Effect of Valemetostat on the Pharmacokinetics of Midazolam and Digoxin (CYP3A and P-gp Substrates): A Phase 1 Drug–Drug Interaction Study in Patients With Refractory or Relapsed Non-Hodgkin Lymphoma

PI-030

Masaya Tachibana[1], Steven Horwitz[2], Eric Jacobsen[3], Shinichi Inaba[1], Yuka Iko[1], Yasuyuki Kakurai[1], Noriaki Kitami[1], **Yang Chen**[4], Yvonne Lau[4]

[1]Daiichi Sankyo Co., Ltd, Tokyo, Japan; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]Daiichi Sankyo Inc., Basking Ridge, NJ, USA

PURPOSE

- The primary objective was to evaluate the effect of repeated doses of valemetostat tosylate (valemetostat) on the pharmacokinetics (PK) of a single dose of midazolam, a sensitive index cytochrome P450 (CYP) 3A substrate, and digoxin, a sensitive index P-glycoprotein (P-gp) substrate, in patients with relapsed or refractory (R/R) non-Hodgkin lymphomas (NHLs) from the drug–drug interaction (DDI) cohort of the DS3201-A-J101 study (NCT02732275)
- The secondary objective was the assessment of safety and tolerability of valemetostat when administered alone or in combination with a single dose of midazolam or digoxin in patients with NHLs

CONCLUSIONS

- Valemetostat has no clinically meaningful DDI with sensitive index CYP3A substrates and has a potentially weak DDI (< 30% increase) with sensitive index P-gp substrates
- Valemetostat 200 mg/day in 28-day cycles was well tolerated and treatment-emergent adverse events (TEAEs) were manageable by routine patient monitoring and supportive care
  - TEAEs were similar to those reported in the overall patient population of the DS3201-A-J101 study[1]

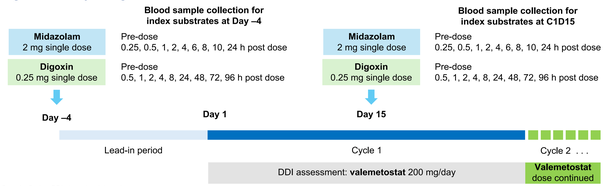
BACKGROUND

- Valemetostat is a first-in-class, oral, dual inhibitor of enhancer of zeste homolog (EZH)2 and EZH1, approved in Japan for the treatment of R/R adult T-cell leukemia/lymphoma (ATLL) and R/R peripheral T-cell lymphoma (PTCL)[2,3]
- Preclinical studies demonstrated that valemetostat is primarily metabolized by CYP3A4 and is a substrate of P-gp[4]
  - In previous DDI studies, valemetostat exposure increased upon coadministration of either itraconazole (a P-gp and strong CYP3A inhibitor) or fluconazole (a moderate CYP3A inhibitor),[4] and decreased after coadministration of rifampicin (a strong CYP3A and P-gp inducer)[5]
- In vitro, valemetostat inhibits the metabolism of midazolam via CYP3A4 as well as the P-gp–mediated transport of digoxin[3]
  - A static mechanistic model predicted an area under the plasma concentration–time curve (AUC) ratio for midazolam combined with valemetostat versus midazolam alone of 1.3 (data on file)
  - The ratio between the intestinal luminal concentration of valemetostat 200 mg/day and the in vitro half-maximal inhibitory concentration (IC_{50}) of valemetostat for digoxin (18.2 µmol/L) was 90
  - Both results exceeded the cutoff values of 1.25 and 10, respectively, for determining whether in vivo studies are needed[6,7]

METHODS

- This study was a DDI cohort-specific sub-study, and is a part of the first-in-human, multicenter, open-label, phase 1 dose-escalation and dose-expansion trial of valemetostat monotherapy in patients with B- and T-cell NHLs[1]
- Eligible adult patients with confirmed diagnosis of NHL, as defined by the 2016 World Health Organization criteria,[8] received valemetostat 200 mg/day in continuous 28-day treatment cycles and single doses of midazolam 2 mg and digoxin 0.25 mg on Day –4 and Cycle 1 Day 15 (C1D15) (**Figure 1**)
- Plasma concentrations of midazolam, digoxin, and valemetostat were assessed at pre-dosing and numerous time points post-dosing using validated liquid chromatography–tandem mass spectrometry methods
- Maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), AUC up to last quantifiable time point (AUC_{last}), AUC extrapolated to infinity (AUC_{inf}), elimination rate constant (K_{el}), half-life ($t_{1/2}$), oral clearance (CL/F), and the apparent volume of distribution (Vz/F) of midazolam, digoxin, and valemetostat (total and unbound) were assessed by noncompartmental analysis

Figure 1. Study design



C, cycle; D, day; DDI, drug–drug interaction.

