Ulviprubart Pharmacokinetics, Pharmacodynamics, and Safety: Phase 1 Study Results in Patients With Inclusion Body Myositis

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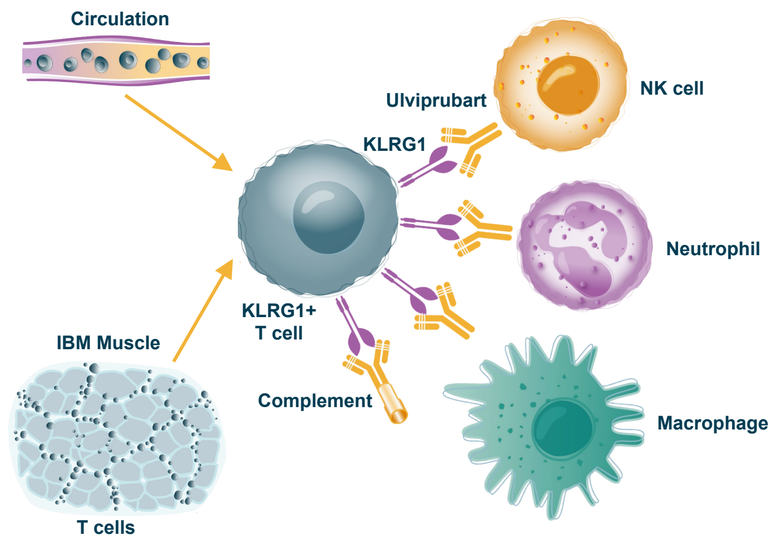
Introduction

- Inclusion body myositis (IBM) is a rare, progressive autoimmune disease characterized by invasion and destruction of healthy muscle by highly differentiated cytotoxic CD8+ T cells[1,2]
  - A mean of 70−82% of the blood and mean of 85% of the myofiber-invading and 79% of the myofiber surface CD8+ T-cell populations in IBM have been reported to express the cell surface receptor killer cell lectin-like receptor G1 (KLRG1)[3-5]
  - Patients with IBM can experience profound functional impairment, including loss of grip strength, difficulty walking, and/or dysphagia, which can negatively impact their mental health and lead to caregiver dependency[1,2,6,7]
- As no disease-modifying therapies exist for patients with IBM,[8] there is a high unmet need for a safe and efficacious therapy
- Ulviprubart, a monoclonal antibody that targets KLRG1, is designed to selectively deplete cytotoxic KLRG1+ T cells and may have clinical activity in patients with IBM (**Figure 1**)

Figure 1. Schematic of ulviprubart-mediated KLRG1+ T-cell depletion by NK cells, neutrophils, macrophages, and complement



IBM, inclusion body myositis; KLRG1, killer cell lectin-like receptor G1; NK, natural killer.

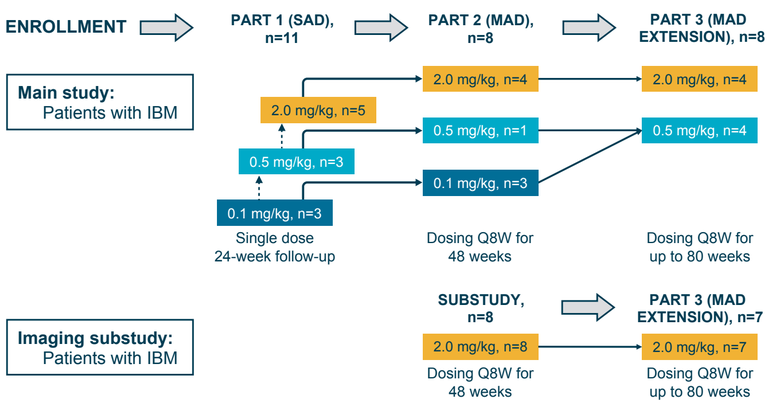
- Here, we describe pharmacodynamic (PD), pharmacokinetic (PK), and safety results from a first-in-human study of ulviprubart in patients with IBM

