Valmecostat (DS-3201, EZHARMA®) is an orally administered dual inhibitor of enhancer of zeste homolog EZH1 and EZH2, which was approved for the treatment of patients with relapsed/refractory (R/R) adult T-cell leukemia/lymphoma (ATL) in Japan in September 2022 and is under development for other cancers. The objectives of this study were to determine (i) the valmecostat exposure range which provided satisfactory efficacy and acceptable safety or tolerability in R/R ATL patients, (ii) whether there were any clinically identifiable subpopulations that would warrant a dosing regimen other than the recommended dose (200 mg QD), and iii) a dose adjustment guidance due to platelet count decreased.

Methods and results

Landmark Exposure-Response Analyses
- The analysis was conducted using data from Studies DS3201-A-J101 and DS3201-A-J201 with non-Hodgkin’s lymphoma (NHL), including ATL. Patients with ATL were included for efficacy endpoints and the whole population of NHL were analyzed for safety with wider dose range (Table 1).

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Population</th>
<th>N</th>
<th>Dose (mg)</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR by central assessment</td>
<td>ATL</td>
<td>25</td>
<td>200 mg</td>
<td>Efficacy</td>
</tr>
<tr>
<td>ORR by investigator</td>
<td>ATL</td>
<td>39</td>
<td>150-200 mg</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Neutrophil count decreased (Grade &gt;=3)</td>
<td>NHL</td>
<td>102</td>
<td>150-300 mg</td>
<td>Safety</td>
</tr>
<tr>
<td>Platelet count decreased (Grade &gt;=3)</td>
<td>NHL</td>
<td>102</td>
<td>150-300 mg</td>
<td>Safety</td>
</tr>
<tr>
<td>Dose reduction due to AEs</td>
<td>NHL</td>
<td>102</td>
<td>150-300 mg</td>
<td>Safety</td>
</tr>
<tr>
<td>Any AEs with Grade &gt;=3</td>
<td>NHL</td>
<td>102</td>
<td>150-300 mg</td>
<td>Safety</td>
</tr>
</tbody>
</table>

- Slightly positive association with exposure was observed for efficacy endpoints while it was steeper for all safety endpoints (Fig. 1).
- Each of these outcome variables were dichotomous, therefore logistic regression was performed.
- The candidate covariates were investigated by full model approach with regularized estimation of covariate effects via Spike and Slab priors in a Bayesian framework.
- For all endpoints, positive exposure-response relationship was confirmed (Fig. 2).
- Only the baseline blood counts for the corresponding safety outcomes were identified as covariates with substantial impact (Fig. 2).
- The models were also used to establish a region of practical equivalence (ROPE), that provides satisfactory efficacy and acceptable safety.
  - Satisfactory efficacy: probability of objective response of greater than 30% for typical patients.
  - Acceptable safety: probability of dose reduction due to AE of less than 50% for 90% of patients.
  - A ROPE of (0 to 1255 ng/hr/mL) and modified ROPE with direct empirical support of (184 to 887 ng/hr/mL) were estimated as target exposure ranges (Fig. 3 left).
  - Simulations suggested that 200 mg QD dosing is most likely to achieve exposures within the modified ROPE for subpopulations of interest (Fig. 3 right).
- These analyses were conducted using R 4.0.3.

Conclusions
- The landmark analyses confirmed the positive exposure-response relationship for all endpoints and established the target exposure range (ROPE), that provides satisfactory efficacy and acceptable safety of recommended dose (200 mg QD) of valmecostat.
- The longitudinal analysis adequately characterized the time-course of platelet counts with spontaneous partial recovery from the nadir. The adaptive simulation predicted the risk of recurrent G4 platelet count decreased with or without dose adjustment. The dose adjustment guidance based on platelet count was justified.
- These analyses justified the recommended dose of 200 mg QD and dose adjustment for patients with R/R ATL.

Methods and results (cont.)

Fig. 3 Estimated ROPE based on the definition (left) and expected exposure range of subpopulation administered 200 mg QD (right). The light and dark gray areas indicate the ROPE and modified ROPE, respectively.

Fig. 4 Observed platelet count data after administration of valmecostat by exposure level.

Fig. 5 Schematic representation of the longitudinal exposure-response model for platelet count decreased.

Fig. 6 Predicted frequency of Grade 4 platelet count decreased with or without dose adjustment.