Depletion of KLRG1⁺ T cells in a First-in-Human Clinical Trial of ABC008 in Inclusion Body Myositis (IBM)

Poster L07

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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 naïve, central memory, and regulatory T cells (Tregs).
- ABC008 has been designed to treat diseases mediated by highly cytotoxic T cells, including IBM[2], T cell large granular lymphocytic leukemia (T-LGLL), and mature T and NK cell malignancies. IBM[4] and rheumatoid arthritis[5] 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 *in vivo* cynomolgus monkey depletion of KLRG1⁺ T cells by subcutaneous (SC) administration of ABC008.
- We also report the preliminary safety, pharmacokinetic (PK), pharmacodynamics (PD), and efficacy in the first cohort (N=3) of an ongoing single ascending dose (SAD), first-in-human Phase 1 study of ABC008 in patients with IBM (NCT04659031).

2. ABC008 Mechanism of Action and Nonclinical Data

Figure 1. ABC008 Mechanism of Action: ADCC, ADCP, and CDC

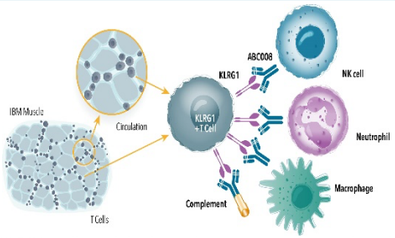


Figure 1. ABC008 binds to KLRG1⁺ cells and depletes them via immune-mediated mechanisms of antibody dependent cell-mediated cytotoxicity (ADCC) and phagocytosis (ADCP) and complement dependent cytotoxicity (CDC).

Figure 2. ABC008 SC Depletion of Cynomolgus Monkey CD8⁺ KLRG1⁺ T Cells

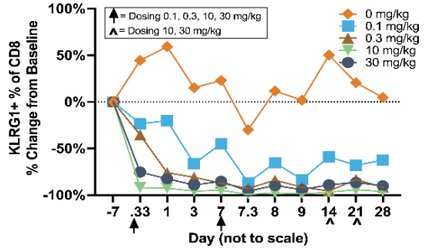


Figure 2. 1-month toxicology study of ABC008 SC in cynomolgus monkey.

3. Clinical 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 efficacy
- **Inclusion criteria:**
  - IBM diagnosis (ENMC Criteria 2011)
  - IBM functional rating scale (IBMFRS) ≤38
- **Planned dose cohorts of a single dose of ABC008 SC**
  - 0.1 mg/kg (completed)
  - 0.5 mg/kg (enrolling)
  - 2.0 and 5.0 mg/kg (planned)
- **Assessments:**
  - Safety: Adverse events (AEs), vital signs, physical examinations, electrocardiograms (ECGs), and laboratory tests including herpes viruses' viral loads
  - PK and PD (flow cytometry)
  - Efficacy: IBMFRS, IBM functional assessment (sIFA), modified Timed Up and Go (mTUG), manual muscle testing (MMT12).

4. First Cohort Demographics

Table 1

N	AGE (years) (Mean ± SD)	MALE SEX (n [%])	WHITE RACE (n [%])	WEIGHT (kg) (Mean ± SD)	IBM DISEASE DURATION (years) (Mean ± SD)
3	64 ± 11.4	3 (100)	3 (100)	94.5 ± 16.06	9.8 ± 5.79

5. First Cohort Safety Observations

- No moderate or severe or serious AEs, discontinuations due to AEs, or deaths
- No significant findings on vital signs, ECGs, or clinical laboratories other than mild reduction in muscle enzymes (e.g., creatine kinase) and expected changes in lymphocyte counts.

We thank investigators, site staff, and especially the patients who have contributed their time and efforts to this study.

References

1. Engel AG, et al. Ann Neurol 1984.
2. Greenberg SA. Nat Rev Rheum 2019.
3. Greenberg SA, et al. Brain 2019.
4. Greenberg SA, et al. Brain 2016.
5. Gorodetskiy VR, et al. Rheumatol Int 2021.

