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Phase 2/3 study of ulviprubart in inclusion body myositis: Study design, patient characteristics, and topline results

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Disclosure Statement

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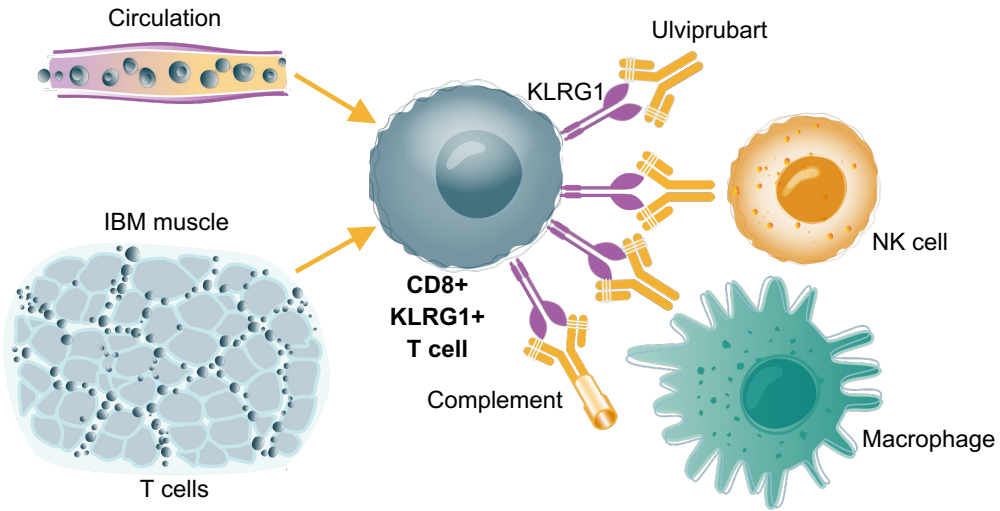
Introduction

- Ulviprubart is a humanized monoclonal antibody that selectively depletes cytotoxic CD8+ KLRG1+ T cells by targeting KLRG1 expressed on most IBM muscle–infiltrating T cells[1]
- The objective of this randomized, double-blind study was to evaluate the efficacy and safety of ulviprubart in the treatment of patients with IBM



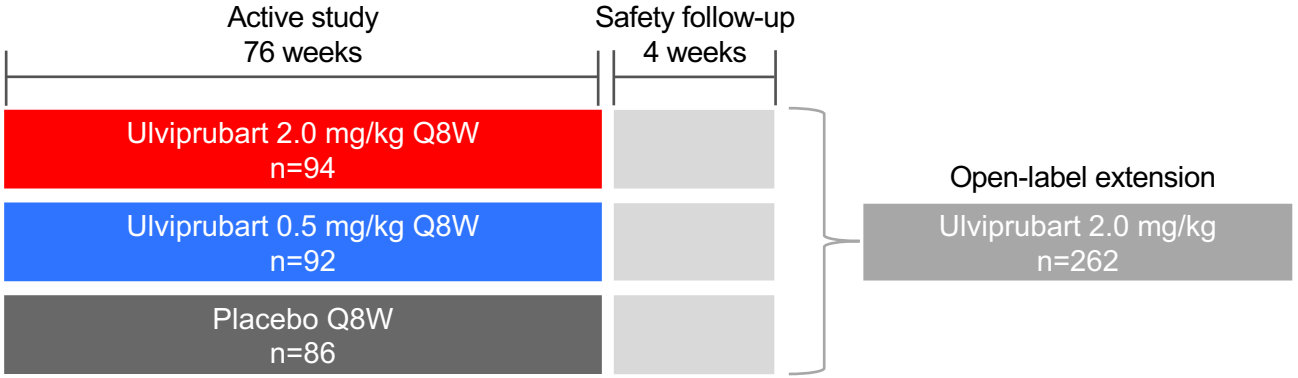
IBM, inclusion body myositis; KLRG1, killer cell lectin-like receptor G1; NK, natural killer. 1. Matsubara S, et al. *J Neuropathol Exp Neurol*. 2022;81(10):825-35.

Study design

- This phase 2/3 randomized, double-blind, placebo-controlled, global study was conducted at 45 sites in Australia, Belgium, Canada, France, Germany, the United Kingdom, and the United States

Key eligibility criteria

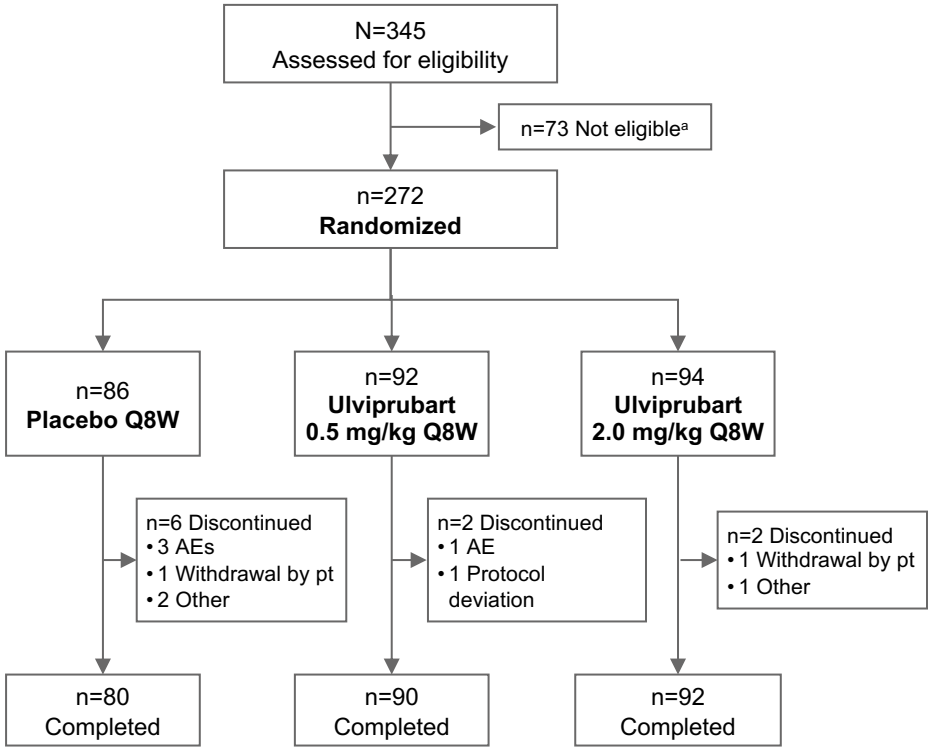
- Patients with IBM defined by 2011 ENMC criteria[1]
- Age ≥40 years
- Able to complete the mTUG test
- Receiving <7.5 mg/day oral prednisone or equivalent at screening
- No use of other immunosuppressants