  - PK values were calculated using version 8.1 of Phoenix WinNonlin (CERTARA; Radnor, PA, USA) and statistical analyses were performed using Statistical Analysis System (SAS Institute, Cary, NC, USA) versions 9.3
- Safety was evaluated by reporting and monitoring TEAEs according to the Common Terminology Criteria for Adverse Events version 4.0

RESULTS

- Twenty-four patients with R/R NHLs were enrolled, including 17 with PTCL (71%), 5 with ATLL (21%), and 2 with cutaneous T-cell lymphoma (8%) (**Table 1**)
  - The median (range) age of patients was 63 (23–85) years, and most were male (63%) and white (63%)
- Of 24 patients, 15 and 16 were evaluable for PK analyses of midazolam and digoxin, respectively
  - Nine patients were excluded from the midazolam subgroup due to lack of valemetostat (n = 5) and/or midazolam dosing (n = 6) at the required time points, protocol violation (n = 1), and/or missing PK data (n = 2)
  - For the digoxin subgroup, 8 patients were excluded due to lack of valemetostat (n = 5) and/or digoxin dosing (n = 6), and/or missing PK data (n = 2)

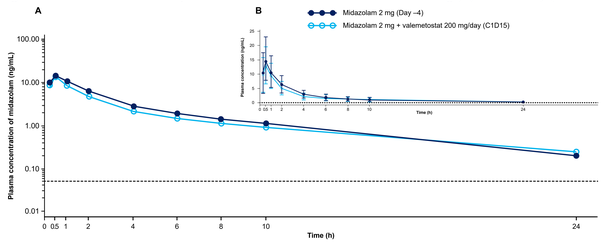
Table 1. Patient characteristics and demographics at baseline

Parameter	Total[a] N = 24
Age, median (min, max), years	63 (23, 85)
Male, n (%)	15 (62.5)
Eastern Cooperative Oncology Group performance status score, n (%)	
0	11 (45.8)
1	13 (54.2)
Non-Hodgkin lymphoma subtype, n (%)	
Peripheral T-cell lymphoma	17 (70.8)
Anaplastic large cell lymphoma	1 (5.9)
Angioimmunoblastic T-cell lymphoma	6 (35.3)
Peripheral T-cell lymphoma not otherwise specified	8 (47.1)
Other T-cell lymphoma	2 (11.8)
Adult T-cell leukemia/lymphoma	5 (20.8)
Cutaneous T-cell lymphoma	2 (8.3)
Prior lines of therapy, median (min, max)	2.5 (1, 7)
Prior hematopoietic stem cell transplantation, n (%)	5 (20.8)
Autologous transplant	2 (40.0)
Allogeneic transplant	3 (60.0)
Hepatic function, n (%)	
Normal	21 (87.5)
Mild impairment[b]	2 (8.3)
Missing	1 (4.2)

[a]Percentage was calculated using the number of patients in the column heading as the denominator. [b]Classification according to the National Cancer Institute Organ Dysfunction Working Group.

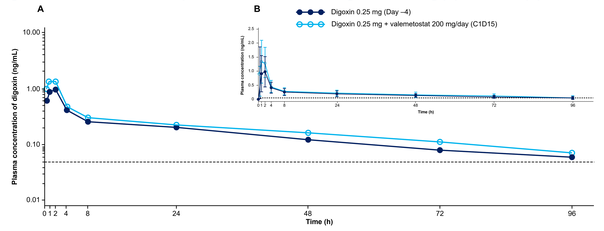
  - All eligible participants were included in the safety population
    - Two patients discontinued the study treatment before completing C1 due to clinical progression
  - The mean plasma concentration–time profiles of midazolam and digoxin on Day –4 and C1D15 are shown in **Figures 2** and **3**

Figure 2. Time course of mean plasma concentrations of midazolam: semi-log (A) and linear (B) scales



Data points are mean ± SD. Dashed line represents lower limit of quantification (0.05 ng/mL). C, cycle; D, day; SD, standard deviation.

Figure 3. Time course of mean plasma concentrations of digoxin: semi-log (A) and linear (B) scales



Data points are mean ± SD. Dashed line represents lower limit of quantification (0.05 ng/mL). C, cycle; D, day; SD, standard deviation.

