

Efficacy and safety of ponsegromab in non-small cell lung cancer and cachexia: a subgroup analysis of the PROACC-1 phase 2 study

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Objective

To report body weight changes from baseline and safety of ponesgromab vs placebo in a subset of patients with NSCLC in the randomized, double-blind, phase 2 PROACC-1 (part A) study in patients with cancer cachexia

Conclusions

- Among patients with NSCLC, cachexia, and elevated GDF-15 levels, GDF-15 inhibition with ponesgromab through 12 weeks of treatment resulted in body weight and skeletal muscle gains
- Ponesgromab was generally well tolerated, with the frequency of adverse events similar to that of placebo



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Abbreviations: BMI, body mass index; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FAAC1, Functional Assessment of Anorexia/Cachexia Therapy; FAAC1-5IASS, 5-item anorexia-related symptoms scale; FAAC1-ACS, anorexia-cachexia subscale; GDF-15, growth differentiation factor 15; IQR, interquartile range; MMRM, mixed model repeated measures; NSCLC, non-small cell lung cancer; PGI-S, Patient Global Impression of Severity; PRO, patient-reported outcome; Q4W, every 4 weeks; R, randomization; SC, subcutaneous; SD, standard deviation; TEAE, treatment-emergent adverse event.

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Background

- Cachexia, a common complication in patients with cancer, is characterized by loss of body weight and skeletal muscle^{1,2}
- Cancer cachexia is associated with reduced survival, cancer treatment response, and quality of life³
- Growth differentiation factor 15 (GDF-15), a stress-induced cytokine, is implicated in the pathogenesis of cachexia and is an emerging therapeutic target^{4,5}
- Ponesgromab is a humanized monoclonal antibody that selectively binds and inhibits unbound GDF-15⁵⁻⁷
- The primary analysis of the randomized, double-blind, phase 2 PROACC-1 study (NCT05546476) demonstrated improved body weight, appetite, cachexia symptoms, and overall physical activity with ponesgromab vs placebo in patients with cancer (NSCLC, pancreatic, or CRC), cachexia, and elevated GDF-15 levels⁵
 - The safety profile of ponesgromab was similar to that of placebo⁵
- This is a subgroup analysis of the patients with NSCLC enrolled in PROACC-1

Methods

Study Design

- PROACC-1 was a phase 2 study of ponesgromab vs placebo in patients with NSCLC, pancreatic cancer, or CRC who had cachexia and elevated GDF-15 levels⁵ (**Figure 1**)
 - Cachexia was defined as involuntary weight loss of >5% within the previous 6 months or >2% in patients with a BMI of <20 kg/m², based on the Fearon international consensus criteria⁸
- In Part A, patients were randomized 1:1:1:1 to receive ponesgromab 100, 200, or 400 mg, or matching placebo, all SC Q4W for 12 weeks (3 doses in total)
- The primary endpoint was change in body weight from baseline to Week 12
- Secondary endpoints included change in lumbar skeletal muscle index, safety and tolerability, and PROs

Statistical Analysis

- Descriptive summaries of data are provided as n (%), median (IQR), or mean (SD), as appropriate
- Change from baseline in body weight was analyzed by an MMRM model and fitted to post-treatment dosing timepoints (Weeks 4, 8, and 12)

PROs

- PGI-S for appetite assesses patient-reported severity of appetite loss on a 5-point scale from "none" to "very severe"
- FAAC1-ACS measures symptoms of patients with anorexia or cachexia on a scale of 0 (worst) to 48 (best)
- FAAC1-5IASS measures appetite-related symptoms on a scale of 0 to 20; higher scores indicate fewer symptoms

