

Pharmacokinetics, pharmacodynamics, and safety profile of ulivprubart: Results from a 48-week, open-label, phase 1 study in patients with inclusion body myositis

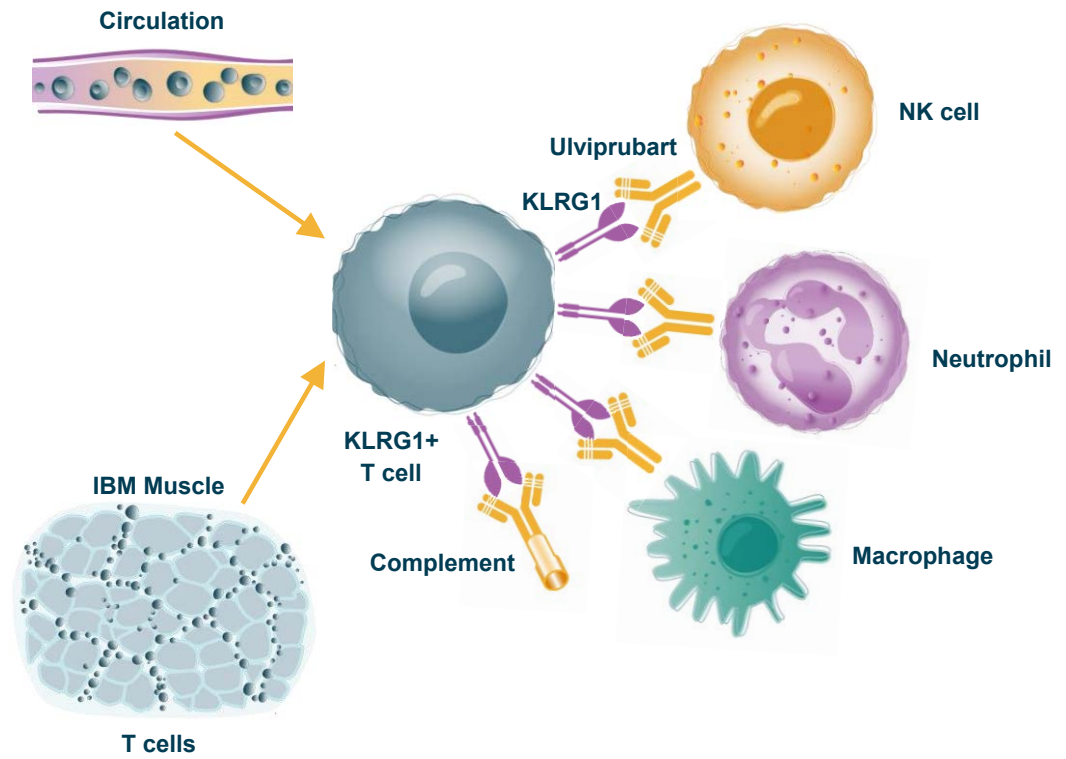
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Introduction

- 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 79% of the muscle myofiber-invading 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
- Ulivprubart, 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 ulivprubart-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.