Primary efficacy endpoint	Secondary efficacy endpoints	Key safety endpoints
Mean change from baseline in IBMFRS score at week 76	Mean change from baseline in MMT12, dominant hand and quadriceps dynamometry, and mTUG at week 76	TEAEs, serious TEAEs, and AEs of special interest

AE, adverse event; ENMC, European Neuro Muscular Centre; IBM, inclusion body myositis; IBMFRS, inclusion body myositis functional rating scale; MMT12, manual muscle testing 12; mTUG, modified timed up and go; Q8W, every 8 weeks; TEAE, treatment-emergent adverse event. **1.** Rose MR. *Neuromuscul Disord*. 2013;23:1044-55.

Patient disposition and baseline characteristics



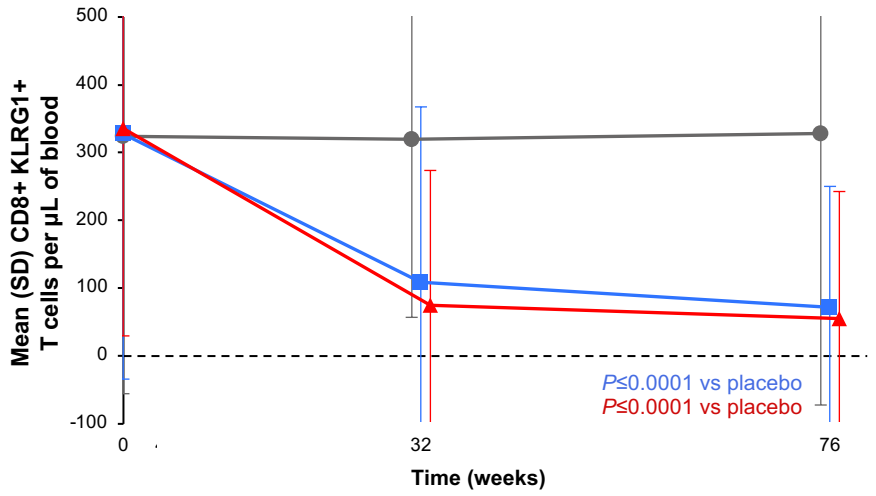
Baseline demographics and clinical characteristics

	Placebo (n=86)	Ulviprubart 0.5 mg/kg (n=92)	Ulviprubart 2.0 mg/kg (n=94)
Age, mean (SD), years <65 years, n (%) ≥65 years, n (%)	68.5 (7.6) 21 (24.4) 65 (75.6)	67.9 (7.0) 29 (31.5) 63 (68.5)	67.9 (8.7) 28 (29.8) 66 (70.2)
Sex, male, n (%)	60 (69.8)	61 (66.3)	65 (69.1)
Race, White, n (%)	73 (84.9)	86 (93.5)	84 (89.4)
Weight, mean (SD), kg	82.5 (21.1)	83.2 (17.5)	84.8 (18.6)
BMI, mean (SD), kg/m^2	27.0 (5.1)	27.4 (5.0)	27.7 (4.6)
IBMFRS score, mean (SD)	27.8 (5.3)	27.1 (5.2)	27.0 (4.5)
Time from diagnosis, mean (SD), years	4.2 (3.8)	3.7 (2.9)	4.0 (3.1)
Time from symptom onset, mean (SD), years	8.7 (4.9)	8.9 (5.2)	9.2 (4.7)
CD8+ KLRG1+ T cells, cells/μL of blood, mean (SD)	324.3 (379.8)	327.4 (361.4)	335.5 (305.8)

[a]65 patients could not perform the mTUG, failed to meet inclusion criteria, or met exclusion criteria. AE, adverse event; BMI, body mass index; IBMFRS, inclusion body myositis functional rating scale; KLRG1, killer cell lectin-like receptor G1; mTUG, modified timed up and go; pt, patient; Q8W, every 8 weeks.