Results

Patients

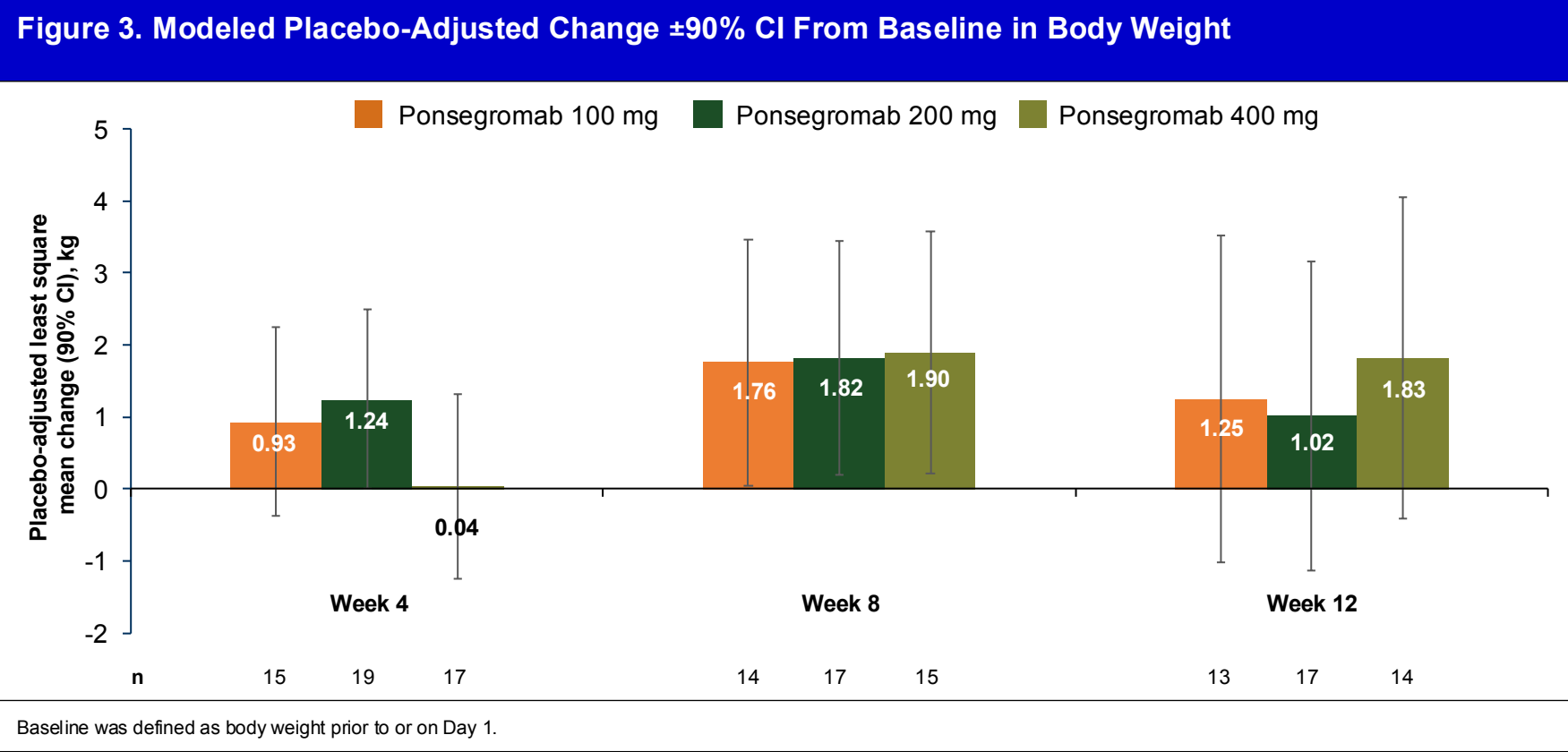
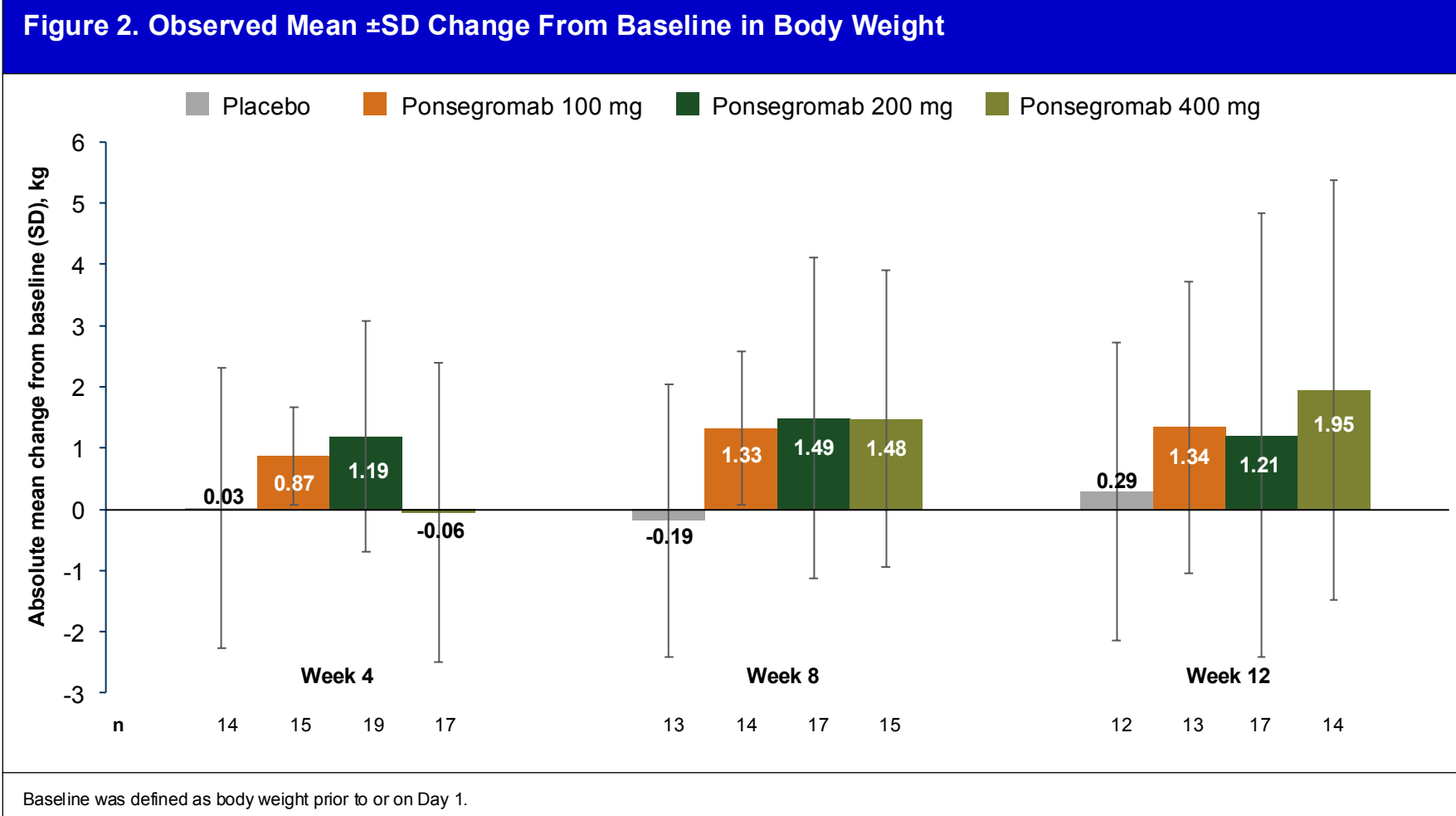
- Overall, 74 patients (39.6% of the overall study population of 187 randomized patients) had NSCLC
- Demographics and baseline characteristics of the NSCLC subgroup are shown in **Table 1**
 - Baseline mean $\pm$ SD body weight was 55.0 $\pm$ 13.0 kg
 - More than half of the patients (58.1%) had a BMI of <20 kg/m², and 43.2% had $\geq$ 10% body weight loss over the prior 6 months
 - There was an imbalance in the frequency of Stage 4 cancer across treatment groups; 46.7% of patients in the placebo group had Stage 4 disease compared with 70.6%, 76.2%, and 81.0% in the ponesgromab 100-, 200-, and 400-mg groups
 - The majority (87.8%) of patients were actively receiving systemic anticancer therapy
- Overall, the median baseline GDF-15 level was 2701 pg/mL (IQR, 2114-4094 pg/mL)

