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

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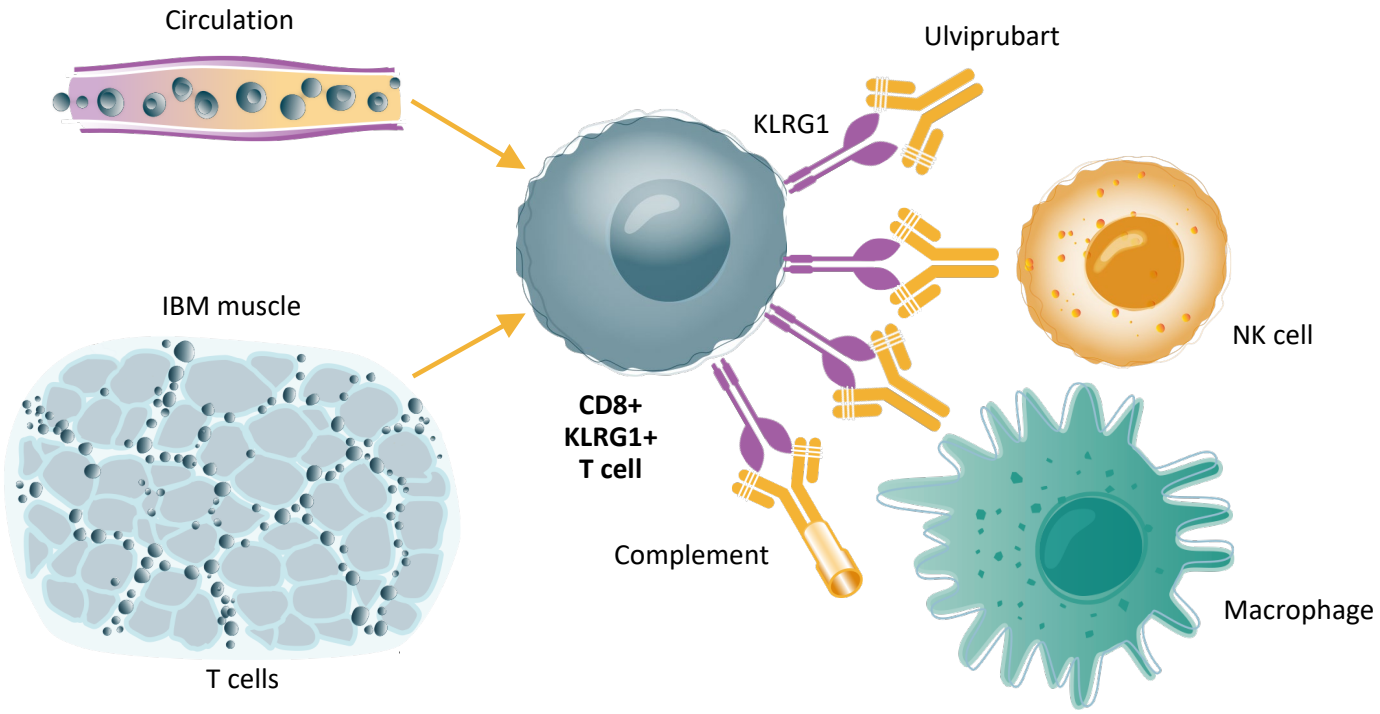
Introduction

- 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



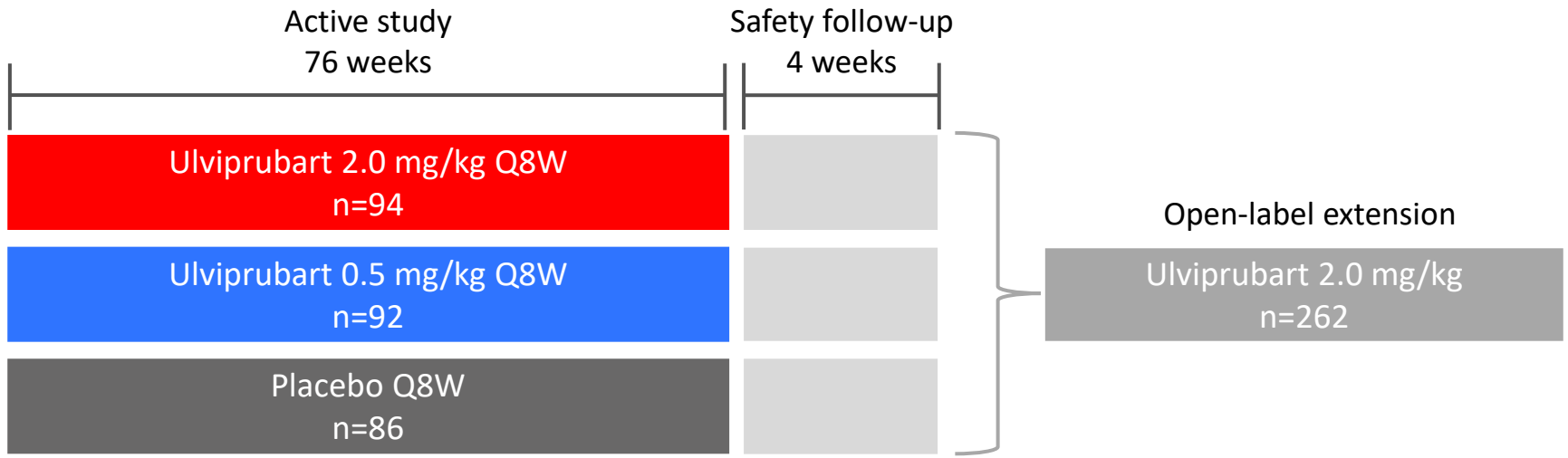
IBM, inclusion body myositis; KLRG1, killer cell lectin-like receptor G1; NK, natural killer. **1.** Matsubara S, et al. *J Neuropathol Exp Neurol*. 2022;81(10):825-35.