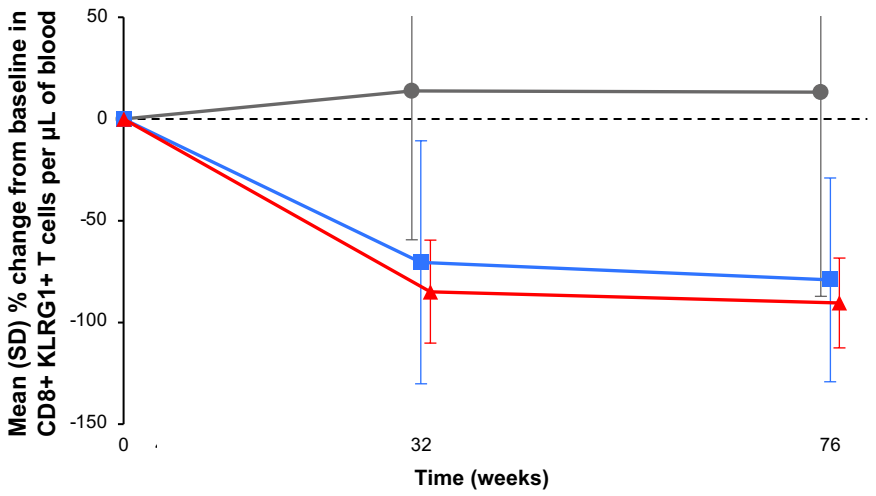
Both doses of ulviprubart achieved deep depletion of blood CD8+ KLRG1+ T cells

Mean CD8+ KLRG1+ T cells



Patients, n			
Placebo	85	71	78
Ulviprubart 0.5 mg/kg	92	72	85
Ulviprubart 2.0 mg/kg	93	80	85

Mean percentage change from baseline in CD8+ KLRG1+ T cells

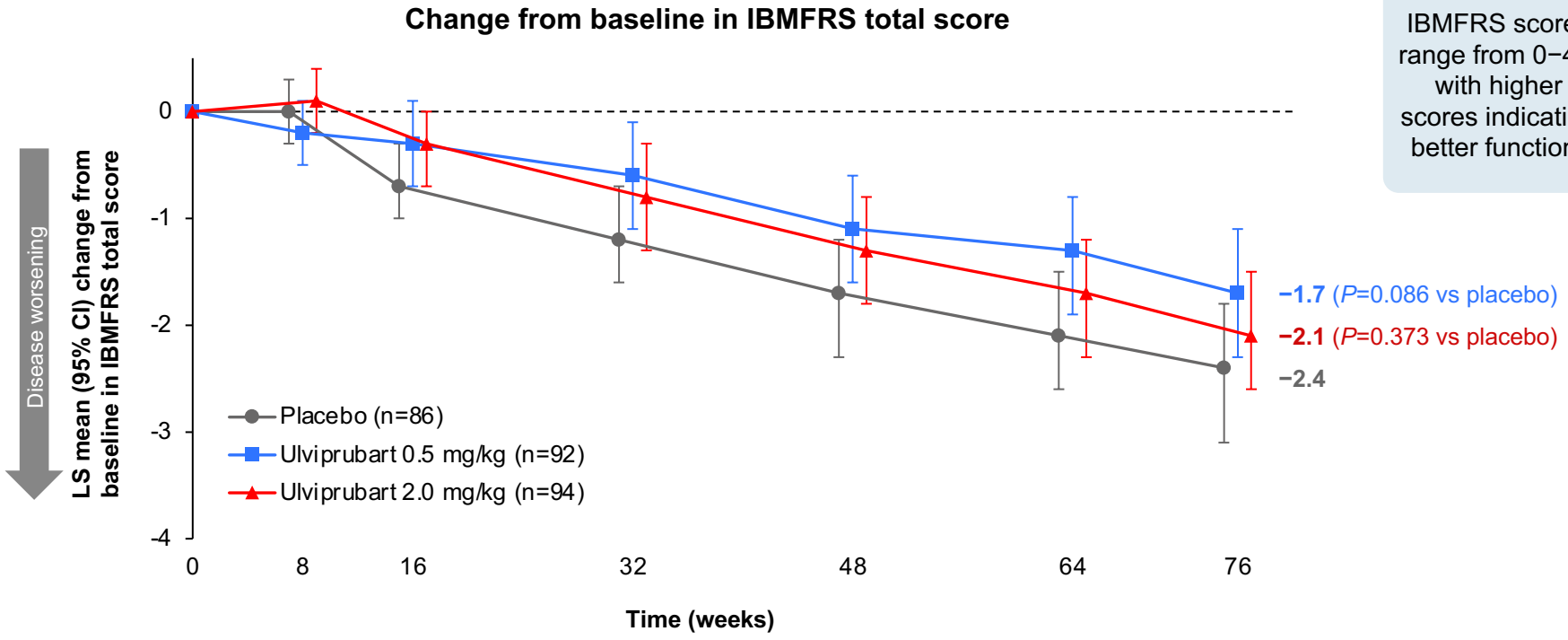


	85	71	78
	92	72	85
	93	79	84

Placebo Ulviprubart 0.5 mg/kg Ulviprubart 2.0 mg/kg

Mean CD8+ KLRG1+ T cell levels were not significantly different between the ulviprubart 0.5 and 2.0 mg/kg groups. KLRG1, killer cell lectin-like receptor G1.

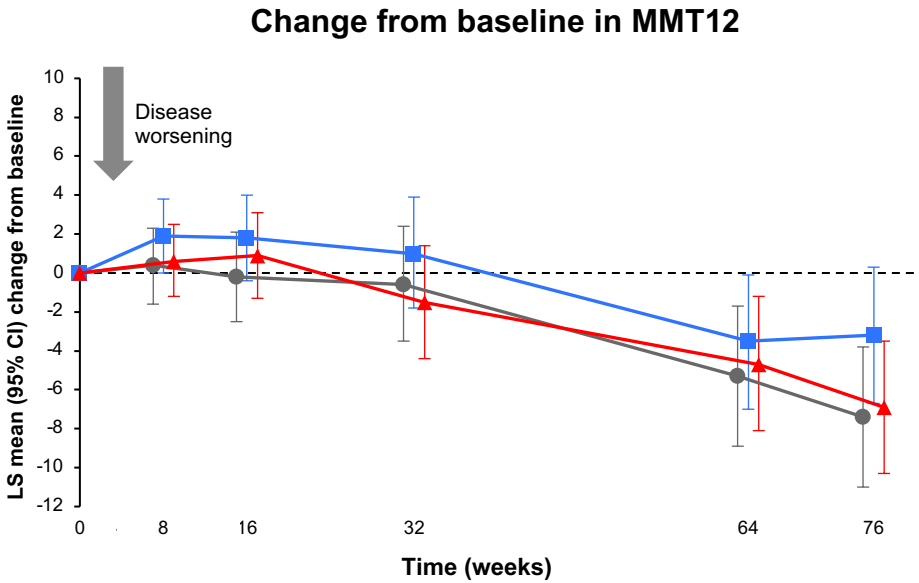
Primary endpoint: IBMFRS total score changes were not significantly different at week 76

