

1. BACKGROUND

- Inclusion body myositis (IBM), a relentlessly progressive autoimmune skeletal muscle disease, has no effective available pharmacological therapy. A prominent pathological feature of IBM is highly differentiated effector CD8⁺ cytotoxic T cells invading non-necrotic myofibers.¹ These cells are relatively resistant to apoptosis and express markers including killer cell lectin-like receptor G1 (KLRG1).^{2,3}
- ABC008, a first-in-class humanized afucosylated monoclonal antibody therapeutic, binds to KLRG1 to selectively deplete highly differentiated T cells, while sparing other blood cell populations, in particular naive, central memory, and regulatory T cells (Tregs).
- ABC008 has been designed to treat diseases mediated by highly cytotoxic T cells, including IBM², T cell large granular lymphocytic leukemia (T-LGLL), and mature T and NK cell malignancies. IBM⁴ and rheumatoid arthritis⁵ may each coexist with T-LGLL and share similar expansions of blood T cell large granular lymphocytes (T-LGLs) which are highly cytotoxic T cells.
- We report the preliminary safety, pharmacokinetics (PK), and pharmacodynamics (PD) in the first three cohorts (N=3 each) of an ongoing single ascending dose (SAD), first-in-human Phase 1 study of ABC008 administered subcutaneously (SC) to patients with IBM (NCT04659031).

2. KLRG1⁺ CELLS AND ABC008 MECHANISM OF ACTION

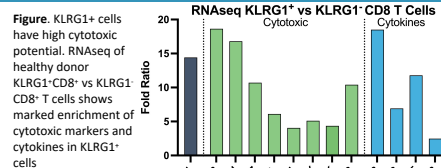
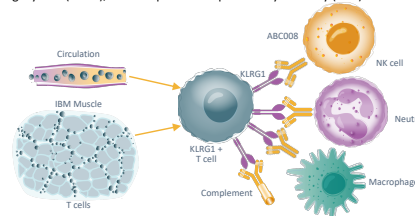


Figure. ABC008 binds to KLRG1⁺ cells and depletes them via immune-mediated mechanisms of antibody dependent cell-mediated cytotoxicity (ADCC), phagocytosis (ADCP), and complement dependent cytotoxicity (CDC).



3. TRIAL OBJECTIVES AND DESIGN

- Objectives for assessment of ABC008:**
 - Primary: Evaluate safety and tolerability
 - Secondary: Evaluate PK and determine Phase 2 doses
 - Exploratory: Evaluate PD and disease severity
- Inclusion criteria:**
 - IBM diagnosis (ENMC Criteria 2011)
- Dose cohorts of a single subcutaneous (SC) ABC008 dose**
 - 0.1 mg/kg
 - 0.5 mg/kg
 - 2.0 mg/kg (ongoing)
- Safety, PK, and PD Assessments:**
 - Safety: Adverse events (AEs), vital signs, physical examinations, electrocardiograms (ECGs), and laboratory tests including selected viral loads
 - PK and PD (flow cytometry)

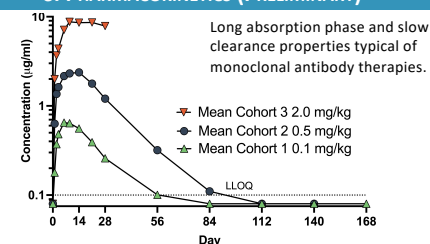
4. POPULATION CHARACTERISTICS

- Gender: 9 male, 2 females
- Age mean (range): 64.9 (51-77) years
- Disease duration mean (range): 8.5 (2-17) years

5. SAFETY OBSERVATIONS

- Self-limited fever, rigors, flushing, nausea, or headache within 24 hours after infusion in 1 of 3 participants at 0.5 mg/kg and 2 of 5 participants at 2.0 mg/kg, likely reflecting acute cell lysis in the setting of significant highly cytotoxic KLRG1⁺CD8⁺ cell burden
- 1 participant with history of recurrent oral herpes with self-limited AE of mild oral herpes ~4 months post ABC008 0.1 mg/kg
- No drug-related severe or serious AEs
- No lymphopenia or neutropenia

6. PHARMACOKINETICS (PRELIMINARY)



7. PHARMACODYNAMICS – DEPLETION OF HIGHLY CYTOTOXIC KLRG1⁺CD8⁺ T CELLS

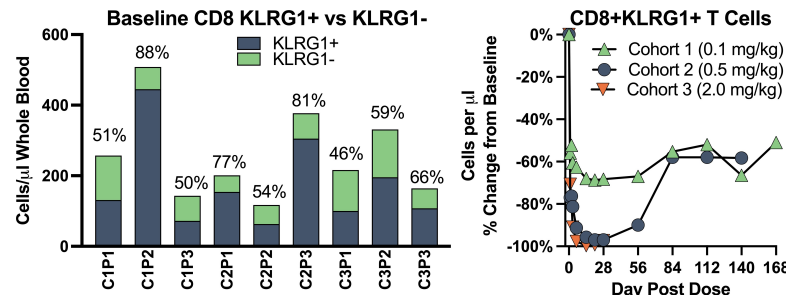


Figure. (Left) Baseline CD8 and KLRG1⁺CD8 T cells in 9 patients (e.g., C1P1 = cohort 1, patient 1). (Right) Single SC dose of ABC008 results in sustained depletion of CD8⁺KLRG1⁺ T cells (Day 28 depletion mean 68%-97%) through at least Day 56 Cohort 1 N=3 to Day 168; Cohort 2 N=3 to Day 140; Cohort 3 N=3 to Day 28

8. SPARING OF PROTECTIVE REGULATORY T CELLS AND CENTRAL MEMORY T CELLS

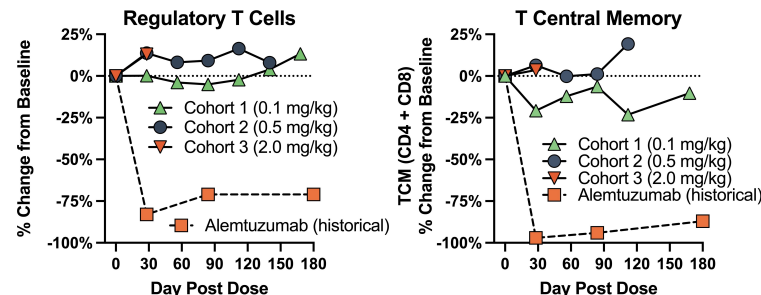


Figure ABC008 spares protective regulatory T cells and central memory T cells, in contrast to the T cell depleter alemtuzumab (based on published historical data from multiple sclerosis trials) Cohort 1 N=3 to Day 168; Cohort 2 N=3 to Day 140; Cohort 3 N=3 to Day 28

CONCLUSIONS

In IBM patients, single SC doses of ABC008 0.1, 0.5, and 2.0 mg/kg selectively depleted KLRG1⁺ CD8⁺ T cells. This along with the preliminary safety profile supports further development of ABC008.

REFERENCES

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