

Impact of anti-cytosolic nucleotidase 1A antibody status on disease phenotype and therapeutic response to ulviprubart in inclusion body myositis

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Presented at the 2026 European Alliance of Associations for Rheumatology, London, UK; Presentation number: OP0164



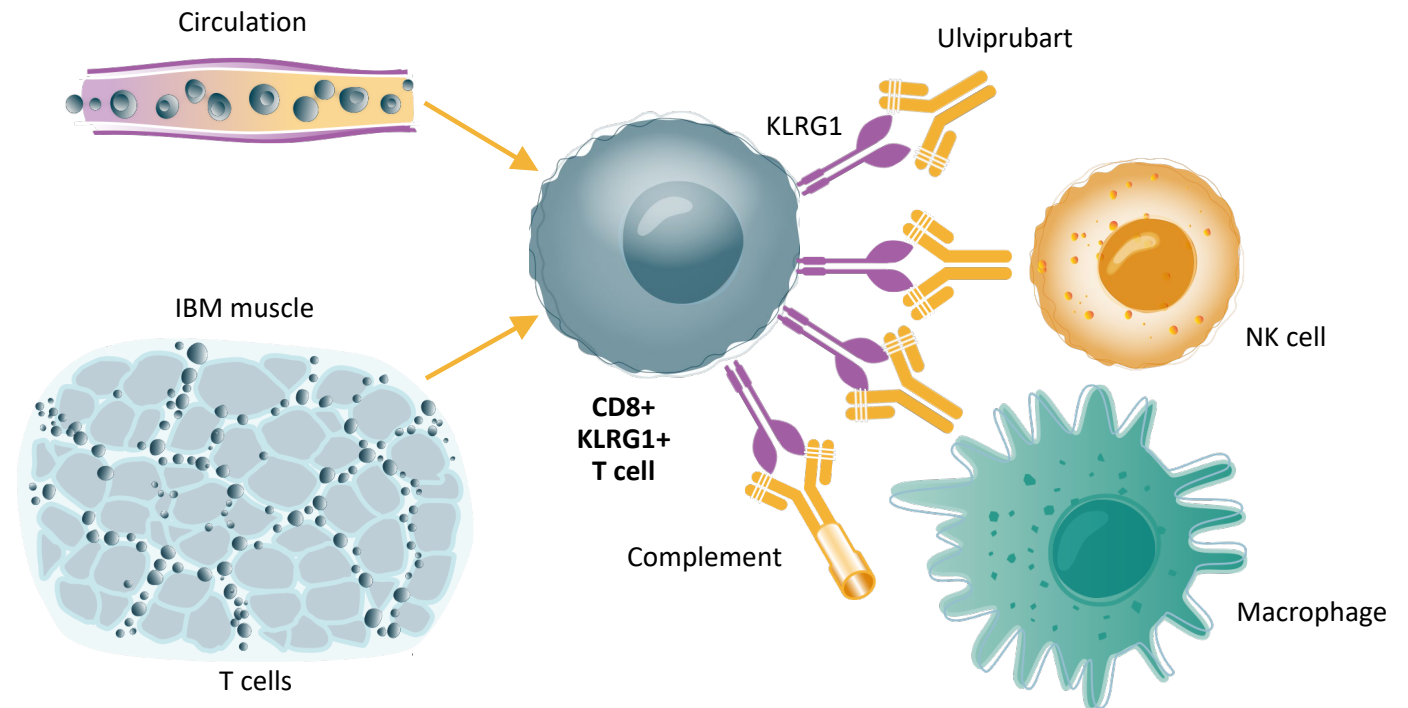
Disclosure statement

Pedro M. Machado has received grants and/or honoraria from Abbvie, Abcuro, BMS, Celgene, Eli Lilly, Galapagos/Alfasigma, Greywolf, Janssen, MSD, Novartis, Orphazyme, Pfizer, Roche, and UCB; he has also served as UK Chief Investigator and site PI for the ABC008 study



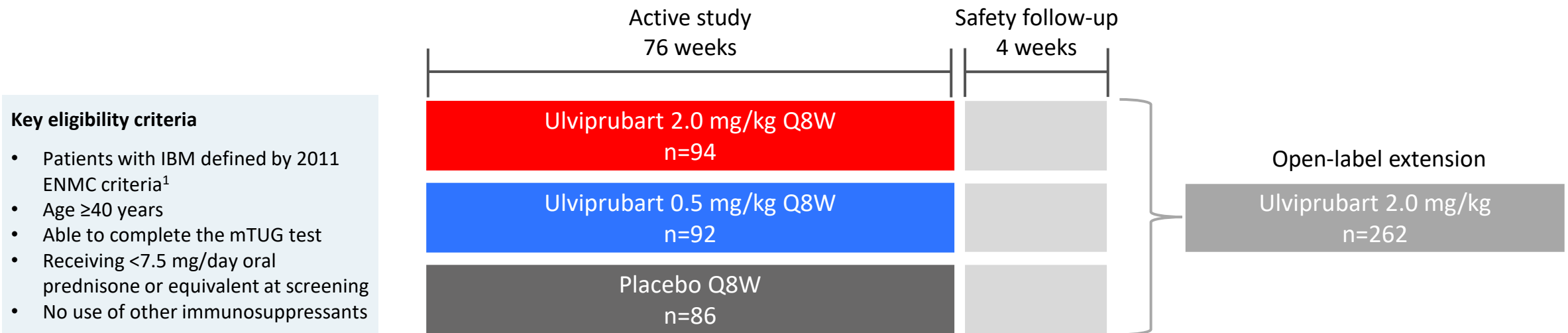
Introduction

- Ulviprubart is a humanized monoclonal antibody that selectively depletes cytotoxic CD8+ KLRG1+ T cells by targeting KLRG1 expressed on most IBM muscle-infiltrating T cells¹
- The objective of this randomized, double-blind study was to evaluate the efficacy and safety of ulviprubart in the treatment of patients with IBM