Table 1. Baseline Demographics and Disease Characteristics						
	Placebo n=15	Ponesgromab combined n=59	Ponesgromab 100 mg n=17	Ponesgromab 200 mg n=21	Ponesgromab 400 mg n=21	All patients N=74
Median age (IQR), years	67.0 (61.0-71.0)	69.0 (62.0-76.0)	69.0 (74.0-79.0)	67.0 (60.0-71.0)	67.0 (60.0-74.0)	69.0 (61.0-75.0)
Male, n (%)	11 (73.3)	40 (67.8)	10 (58.8)	16 (76.2)	14 (66.7)	51 (68.9)
Body weight, mean (SD), kg	52.2 (6.8)	55.8 (14.1)	49.4 (10.0)	60.1 (17.9)	56.6 (11.1)	55.0 (13.0)
BMI, median (IQR), kg/m ²	18.4 (16.4-20.5)	19.5 (17.5-21.6)	18.7 (17.6-20.2)	19.6 (17.4-22.8)	20.1 (17.8-23.6)	19.4 (17.3-21.3)
BMI, n (%)						
<20 kg/m ²	11 (73.3)	32 (54.2)	12 (70.6)	11 (52.4)	9 (42.9)	43 (58.1)
20 to <25 kg/m ²	4 (26.7)	21 (35.6)	5 (29.4)	8 (38.1)	8 (38.1)	25 (33.8)
$\geq$ 25 kg/m ²	0	6 (10.2)	0	2 (9.5)	4 (19.0)	6 (8.1)
Percentage weight loss in 6 months before screening, n (%)						
<5%	4 (26.7)	11 (18.6)	5 (29.4)	5 (23.8)	1 (4.8)	15 (20.3)
5% to <10%	6 (40.0)	21 (35.6)	7 (41.2)	4 (19.0)	10 (47.6)	27 (36.5)
10% to <15%	3 (20.0)	12 (20.3)	2 (11.8)	6 (28.6)	4 (19.0)	15 (20.3)
$\geq$ 15%	2 (13.3)	15 (25.4)	3 (17.6)	6 (28.6)	6 (28.6)	17 (23.0)
Cancer stage, n (%)						
Stage 1	0	1 (1.7)	1 (5.9)	0	0	1 (1.4)
Stage 2	1 (6.7)	0	0	0	0	1 (1.4)
Stage 3	7 (46.7)	13 (22.0)	4 (23.5)	5 (23.8)	4 (19.0)	20 (27.0)
Stage 4	7 (46.7)	45 (76.3)	12 (70.6)	16 (76.2)	17 (81.0)	52 (70.3)
Actively receiving anticancer therapy*, n (%)	13 (86.7)	52 (88.1)	16 (94.1)	19 (90.5)	17 (81.0)	65 (87.8)
ECOG PS, n (%)						
0	2 (13.3)	9 (15.3)	3 (17.6)	5 (23.8)	1 (4.8)	11 (14.9)
1	9 (60.0)	44 (74.6)	12 (70.6)	15 (71.4)	17 (81.0)	53 (71.6)
2	3 (20.0)	6 (10.2)	2 (11.8)	1 (4.8)	3 (14.3)	9 (12.2)
3	1 (6.7)	0	0	0	0	1 (1.4)
Median serum GDF-15 level (IQR)*, pg/mL	2698.0 (2193.0-3507.0)	2721.0 (2084.0-4787.0)	3210.0 (2467.0-3903.0)	2427.0 (2127.0-3862.0)	3179.0 (1899.0-5599.0)	2700.5 (2114.0-4094.0)

