Activin type II receptor blockade for treatment of muscle depletion in COPD: A randomized trial

Michael I. Polkey, Jens Praestgaard, Amy Berwick, Frits M. E. Franssen, Dave Singh, Michael C. Steiner, Richard Casaburi, Hanns-Christian Tillmann, Estelle Lach-Trifilieff, Ronenn Roubenoff, and Daniel S. Rooks

ONLINE DATA SUPPLEMENT

ONLINE SUPPLEMENTARY MATERIAL

Table E1. Inclusion and exclusion criteria

Inclusion criteria
Patients eligible for inclusion in this study had to fulfill all of the following criteria: 1. Written informed consent was obtained before any assessment was performed. 2. Males and sterile or post-menopausal females aged 40 to 80 years. Women were postmenopausal or surgically sterile females who were at least 12 months beyond natural or surgically-induced menopause (e.g., tubal ligation, bilateral oophorectomy or total hysterectomy as confirmed by surgical note). Natural menopause was defined as ≥12 continuous months of spontaneous amenorrhea or 6 months of amenorrhea with follicle stimulating hormone (FSH) level indicative of postmenopausal status. All women, regardless of age, were required to have a negative pregnancy test result at Screening and at Baseline. 3. Smoking history of at least 10 pack-years. 4. Diagnosis of COPD according to GOLD guidelines, with a post-bronchodilator FEV_1 <80% predicted and FEV_1/FVC ratio <0.70. 5. BMI <20 kg/m^2 or skeletal muscle mass index by DXA <7.25 kg/m^2 for men or <5.45 kg/m^2 for women. 6. In general stable health, including managed COPD, by past medical history, physical examination, vital signs at Baseline as determined by the Investigator.
Exclusion criteria
Patients fulfilling any of the following criteria were not eligible for inclusion in this study: 1. Patients with MRC dyspnea Grade 5 (i.e. patients too breathless to leave the house or breathless when dressing). 2. Plans for lung transplantation or lung reduction surgery within four months of enrollment. 3. Patients participating in a formal pulmonary rehabilitation program within 3 months of dosing. 4. History of malignancy of any organ system (other than excised non-melanomatous carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there was an evidence of local recurrence or metastases. 5. Diseases other than cancer known to cause cachexia or muscle atrophy, including but not limited to congestive heart failure of any stage, chronic kidney disease with estimated Glomerular Filtration Rate (GFR) <30 mL/min using the Modification of Diet in Renal Disease (MDRD) equation, rheumatoid arthritis, primary myopathy, stroke, Human Immunodeficiency Virus (HIV) infection, tuberculosis or other chronic infection, uncontrolled diabetes mellitus, etc. 6. Any other clinically relevant disease or disorder e.g., infectious/viral disease (including hepatitis B or C), cardiovascular (including unstable ischemic heart disease, arrythmia, cardiomyopathy, uncontrolled hypertension), pulmonary disease other than COPD, gastrointestinal, liver, renal, neurological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment, past or present, which in the opinion of the Investigator could either put the patient at risk by participation in the study or could influence the results of the study or the patient's ability to participate in the study.