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

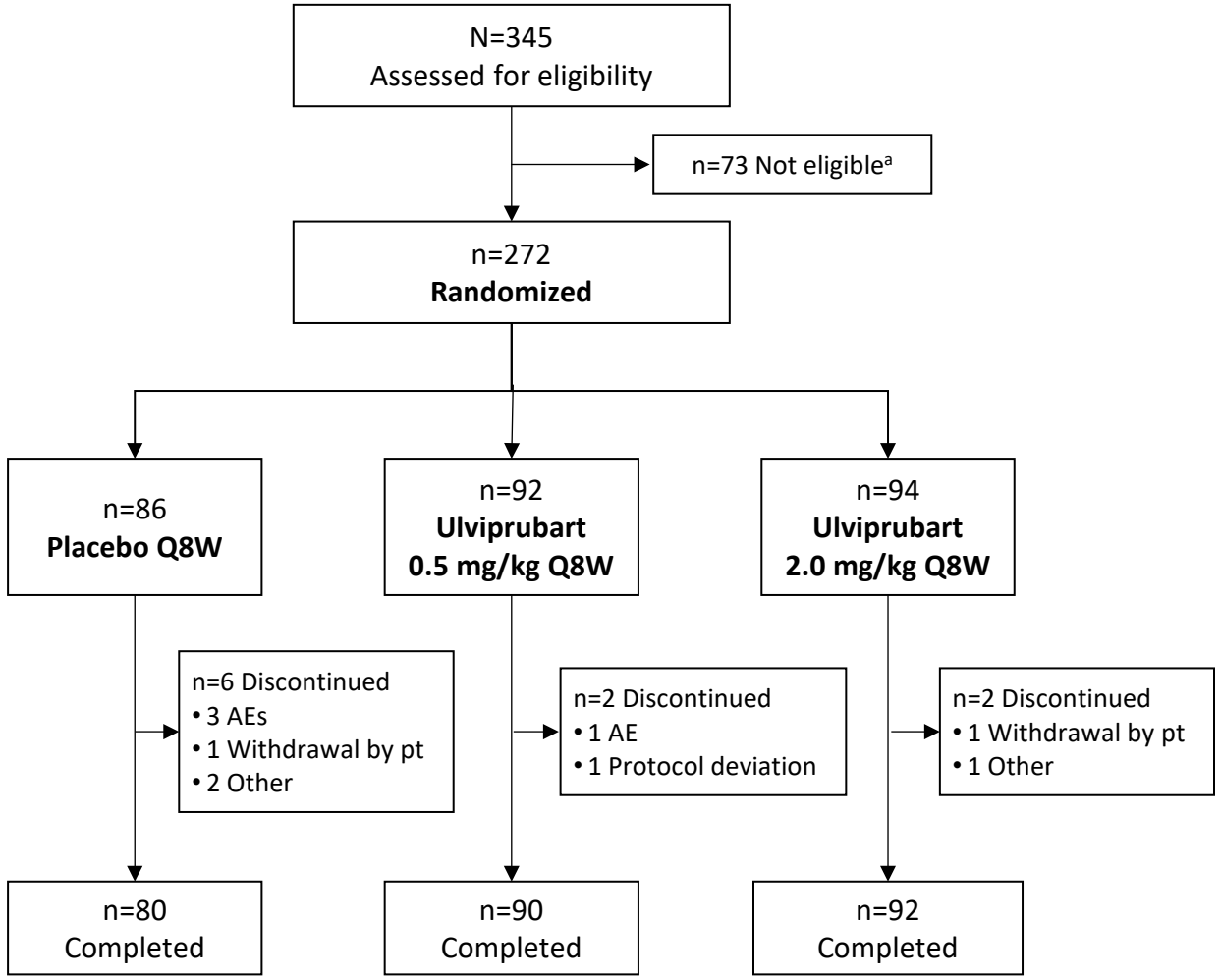


Primary efficacy endpoint	Secondary efficacy endpoints	Key safety endpoints
Mean change from baseline in IBMFRS score at week 76	Mean change from baseline in MMT12, mTUG, and dominant hand and quadriceps dynamometry at week 76	TEAEs, serious TEAEs, and AEs of special interest