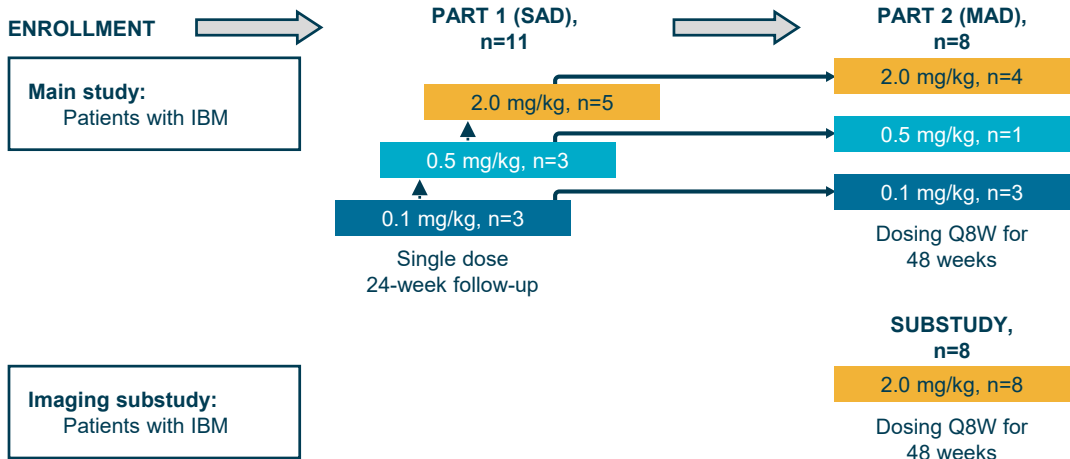
- Here, we describe pharmacokinetic (PK), pharmacodynamic (PD), and safety results from a first-in-human study of ulivprubart in patients with IBM

Methods

Study design and patients

- In this phase 1, open-label study (NCT04659031), initial patients received subcutaneous ulivprubart (0.1, 0.5, or 2.0 mg/kg) as a single dose (Part 1 single-ascending dose [SAD]) and approximately 6–12 months later were dosed once every 8 weeks (Q8W) for up to 48 weeks (Part 2 multiple-ascending dose [MAD]); later patients (in a substudy) received initial multiple dosing of 2.0 mg/kg Q8W for up to 48 weeks (**Figure 2**)
- Key eligibility criteria included formal diagnosis of IBM⁹ 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. IBM, inclusion body myositis; MAD, multiple-ascending dose; Q8W, every 8 weeks; SAD, single-ascending dose.

Assessments and analyses

- PK, PD, and safety results from Part 1 (SAD), Part 2 (MAD), and the substudy were analyzed descriptively
- PK parameters for ulivprubart 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 (V_z/F)
- PD assessments evaluated blood immune cells, including KLRG1-expressing CD8+ and CD4+ T cells, regulatory T cells, and B cells
- PK/PD analyses were performed as follows:
 - Part 1 (SAD):
 - Within 2 hours prior to ulivprubart administration on day 1 (predose)
 - After ulivprubart 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 treatment (EOT)
 - Part 2 (MAD) and the substudy:
 - Predose at screening or on day 1 and predose at weeks 8, 16, 24, 32, 40, and 48 (end of MAD study)
 - After administration at weeks 1, 4, 12, and at the EOT
- Safety assessments included treatment-emergent adverse event (TEAE) monitoring, electrocardiograms, laboratory data, vital signs, and physical examinations; a panel of common herpes infection 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.

Pharmacokinetics of ulivprubart

- Following a single dose, ulivprubart displayed a long absorption phase, slow clearance, and a $t_{1/2}$ of 21 days (2 mg/kg group) (**Figure 3**; **Table 2**)

Figure 3. Serum concentrations of ulivprubart over time after single-dose administration

