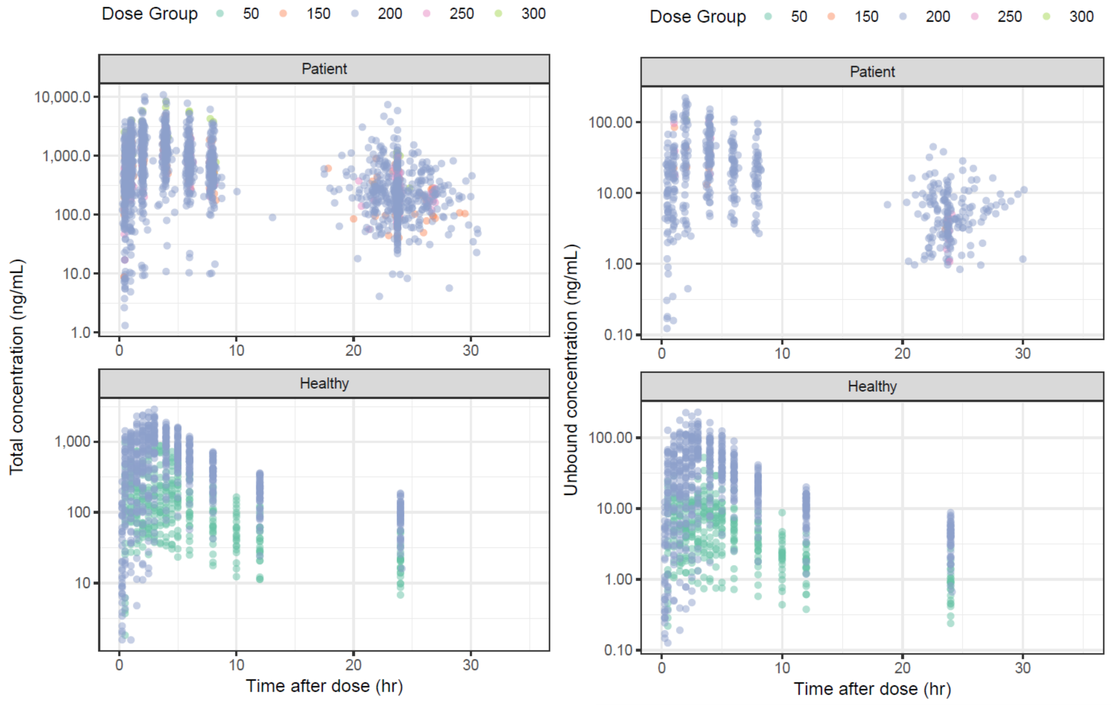
Methods and results

- The brief summary of the five clinical studies (two patient studies and three healthy volunteer studies) used in the modeling is shown in **Table 1**.
- The pooled population included 102 patients with NHL and 72 healthy subjects with 3162 total and 1871 unbound valemetostat observations.
- Only Study J101 applied a sparse sampling (peak and trough) for unbound concentrations while rich sampling data were available in the other studies.
- Study J101 applied different measurement methods for unbound concentrations.
- Some patients had missing AAG in Study J101.
- Observed PK data in the dataset are shown in **Fig. 1**. Higher total valemetostat concentration in patients compared to healthy subjects was observed while unbound valemetostat concentration was similar.

Table 1 Brief description of the clinical studies used in population PK analysis

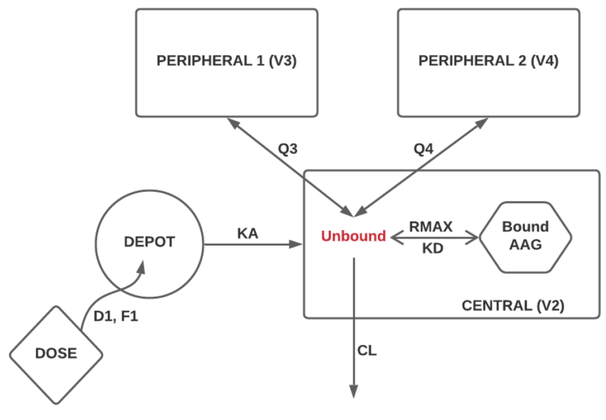
Study	Description	N	Dose
J101	First-in-human study in patients with non-Hodgkin's lymphoma	77	150-300 mg
J201	Phase 2, single-arm study in patients with relapsed or refractory adult T-cell leukemia/lymphoma	25	200 mg
J107	Phase 1 study to evaluate the effect of rifampicin in healthy subjects	20	200 mg
J109	Phase 1 study to evaluate the effect of low-fat meal in healthy subjects	28	200 mg
U106	Phase 1 study to assess the PK in patients with hepatic impairment	24	50 mg

