Safety and Efficacy Data of AK002, an Anti-Siglec-8 Monoclonal Antibody, in Patients with Indolent Systemic Mastocytosis (ISM): Results from a First-in-Human, Open-label Phase 1 Study

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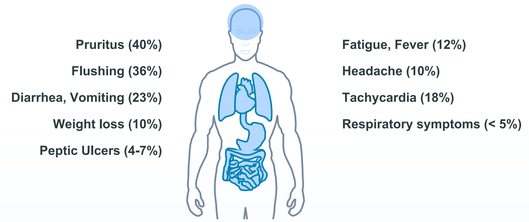
BACKGROUND

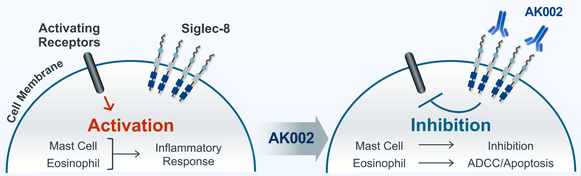
- Systemic mastocytosis (SM) is a group of proliferative disorders characterized by mast cell accumulation and activation in multiple organ systems: most commonly in bone marrow; with or without skin involvement
- Indolent Systemic Mastocytosis (ISM) is the most common form of SM, estimated to affect ~30,000 people in the United States
- Although patients with ISM present with a stable or slowly progressing clinical course, the symptoms associated with this disease significantly affect quality of life

Figure 1. Common ISM Symptoms



- No approved therapies – current treatment options (steroids, antihistamines, and mast cell stabilizers) have limited efficacy
- There is a significant medical unmet need for novel therapies

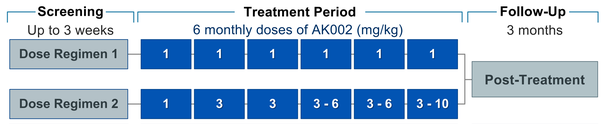
Figure 2. AK002 Mechanism of Action



- Siglec-8 is an inhibitory receptor selectively expressed on human eosinophils and mast cells, and therefore represents a novel target for the treatment of ISM
- AK002 is a novel, humanized, non-fucosylated IgG1 monoclonal antibody to Siglec-8
- Engagement of Siglec-8 receptor by AK002 triggers:
  - Antibody dependent cell mediated cytotoxicity (ADCC) against eosinophils (blood)
  - Inhibition of mast cells and apoptosis of tissue eosinophils (tissue)
- This Phase 1 study evaluated single ascending doses and multiple doses of AK002 in ISM
- Here we present results from the multiple dose arm of the study

METHODS

Figure 3. Study Design



- Confirmed ISM diagnosis
- Active symptoms:
  - Flushing
  - Pruritus
  - Diarrhea
  - Anaphylaxis

Primary Objective:
- Safety and tolerability of multiple doses of AK002

Secondary Objectives:
- Patient reported outcomes:
  - Mastocytosis Symptom Questionnaire (MSQ)
  - Mastocytosis Activity and Symptom Severity (MAS)
  - Mastocytosis Quality of Life (MC-QoL)

- Monthly visits
- Safety, tolerability, PD, and efficacy measures are assessed

INCLUSION CRITERIA
- Adults (18 to 85 years old)
- Confirmed diagnosis of ISM based on World Health Organization (WHO) criteria
- Presence of at least 1 of the following ISM related symptoms:
  - Flushing (at least 1 episode per week)
  - Pruritus (minimum MAS score of 4)
  - Diarrhea (minimum MAS score of 4)
  - Anaphylaxis (at least 1 episode [grade 2 or higher] within the last 12 months)

EXCLUSION CRITERIA
- Presence of an associated hematologic non-mast cell lineage disorder or mast cell leukemia
- Use during the 30 days before screening of omalizumab (Xolair®), immunosuppressive drugs, or systemic corticosteroids with a daily dose >10 mg prednisone or equivalent

Figure 4. Daily Symptom Intensity PRO (MSQ and MAS)

Symptoms
1. Itching
2. Hives
3. Flushing
4. Abdominal Pain
5. Diarrhea
6. Headache
7. Fatigue
8. Difficulty Concentrating
9. Muscle Pain
10. Joint Pain

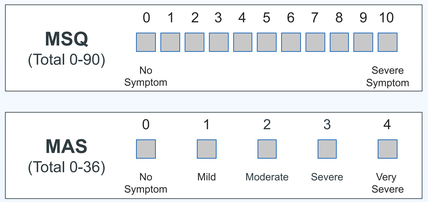


Figure 5. Biweekly Quality of Life Assessment (MC-QoL)

Domains
1. Symptoms
2. Social Life / Functioning
3. Emotions
4. Skin

Figure 5. MC-QoL PRO has 27 questions to assess quality of life improvements in 4 domains: Symptoms (diarrhea, fatigue, headache, muscle or joint pain, difficulty concentrating; limited sleep, tired during the day due to not sleeping well; feeling less capable, lack of motivation), Social Life/Functioning (limited in daily life in school/university/work, sexual activity, leisure time, relationships; change of food/drink, burdened by symptoms, choice of wear restricted; uncomfortable in public), Emotions (afraid of allergic reaction, wrong treatment, worsening of mastocytosis; feeling alone with illness, concerned, sad), and Skin (itching, skin redness/swelling, flushing). All domain scores and the total score are linearly transformed to a 0-100 scale