*Receiving any systemic anticancer therapy at randomization. *Using the Investigational Use Only Roche Elecsys GDF-15 assay.

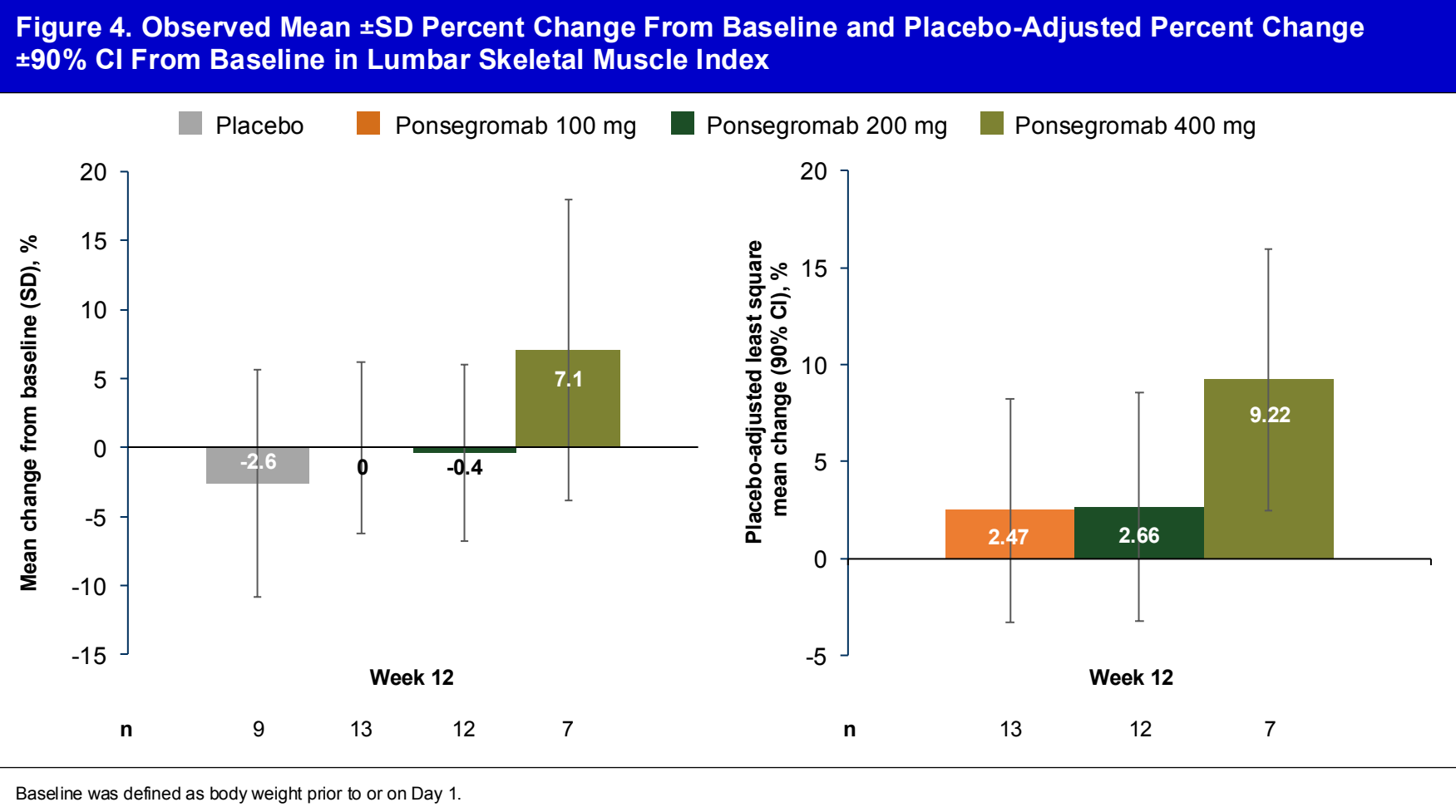
Change From Baseline in Body Weight

- Increases in body weight were observed in all the ponesgromab groups at Week 12 vs placebo (**Figure 2**)
- Least squares mean change in body weight from baseline to Week 12 with placebo and ponesgromab 100, 200, and 400 mg was 0.00 (90% CI, -1.64, 1.64), 1.25 (90% CI, -0.35, 2.85), 1.02 (90% CI, -0.37, 2.41), and 1.83 kg (90% CI, 0.32, 3.34), respectively
- At Week 12, placebo-adjusted least squares mean body weight gain with ponesgromab 100, 200, and 400 mg was 1.25 (90% CI, -1.01, 3.52), 1.02 (90% CI, -1.13, 3.16), and 1.83 kg (90% CI, -0.41, 4.06), respectively (**Figure 3**)