Study design

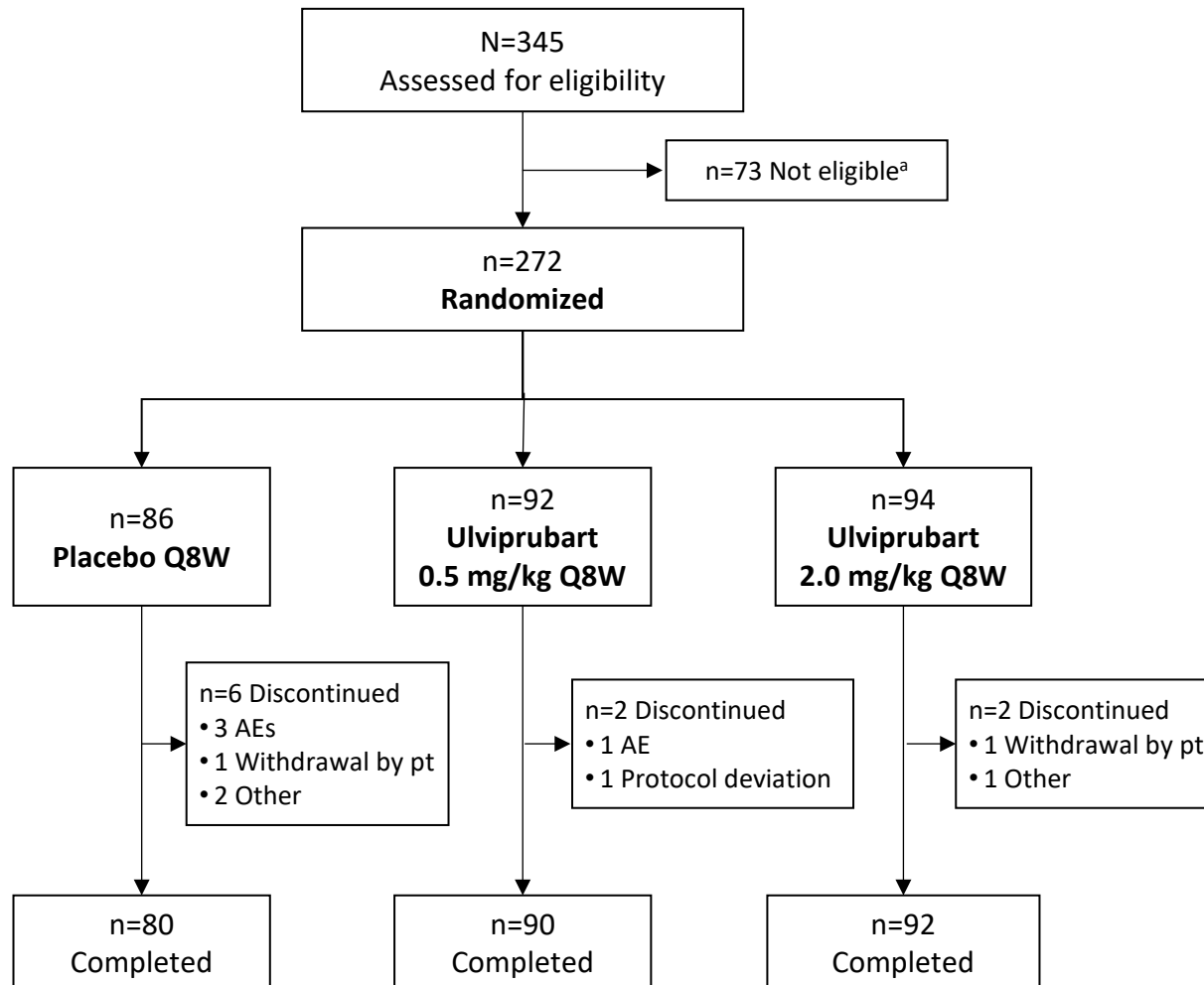
- This phase 2/3 randomized, double-blind, placebo-controlled, global study was conducted at 45 sites in Australia, Belgium, Canada, France, Germany, the United Kingdom, and the United States



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



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)

^a65 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.



