Preliminary Clinical Data From a Phase 1b Study of Mavorixafor and Ibrutinib in Patients With Waldenström's Macroglobulinemia With *MYD88* and *CXCR4* Mutations

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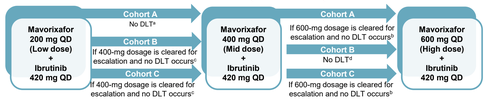
Background

- Waldenström's macroglobulinemia (WM) is a rare B-cell lymphoproliferative disorder characterized by increased clonal immunoglobulin M (IgM)-secreting cells[1,2]
- Most patients with WM (>90%) have somatic mutations in the myeloid differentiation factor 88 (*MYD88*) gene, and a subset (30%–40%) also have Warts, Hypogammaglobulinemia, Infections, Myelokathexis syndrome (WHIM)-like activating mutations in C-X-C chemokine receptor 4 *(CXCR4^{WHIM})*[3,4]
- The presence of *CXCR4^{WHIM}* is associated with higher disease burden with higher serum IgM levels and increased risk of developing symptomatic hyperviscosity syndrome[5]
- The presence of *CXCR4^{WHIM}* impacts response to Bruton tyrosine kinase inhibitors (BTKi) in patients with WM, as manifested by delayed response, inferior depth of response, and/or shorter progression-free survival[6,7]
- Inhibition of *CXCR4* has been shown to sensitize *CXCR4^{WHIM}*-expressing cells to ibrutinib[8,9]
- Mavorixafor, an oral small-molecule antagonist of CXCR4, has been shown to inhibit C-X-C chemokine ligand 12 (CXCL12) binding and extracellular signal-regulated kinase hyperactivation and protein kinase B (AKT) hyperactivation for many *CXCR4* mutations in vitro[10]
- Mavorixafor has been shown to be well tolerated and active in combination with standard of care in clinical studies for other solid malignancies[11,12]

Methods

- This ongoing phase 1b, open-label, multicenter, single-arm study examines intrapatient dose escalation, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of mavorixafor in combination with ibrutinib
- Eligibility includes age ≥18 years, clinicopathological WM diagnosis, indication for treatment using consensus panel criteria[2,13], measurable disease, 0–3 prior therapies, confirmed *MYD88^{L265P}* and *CXCR4^{WHIM}* mutations, and ability to provide written informed consent
- Patients are initiated on mavorixafor 200 mg and ibrutinib 420 mg, both oral and once daily (QD). Mavorixafor escalation to 400 mg occurs after 28 days if no dose-limiting toxicities (DLTs) are observed and to 600 mg after 400 mg is deemed tolerable (<2/6 DLTs) (Figure 1)
- Patients are followed for adverse events (AEs) and change from baseline in IgM and hemoglobin (Hgb), PK, and PD (peripheral white blood cell [WBC] counts)
- **Interim early data analysis was performed with data cutoff at April 15, 2021**

Figure 1. Trial Design (NCT04274738)



DLT, dose-limiting toxicity; QD, once daily.
[a]If DLT occurs, patient is withdrawn.
[b]If dose escalation not cleared, patient remains at current dose level. If dose escalation is cleared but DLT occurs, patient stays in the study after dose de-escalation.
[c]If dose escalation is not cleared, patient remains at current dose level. If dose escalation is cleared but DLT occurs, patient is withdrawn.
[d]If DLT occurs, patient stays in the study after dose de-escalation.
Cohort A will continue to receive 400 mg until 600 mg is deemed tolerable by Cohort B. Once 600 mg is deemed tolerable, all enrolled patient doses may escalate to 600 mg, and additional patients enrolled will start at 200 mg and their doses will escalate to 600 mg.

Primary Objectives

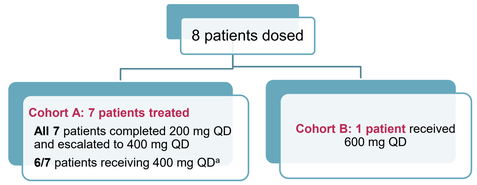
- To report preliminary findings from our ongoing phase 1b study that examines the safety and efficacy of mavorixafor in combination with ibrutinib in patients with WM with *MYD88* and *CXCR4* mutations
- Safety: DLTs
- Clinical assessment of drug activity is defined as change from baseline in IgM and Hgb, measured monthly, during dose escalation
- PK parameters of mavorixafor and ibrutinib during dose-escalation phase
- PD changes in maximum WBC during dose-escalation phase

Results

Patient Disposition

- Patient disposition as of April 15, 2021, is shown in Figure 2
- 8 patients were enrolled in the study
- 4 patients have been treated for ≥6 28-day cycles
- Median duration of treatment was 156 days
- 1 patient had a dose de-escalation (400 mg to 200 mg) due to an AE of gastroesophageal reflux disease (GERD)

Figure 2. Patient Disposition



QD, once daily.
[a]As of April 15, 2021.