7. Patients whose status post splenectomy or organ transplant, on anti-Tumor Necrosis Factor (TNFα) medication, or were immunocompromised (e.g. IgA or other immunoglobulin)
8. Hospitalization within 14-days prior to Screening.
9. Hemoglobin concentration below 11.0 g/dL at Screening.
10. Liver disease or liver injury as indicated by abnormal liver function tests such as Serum Glutamic Oxaloacetic Transaminase (SGOT) Aspartate Amino Transferase (AST), Serum Glutamic Pyruvate Transaminase (SGPT) Alanine Amino Transferase (ALT), Gammaglutamyl transferase (γ-GT), alkaline phosphatase, or serum bilirubin (other than Gilbert's Disease). The Investigator was guided by the following criteria:
    - Any single transaminase listed above should have not exceeded 3x upper limit of normal (ULN).
    - If the total bilirubin concentration increased above 1.5 x ULN, total bilirubin should have been differentiated into the direct and indirect reacting bilirubin. Total serum bilirubin should not have exceeded 2 x ULN.
11. Diseases known to cause malabsorption of protein or energy, such as inflammatory bowel disease, celiac disease, short bowel syndrome, pancreatic insufficiency, etc.
12. Patients weighing <40 kg or ≥120 kg.
13. Usual dietary intake <20 kcal/kg and 0.6 g protein/kg estimated by a diet evaluation.
14. Use of any prescription drugs known to affect muscle mass, including androgen supplements, anti-androgens (such as Luteinizing hormone release hormone (LHRH) agonists), anti-estrogens (tamoxifen, etc.) recombinant human growth hormone (rhGH), insulin, oral beta agonists, megestrol acetate, dronabinol, metformin, etc.
15. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever was longer; or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations.
16. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
17. Patients with known claustrophobia, double above-knee leg amputee, presence of pacemaker and/or ferromagnetic material in their body that would prohibit MRI imaging.
18. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant.
20. Any history of bleeding diathesis.
21. Taking heparin, Coumadin, Plavix, or any other anticoagulant at the time of Screening.
22. Chronic aspirin or non-steroidal anti-inflammatory use.
23. Allergy to lidocaine, bupivacaine or other drug or material used in obtaining the biopsy.
24. Active infection or chronic skin conditions that prevent access to the biopsy area.

Table E2. Adverse events according to treatment groups

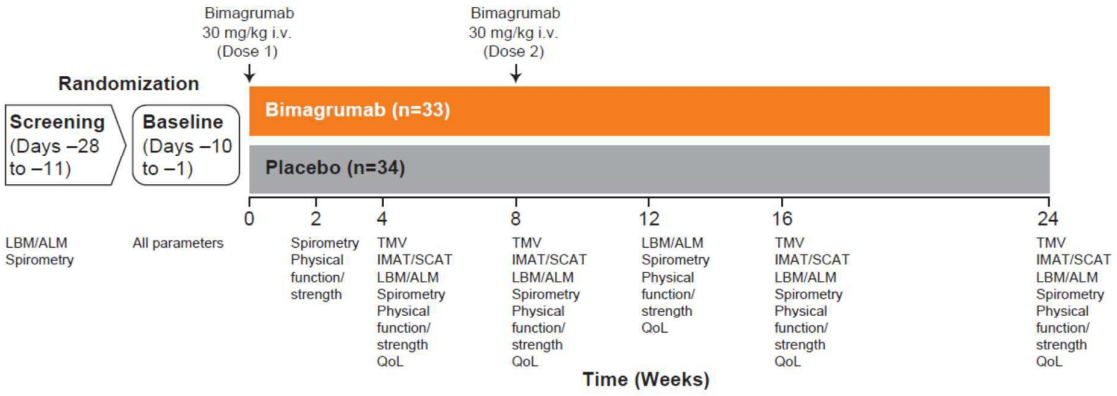
Summary of AEs[†]	**Bimagrumab (n=33)**	**Placebo (n=34)**	**Total (n=67)**
Participants with AE(s)	33 (100)	31 (91.2)	64 (95.5)
Muscle spasms	26 (78.8)*	16 (47.1)	42 (62.7)
Acute exacerbation of COPD	16 (48.5)	13 (38.2)	29 (43.3)
Muscle twitching	15 (45.5)	9 (26.5)	24 (35.8)
Muscle tightness	18 (54.5)***	5 (14.7)	23 (34.3)
Pain in extremity	8 (24.2)	7 (20.6)	15 (22.4)
Myalgia	7 (21.2)	6 (17.6)	13 (19.4)
Pruritus	5 (15.2)	7 (20.6)	12 (17.9)
Headache	3 (9.1)	8 (23.5)	11 (16.4)
Diarrhea	7 (21.2)	3 (8.8)	10 (14.9)
Dyspnea	5 (15.2)	5 (14.7)	10 (14.9)
Cough	4 (12.1)	5 (14.7)	9 (13.4)
Back pain	4 (12.1)	4 (11.8)	8 (11.9)
Erythema	4 (12.1)	4 (11.8)	8 (11.9)
Abnormal feeling	4 (12.1)	3 (8.8)	7 (10.4)
Dizziness	3 (9.1)	3 (8.8)	6 (9)
Pneumonia	3 (9.1)	3 (8.8)	6 (9)
Upper respiratory tract infection	2 (6.1)	4 (11.8)	6 (9)
Fatigue	2 (6.1)	3 (8.8)	5 (7.5)
Musculoskeletal stiffness	3 (9.1)	2 (5.9)	5 (7.5)