  - Median T_{max} values on Day –4 and C1D15 showed that both midazolam and digoxin were rapidly absorbed when administered alone and in the presence of valemetostat (**Table 2**)

Table 2. PK values of midazolam and digoxin on Days –4 and C1D15

Parameters	Midazolam alone (Day –4)	Midazolam + valemetostat (C1D15)	Digoxin alone (Day –4)	Digoxin + valemetostat (C1D15)
n	15	15	16	16
C_{max}, ng/mL	15.6 (7.34)	14.4 (5.62)	1.30 (0.540)	1.69 (0.709)
T_{max}, h[a]	0.50 (0.25, 1.75)	0.50 (0.25, 1.27)	1.04 (0.50, 2.05)	1.17 (0.42, 2.25)
AUC_{last}, ng·h/mL	44.6 (20.0)	38.5 (17.4)	15.7 (8.29)	19.0 (7.56)
AUC_{inf}, ng·h/mL	47.4 (20.3)	42.0 (18.9)	19.8 (1.60)[b]	24.3 (5.37)[c]
$t_{1/2}$, h	6.04 (2.33)	6.26 (2.13)	53.0 (11.4)[d]	50.0 (15.5)[e]

All parameters are expressed as mean (standard deviation). [a]T_{max} expressed as median (min, max). [b]n = 3. [c]n = 6. [d]n = 13. [e]n = 15.
AUC, area under the plasma concentration–time curve; AUC_{inf}, AUC extrapolated to infinity; AUC_{last}, AUC up to last quantifiable time point; C, cycle; C_{max}, maximum plasma concentration; D, day; PK, pharmacokinetic; T_{max}, time to reach C_{max}; $t_{1/2}$, half-life.

  - Coadministration of valemetostat with midazolam and digoxin slightly decreased midazolam mean C_{max}, AUC_{last}, and AUC_{inf}, and increased digoxin exposure parameters (**Table 3**)

Table 3. Comparison of pharmacokinetics parameters for midazolam and digoxin when administered alone or with valemetostat

Drug (dose)	Parameter	GMR (90% CI)
Midazolam (2 mg) + valemetostat (200 mg) / Midazolam (2 mg) alone, n = 15	C_{max}, ng/mL	0.966 (0.769–1.21)
	AUC_{last}, ng·h/mL	0.874 (0.745–1.03)
Digoxin (0.25 mg) + valemetostat (200 mg) / Digoxin (0.25 mg) alone, n = 16	C_{max}, ng/mL	1.30 (1.07–1.57)
	AUC_{last}, ng·h/mL	1.27 (1.06–1.52)

AUC_{last}, area under the plasma concentration–time curve up to last quantifiable time point; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric least square mean ratios.

  - All patients (N = 24) reported at least 1 TEAE after C1D1 (**Table 4**)
    - The most common TEAEs (≥ 40% of patients) were dysgeusia, anemia, diarrhea, and platelet count decreased
    - Most common Grade ≥ 3 TEAEs were anemia, neutrophil count decreased, and platelet count decreased

Table 4. Safety events in the drug–drug interaction cohort

Preferred terms, n (%)	Midazolam + digoxin[a] (N = 24)	Valemetostat only[b] (N = 24)	Valemetostat + midazolam + digoxin[c] (N = 21)[d]	Overall[a] (N = 24)
Patients with TEAEs	12 (50.0)	16 (66.7)	13 (61.9)	24 (100.0)
Dysgeusia	0	1 (4.2)	1 (4.8)	12 (50.0)
Anemia	1 (4.2)	2 (8.3)	3 (14.3)	11 (45.8)
Diarrhea	0	2 (8.3)	2 (9.5)	11 (45.8)
Platelet count decreased	0	1 (4.2)	3 (14.3)	10 (41.7)
Alopecia	0	1 (4.2)	0	7 (29.2)
Fatigue	1 (4.2)	2 (8.3)	0	7 (29.2)
Neutrophil count decreased	0	0	3 (14.3)	6 (25.0)
Headache	1 (4.2)	3 (12.5)	0	5 (20.8)
Dyspnea	0	0	3 (14.3)	4 (16.7)
Grade ≥ 3 TEAE				
Patients with Grade ≥ 3 TEAEs	4 (16.7)	5 (20.8)	5 (23.8)	16 (66.7)
Anemia	0	1 (4.2)	1 (4.8)	6 (25.0)
Neutrophil count decreased	0	0	2 (9.5)	4 (16.7)
Platelet count decreased	0	1 (4.2)	1 (4.8)	4 (16.7)
Hypertension	1 (4.2)	0	0	3 (12.5)
Disease progression	0	1 (4.2)	0	2 (8.3)
Neutropenia	1 (4.2)	1 (4.2)	0	2 (8.3)
White blood cell count decreased	0	0	2 (9.5)	2 (8.3)

[a]Onset from Day –4 to Day –1/0. [b]Onset from C1D1 to C1D14. [c]Onset from C1D15 to C1D28. [d]Number excludes 3 patients who did not received at least one of the three drugs (valemetostat, midazolam, or digoxin) on C1D15. [d]Onset after C1D1.
C, cycle; D, day; TEAE, treatment-emergent adverse event.

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