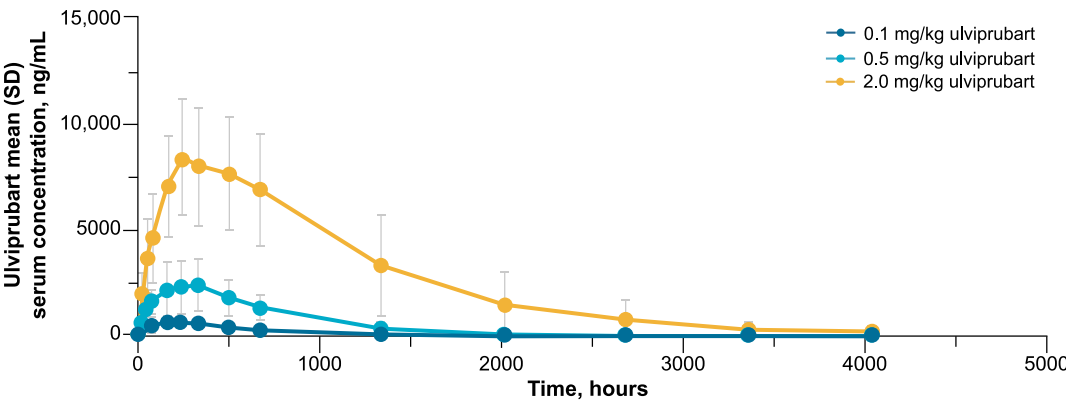


Table 2. Ulivprubart pharmacokinetic parameters after single-dose administration

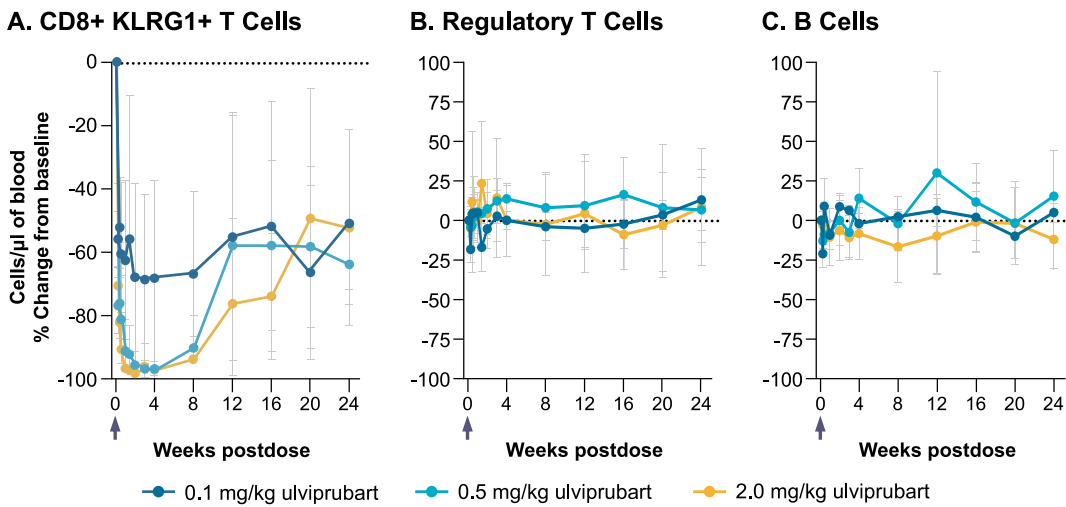
	Ulivprubart 0.1 mg/kg n=3	Ulivprubart 0.5 mg/kg n=3	Ulivprubart 2.0 mg/kg n=5
C_{max} , ng/mL	721 (175)	2626 (1224)	9274 (2520)
T_{max} , days	10 (4)	13 (2)	12 (5)
$t_{1/2}$, days	12 (6)	14 (5)	21 (9)
AUC_{0-inf} , ng·h/mL	443,019 (103,405)	1,971,078 (972,424)	11,163,765 (5,795,408)
CL/F, mL/h	23 (9)	29 (15)	18 (8)
V_z/F , mL	8755 (2654)	14,655 (11,516)	11,110 (1927)

Data shown are mean (SD). AUC, area under the concentration-time curve; CL/F, apparent clearance; C_{max} , maximum observed concentration; T_{max} , time to maximum observed concentration; $t_{1/2}$, terminal half-life; V_z/F , apparent terminal volume of distribution.