Baseline Characteristics

Table 1. Demographics, Clinical Characteristics and Mutational Status of All Patients

Characteristic	
Patients with both *MYD88* and *CXCR4* mutations, n (%)	8 (100)
Mean age (range),y	67 (38–80)
Male sex, n (%)	6 (75)
Mean disease duration (range),y	4.5 (0–11)
Mean prior lines of treatment, n (range)[a] Frontline therapy, n (%) Relapse/refractory therapy, n (%)	1 (0–3) 3 (37.5) 5 (62.5)
Median baseline IgM levels (range)[b], g/L	39.75 (11.88–58.50)
Median baseline hemoglobin levels (range)[c], g/L	110.5 (76–161)
Median baseline platelet levels (range)[d], 10^9/L	189 (108–453)
Patients with baseline extramedullary disease, n (%)	3 (38)
Patient baseline IPSS WM score, n	Low–2 Intermediate–3 High–3
CXCR4 mutational status Frameshift mutation, n (%) Nonsense mutation, n (%)	 4 (50) 4 (50)

CXCR4, C-X-C chemokine receptor 4; IgM, immunoglobulin M; IPSS, International Prognostic Scoring System; *MYD88*, myeloid differentiation factor 88; WM, Waldenström's macroglobulinemia.
[a]3 patients were previously untreated.
[b]Normal range, 0.5–2 g/L.
[c]Normal range: male, 138–172 g/L; female, 121–151 g/L.
[d]Normal range, 150–400 10^9/L.

Mavorixafor and Ibrutinib Combination Therapy Is Well Tolerated to Date[a]

- No serious AEs were reported
- 77% of AEs were mild (Common Terminology Criteria for Adverse Events grade 1)
- 18 AEs were related to combination therapy, 13 were attributed to ibrutinib treatment only and 6 to mavorixafor use only[b]
  - AEs related to use of mavorixafor only occurred in 2 patients and were grade 1 or grade 2 and included nausea, acid reflux, constipation, elevated WBC count, and worsening pain/numbness in the shoulder/hands/wrists
- 3 DLT AEs were reported in 2 patients (Table 2)

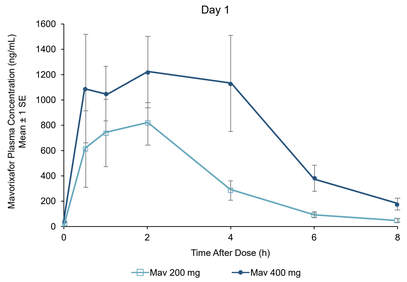
Table 2. DLT AEs

AE	Grade	Causality
Hypertension	3	Combination therapy
Worsening pain and numbness in right shoulder, bilateral hands/wrists[c]	2	Possibly mavorixafor
Worsening pain, numbness, and tingling in left hand and shoulder[d]	3	Ibrutinib

AE, adverse events; CTCAE, Common Criteria for Adverse Events; DLT, dose-limiting toxicity.
[a]Interim early data analysis performed with data cutoff at April 15, 2021.
[b]Only AEs with a completed assessment for a causal relationship to the study drug(s) at the time of the data cutoff are included.
[c]Upon review with the investigator post the data cut, the AE does not meet DLT criteria per protocol and is pending removal of the DLT flag.
[d]Upon review with the investigator post data cut, the AE does not meet Grade 3 CTCAE criteria and is pending downgrade to Grade 2 and removal of the DLT flag.

Dose-Dependent Increases in Plasma Levels of Mavorixafor

Figure 3. Plasma Levels of Mavorixafor[a]

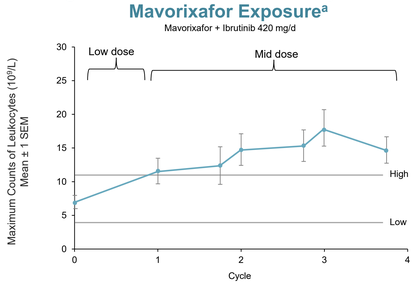


[a]Data cutoff at March 15, 2021.