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

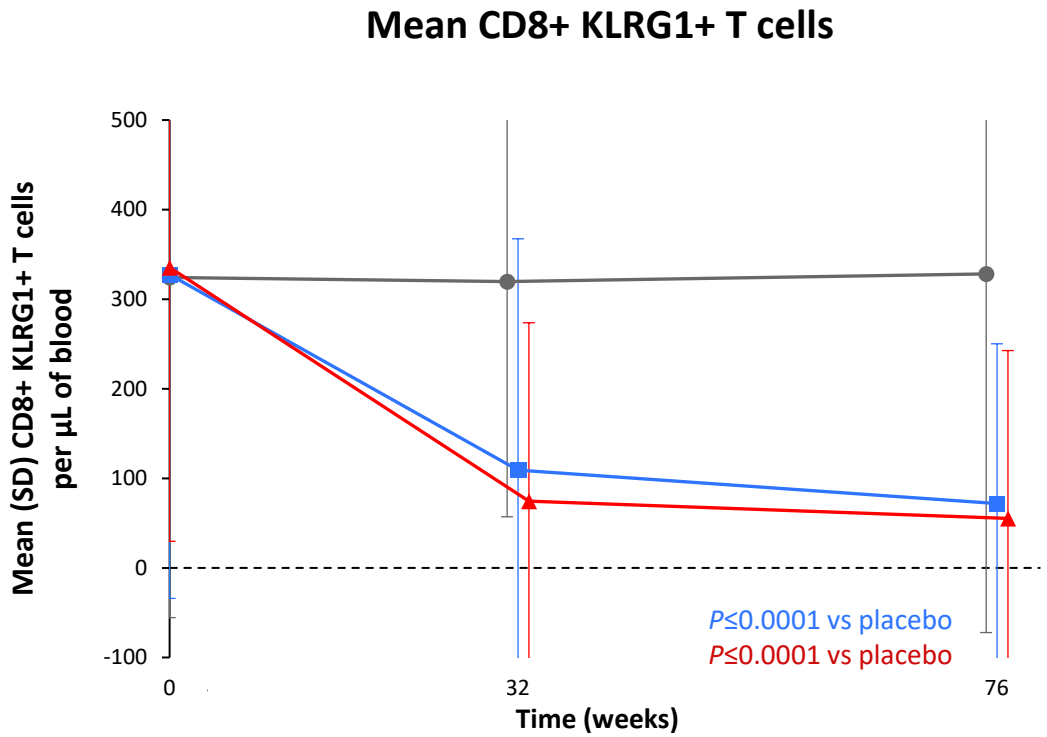


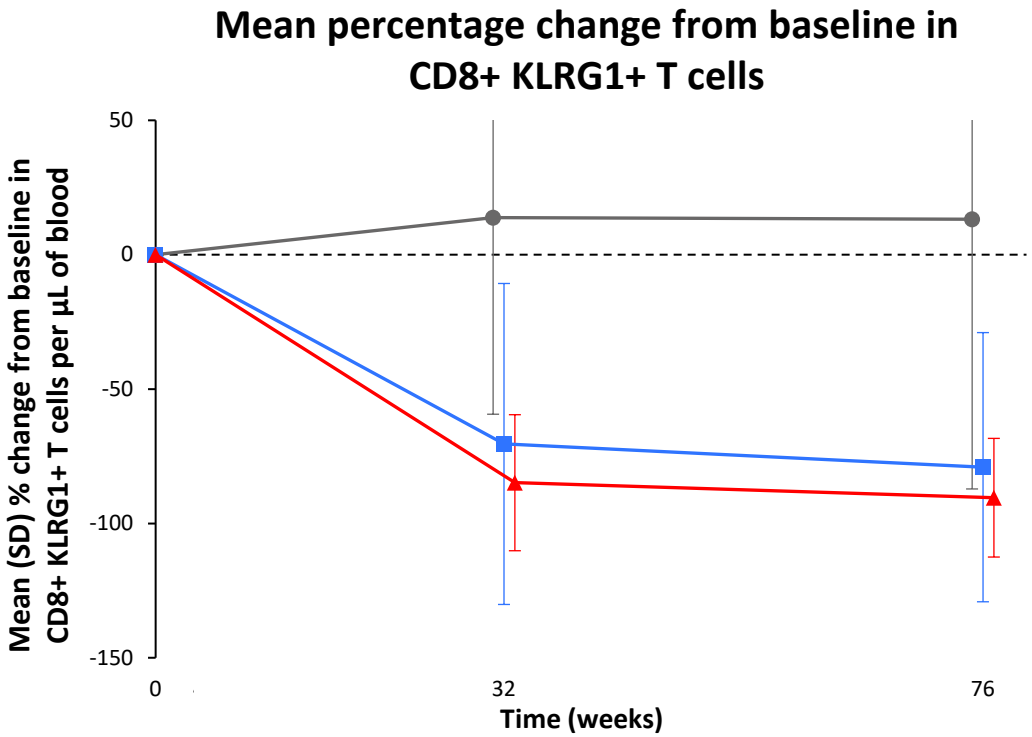
Baseline demographics and clinical characteristics