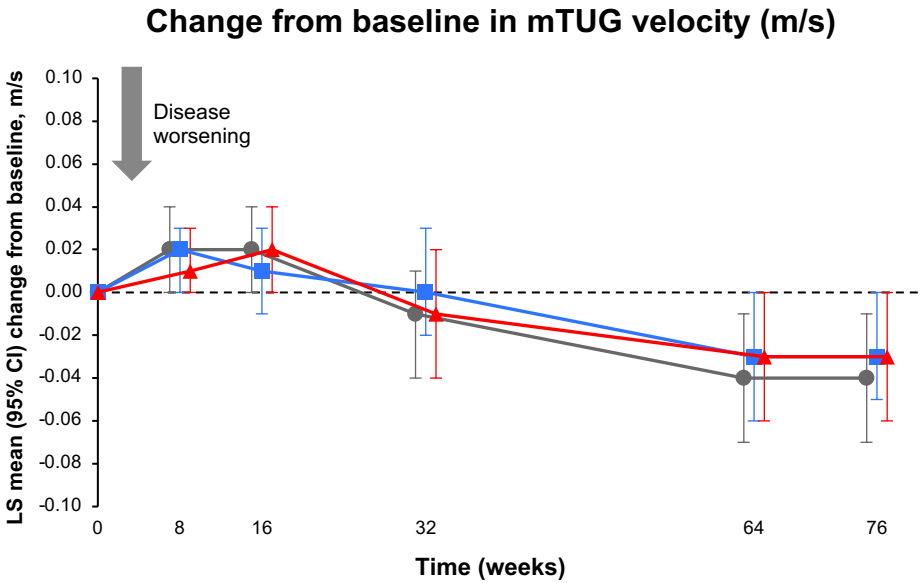


IBMFRS scores range from 0−40, with higher scores indicating better function[1]

Changes from baseline to week 76 are indicated. IBMFRS, inclusion body myositis functional rating scale; LS, least squares. 1. Jackson CE, et al. *Muscle Nerve*. 2008;37(4):473-6.

Changes in MMT12 and mTUG velocity were not significantly different with ulviprubart vs placebo