Pustular rash	3 (9.1)	2 (5.9)	5 (7.5)
Acne	3 (9.1)	1 (2.9)	4 (6)
Increased blood CPK	2 (6.1)	2 (5.9)	4 (6)
Contusion	2 (6.1)	2 (5.9)	4 (6)
Depression	1 (3)	3 (8.8)	4 (6)
Ecchymosis	2 (6.1)	2 (5.9)	4 (6)
Hemoglobinuria	2 (6.1)	2 (5.9)	4 (6)
Musculoskeletal chest pain	3 (9.1)	1 (2.9)	4 (6)
Nasopharyngitis	4 (12.1)	0 (0)	4 (6)
Paresthesia	3 (9.1)	1 (2.9)	4 (6)
Increased ALT, AST, GGT	3 (9.1)	0 (0)	3 (4.5)
Arthralgia	2 (6.1)	1 (2.9)	3 (4.5)
Increased blood glucose	2 (6.1)	1 (2.9)	3 (4.5)
Gastroenteritis	2 (6.1)	1 (2.9)	3 (4.5)
Hematoma	2 (6.1)	1 (2.9)	3 (4.5)
Nausea	2 (6.1)	1 (2.9)	3 (4.5)
Sinusitis	3 (9.1)	0 (0)	3 (4.5)
Skin abrasion	1 (3.0)	2 (5.9)	3 (4.5)
Skin exfoliation	0 (0)	3 (8.8)	3 (4.5)

[†]AEs >3% in total have been listed; data presented as n (%).*P=0.011; ***P<0.001.

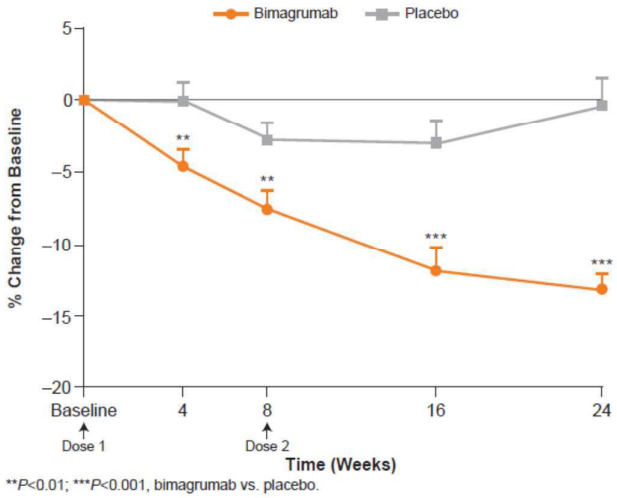
AEs=adverse events; ALT=alanine aminotransferase; AST=aspartate aminotransferase; COPD=chronic obstructive pulmonary disease, CPK=creatine phosphokinase; GGT=gamma-glutamyl transpeptidase.

Figure E1. Trial overview



ALM=appendicular lean mass, IMAT=intermuscular adipose tissue, LBM=lean body mass, QoL=quality of life, SCAT=subcutaneous adipose tissue, TMV=thigh muscle volume.