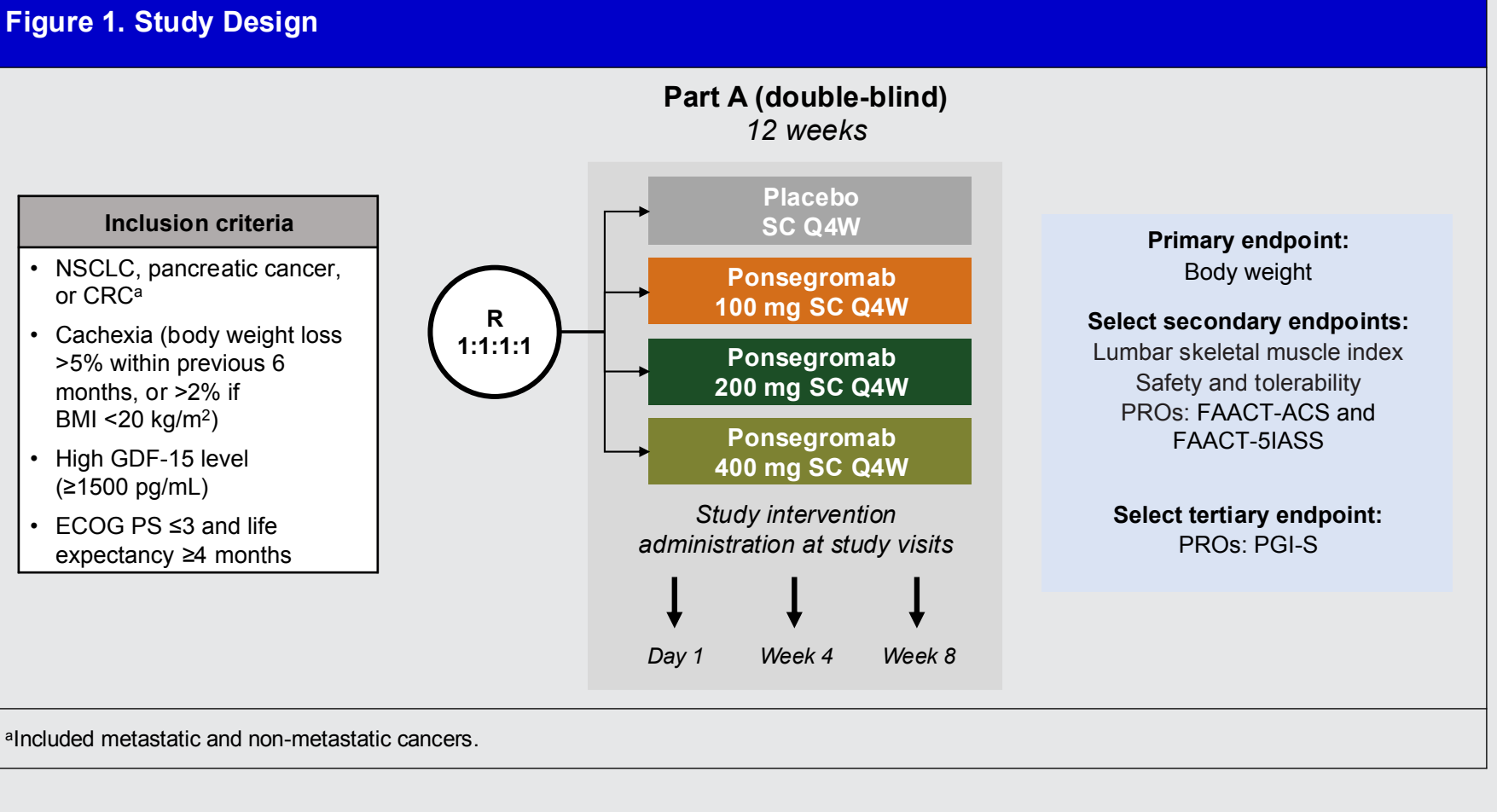
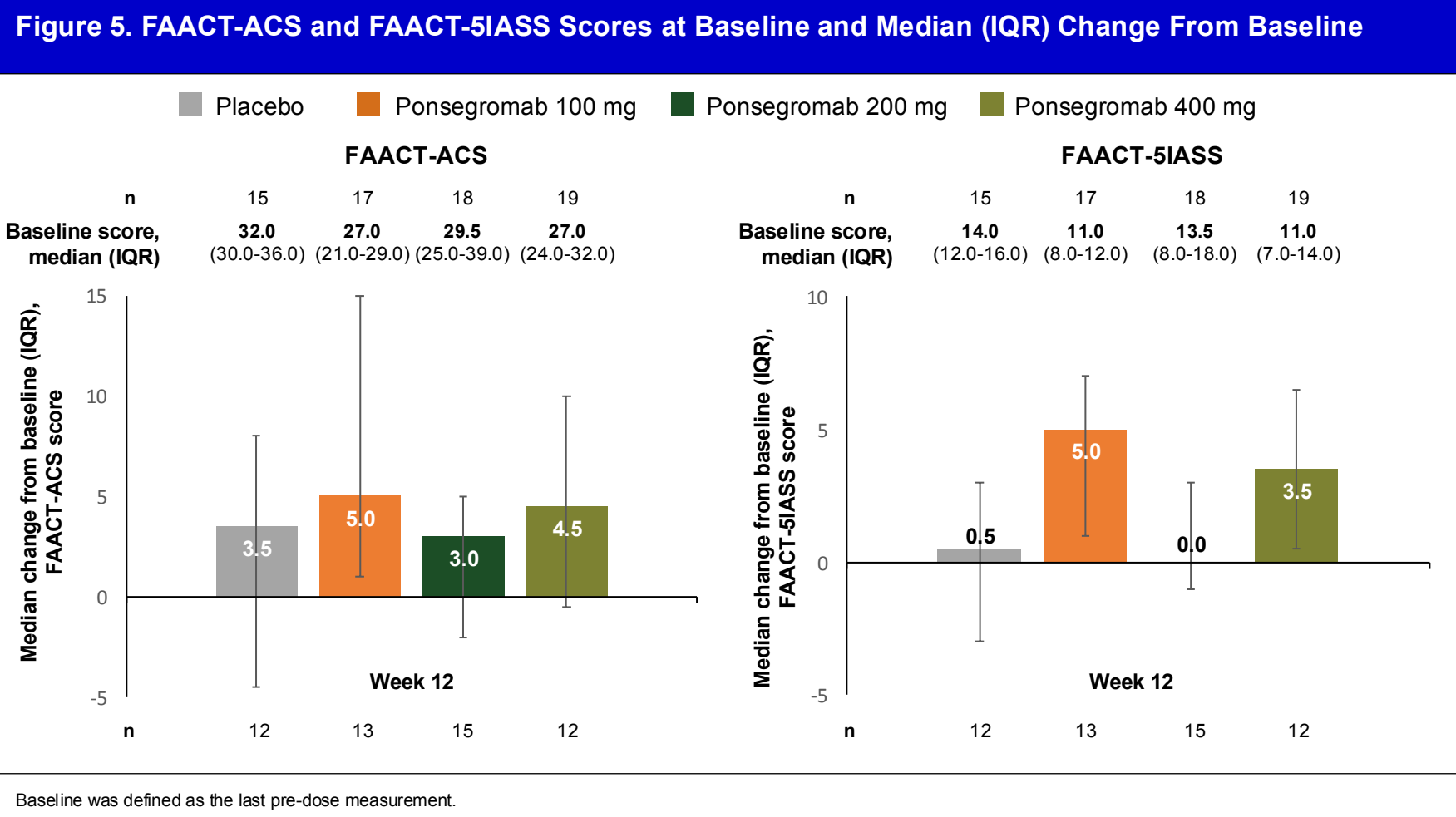
Change From Baseline in Lumbar Skeletal Muscle Index