	Placebo (n=86)	Ulviprubart 0.5 mg/kg (n=92)	Ulviprubart 2.0 mg/kg (n=94)
Age, mean (SD), years	68.5 (7.6)	67.9 (7.0)	67.9 (8.7)
<65 years, n (%)	21 (24.4)	29 (31.5)	28 (29.8)
≥65 years, n (%)	65 (75.6)	63 (68.5)	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



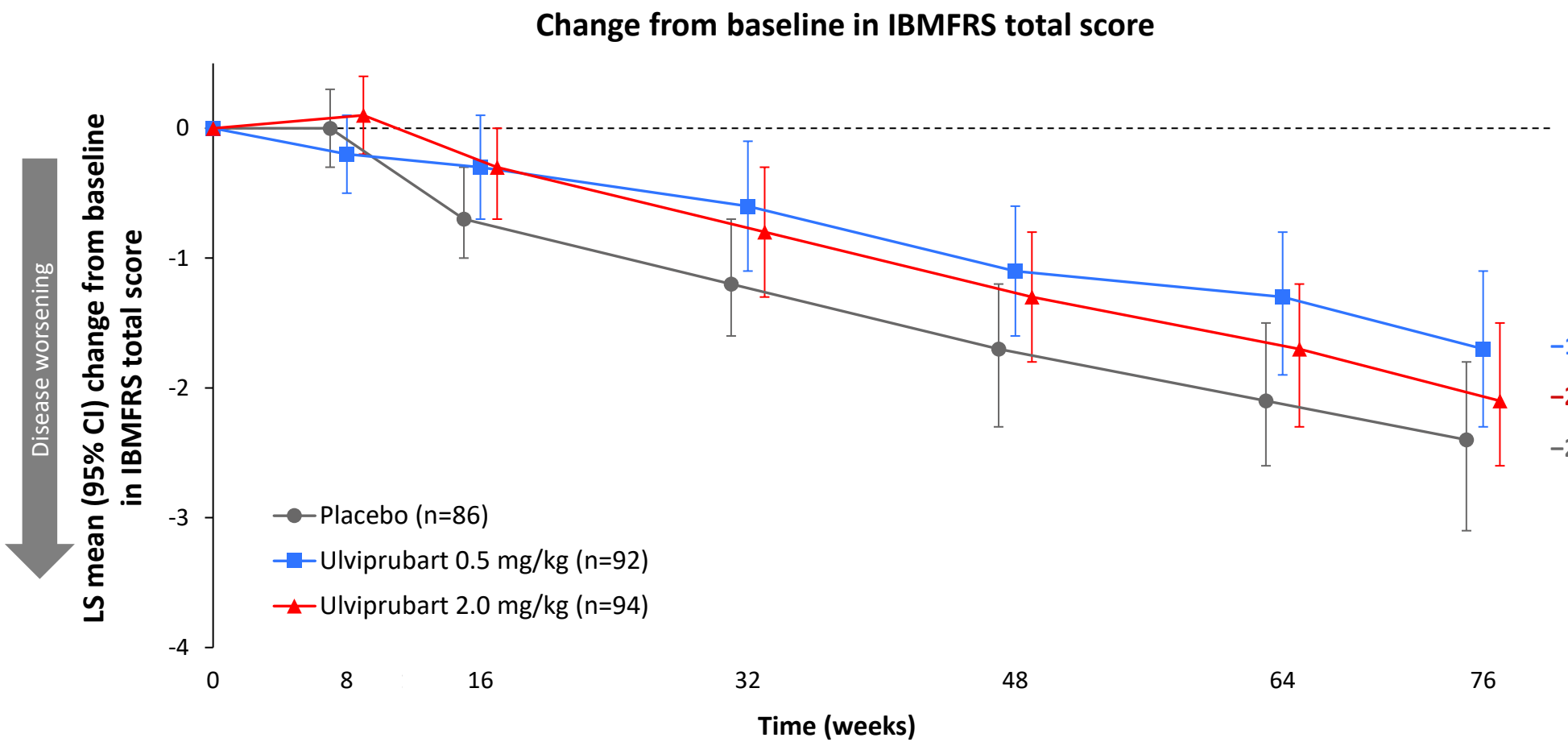


Patients, n						
Placebo	85	71	78	85	71	78
Ulviprubart 0.5 mg/kg	92	72	85	92	72	85
Ulviprubart 2.0 mg/kg	93	80	85	93	79	84

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.