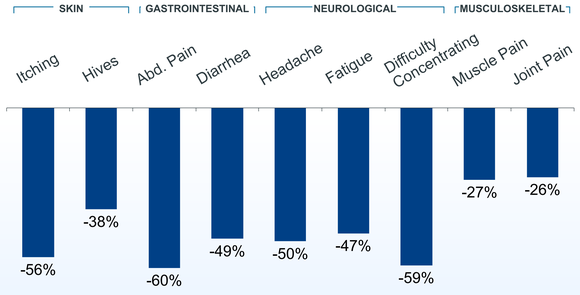
RESULTS

Table 1. Baseline Characteristics

	Multi-dose Patients (N=12)
Age, Median Years (Range)	47 (34-66)
Female, %	75%
White, %	100%
BMI, Median (Range)	26 (20-39)
MSQ Total Symptom Score (0-90), Mean (Median)[a]	32.1 (33.3)
MAS Total Symptom Score (0-36), Mean (Median)[b]	14.2 (15.7)
MC-QoL Total Score (0-108), Mean (Median)[b]	59.5 (64.8)

a 8 patients have recorded baseline MSQ
b n=11

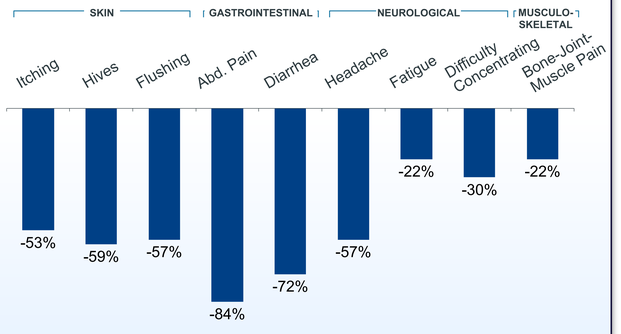
Figure 6. Improvement in Symptoms (MSQ)



Median MSQ % Δ from Baseline to Week 21-22

8 patients included in MSQ analysis. 3 patients from multi-dose cohort enrolled before MSQ PRO was available
Mean baseline: itching (3.7), hives (4.2), abdominal pain (3.4), diarrhea (2.9), headache (3.7), fatigue (5.1), difficulty concentrating (3.9), muscle pain (3.6), joint pain (3.4)

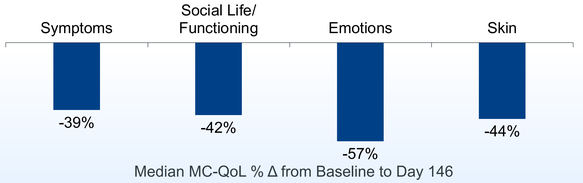
Figure 7. Improvement in Symptoms (MAS)



Median MAS % Δ from Baseline to Week 21-22

Mean baseline: itching (1.8), hives (1.6), flushing (1.7), abdominal pain (1.4), diarrhea (1.0), headache (1.5), fatigue (2.2), difficulty concentrating (1.6), bone-joint-muscle pain (2.0)

Figure 8. Improvement in Quality of Life (MC-QoL)

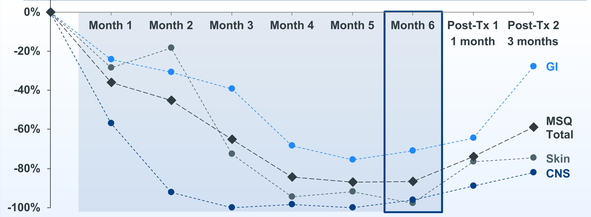


Median MC-QoL % Δ from Baseline to Day 146

Mean baseline: symptoms (64), social life/function (69), emotions (48), skin (51)

Figure 9. ISM Patient Case Study

Medical History
- 43 year old woman
- Diagnosed with ISM in 1993
- Suffered from severe ISM symptoms for over 20 years despite treatment
  - History of ranitidine, fexofenadine, and steroids use
- Chief symptoms were gastrointestinal, headache and itchy skin



- **98% reduction in skin domain** (flushing, itching, and hives)
- **96% reduction in CNS domain** (headache, difficulty concentrating, fatigue)
- **71% reduction in GI domain** (abdominal pain and diarrhea)

Safety Summary

- Generally well-tolerated
- The most common drug-related adverse event was infusion-related reactions all of which were mild to moderate
  - These may include feeling of warmth, headache, erythema, fatigue, and dizziness
- No drug related serious adverse events

CONCLUSIONS

- AK002, a humanized Siglec-8 antibody, demonstrates substantial improvement across all ISM symptoms
- Significant and consistent improvements reported in symptoms and quality of life using three different PROs
- AK002 was generally well-tolerated
- These results suggest AK002 may be a novel treatment for ISM

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