A Phase 1b/2 study of the anti-myostatin adnectin RG6206 (BMS-986089) in ambulatory boys with Duchenne muscular dystrophy

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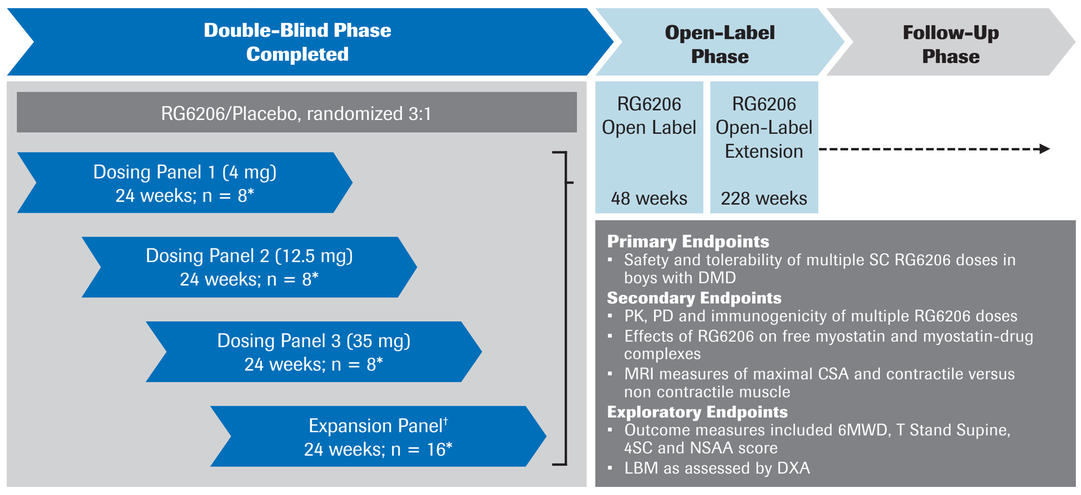
Introduction

- DMD is an X-linked, recessive neuromuscular disorder resulting in a loss of function of dystrophin protein and progressive muscle degeneration from early childhood.[1,2]
- Inhibition of myostatin, a negative regulator of muscle growth[3], has been shown to increase skeletal muscle mass in several species including humans.[3,4]
- RG6206 (BMS-986089) is a fully human anti-myostatin adnectin modified by the addition of an IgG-Fc tail to prolong half-life.[5]
  - RG6206 inhibits myostatin activity by binding to serum-free myostatin or myostatin-ActRIIB complex and inhibiting downstream pSmad2/3 signaling via the inhibition of ALK4/5 (signaling receptor) recruitment.
  - RG6206 is administered subcutaneously with weekly dosing at home.[5]
  - In a Phase 1 healthy volunteer trial (NCT02145234)[6] RG6206 treatment reduced levels of free myostatin from baseline by a maximum of 96%.
    - This was associated with increases in thigh muscle volume and total LBM that were dependent on RG6206 dose and magnitude of free myostatin suppression.[7]

Method and Study Design

- Phase 1b/2 study of the novel anti-myostatin adnectin RG6206 in ambulatory boys with DMD, aged 5–10 years (NCT02515669).[8]
- Forty-three boys were randomized to receive weekly SC doses of RG6206 (4–50 mg) or placebo (Figure 1).[8]

Figure 1. NCT02515669: Design of a Phase 1b/2 MAD study in ambulatory boys with DMD aged 5–10 years[7,8]



*n, numbers per protocol; †Expansion panel utilizes the same dose as Dosing Panel 3.

Table 1: NCT02515669: Demographics and baseline characteristics*

	Placebo	Panel 1 RG6206	Panel 2 RG6206	Panel 3 RG6206	Expansion Panel RG6206
n	11	7	6	6	13
RG6206 dose, mg **≥ 15 kg** **≥ 15 to ≤ 45 kg** **> 45 kg**	N/A	4	12.5 20	35 50	35 50
Age, mean years (SD)	8.8 (1.3)	8.0 (2.2)	8.0 (1.8)	7.7 (2.3)	8.2 (1.6)
Age, n **5–6 years** **≥ 6–10 years**	1 10	3 4	1 5	3 3	3 10
Screening weight, mean kg (SD)	29.7 (7.6)	26.1 (6.4)	27.8 (6.6)	27.5 (6.7)	28.1 (9.0)
Screening weight, n **≤ 45 kg** **> 45 kg**	10 1	7 0	6 0	6 0	12 1
Myostatin, median pg/mL (min–max)	1071 (500–2745)	835 (611–1006)	1114 (538–3552)	1447 (703–2143)	835 (492–1580)

Forty patients received daily doses of corticosteroids – three patients received intermittent doses.
*All treated subjects.