6. PK and PD: ABC008 0.1 mg/kg SC in IBM Patients 001, 002, 003

Figure 3. Depletion of CD8⁺KLRG1⁺ T Cells

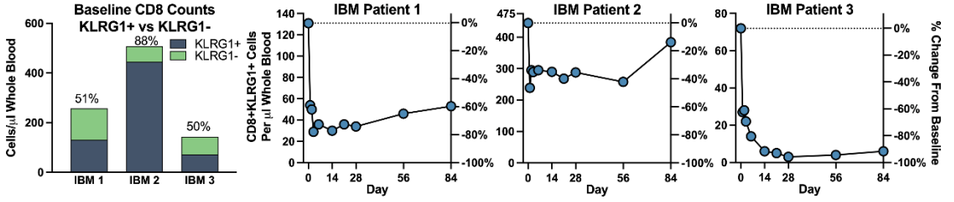


Figure 4. Depletion of CD8⁺CD57⁺ T-LGLs

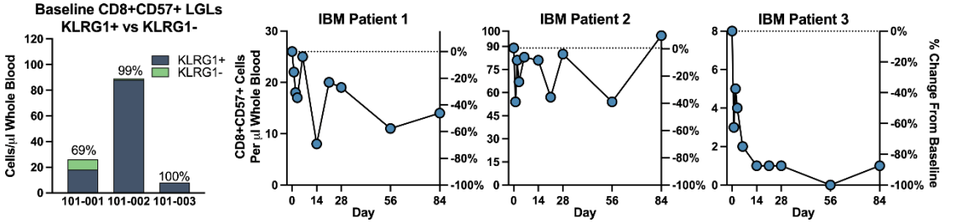


Figure 5. Regulatory T Cell Sparing Tregs

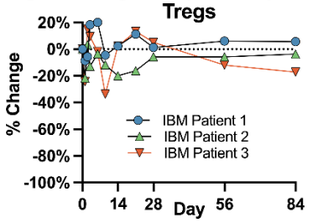
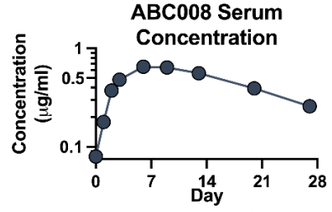


Figure 6. Pharmacokinetics



Figures 3-5: ABC008 results in CD8⁺KLRG1⁺ T cell (mean 68%, 35-96%) and T-LGL (mean 41%, range 5-93%) depletion at Day 28, sustained through at least Day 56, with sparing of Tregs. KLRG1⁺ cells comprised 50-88% of blood CD8⁺ T cells and 69-100% of blood T-LGLs at Baseline. **Figure 6:** Following SC administration, ABC008 displays a long absorption phase and slow clearance properties typical of monoclonal antibody therapies.

7. First Cohort Disease Severity Measures

Table 2

Patient No.	sIFA	IBMFRS	mTUG (sec)	MMT12
001	20	35	5.27	201
002	71	25	18.0	173
003	57	30	6.47	200

Figure 7. Disease Severity Baseline + Changes

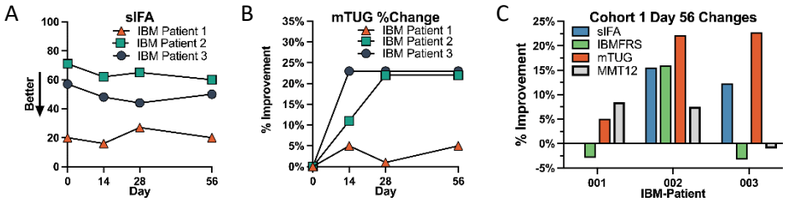


Figure 7. Disease severity measures. (A, B) sIFA absolute score changes and mTUG percent changes from baseline over 56 days. (C) Outcome summary changes at Day 56.

- Preliminary evaluations demonstrated functional improvement, as measured by several IBM efficacy assessments
- The most pronounced improvements were seen in Patient 002, who had the greatest level of IBM disease severity at baseline

CONCLUSIONS

- **In IBM patients, a single SC dose of ABC008 0.1 mg/kg selectively depleted KLRG1⁺ CD8⁺ T cells with no apparent safety signals**
  - **ABC008 depleted T-LGLs**
  - **ABC008 did not deplete T regs**
- **The second ABC008 dose cohort (0.5 mg/kg) is now enrolling**
  - **Preliminary data show a dose response for T-LGL depletion**
- **Based on these results, a study to evaluate ABC008 for the treatment of T-LGLL is planned**
- **Evaluation of additional dose cohorts of ABC008 and KLRG1⁺ T cell and T-LGL depletion over time in IBM patients will inform dose and dose schedule for ABC008 in upcoming studies.**

Study sponsored by Abcuro, Inc.