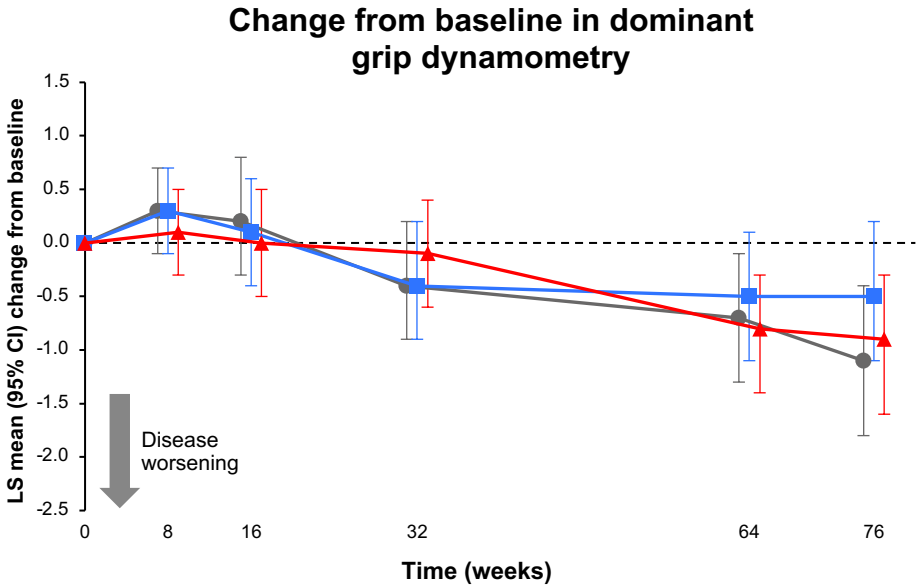


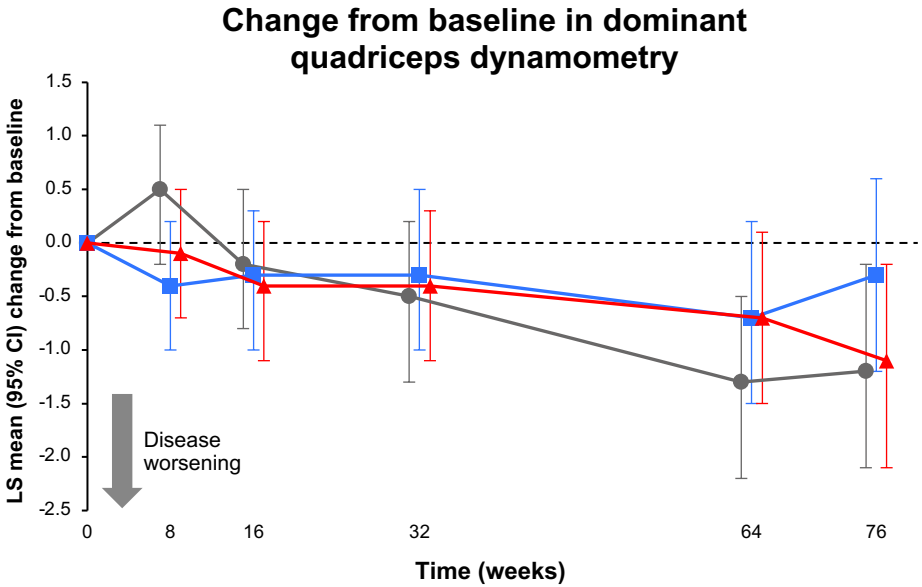


Placebo (n=86) Ulviprubart 0.5 mg/kg (n=92) Ulviprubart 2.0 mg/kg (n=94)

Changes from baseline with ulviprubart were not statistically significantly different vs placebo at any time point. LS, least squares; m/s, meters per second; MMT12, manual muscle testing 12; mTUG, modified timed up and go.

Dynamometry results were similar with ulviprubart and placebo





Placebo (n=86[a]) Ulviprubart 0.5 mg/kg (n=92) Ulviprubart 2.0 mg/kg (n=94)

Changes from baseline with ulviprubart were not statistically significantly different vs placebo at any time point. [a]n=85 for dominant quadriceps dynamometry. LS, least squares.

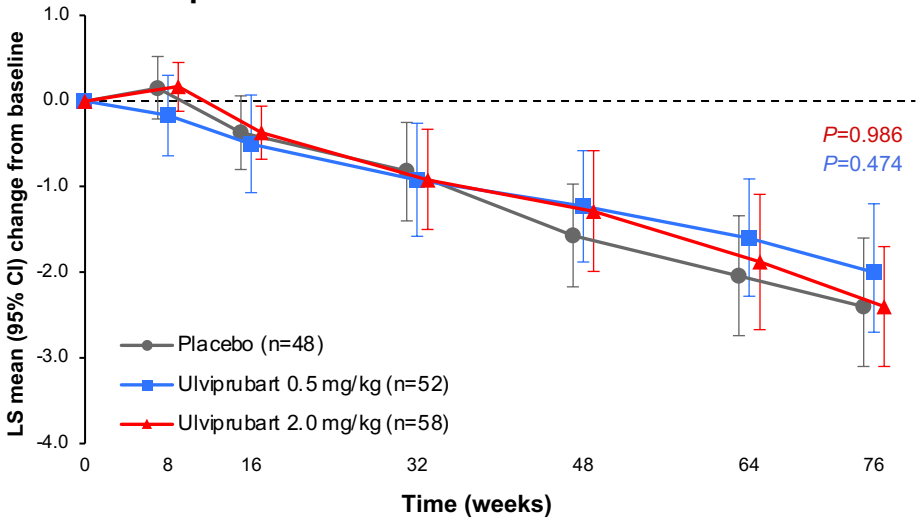
Baseline demographic data were balanced across cohorts within subgroups of patients with baseline IBMFRS scores <29 and ≥29

	Baseline IBMFRS score <29			Baseline IBMFRS score ≥29		
	Placebo (n=53)	Ulviprubart 0.5 mg/kg (n=54)	Ulviprubart 2.0 mg/kg (n=60)	Placebo (n=33)	Ulviprubart 0.5 mg/kg (n=38)	Ulviprubart 2.0 mg/kg (n=34)
Age, mean (SD), years	69.9 (7.4)	68.7 (6.4)	68.8 (8.3)	66.1 (7.5)	66.7 (7.6)	66.3 (9.3)
<65 years, n (%)	9 (17.0)	17 (31.5)	16 (26.7)	12 (36.4)	12 (31.6)	12 (35.3)
≥65 years, n (%)	44 (83.0)	37 (68.5)	44 (73.3)	21 (63.6)	26 (68.4)	22 (64.7)
Sex, male, n (%)	35 (66.0)	38 (70.4)	41 (68.3)	25 (75.8)	23 (60.5)	24 (70.6)
Race, White, n (%)	48 (90.6)	53 (98.1)	52 (86.7)	25 (75.8)	33 (86.8)	32 (94.1)
Weight, mean (SD), kg	80.2 (19.9)	85.1 (16.3)	85.8 (18.2)	86.3 (22.7)	80.6 (19.2)	82.9 (19.5)
BMI, mean (SD), kg/m^2	26.6 (4.7)	27.8 (4.2)	28.0 (4.6)	27.5 (5.9)	26.8 (5.9)	27.2 (4.8)
Time from diagnosis, mean (SD), years	3.1 (2.9)	4.1 (3.6)	3.7 (3.5)	1.9 (2.5)	2.1 (3.5)	1.8 (2.2)
Time from symptom onset, mean (SD), years	8.1 (4.4)	9.2 (4.9)	8.2 (5.7)	5.7 (4.2)	7.1 (4.5)	6.4 (4.5)