Results

- RG6206 was generally well tolerated throughout the 24-week double blind phase (Table 2).
  - No clinically significant changes in safety lab parameters, vital signs or ECG parameters were observed.
  - The most common AEs considered to be related to study drug were cutaneous injection site reactions (RG6206, n = 7, 21.9%), which were mild (except one event of moderate injection site discomfort).
  - Preliminary immunogenicity data from 43 subjects* showed one subject with a low positive ADA titer (prior to dosing and at Day 29), with no post-treatment boost in ADA titer.
- RG6206 serum concentrations increased with dose and were accompanied by a dose-dependant reduction (77-97%) in free myostatin. Maximum myostatin suppression was obtained with the high (35 mg) dose.
- Muscle composition (MRI, DXA) and function (6MWD, T Stand Supine, 4SC and NSAA) were correlated at baseline (Table 3).

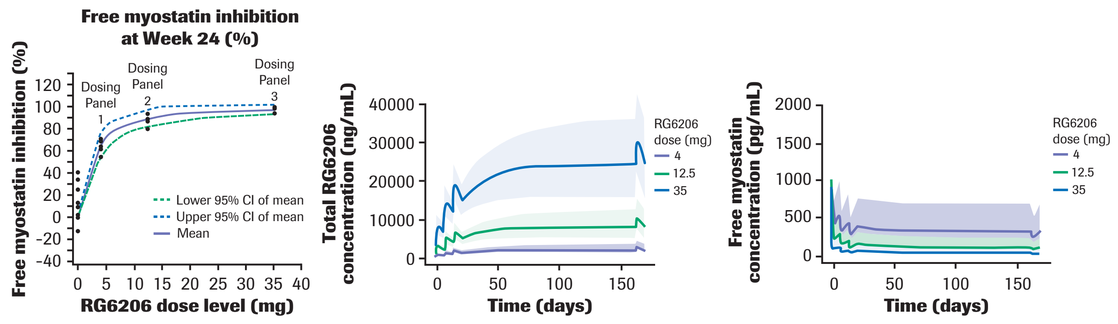
There was no impact of treatment on function and functional endpoints were stable at 24 weeks; however, the study was not powered to demonstrate effects on functional endpoints.

Table 2. NCT02515669: Safety summary*

n (%)	RG6206 (n = 32)	Placebo (n = 11)
Patients experiencing any AEs	28.7 (87.5)	9 (81.8)
Patients experiencing moderate-intensity AEs (No severe-intensity AEs)	4 (12.5) Foot fracture, injection site discomfort, headache, spinal compression fracture	1 (9.1) Vomiting, fall, skull fracture, headache
Patients experiencing SAEs	1 (3.1) Fractures as a result of a fall considered unrelated to study drug	1 (9.0) Fractures as a result of a fall considered unrelated to study drug
Deaths or AEs leading to discontinuation	0 (0)	0 (0)

*During the double-blind phase; Data cut-off: 20 April 2017.

Figure 2. NCT02515669: PK and target engagement



Population PK analysis – lines are the population average and shaded areas represent the 90% prediction interval. Target myostatin suppression for Dosing Panels: 1 = ≥ 50%, 2 = ≥ 85%, 3 and expansion = ≥ 95%.

- Analysis of DXA and MRI data suggests positive effects of RG6206 on muscle.
  - When all dose groups were pooled, a 3.85% increase in LBMI (Figure 3) and a 5.49% increase in contractile CSA of right thigh was observed versus placebo.
  - Baseline serum myostatin levels were not correlated with changes in muscle volume or composition.

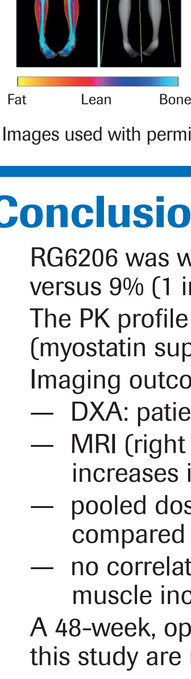
Table 3: NCT02515669: Correlations of imaging and functional tests at baseline

