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The Dramatic Fat Mass Loss Caused by Bimagrumab is Similar in Diabetic and Non-diabetic Patients.

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Bimagrumab is a fully human, ligand-blocking antibody to activin receptors type IIA and type IIB that in obese diabetic patients has been shown to improve body composition dramatically. After 48 weeks of treatment (N=75, allocated 1: 1, bimagrumab intravenously (iv) 10 mg/kg/month: placebo), in the bimagrumab group total body fat mass decreased by 20.5% while at the same time, lean mass increased by 3.6%, both assessed by dual X-ray absorptiometry (DXA). At 24 weeks, fat mass loss was 16.5% in those treated with bimagrumab, while there was little effect on fat or lean mass in the placebo group at either timepoint. In a subset of patients who underwent magnetic resonance imaging, the fat loss effect was greatest for hepatic fat, with a 52% reduction from baseline to week 48, and for abdominal visceral fat, where a 34% decrease was observed over the same interval (Heymsfield SB et al. JAMA Open 2021;4: e2033457).

Most drugs for obesity are less effective in diabetics, so to evaluate the efficacy of bimagrumab on fat mass in non-diabetics, we undertook a pooled analysis of patient-level data from 6 clinical studies of bimagrumab previously conducted to assess muscle anabolic activity and/or clinical safety. Criteria for study selection included at least 24 weeks of therapeutic drug exposure, DXA performed at baseline and at least 2 additional time points. Studies that recruited patients with known, underlying primary diseases of adipose tissue or muscle were excluded. Of the 568 subjects in these 6 studies, 7 were identified as diabetic and excluded, leaving 561 subjects in 4 dose groups including placebo (N=204), 70 mg iv monthly (N=43), 210 mg iv monthly (N=75), or a top dose group comprising 700 mg iv once monthly or 10 mg/kg iv once monthly or 30 mg/kg iv q8w x 2 (total N=239). A dose- and time-dependent effect of bimagrumab on fat loss was observed and at the 24 week time point, the top dose group lost 14.6% (LS mean (95% CI) 13.2% - 16.0%) of total body fat mass, while the placebo group increased their fat mass by 2.4% (0.9% - 3.8%). Approximately 41% of the subjects in this pooled analysis were overweight or obese, which is a potential limitation of this study since all subjects in the diabetes study were overweight or obese, however this likely does not affect the conclusion since no effect of baseline BMI on % initial body fat lost at week 24 was

seen. Thus, unlike most other drugs for obesity, the efficacy of bimagrumab is very similar in both diabetic patients and in non-diabetic patients.

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