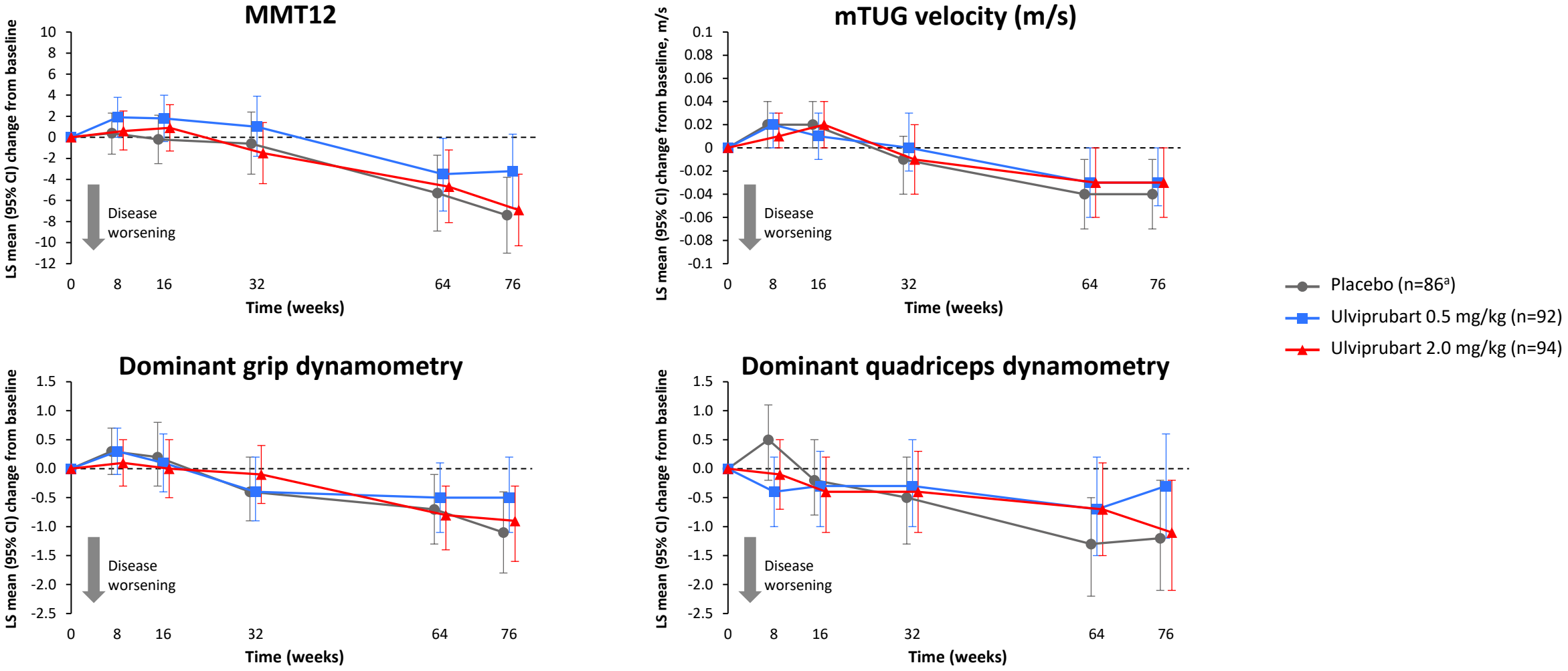
Primary endpoint: IBMFRS total score changes were not significantly different at week 76



IBMFRS scores range from 0–40, and higher scores indicate better function[1]

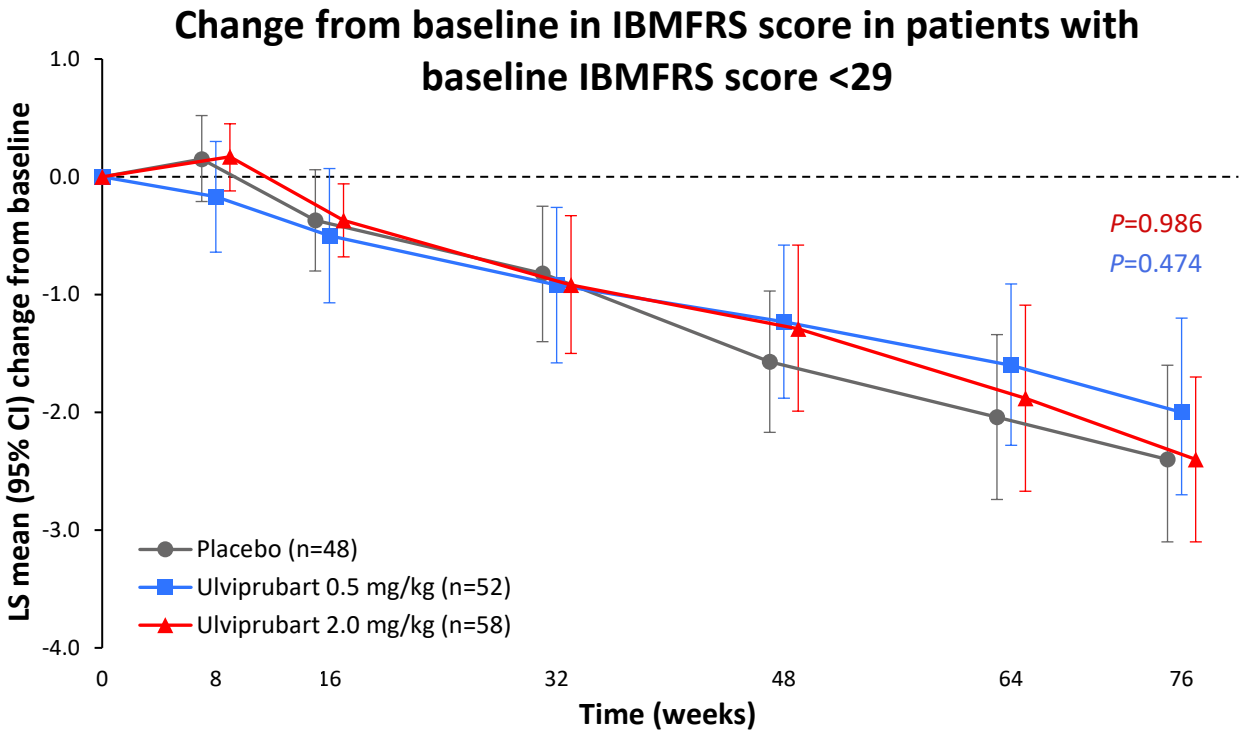
Changes from baseline to week 76 are indicated. IBMFRS, Inclusion Body Myositis Functional Rating Scale; LS, least squares. **1.** Jackson CE, et al. *Muscle Nerve*. 2008;37(4):473-6.