Baseline characteristics of patients grouped by anti-cN1A antibody status

- Autoantibodies against cN1A serve as supportive diagnostic markers in IBM, with varying levels of evidence regarding their association with disease severity^{1,2}
- Baseline characteristics were generally similar between groups defined by anti-cN1A status, except for swallowing impairment, which was more frequent and severe in the anti cN1A+ group

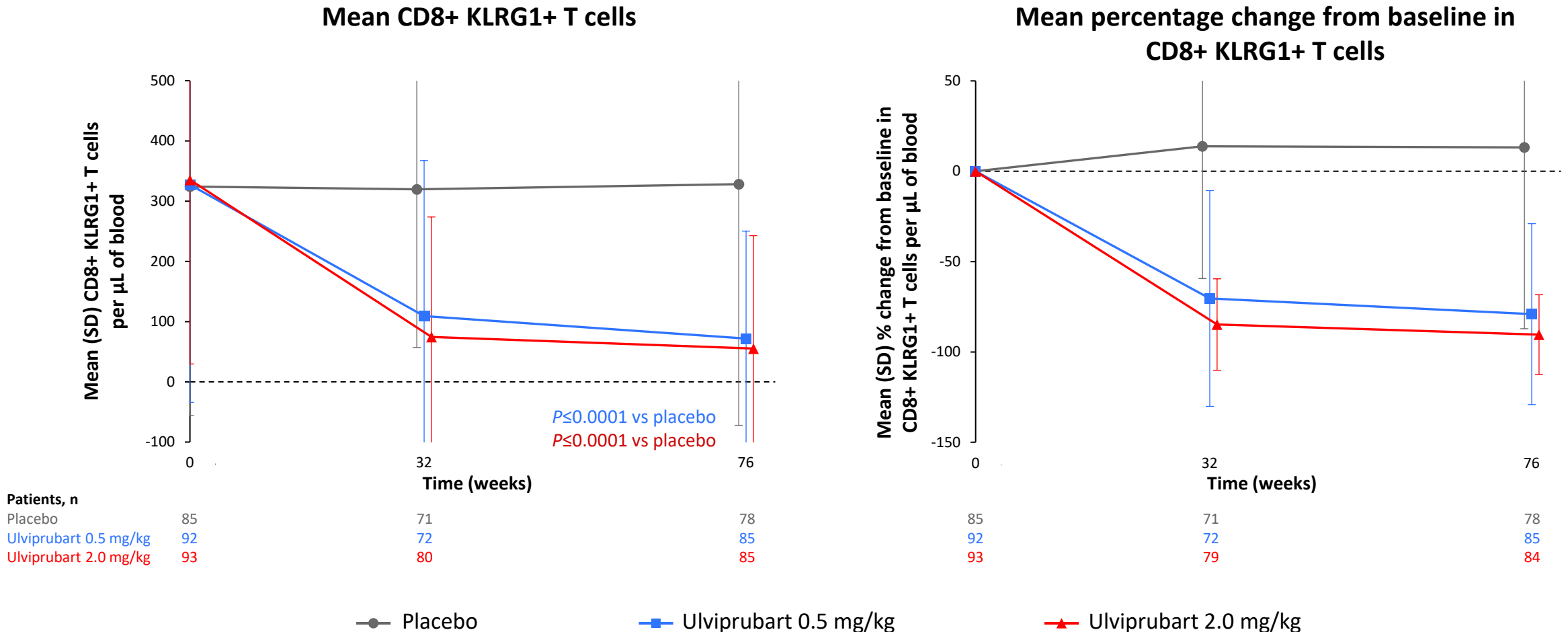
Baseline demographics and clinical characteristics

	Anti-cN1A+ (n=171) ^{a,b}	Anti-cN1A- (n=101)
Age, mean (SD), years	67.8 (7.7)	68.5 (8.0)
Sex, male, n (%)	114 (66.7)	72 (71.3)
Age of symptom onset, mean (SD), years	60.3 (8.3)	60.6 (9.0)
Age of diagnosis, mean (SD), years	65.1 (8.1)	65.1 (8.2)
IBMFRS score, mean (SD)	27.1 (5.0)	27.6 (4.9)
MMT, mean (SD)	177.6 (25.9)	179.8 (27.3)
mTUG, mean (SD), seconds	18.9 (26.6)	18.6 (24.1)
Grip strength, dominant, mean (SD), kg	11.5 (6.5)	11.8 (7.9)
Quadriceps strength, dominant, mean (SD), kg	10.9 (7.6)	11.0 (7.8)
EAT-10 score ≥ 3 , n (%) ^c	82 (48.0)*	29 (28.7)
EAT-10 total score, mean (SD) ^c	5.7 (6.9)**	2.9 (4.3)

Anti-cN1A detection was performed using ELISA. EAT-10 scores ≥ 3 indicate dysphagia.³ Comparisons between groups at baseline were made using Fisher's exact or chi-square test for categorical variables and t-test for numeric variables. ^aIncludes patients who were positive or borderline for anti-cN1A antibody at baseline; ^bA sensitivity analysis excluding borderline cases (n=19, 7%) yielded similar results to the primary analysis; ^cn=139 for anti-cN1A+ and n=82 for anti-cN1A-. *P<0.0001 for anti-cN1A+ vs anti-cN1A- group; **P=0.001 for anti-cN1A+ vs anti-cN1A- group. cN1A, cytosolic nucleotidase1A; EAT-10, Eating Assessment Tool; ELISA, enzyme-linked immunosorbent assay; IBM, inclusion body myositis; IBMFRS, Inclusion Body Myositis Functional Rating Scale; MMT, Manual Muscle Testing; mTUG, modified Timed Up and Go. 1. Lilleker JB, et al. *Neuromuscul Disord*. 2024;37:36-51. 2. Salam S, et al. *Clin Exp Rheumatol*. 2022;40(2):384-93. 3. Belafsky PC, et al. *Ann Otol Rhinol Laryngol*. 2008;117(12):919-24.



