AK002, a Novel Humanized Monoclonal Antibody to Siglec-8, Inhibits Mast Cell Activity and Depletes Eosinophils in Ex Vivo Bone Marrow Tissue from Patients with Systemic Mastocytosis

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**BACKGROUND**

- Systemic Mastocytosis (SM) is a rare disease characterized by the clonal proliferation and accumulation of mast cells in the bone marrow, respiratory and gastrointestinal tracts, and organs such as the skin, liver, spleen, and brain.
- Common symptoms include pruritus, flushing, headache, cognitive impairment, fatigue, diarrhea, abdominal pain, hypotension and skin lesions, as well as an increased risk for osteoporosis and anaphylaxis.
- SM is currently managed with antihistamines, cromolyn sodium, and leukotriene blocking agents, which lack efficacy in many patients.
- In addition, glucocorticoids can provide temporary relief in some cases, however long-term treatment with steroids is not appropriate due to their many side effects.

**METHODS**

- **Patient numbers**: 12 healthy subjects and 7 SM patients
- **Bone marrow aspirates and blood**: Obtained from patients
- **AK002 Single dose**: SD from 1 SM patient
- **AK002 Antibody**: Reduced the expression of SM markers, CD25 and CD69 on bone marrow mast cells from SM patients
- **CD25 and CD69 expression**: Significantly elevated on bone marrow mast cells from SM patients consistent with previous experiments
- **Bone marrow aspirates and blood**: Obtained from patients
- **AK002 significantly reduced ex vivo bone marrow eosinophils, but not mast cells, from SM patients consistent with previous experiments

**RESULTS**

- **Siglec-8 is highly expressed on mature bone marrow eosinophils from SM patients**
- **AK002 significantly reduced ex vivo bone marrow eosinophils, but not mast cells, from SM patients consistent with previous experiments

**CONCLUSIONS/DISCUSSION**

- **Siglec-8 was robustly expressed on diseased mast cell surface markers and decreased mast cell mediators in SM patient bone marrow, suggestive of broad mast cell inhibition**
- **AK002 reduced the expression of cytokines and chemokines in bone marrow that were also elevated in serum of SM patients compared to healthy subjects**
- **Multiple cytokines, including IL-2, 5, 6, 8, 9, 13, 15, 16 and TNFα were significantly elevated in serum of SM patients compared to healthy subjects**

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**Figure 1. AK002 Mechanism of Action**

**Figure 2. AK002 Mechanism of Action**

**Figure 3. SM Patient Bone Marrow Mast Cells Express Siglec-8 and Display a Diseased Phenotype**

**Figure 4. AK002 Significantly Reduced Eosinophils in ex vivo SM Patient Bone Marrow**

**Figure 5. AK002 Reduced the Expression of CD25 and CD69 on ex vivo Bone Marrow Mast Cells from SM Patients**

**Figure 6. AK002 Reduced the Level of Mast Cell-Associated Mediators Produced in Supernatant of Cultured Bone Marrow Cells**

**Figure 7. SM Patients Display Elevated Levels of Serum Cytokines and Chemokines Compared to Healthy Subjects**