Methods

Study design and patients

- In this phase 1, open-label study (NCT04659031), initial patients received subcutaneous ulviprubart (0.1, 0.5, or 2.0 mg/kg) as a single dose (Part 1 single-ascending dose [SAD]) prior to dosing every 8 weeks (Q8W) approximately 6−12 months later, while later patients received 2.0 mg/kg ulviprubart Q8W; patients received ulviprubart for up to 18 months (**Figure 2**)
- Key eligibility criteria included formal diagnosis of IBM[9] and age ≥40 years

Figure 2. Study design and patient disposition



In Part 1 (SAD), dose cohorts opened sequentially following review of each by a Safety Monitoring Committee. Patients who completed Part 1 were eligible to participate in Part 2 (MAD) at the same dose level. Patients who completed Part 2 were eligible to participate in Part 3 (MAD Extension); patients who received 0.1 and 0.5 mg/kg ulviprubart in Part 2 will receive 0.5 mg/kg ulviprubart in Part 3, and patients who received 2.0 mg/kg ulviprubart in Part 2 will continue on 2.0 mg/kg ulviprubart in Part 3. IBM, inclusion body myositis; MAD, multiple-ascending dose; Q8W, every 8 weeks; SAD, single-ascending dose.

Assessments and analyses

- PD, PK, and safety results were analyzed descriptively
- PD assessments evaluated blood immune cells, including KLRG1-expressing CD8+ and CD4+ T cells, regulatory T cells, and B cells
- PK parameters for ulviprubart included: Maximum observed concentration (C_{max}), time to maximum observed concentration (T_{max}), terminal half-life ($t_{1/2}$), area under the concentration-time curve (AUC), apparent clearance (CL/F), and apparent terminal volume of distribution (Vz/F)
- PD and PK analyses were performed as follows:
  - Part 1 (SAD):
    - Within 2 hours prior to ulviprubart administration on day 1 (predose)
    - After ulviprubart administration: On days 2, 3, 4, and 11, at weeks 1, 2, 3, and 4, then every 4 weeks thereafter, and at the end of study (EOS)
  - Part 2 (MAD) and the substudy:
    - At screening and predose on day 1 and at weeks 8, 16, 24, 32, 40, and 48 (end of MAD study)
    - After administration at weeks 1, 4, 12, and at the EOS
  - Part 3 (MAD Extension):
    - Predose on day 1 (ie, week 48 above)
    - After ulviprubart administration (up to 18 months): On days 113 (week 16), 122, and 178
- Safety assessments included treatment-emergent adverse event (TEAE) monitoring, electrocardiograms, laboratory data, vital signs, and physical examinations; a panel of common herpes viruses were monitored throughout the trial, and other viral load testing was performed as medically indicated

Results

Patient demographics and baseline characteristics

- Nineteen patients were enrolled (0.1 mg/kg, n=3; 0.5 mg/kg, n=3; 2.0 mg/kg, n=13)
  - Demographics and baseline characteristics are shown in **Table 1**