Fig. 1 Observed total (**left**) and unbound (**right**) PK data in the dataset



- The target-mediated drug disposition model with quasi-equilibrium approximation, which ignored target-mediated elimination was employed to describe both total and unbound concentration, while binding protein was not the therapeutic target of this drug (**Fig. 2**).
- Valemetostat disposition was well described by a three-compartment model with sequential zero-/first-order absorption and a saturable binding submodel in the central compartment to characterize total and unbound valemetostat.
- The unbound valemetostat disposition was parameterized in terms of total binding capacity (RMAX) and binding affinity (KD). RMAX was modeled as a function of AAG, which explained large amount of variability of total valemetostat PK.
- Covariates evaluated in the population PK modeling included AAG, weight, age, Cockcroft-Gault calculated creatinine clearance based on total body weight, albumin, sex, race or country of origin (Japan versus USA), and population (patients versus healthy subjects). Missing AAG data were imputed using a multivariate log-linear regression model with other PK model covariates as predictors.
- These covariates were evaluated based on the full covariate modeling approach considering correlation or collinearity in predictors.
- Since one of the patient studies used different assay for unbound concentration, an adjustment factor was estimated.
- These analyses were conducted using NONMEM® 7.5 and R 4.0.3.

Fig. 2 Schematic representation of the simultaneous model for both total and unbound valemetostat



Methods and results (cont.)

- While total valemetostat exposure increased with increasing AAG, there was little variation in unbound exposure with AAG (**Figs. 3 and 4**), which suggested that the high variation of total exposure due to AAG could be clinically not significant and that the difference in AAG between healthy subjects and patients contributed to the deference in total exposure through unbound fraction.
- The other covariates in the model (e.g. body weight, sex and race) had a minimal impact on valemetostat exposure (**Fig. 5**).

Fig. 3 The relationship between total and unbound exposure metrics and unbound fraction and AAG

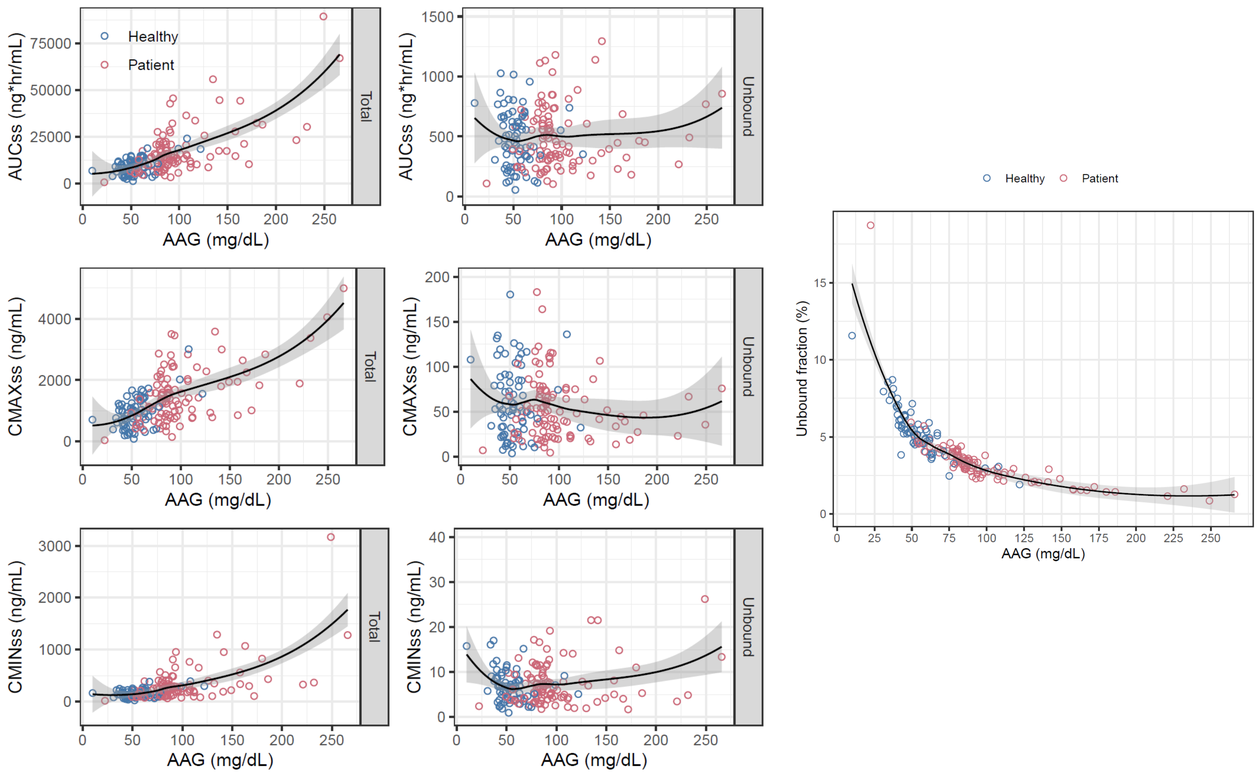


Fig. 4 The effect of AAG on the time-course of total and unbound plasma concentration and fraction unbound