- Observed change from baseline in lumbar skeletal muscle index at Week 12 with placebo and ponesgromab 100, 200, and 400 mg was -2.6%, 0%, -0.4%, and 7.1%, respectively (**Figure 4**)
- At Week 12, placebo-adjusted least squares mean percent change in lumbar skeletal mass index with ponesgromab 100, 200, and 400 mg was 2.47% (90% CI, -3.31, 8.25), 2.66% (90% CI, -3.25, 8.57), and 9.22% (90% CI, 2.47, 15.96) (**Figure 4**)



PROs

- At baseline, many patients had no or only mild appetite loss based on the PGI-S appetite scale, precluding a meaningful assessment of improved appetite in these patients
 - No and mild appetite loss were reported by 5 (33.3%) and 3 patients (20.0%) in the placebo group, 2 (11.8%) and 5 (29.4%) in the ponesgromab 100 mg group, 6 (33.3%) and 3 (16.7%) in the ponesgromab 200 mg group, and 2 (10.5%) and 7 (36.8%) in the ponesgromab 400 mg group, respectively
- Baseline FAAC1-ACS and FAAC1-5IASS scores and change from baseline at Week 12 are shown in **Figure 5**
 - The NSCLC patient subgroup was not powered for detecting statistically significant changes in these outcomes