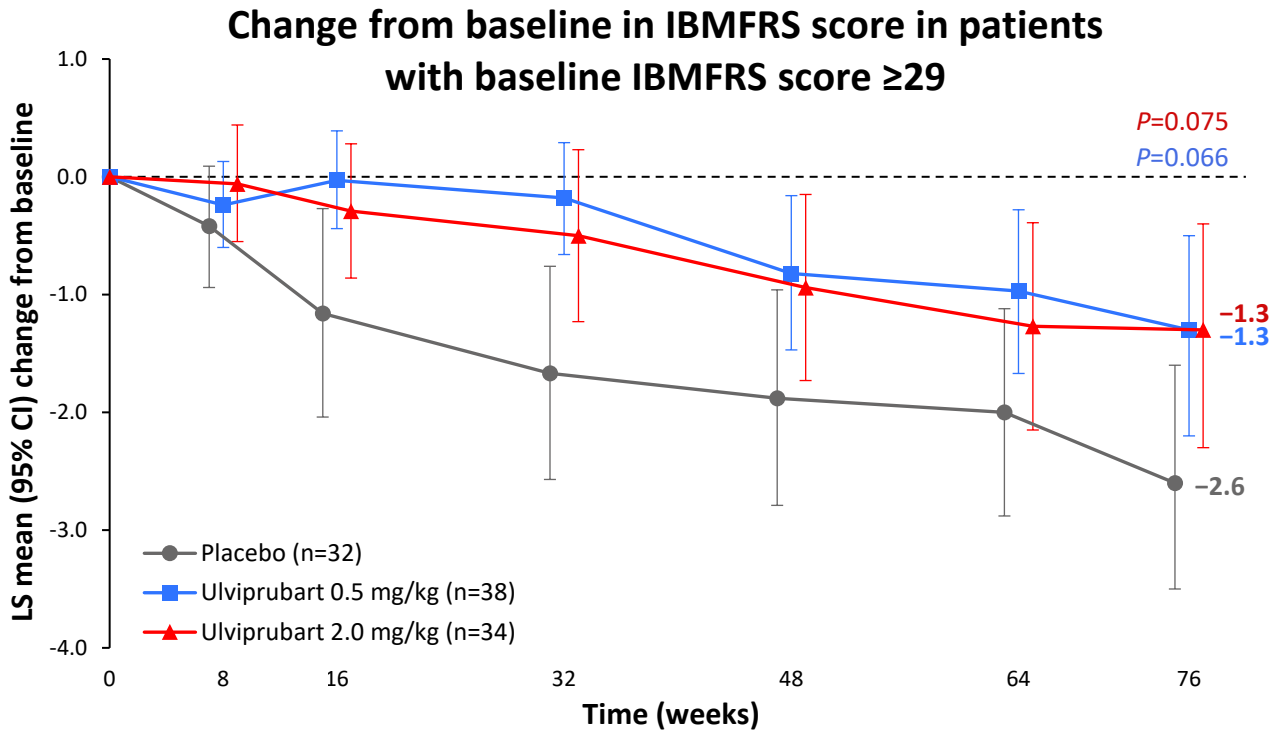
Changes in MMT12, mTUG velocity, and dynamometry were not significantly different with ulviprubart vs placebo



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; m/s, meters per second; MMT12, Manual Muscle Testing 12; mTUG, modified Timed Up and Go.