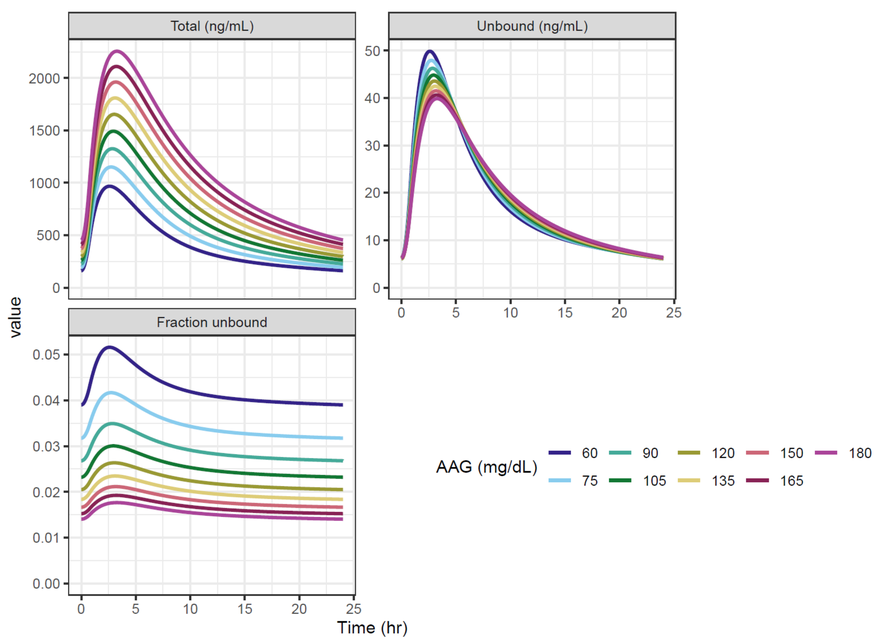
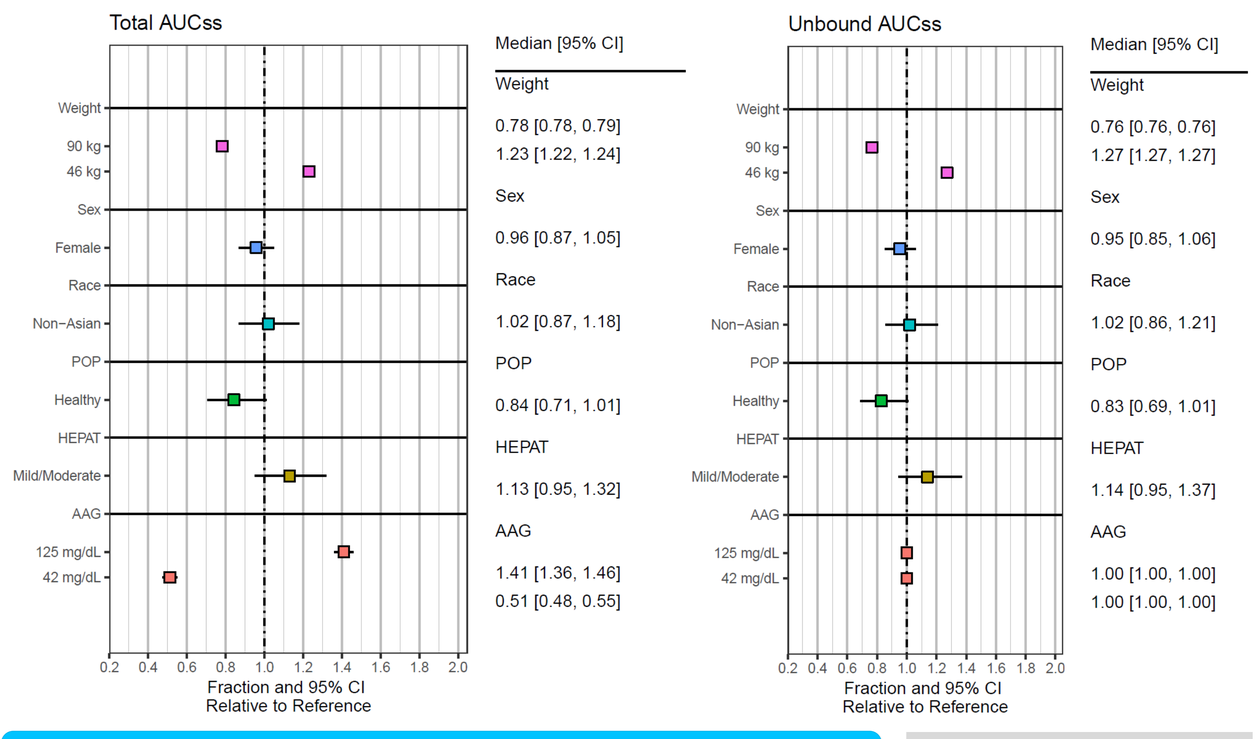


Fig. 5 The effect of each covariate in the final model on the total and unbound AUCss



Conclusions

A single simultaneous population pharmacokinetic model appropriately described both total and unbound valemetostat concentrations in patients with NHL and healthy subjects. Binding of valemetostat to AAG had the highest impact on total valemetostat pharmacokinetics but had little on unbound.

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