Table 1. Patient demographics and baseline characteristics

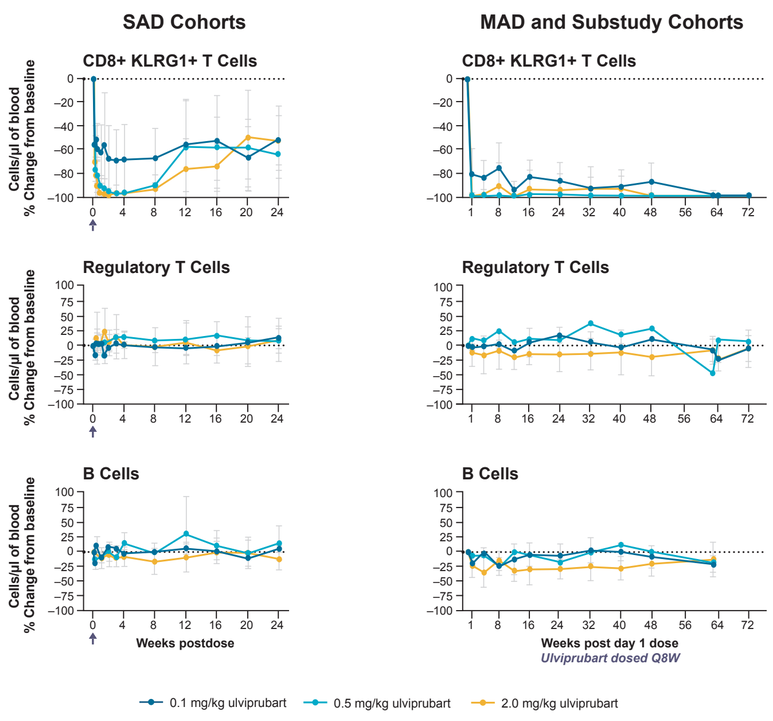
	Part 1 (SAD) n=11	Part 2 (MAD) n=8	Substudy n=8
Age, median (range), years	64 (51−77)	67 (52−77)	69 (46−79)
Male, n (%)	9 (82)	7 (88)	6 (75)
Race			
White, n (%)	10 (91)	8 (100)	7 (88)
Disease duration, median (range), years	7.2 (0.2−17)	7.3 (3.3−18)	6.4 (1.4−18)

MAD, multiple-ascending dose; SAD, single-ascending dose.

Pharmacodynamic effects of ulviprubart

- Depletion of peripheral CD8+ KLRG1+ and CD4+ KLRG1+ T cells was evident on day 1 postdose, with mean CD8+ KLRG1+ T-cell maximum depletions of 69%, 97%, and 98% achieved by weeks 2–3 after a single dose of 0.1, 0.5, and 2.0 mg/kg ulviprubart, respectively, in Part 1 (SAD) (**Figure 3**)
  - Depletion was sustained with up to 72 weeks of MAD dosing (**Figure 3**)
- Protective regulatory T cells and B cells (cells that do not express KLRG1) were preserved (**Figure 3**)

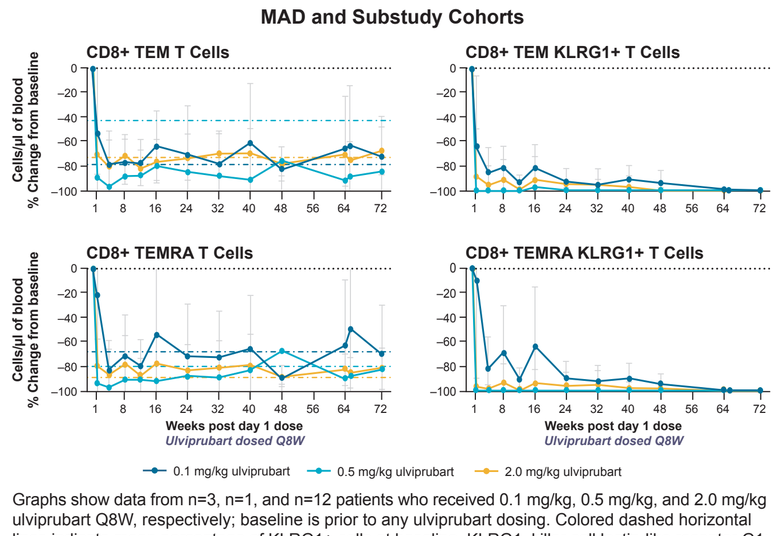
Figure 3. Mean (SD) changes in immune cells over time (SAD; MAD and substudy cohorts)



Graphs on the left show data from n=3, n=3, and n=5 patients who received a single dose of 0.1 mg/kg, 0.5 mg/kg, or 2.0 mg/kg ulviprubart, respectively; baseline is prior to ulviprubart dosing, and purple vertical arrow indicates time of ulviprubart administration. Graphs on the right show data from n=3, n=1, and n=12 patients who received 0.1 mg/kg, 0.5 mg/kg, and 2.0 mg/kg ulviprubart Q8W, respectively; baseline is prior to any ulviprubart dosing. One B cell assessment was taken between weeks 48 and 72 in the MAD extension. KLRG1, killer cell lectin-like receptor G1; MAD, multiple-ascending dose; Q8W, every 8 weeks; SAD, single-ascending dose.