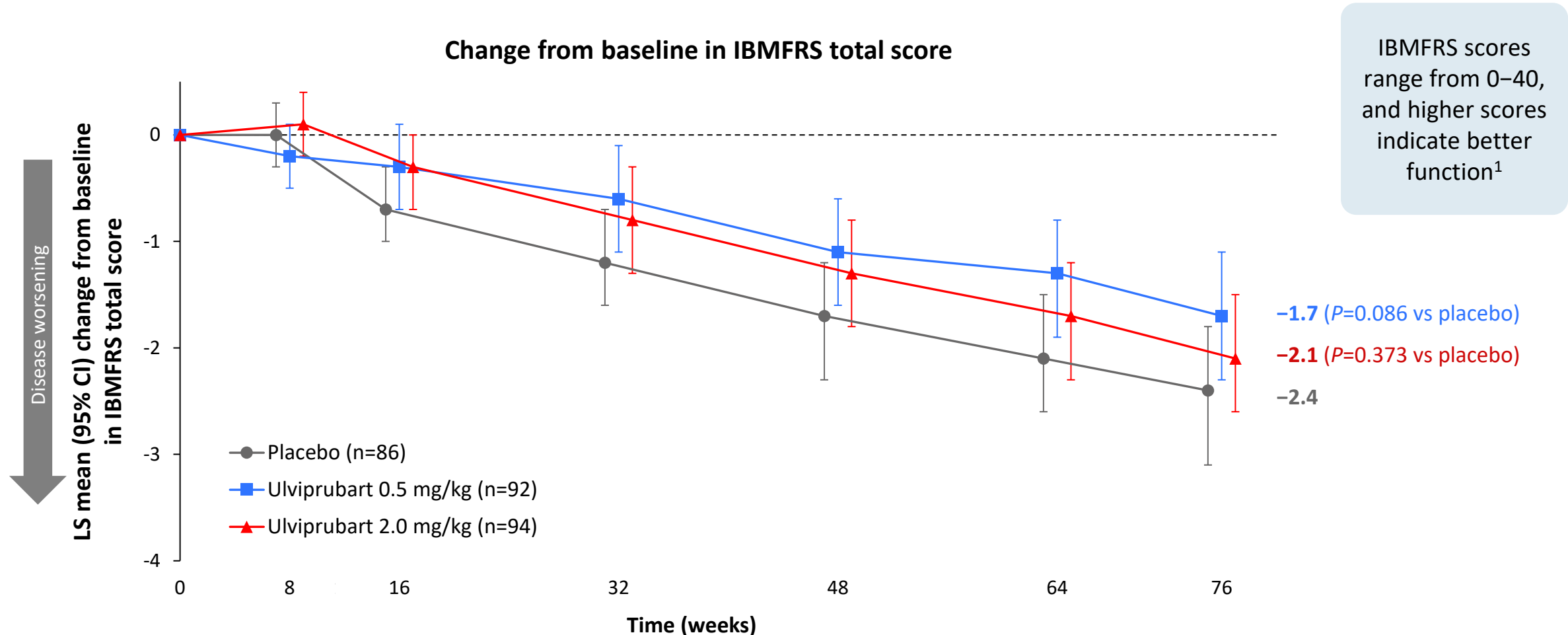
Both doses of ulviprubart achieved deep depletion of blood CD8+ KLRG1+ T cells



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.