Safety

- All-cause and treatment-related TEAEs occurred in 69.5% and 8.5% of ponesgromab-treated patients and 66.7% and 6.7% of placebo-treated patients, respectively (**Table 3**)
- No treatment-related deaths occurred. However, there were 2 deaths in the placebo group, 2 deaths in the ponesgromab 100-mg group, and 4 deaths in each of the ponesgromab 200- and 400-mg groups, all in patients with Stage 4 cancer (**Table 4**)
 - In the placebo group, the primary cause of death was cerebral infarction and cancer
 - In the combined ponesgromab group, cancer was considered the primary cause of death in 5 cases; the remaining deaths were primarily due to pneumonia (2 cases), enterocolitis, neutropenic sepsis, and general health deterioration that were unrelated to treatment
- Permanent discontinuation of study treatment due to TEAEs occurred in 7 patients (11.9%) who received ponesgromab
- The most frequent all-cause TEAEs in patients receiving placebo or ponesgromab are shown in **Table 5**

Table 3. Safety Summary					
	Placebo n=15	Ponesgromab combined n=59	Ponesgromab 100 mg n=17	Ponesgromab 200 mg n=21	Ponesgromab 400 mg n=21
All cause, n (%)					
TEAEs	10 (66.7)	41 (69.5)	13 (76.5)	14 (66.7)	14 (66.7)
Grade 1/2	5 (33.3)	18 (30.5)	7 (41.2)	7 (33.3)	4 (19.0)
Grade 3/4	3 (20.0)	13 (22.0)	4 (23.5)	3 (14.3)	6 (28.6)
Grade 5	2 (13.3)	10 (16.9)	2 (11.8)	4 (19.0)	4 (19.0)
Serious TEAEs	2 (13.3)	18 (30.5)	4 (23.5)	6 (28.6)	8 (38.1)
Permanent discontinuation from any study intervention due to TEAE	2 (13.3)	7 (11.9)	1 (5.9)	3 (14.3)	3 (14.3)
Treatment related, n (%)					
TEAEs	1 (6.7)	5 (8.5)	1 (5.9)	3 (14.3)	1 (4.8)
Grade 1/2	1 (6.7)	5 (8.5)	1 (5.9)	3 (14.3)	1 (4.8)
Grade 3/4	0	0	0	0	0
Grade 5	0	0	0	0	0
Serious TEAEs	0	0	0	0	0
Permanent discontinuation from any study intervention due to TEAE	0	0	0	0	0

Table 4. Summary of Deaths by Stage of Cancer					
	Placebo n=15	Ponesgromab combined n=59	Ponesgromab 100 mg n=17	Ponesgromab 200 mg n=21	Ponesgromab 400 mg n=21
Stage 1-3					
No. of patients	7	13	4	5	4
Deaths, n (%)	0	0	0	0	0
Stage 4					
No. of patients	7	45	12	16	17
Deaths, n (%)	2 (28.6)	10 (22.2)	2 (16.7)	4 (25.0)	4 (23.5)

Table 5. Most Frequent All-Cause TEAEs in $\geq$ 5% of Patients*					
TEAEs, n (%)	Placebo n=15	Ponesgromab combined n=59	Ponesgromab 100 mg n=17	Ponesgromab 200 mg n=21	Ponesgromab 400 mg n=21
Asthenia	0	5 (8.5)	1 (5.9)	2 (9.5)	2 (9.5)
Pneumonia	2 (13.3)	4 (6.8)	0	2 (9.5)	2 (9.5)
Diarrhea	2 (13.3)	4 (6.8)	0	2 (9.5)	2 (9.5)
Constipation	0	4 (6.8)	1 (5.9)	1 (4.8)	2 (9.5)
Dyspnea	0	4 (6.8)	1 (5.9)	0	3 (14.3)
Anemia	2 (13.3)	3 (5.1)	1 (5.9)	1 (4.8)	1 (4.8)
Rash	1 (6.7)	3 (5.1)	0	2 (9.5)	1 (4.8)
Malignant neoplasm progression	1 (6.7)	3 (5.1)	0	2 (9.5)	1 (4.8)
Decreased appetite	2 (13.3)	2 (3.4)	1 (5.9)	1 (4.8)	0

*TEAEs occurring in $\geq$ 5% of patients overall.