- Effector CD8+ T-cell populations (T effector memory cell [TEM] and TEMs expressing CD45RA [TEMRA]) were depleted to the extent of their KLRG1 expression (**Figure 4**)

Figure 4. Mean (SD) changes in immune cells over time (MAD and substudy cohorts)

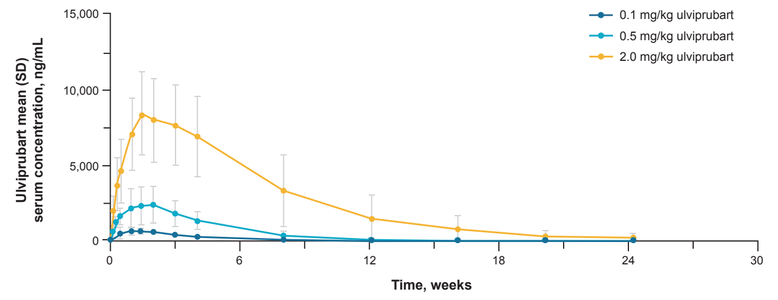


Graphs show data from n=3, n=1, and n=12 patients who received 0.1 mg/kg, 0.5 mg/kg, and 2.0 mg/kg ulviprubart Q8W, respectively; baseline is prior to any ulviprubart dosing. Colored dashed horizontal lines indicate mean percentage of KLRG1+ cells at baseline. KLRG1, killer cell lectin-like receptor G1; MAD, multiple-ascending dose; Q8W, every 8 weeks; TEM, T effector memory cell; TEMRA, TEMs expressing CD45RA.

Pharmacokinetics of ulviprubart

- Following a single dose, ulviprubart displayed a long absorption phase, slow clearance, and a $t_{1/2}$ of 21 days (2 mg/kg group) (**Figure 5**)

Figure 5. Serum concentrations of ulviprubart over time after single-dose administration



Safety

- No treatment-related serious TEAEs or discontinuations due to TEAEs were reported (**Table 2**)
- The most common treatment-related TEAE was injection-related reaction; injection-related reactions occurred with 6 of the 208 (3%) total doses of ulviprubart administered across all patients, and those 6 reactions only occurred with the first dose
- No clinically significant reactivations of latent viral infections were observed

Table 2. Safety summary

Adverse events	Patients with IBM, N=19 n (%)
Any TEAE (grade 1 or 2, n=17; grade 3, n=2)	19 (100)
Severe TEAEs (grade 3)	2 (11)
Treatment-related TEAEs (grade 1 or 2)	11 (58)
Severe treatment-related TEAEs	0
Serious TEAEs (grade 1 or 2, n=2; grade 3, n=2)	4 (21)
Treatment-related serious TEAEs	0
Discontinuations due to TEAEs	0
Most common TEAEs (occurring in ≥25% of patients)	
Fall	14 (74)
Injection-related reaction	6 (32)
Pain in extremity	6 (32)
Skin laceration	6 (32)
Upper respiratory tract infection	6 (32)
Arthralgia	5 (26)
Skin abrasion	5 (26)

IBM, inclusion body myositis; TEAE, treatment-emergent adverse event.

Conclusions

- Ulviprubart led to deep and selective depletion of peripheral blood KLRG1+ T cells in patients with IBM in this first-in-human study without impacting regulatory T or B cells
- Ulviprubart displayed PK properties consistent with other therapeutic monoclonal antibodies[10]
- Together with the favorable safety profile, these data support the continued development of ulviprubart

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Disclosures

M Needham, RD Henderson, and C Liang: Abcuro, Inc. − Consultant; **D Soler-Ferran and HJ Wilkins:** Abcuro, Inc. – Employment; **SA Greenberg:** Abcuro, Inc. – Founder; Consultant

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