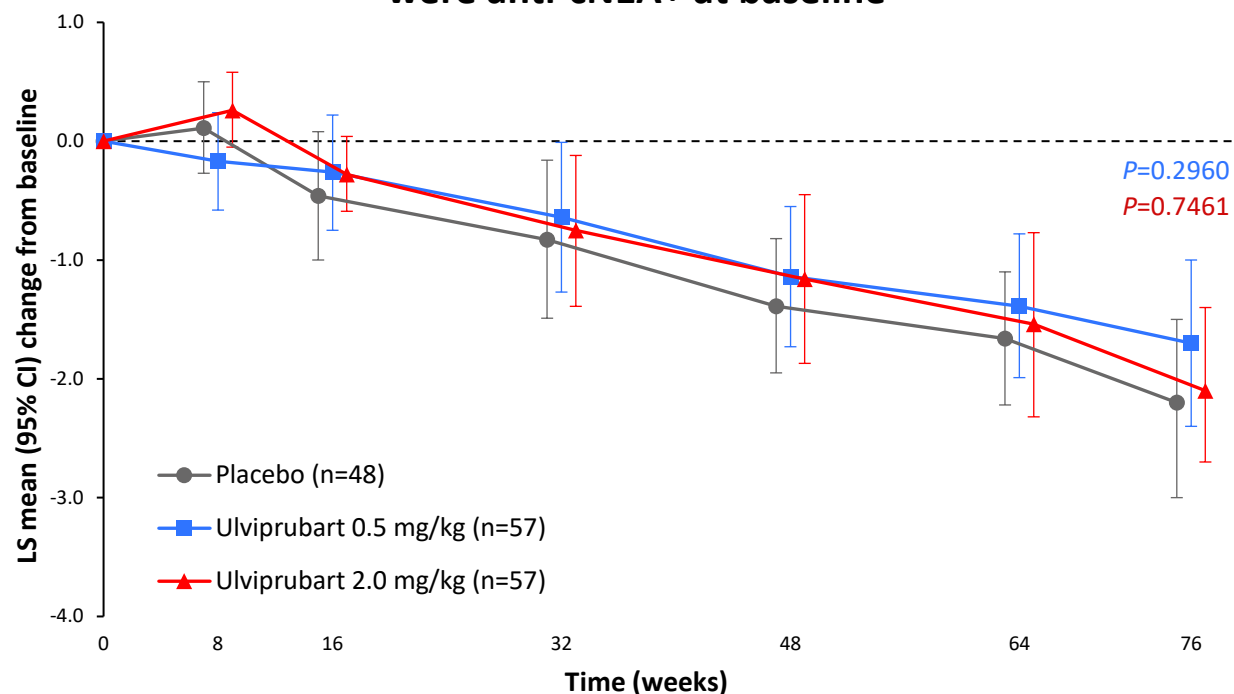


Primary endpoint: IBMFRS total score changes were not significantly different at week 76

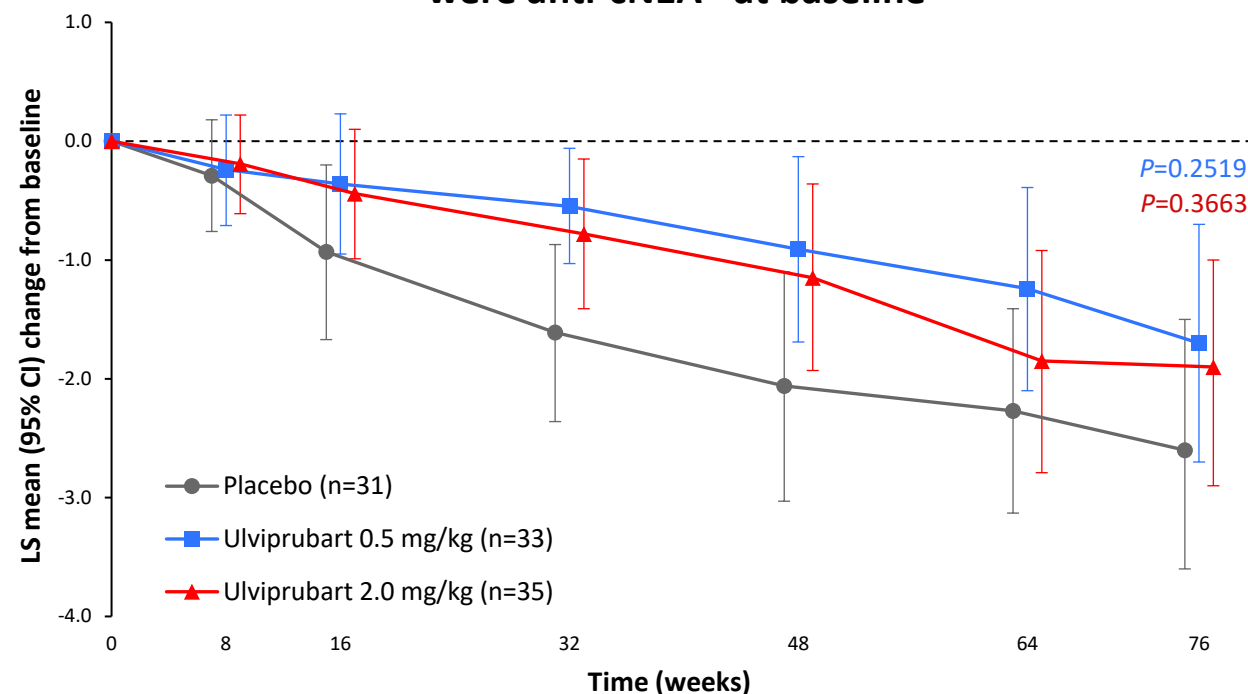


Anti-cN1A antibody status did not have an impact on IBMFRS changes with ulviprubart vs placebo

Change from baseline in IBMFRS score in patients who were anti-cN1A+ at baseline^a