- Mavorixafor and ibrutinib exposures were consistent with previous single-agent studies[10,14]
- No apparent drug–drug interactions between mavorixafor and ibrutinib were observed

Mavorixafor With Ibrutinib Induces Mobilization of Leukocytes

Figure 4. Mobilization of Leukocytes With Mavorixafor Exposure[a]



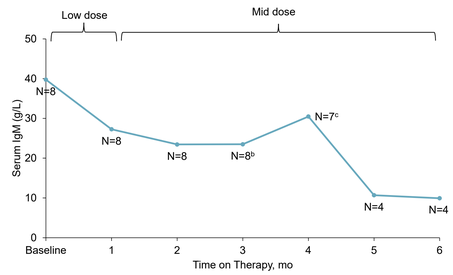
[a]Interim early data analysis performed with data cutoff at April 15, 2021.

- Mavorixafor exposures tracked with increases in key WBC counts in all patients (Figure 4)

Results (continued)

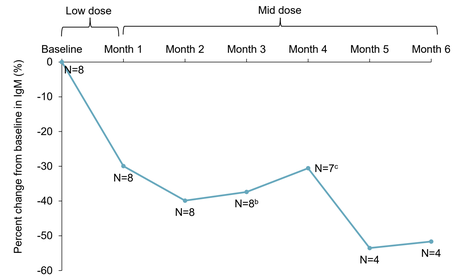
Decrease in Serum IgM Levels Over Time During Dose Escalation[a]

Figure 5A. Median Serum IgM Levels



- Median absolute serum IgM levels decreased to 9.93 g/L (N=4) (range 0.87–37.36 g/L) at 6 months from pretreatment levels of 23.56 g/L (N=4) (Figure 5A)

Figure 5B. Median Percentage Change From Baseline in IgM Levels

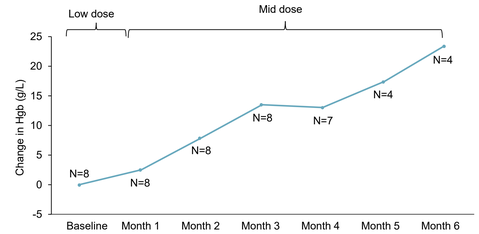


- 2 of 4 patients at 6 months had ≥50% reduction in serum IgM from baseline; 1 of 4 patients at 6 months had ≥ 90% reduction in serum IgM from baseline and had absolute IgM levels within normal range (Figure 5B)

IgM, immunoglobulin M
[a]Interim early data analysis performed with data cutoff at April 15, 2021.
[b]IgM data of Patient 105-001 collected on May 10, 2021, were used to ensure 3 months' follow-up time.
[c]Participant 106-001 study treatment withheld due to an AE the week prior to month 4 IgM sample collection.

Median Hgb Levels Increased Toward Normal Over Time[a]

Figure 6. Median Change From Baseline in Hgb[b]



- Patients with pretreatment Hgb below normal had increases in Hgb during treatment; Hgb levels approached normal levels
- Median Hgb increased by >20 g/L for patients on treatment for 6 cycles (n=4) (Figure 6)

Hgb, hemoglobin
[a]Interim early data analysis performed with data cutoff at April 15, 2021.
[b]Hgb data of Patient 105-001 collected on May 7, 2021, were used to ensure 3 months' follow-up time.

- All patients experienced reduction in IgM levels and no patients progressed (as defined by International Workshop on Waldenström's Macroglobulinemia, IWWM) while on treatment
- Additional data including clinical response based on IWWM criteria are expected to be presented later in 2021

Conclusions

- Mavorixafor in combination with ibrutinib has been well tolerated in WM patients with *MYD88* and *CXCR4* mutations, with cohorts completing the low (200 mg) and mid (400 mg) QD levels; dose escalation at the highest (600 mg) QD level continues
- Mavorixafor and ibrutinib exposures were consistent with previous single-agent studies, suggesting no drug–drug interactions, and mavorixafor exposures tracked with increases in key WBC counts
- Combination of mavorixafor with ibrutinib led to a rapid and clinically important decrease in IgM levels and increase in Hgb levels
- Further follow-up of our ongoing study will help define the potential of combination therapy (mavorixafor and ibrutinib) to improve clinical response to BTKi in patients with *MYD88* and *CXCR4* mutations

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