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





- Baseline characteristics for patients with baseline IBMFRS score <29 vs ≥29 were similar apart from time since diagnosis and since symptom onset, which were slightly longer in the group with more severe disease

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

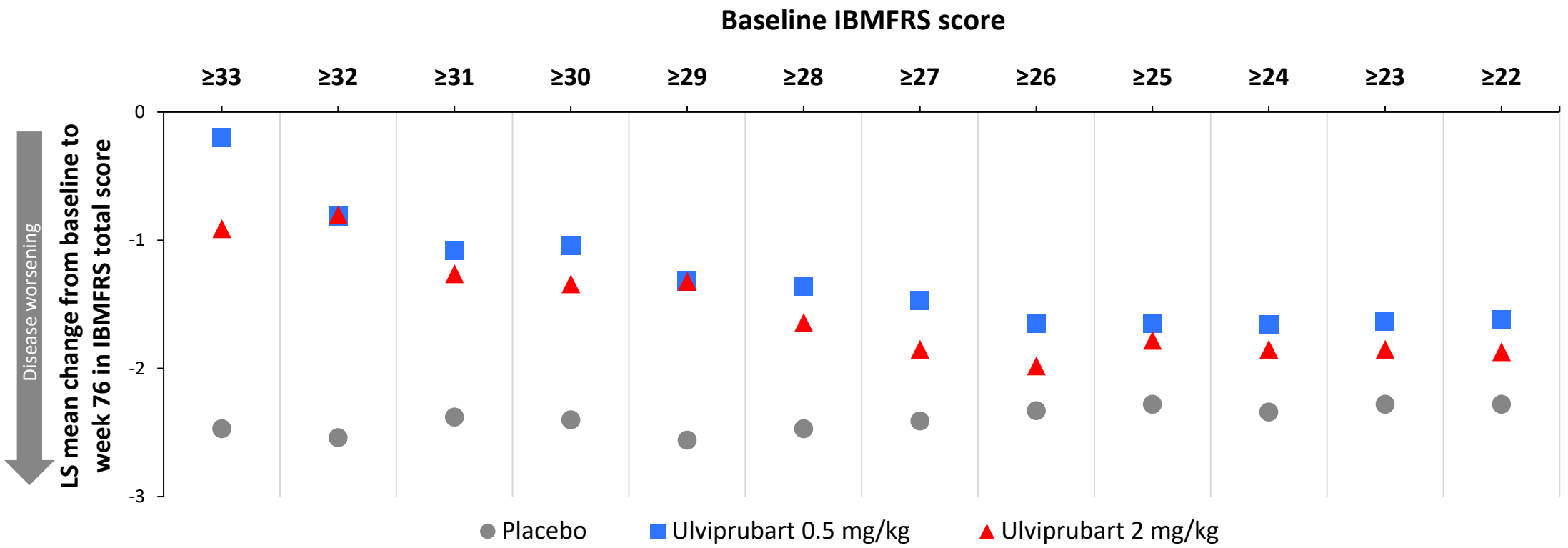
Data for timepoints 8, 16, 32, 48, and 64 are mean estimates and remain to be validated. Patient numbers for changes from baseline at week 76 are shown. IBMFRS, Inclusion Body Myositis Functional Rating Scale; LS, least squares.

Trends suggesting slowed disease progression in patients with baseline IBMFRS score ≥29 were also observed in key secondary endpoints

Change from baseline to week 76	Placebo	Ulviprubart 0.5 mg/kg	Ulviprubart 2.0 mg/kg
MMT12, n	32	38	33
Mean (SD)	**–3.3** (15.0)	**–0.5** (14.4)	**–2.1** (11.9)
Median	–2	–1.5	–2
mTUG, n	30	37	32
Mean (SD), m/s	**–0.02** (0.17)	**0.02** (0.13)	**0.03** (0.16)
Median, m/s	0	0	0
Grip dynamometry, n	32	38	34
Mean (SD)	**–1.2** (4.1)	**–0.2** (2.9)	**–1.4** (3.2)
Median	–1.3	–0.5	–1.3
Quadriceps dynamometry, n	28	37	31
Mean (SD)	**–0.1** (3.7)	**0.5** (4.3)	**–1.7** (5.5)
Median	–0.1	0.2	–1.2

Changes from baseline with ulviprubart were not statistically significantly different vs placebo at any time point. IBMFRS, Inclusion Body Myositis Functional Rating Scale; m/s, meters per second; MMT12, Manual Muscle Testing 12; mTUG, modified Timed Up and Go.

Patients with less severe disease at baseline showed less IBMFRS total score reduction with ulviprubart