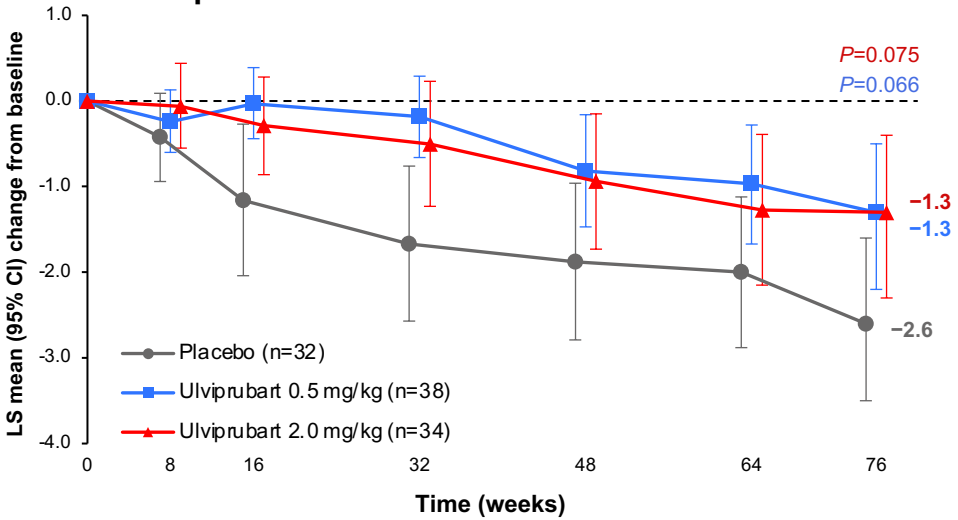
BMI, body mass index; IBMFRS, inclusion body myositis functional rating scale.

Trends suggesting slower reduction in IBMFRS score were seen in patients with baseline IBMFRS score ≥29

Change in IBMFRS score from baseline to week 76 for patients with baseline IBMFRS score <29



Change in IBMFRS score from baseline to week 76 for patients with baseline IBMFRS score ≥29

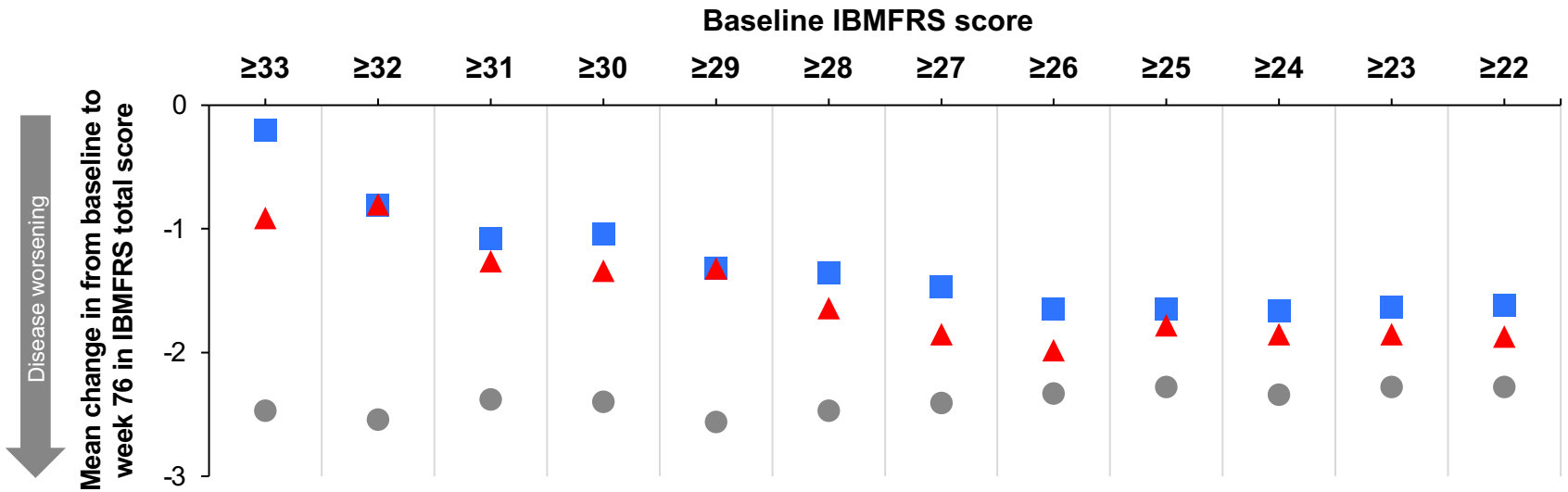


In patients with baseline IBMFRS score ≥29

- There was a difference between ulviprubart and placebo at week 76 that represented a 50% slowing of disease progression
- The most pronounced differences occurred by week 16

Data for timepoints 8, 16, 32, 48, and 64 are mean estimates and remain to be validated. Patient numbers for changes from baseline at week 76 are shown. IBMFRS, inclusion body myositis functional rating scale; LS, least squares.

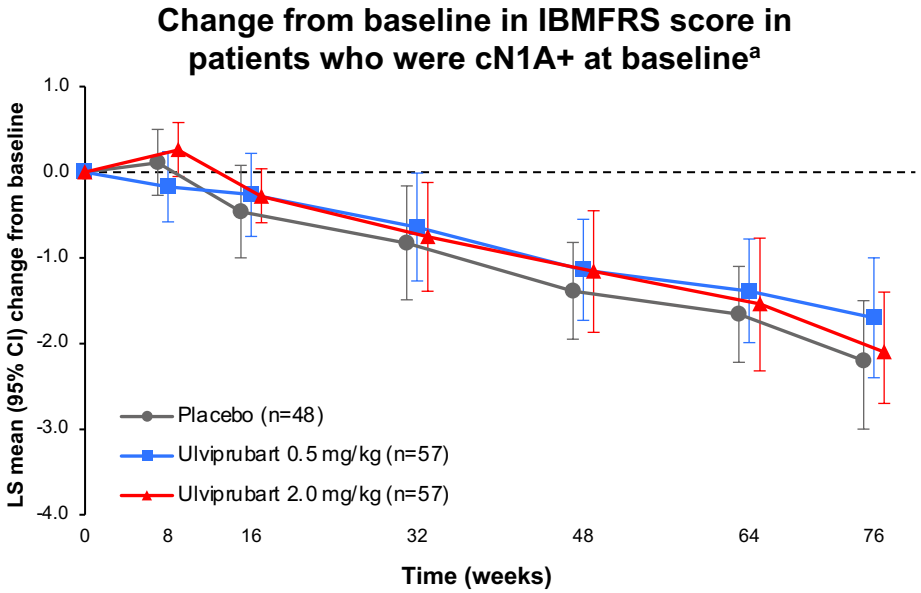
Patients with mild-to-moderate baseline disease severity showed less IBMFRS reduction with ulviprubart