Change from baseline in IBMFRS score in patients who were anti-cN1A- at baseline

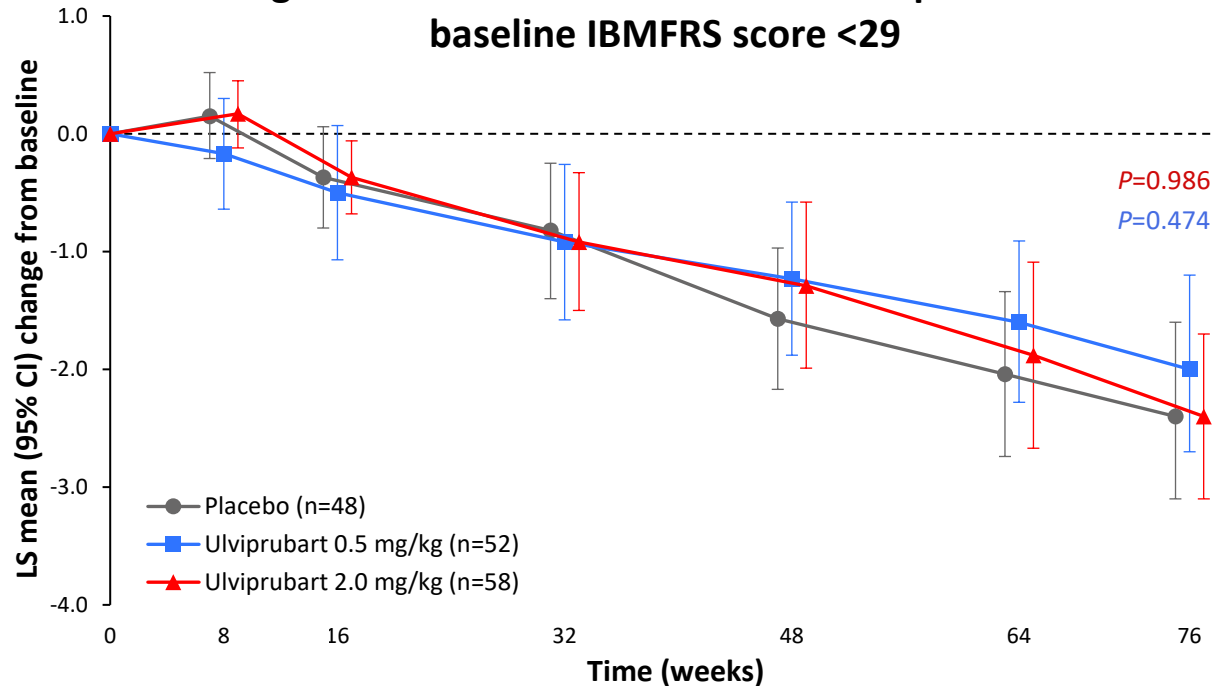


Data for timepoints 8, 16, 32, 48, and 64 are mean estimates and remain to be validated. Patient numbers for changes from baseline at week 76 are shown. ^aIncludes patients who were positive or borderline for anti-cN1A antibody at baseline. cN1A, cytosolic 5'-nucleotidase 1A; IBMFRS, Inclusion Body Myositis Functional Rating Scale; LS, least squares.

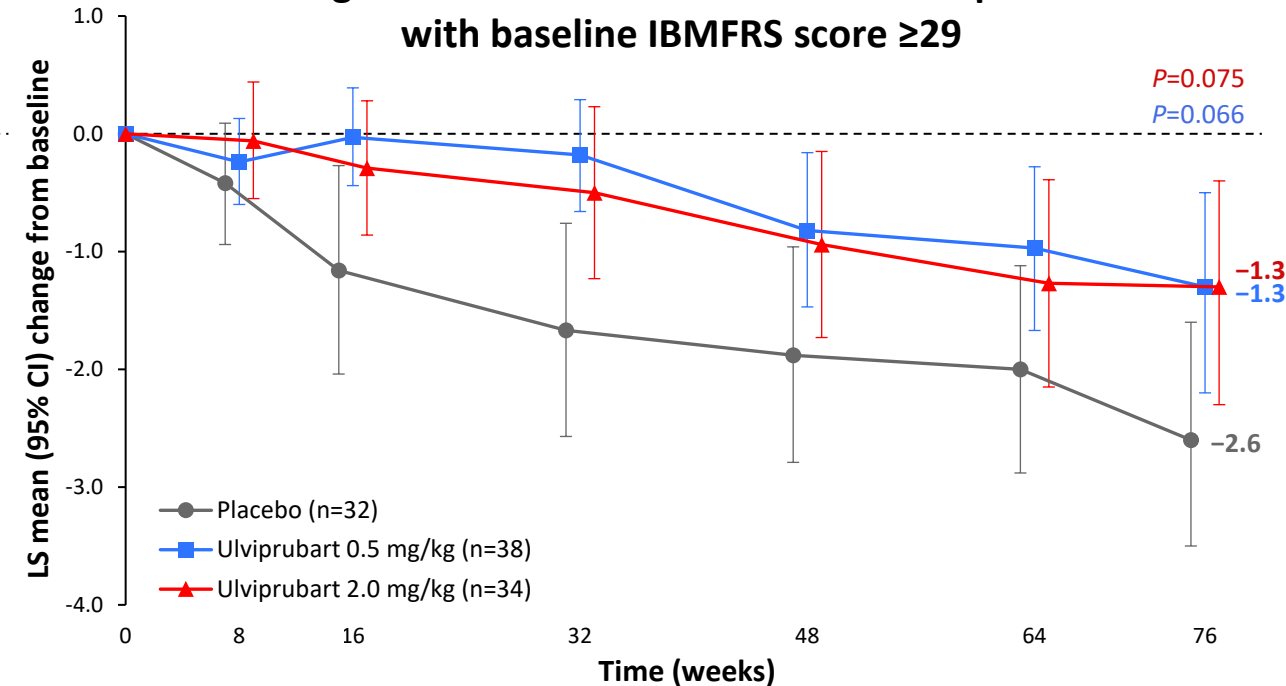


Trends suggesting slower reduction in IBMFRS score were seen in patients with baseline IBMFRS score ≥ 29