	6MWD	T Stand Supine	4SC	NSAA
DXA measurements, R^2 (P value)				
LBM	**0.31 (0.045)**	-0.27 (0.083)	**-0.43 (0.004)**	-0.02 (0.918)
LBM index	**-0.35 (0.024)**	**0.54 (< 0.001)**	**0.45 (0.003)**	**0.37 (0.022)**
Fat mass	-0.24 (0.123)	**0.50 (0.001)**	**0.32 (0.037)**	**-0.57 (< 0.001)**
MRI measurements, R^2 (P value)				
Contractile muscle percentage	**0.44 (0.003)**	**-0.66 (< 0.001)**	**-0.54 (< 0.001)**	**0.68 (< 0.001)**
CSA muscle	0.23 (0.152)	-0.10 (0.534)	-0.25 (0.113)	0.08 (0.631)
CSA contractile muscle	**0.46 (0.002)**	**-0.41 (0.006)**	**-0.52 (< 0.001)**	**0.41 (0.008)**
CSA non-contractile muscle	**-0.34 (0.027)**	**0.52 (< 0.001)**	**0.41 (0.007)**	**-0.56 (< 0.001)**
Lipid fraction, R^2 (P value)	-0.27 (0.155)	**0.62 (< 0.001)**	**0.46 (0.009)**	**-0.64 (< 0.001)**

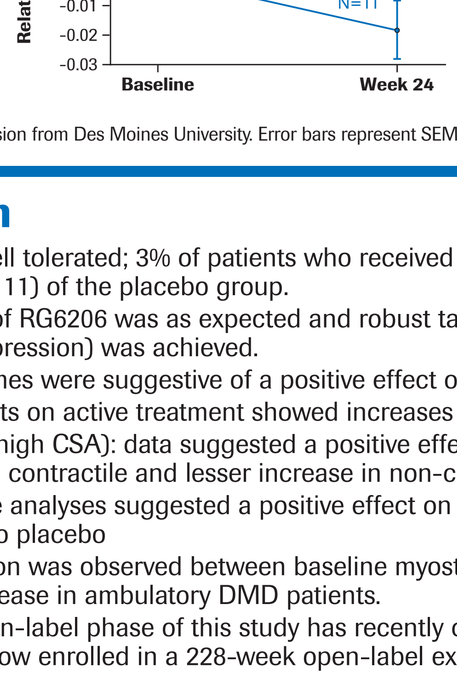
Bold text denotes statistical significance (P = < 0.05). Heat map colors indicate positive (green) or negative (orange) correlations.

Figure 3. NCT02515669: Imaging outcomes (DXA)

DXA provides measures of body fat, lean body tissue and bone mineral content



Patients receiving active treatment had increases in LBM compared with placebo



	Treated pooled (N = 30)	Placebo (N = 11)	Δ treatment–placebo
% LBMI	2.02	-1.82	3.85
Mean LBMI (SEM)	0.02 (0.01)	-0.02 (0.01)	-

Images used with permission from Des Moines University. Error bars represent SEM.

Conclusion

- RG6206 was well tolerated; 3% of patients who received treatment (1 in 32) experienced SAEs versus 9% (1 in 11) of the placebo group.
- The PK profile of RG6206 was as expected and robust target engagement (myostatin suppression) was achieved.
- Imaging outcomes were suggestive of a positive effect of RG6206 treatment on muscle:
  - DXA: patients on active treatment showed increases in LBM compared with placebo
  - MRI (right thigh CSA): data suggested a positive effect on muscle composition with increases in contractile and lesser increase in non-contractile tissue
  - pooled dose analyses suggested a positive effect on muscle growth and composition compared to placebo
  - no correlation was observed between baseline myostatin levels and LBM or contractile muscle increase in ambulatory DMD patients.
- A 48-week, open-label phase of this study has recently concluded. In total, 41 patients from this study are now enrolled in a 228-week open-label extension.

Ongoing RG6206 Pivotal Study for DMD patients

- Phase 2/3 study in ambulatory boys with DMD, aged 6–11 years (NCT03039686).[9]
- This study will evaluate the efficacy, safety and tolerability of RG6206 in ambulatory boys with DMD.
- Planned sites*: North and South America, Belgium, France, Germany, Italy, Netherlands, Spain, Sweden, UK, Japan, Australia.

For further information about the study and eligibility criteria visit www.roche-duchenne-clinicaltrials.com
Or visit https://clinicaltrials.gov/ct2/show/NCT03039686 (NCT03039686).[9]
*Trial status correct as of May 2018

Abbreviations

4SC, 4 stair climb; 6MWD, 6-minute walk distance; ActRIIB, activin receptor type IIB;ADA, anti-drug antibody; AE, adverse event; ALK, anaplastic lymphoma kinase; CSA, cross sectional area; DMD, Duchenne muscular dystrophy; DXA, dual-energy x-ray absorptiometry; ECG, echocardiogram; Fc, fragment crystalizable; Ig, immunoglobulin; LBM, lean body mass; LBMi, lean body mass index; MAD, multiple ascending dose; MRI, magnetic resonance imaging; N/A, not applicable; NSAA, North Star Ambulatory Assessment; PD, pharmacodynamics; PK, pharmacokinetics; SAE, serious adverse event; SC, subcutaneous; SD, standard deviation; SEM, standard error of the mean; T Stand Supine, time to standing from supine.

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