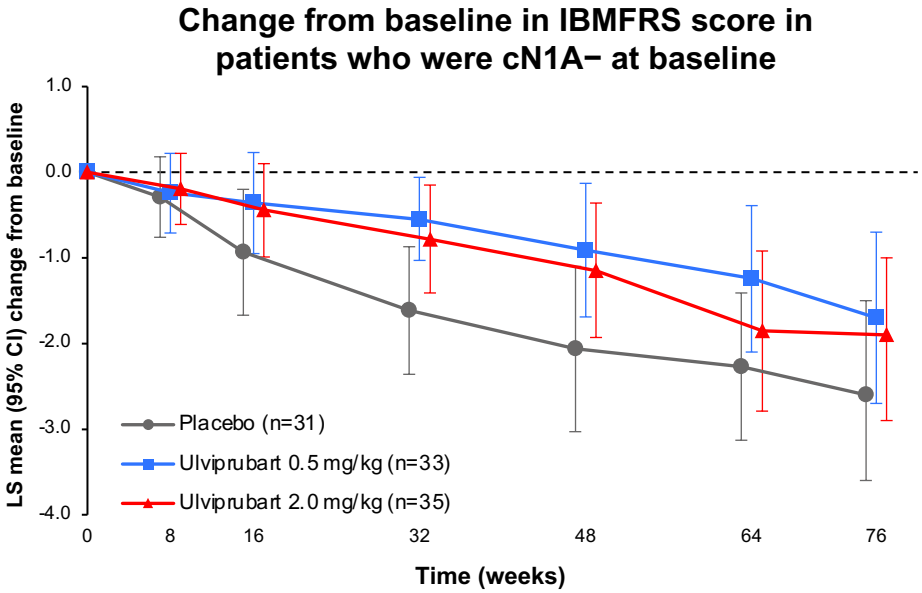


Patients, n												
Placebo	19	24	26	30	32	36	44	49	57	65	72	76
0.5 mg/kg	10	16	24	28	38	45	55	60	66	71	76	79
2.0 mg/kg	11	15	19	29	34	42	47	59	67	73	80	82

IBMFRS, inclusion body myositis functional rating scale.

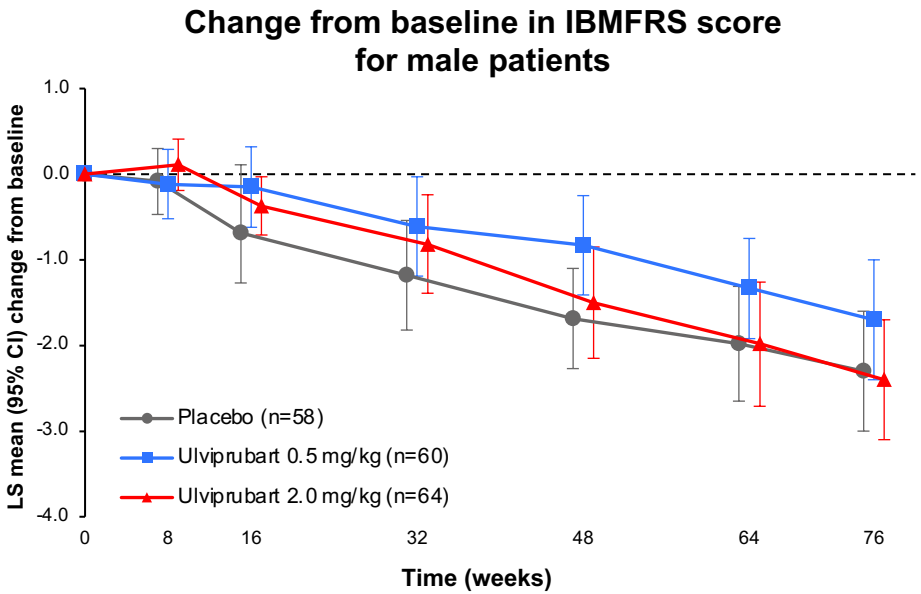
Anti-cN1A antibody status did not have an impact on IBMFRS changes with ulviprubart vs placebo