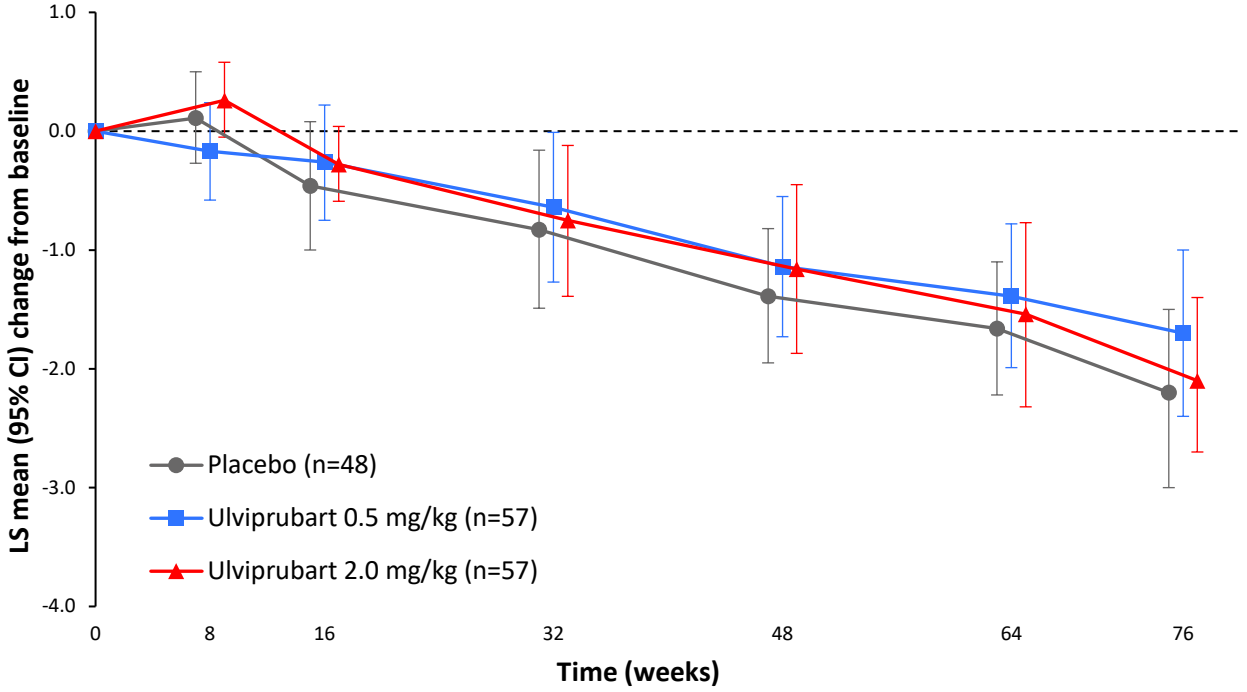


Patients, n												
Placebo	19	24	26	30	32	36	44	49	57	65	72	76
0.5 mg/kg	10	16	24	28	38	45	55	60	66	71	76	79
2.0 mg/kg	11	15	19	29	34	42	47	59	67	73	80	82

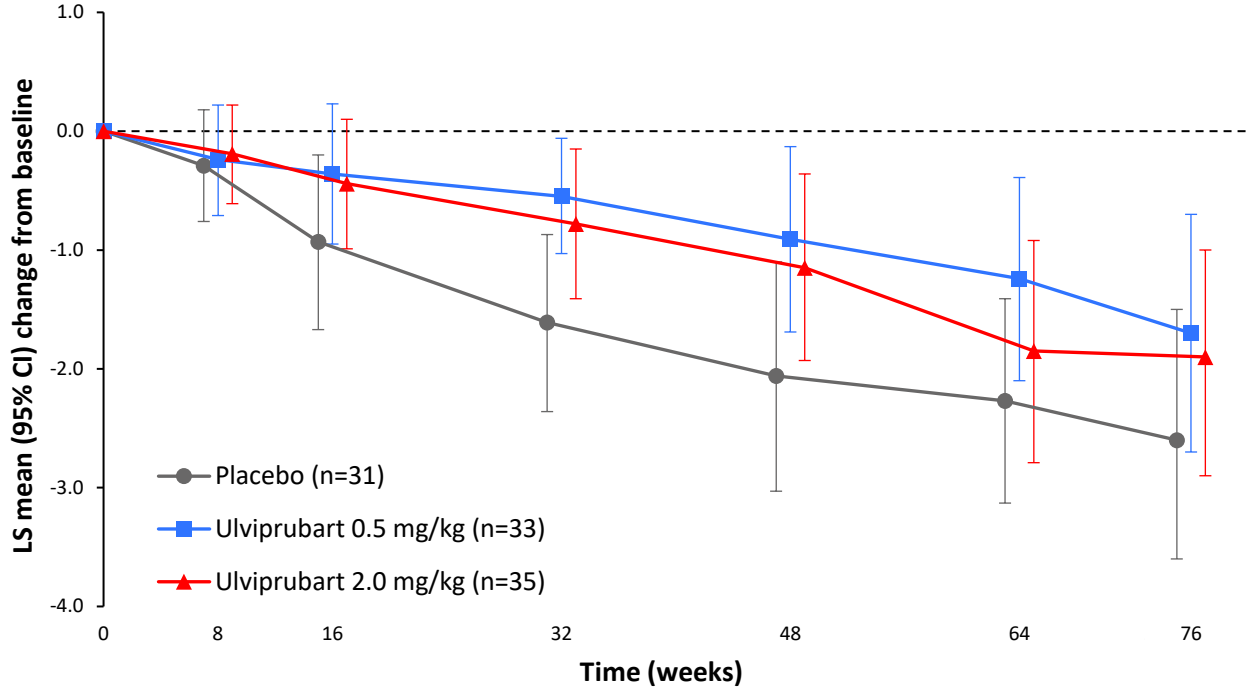
IBMFRS, Inclusion Body Myositis Functional Rating Scale; LS, least squares.

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

Change from baseline in IBMFRS score in patients who were cN1A+ at baseline[a]



Change from baseline in IBMFRS score in patients who were cN1A− at baseline



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.

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
- 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	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.

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

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IBM, inclusion body myositis; IBMFRS, Inclusion Body Myositis Functional Rating Scale.