Change from baseline in IBMFRS score in patients with baseline IBMFRS score < 29



Change from baseline in IBMFRS score in patients with baseline IBMFRS score ≥ 29



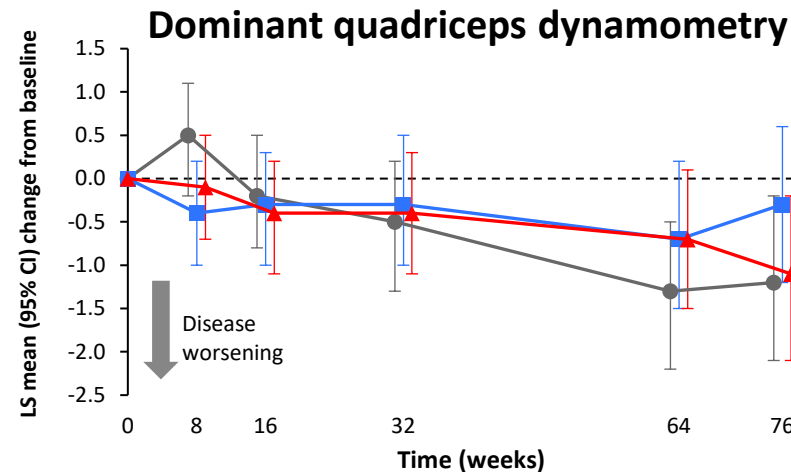
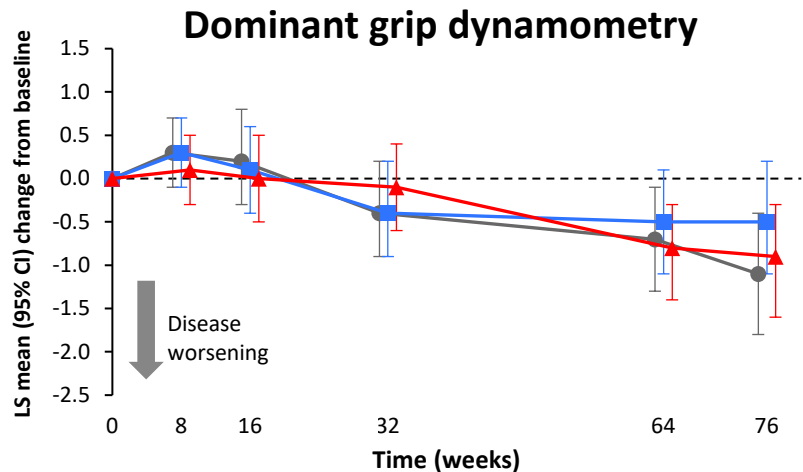
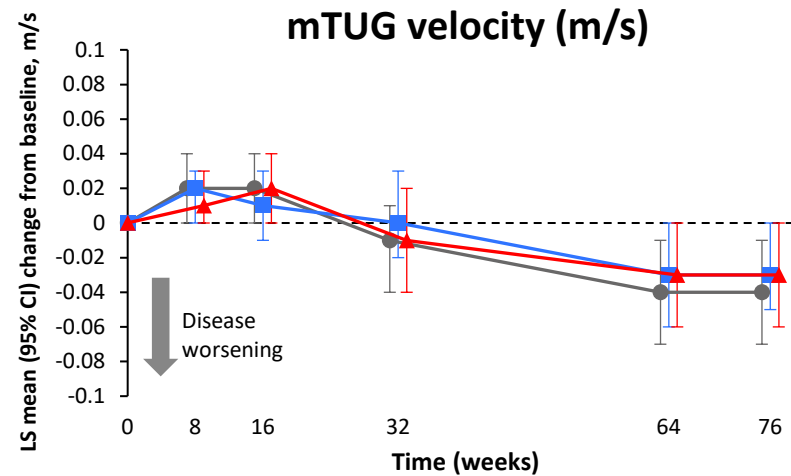
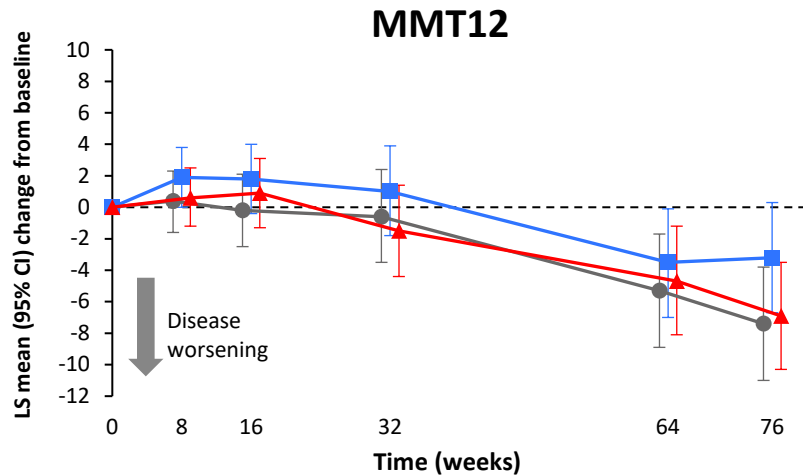
- Baseline characteristics for patients with baseline IBMFRS score < 29 vs ≥ 29 were similar apart from time since diagnosis and since symptom onset, which were slightly longer in the group with more severe disease

In patients with baseline IBMFRS score ≥ 29

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



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. ^an=85 for dominant quadriceps dynamometry. LS, least squares; m/s, meters per second; MMT12, Manual Muscle Testing 12; mTUG, modified Timed Up and Go.