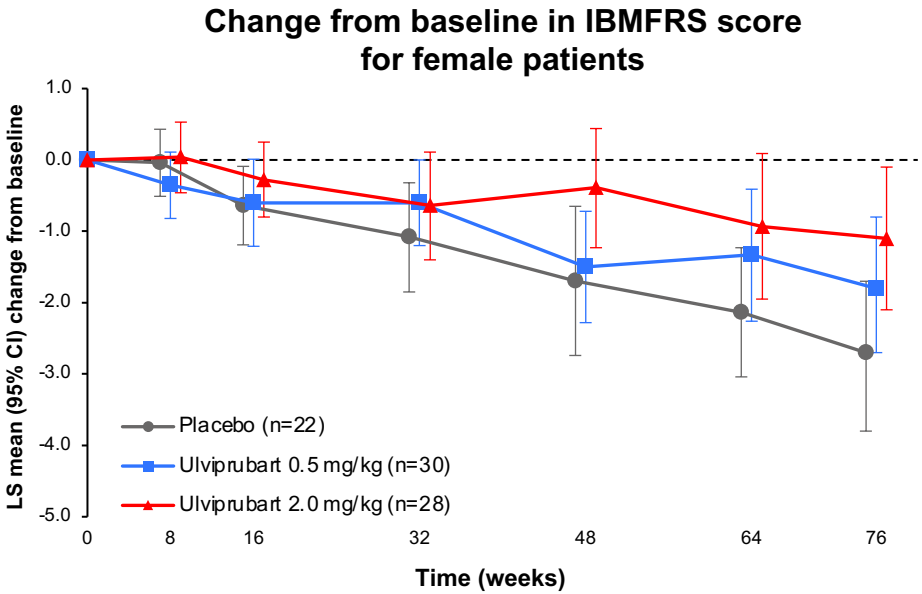




Data for timepoints 8, 16, 32, 48, and 64 are mean estimates and remain to be validated. Patient numbers for changes from baseline at week 76 are shown. [a]Includes patients who were positive or borderline for anti-cN1A antibody at baseline. cN1A, cytosolic 5'-nucleotidase 1A; IBMFRS, inclusion body myositis functional rating scale; LS, least squares.

Changes in IBMFRS scores were similar in men and women receiving ulviprubart and placebo





Data for timepoints 8, 16, 32, 48, and 64 are mean estimates and remain to be validated. Patient numbers for changes from baseline at week 76 are shown. IBMFRS, inclusion body myositis functional rating scale; LS, least squares.

Safety summary

- Overall incidence of TEAEs was similar with ulviprubart and placebo
- No patients receiving ulviprubart had serious TEAEs leading to discontinuation or TEAEs of special interest leading to discontinuation

Patients, n (%)	Placebo (n=86)	Ulviprubart 0.5 mg/kg (n=92)	Ulviprubart 2.0 mg/kg (n=94)
TEAEs	84 (97.7)	92 (100)	91 (96.8)
TEAEs related to study drug	31 (36.0)	54 (58.7)	64 (68.1)
Serious TEAEs	18 (20.9)	8 (8.7)	12 (12.8)
Serious TEAEs related to study drug	0	0	0
Serious TEAEs leading to discontinuation[a]	1 (1.2)	0	0
TEAEs leading to death[b]	2 (2.3)	0	1 (1.1)
TEAEs of special interest[c]	57 (66.3)	70 (76.1)	78 (83.0)
TEAEs of special interest related to study drug	21 (24.4)	42 (45.7)	55 (58.5)
TEAEs of special interest leading to discontinuation	1 (1.2)	0	0

[a]Events of pneumonia aspiration and dehydration unrelated to treatment in 1 patient receiving placebo. [b]Placebo: events of metastatic malignant melanoma unrelated to treatment and acute respiratory failure unrelated to treatment in 1 patient each; ulviprubart 2.0 mg/kg: event of cerebral hemorrhage unrelated to treatment in 1 patient. [c]TEAEs of special interest were infections or symptoms of systemic drug reactions.

TEAE, treatment-emergent adverse event.

Common TEAEs

- Falls were the most common TEAEs and were reported at a similar rate in patients receiving ulviprubart and placebo
- Common TEAEs (in ≥10% of patients) that occurred ≥2 times more often with ulviprubart vs placebo were chills, headache, pyrexia, and nasopharyngitis

Patients, n (%)	Placebo (n=86)	Ulviprubart 0.5 mg/kg (n=92)	Ulviprubart 2.0 mg/kg (n=94)
TEAEs occurring in ≥10% of patients in any group, n (%)			
Fall	44 (51.2)	48 (52.2)	52 (55.3)
Chills	3 (3.5)	21 (22.8)	30 (31.9)
Headache	9 (10.5)	27 (29.3)	22 (23.4)
Arthralgia	20 (23.3)	20 (21.7)	19 (20.2)
Pyrexia	2 (2.3)	12 (13.0)	17 (18.1)
COVID-19	9 (10.5)	15 (16.3)	16 (17.0)
Contusion	13 (15.1)	14 (15.2)	14 (14.9)
Nausea	9 (10.5)	9 (9.8)	13 (13.8)
Pain in extremity	11 (12.8)	13 (14.1)	12 (12.8)
Nasopharyngitis	2 (2.3)	11 (12.0)	12 (12.8)
Fatigue	8 (9.3)	11 (12.0)	11 (11.7)
Diarrhea	8 (9.3)	12 (13.0)	11 (11.7)
Ligament sprain	10 (11.6)	9 (9.8)	10 (10.6)
Skin abrasion	13 (15.1)	4 (4.3)	10 (10.6)
Urinary tract infection	10 (11.6)	13 (14.1)	9 (9.6)
Upper respiratory tract infection	12 (14.0)	12 (13.0)	8 (8.5)
Back pain	6 (7.0)	12 (13.0)	7 (7.4)
Hypertension	10 (11.6)	4 (4.3)	7 (7.4)

There were no safety signals in metabolism, cardiovascular, gastrointestinal, dermatology, or blood. TEAE, treatment-emergent adverse event.

Conclusions

- This randomized, double-blind, placebo-controlled, phase 2/3 study of the efficacy and safety of ulviprubart in patients with IBM did not meet its primary endpoint (assessed by the IBMFRS total score at week 76) or key secondary endpoints
- In a prespecified subgroup analysis, patients with baseline IBMFRS total scores of ≥29 (less severe) showed trends in slowing disease progression based on IBMFRS
- Ulviprubart demonstrated a favorable safety and tolerability profile compared with placebo

IBM, inclusion body myositis; IBMFRS, inclusion body myositis functional rating scale.

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