A PHASE 2 STUDY OF BOMEDEMSTAT (IMG-7289), A LYSINE-SPECIFIC DEMETHYLASE-1 (LSD1) INHIBITOR, FOR THE TREATMENT OF MYELOFIBROSIS (MF)

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INTRODUCTION

Bomedemstat (IMG-7289) is an inhibitor of lysine-specific demethylase-1 (LSD1), an epigenetic regulator critical for self-renewal of malignant myeloid cells and the differentiation of myeloid progenitors. LSD1 with GFI1b licenses maturation of progenitors to megakaryocytes and enables their normal function. In mouse models of MPNs (*Mpl*^{W515L}, *JAK2*^{V617F}), LSD1 inhibition improved peripheral cell counts, spleen volumes, inflammatory cytokines, mutant allele frequencies, marrow fibrosis and overall survival (Jutzi *et al.* 2018).

Based on these data, Bomedemstat was granted FDA Fast-Track status for the treatment of myelofibrosis and essential thrombocythemia.

OBJECTIVES

This multi-center, open-label Phase 2 study evaluated the safety and pharmacodynamics of bomedemstat administered orally once-daily in adult patients with high or intermediate-2 risk MF who were resistant to or intolerant of ruxolitinib.

METHODS

The primary objectives were safety, PK and spleen volume (SV) reduction. Other endpoints included reductions in inflammatory cytokines, total symptom scores (TSS) and bone marrow (BM) fibrosis. Key inclusion criteria included intermediate-2 or high risk (DIPSS) patients with platelet count ≥100K/µL.

Patients in the dose-range finding study (N=18) were treated daily for 12 weeks followed by a washout period of up to 28 days during which imaging and bone marrow assessments were made. Patients in the Phase 2b study (N=18) were treated daily for 24 weeks. Abdominal imaging to measure SV was performed after every 12 weeks of treatment. The MPN10 responses were submitted at each clinic visit. Dosing was tailored using platelet count as a marker of bomedemstat activity on megakaryocyte function. Phase 2a patients started at the presumed *sub*-therapeutic dose of 0.25 mg/kg/d and were up-titrated weekly until the platelet count rested between 50 and 100K/µL. Phase 2b patients started at 0.5 mg/kg/d and were up-titrated until platelet counts rested between 50 and 75K/µL.

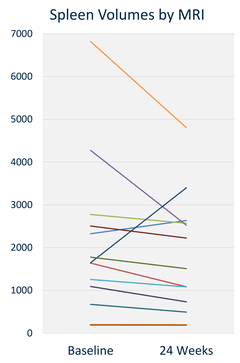
RESULTS

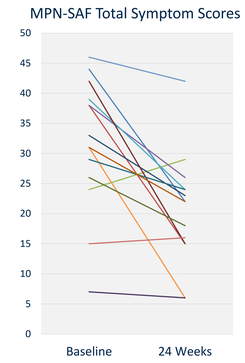
This preliminary analysis includes 36 patients (Phase 2a + Phase 2b). 47% had PMF, 36% PET-MF, 17% PPV-MF. The median patient age was 70 years (34-90) with 61% males. 61% were classified as high risk and 63% had high risk mutations.

The Phase 2a was a dose-range finding study focused on safety and PK. Dose-limiting toxicities were not observed and a maximum tolerated dose (MTD) was not identified. 78% (14/18) completed the 12-week Phase 2a study. The median duration of treatment was 165 days (range 27-562 days).

To study the efficacy of bomedemstat at more therapeutic exposures, changes in the protocol for the Phase 2b portion included higher starting dose, the elimination of the washout period and extension of the study from 12 to 24 weeks. Of the 18 Phase 2b patients, seven remain on-study. Five patients withdrew for AEs, two of which – mucositis and fatigue --were deemed related to bomedemstat. Other early terminations included a patient who died from a fall unrelated to drug, one with progressive disease, one for lack of clinical benefit and two withdrew consent.

Of those who reached 24 weeks, 83% of evaluable patients (10/12) demonstrated a reduction in spleen volume (Figure below left). 86% (N=14) experienced improvement in symptom scores (Figure below right). 71% of patients had a stable or improved BM fibrosis score. 70% (N=30) of patients had stable or improved hemoglobin. >90% of patients with elevated cytokines, e.g., IL-8, showed significant reductions. The median duration of treatment stands at 142 days (21-562) in this ongoing study.





SAFETY

- No dose limiting toxicities
- No deaths on study related to study drug
- Out of 723 AEs reported, 215 were attributed to Bomedemstat
- 4 SAEs attributed to Bomedemstat (all Grade 3)
    - Painful splenomegaly
    - Headache
    - Heart failure
    - Rectal bleeding
- The most common AE related to bomedemstat was dysgeusia (33%)
- Overall, regarded as safe and well tolerated

CONCLUSIONS

- The first-in-class LSD1 inhibitor bomedemstat (IMG-7289) is safe and well tolerated in patients with advanced MF
- Bomedemstat monotherapy has clinical activity in patients with advanced MF
    - Improvements in symptoms, spleen volumes, anemia, and bone marrow fibrosis have been demonstrated
- Phase 2b study enrollment is ongoing in the US, UK and EU
- A similar study of bomedemstat in ET is open (NCT04254978)
- Based on pre-clinical data, a combination study of bomedemstat and a JAK inhibitor is planned

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