Figure E2. Percentage change from baseline in intermuscular adipose tissue

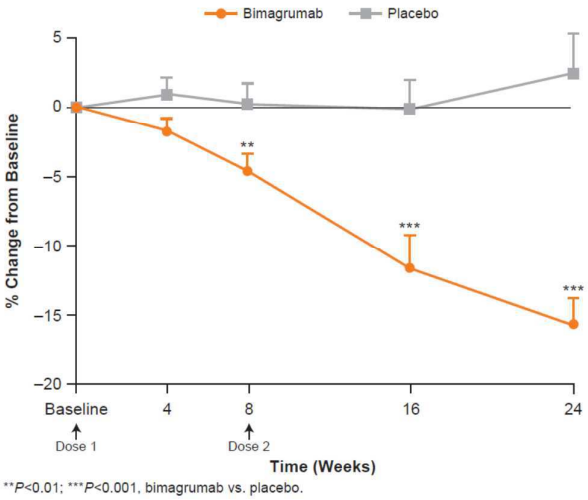


**P<0.01; ***P<0.001, bimagrumab vs. placebo.

Data presented as mean (SE).

SE=standard error.

Figure E3. Percentage change from baseline in subcutaneous adipose tissue

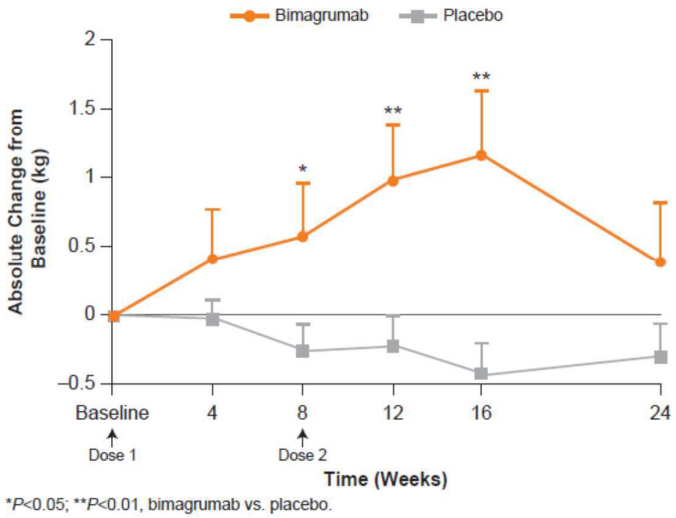


**P<0.01; ***P<0.001, bimagrumab vs. placebo.

Data presented as mean (SE).

SE=standard error.

Figure E4. Absolute change from baseline in total lean body mass

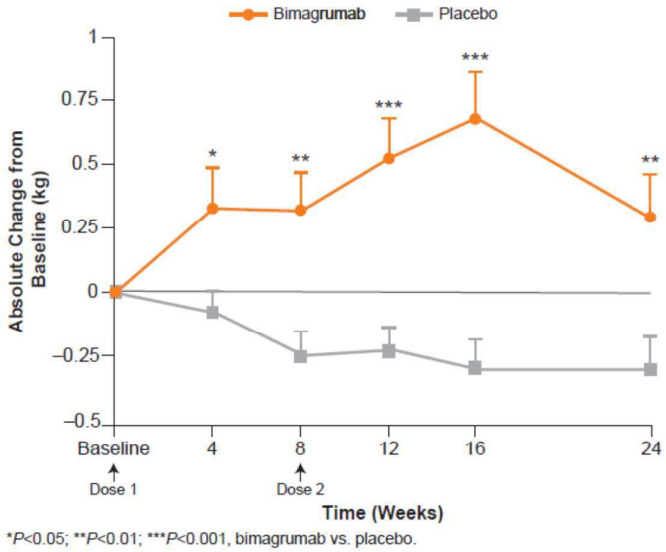


*P<0.05; **P<0.01, bimagrumab vs. placebo.

Data presented as mean (SE).

SE=standard error.

Figure E5. Absolute change from baseline in appendicular lean mass



*P<0.05; **P<0.01; ***P<0.001, bimagrumab vs. placebo.

Data presented as mean (SE).

SE=standard error.