Pharmacodynamic effects of ulivprubart

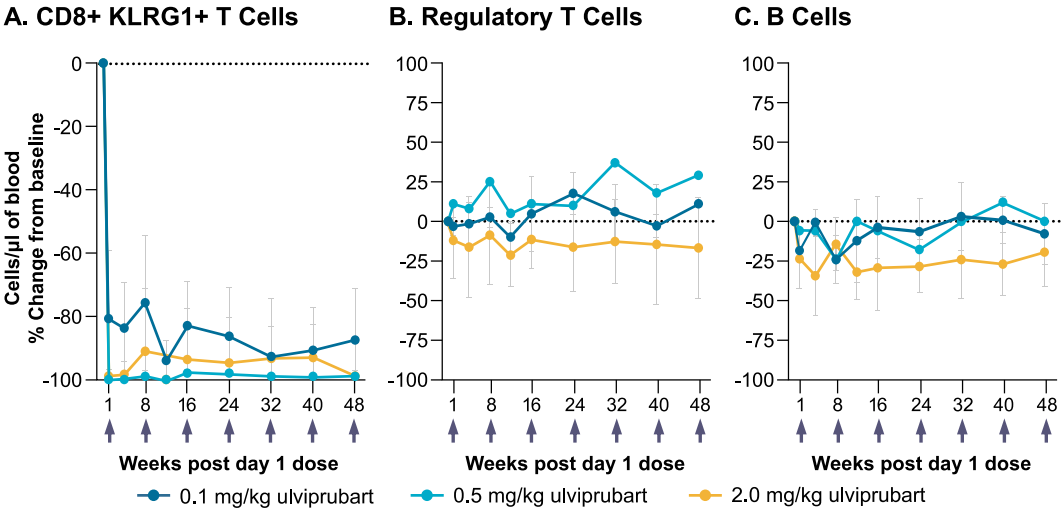
- Depletion of peripheral CD8+ KLRG1+ and CD4+ KLRG1+ T cells was evident on day 1 postdose, with mean CD8+ KLRG1+ T-cell maximum depletions of 69%, 97%, and 98% achieved by weeks 2–3 after a single dose of 0.1, 0.5, and 2.0 mg/kg ulivprubart, respectively, in Part 1 (SAD) (**Figure 4A**)
 - Depletion was sustained throughout Part 2 (MAD) and the substudy (**Figure 5A**)
- Protective regulatory T cells and B cells (cells that do not express KLRG1) were preserved (**Figures 4B/5B** and **4C/5C**, respectively)

Figure 4. Mean (SD) changes in immune cells over time (SAD cohorts)



Data are 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 ulivprubart, respectively. Baseline is prior to ulivprubart dosing. Purple vertical arrow indicates time of ulivprubart administration. KLRG1, killer cell lectin-like receptor G1; SAD, single-ascending dose.

Figure 5. Mean (SD) changes in immune cells over time (MAD and substudy cohorts)



Data are from n=3, n=1, and n=12 patients who received 0.1 mg/kg, 0.5 mg/kg, and 2.0 mg/kg ulivprubart Q8W, respectively. Baseline is prior to any ulivprubart dosing. Purple vertical arrows indicate time of ulivprubart administration. KLRG1, killer cell lectin-like receptor G1; MAD, multiple ascending dose; Q8W, every 8 weeks.

Safety

- No treatment-related serious TEAEs or discontinuations due to TEAEs were reported (**Table 3**)
- The most common treatment-related TEAE was injection-related reaction, which occurred in 6/19 patients (32%); no other treatment-related TEAEs occurred in >2 participants
- No clinically significant reactivations of latent viral infections were observed

Table 3. Safety summary

Patients, n (%)	Overall N=19
Any TEAE (grade 1 or 2, n=17; grade 3, n=2)	19 (100)
Severe TEAE (grade 3)	2 (11)
Treatment-related TEAE (grade 1 or 2)	11 (58)
Severe treatment-related TEAE	0
Serious TEAEs (grade 3, n=2; grade 1 or 2, 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)

TEAE, treatment-emergent adverse event.

Conclusions

- Ulivprubart displayed PK properties consistent with other therapeutic monoclonal antibodies¹⁰
- Ulivprubart 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
- Together with the favorable safety profile, these data support the continued development of ulivprubart

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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