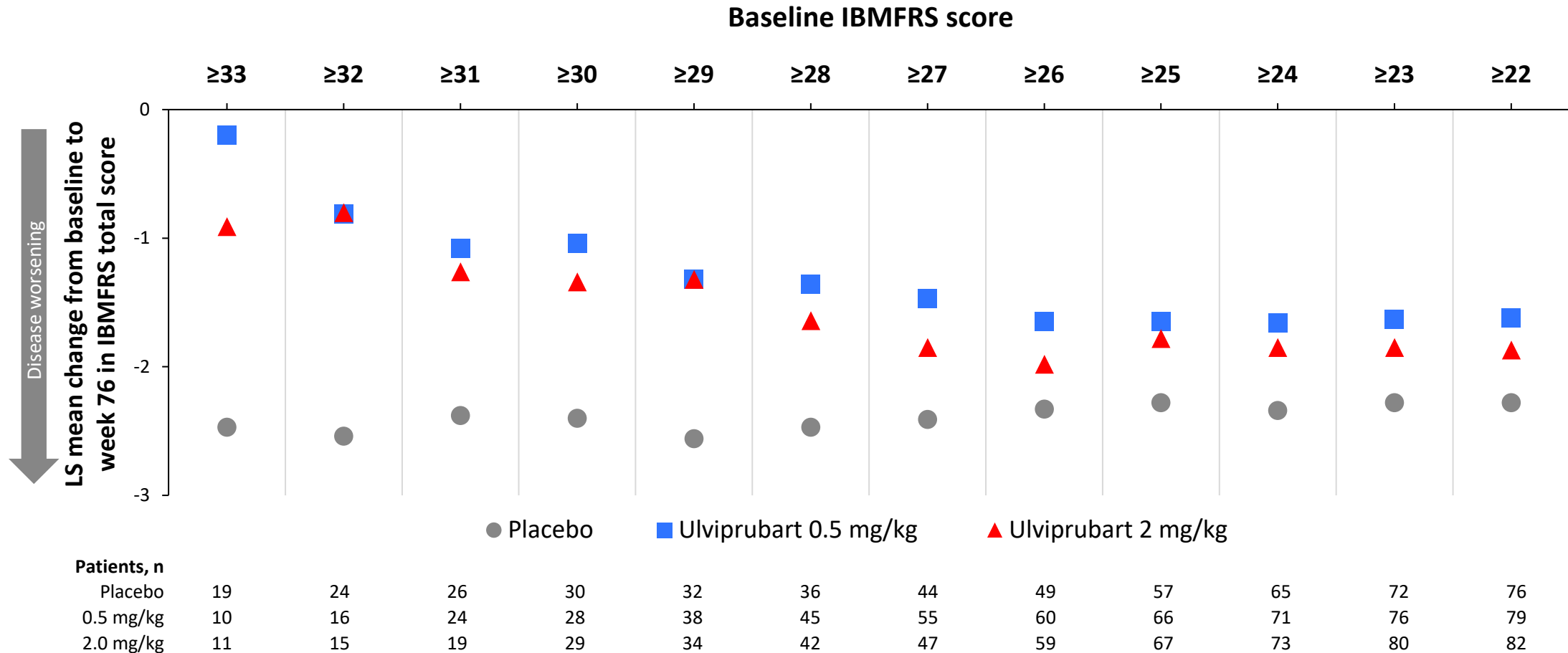
Trends suggesting slowed disease progression in patients with baseline IBMFRS score ≥ 29 were also observed in key secondary endpoints

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



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 $\geq 10\%$ 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

^aEvents of pneumonia aspiration and dehydration unrelated to treatment in 1 patient receiving placebo. ^bPlacebo: 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. ^cTEAEs of special interest were infections or symptoms of systemic drug reactions.



Conclusions

- This randomized, double-blind, placebo-controlled, phase 2/3 study of the efficacy and safety of ulviprubarb in patients with IBM did not meet its primary endpoint (assessed by the IBMFRS total score at week 76) or key secondary endpoints
- At baseline, as indicated by EAT-10 scores, swallowing difficulties were more common among anti-cN1A–positive patients
- Anti-cN1A antibody status did not have an impact on IBMFRS changes with ulviprubarb vs placebo
- In a prespecified subgroup analysis, patients with baseline IBMFRS total scores of ≥ 29 (less severe) showed trends in slowing disease progression based on IBMFRS
- Ulviprubarb demonstrated a favorable safety and tolerability profile compared with placebo

Acknowledgments

- The authors thank all study participants and their families as well as the care teams, investigators, and research staff at participating institutions
- This study was sponsored by Abcuro, Inc.
- The authors thank Peloton Advantage, LLC, an OPEN Health company, for providing medical writing and editorial support, which was sponsored by Abcuro, Inc., in accordance with Good Publication Practice guidelines

