Anamorelin for patients with cancer cachexia: an integrated analysis of two phase 2, randomised, placebo-controlled, double-blind trials

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Summary

Background Cancer anorexia-cachexia syndrome is associated with increased morbidity and mortality. Anamorelin is an oral ghrelin-receptor agonist with appetite-enhancing and anabolic activity. We assessed the effects of anamorelin on body composition, strength, quality of life, biochemical markers, and safety in patients with cancer anorexia-cachexia.

Methods Data were pooled, a priori, from two completed phase 2, multicentre, placebo-controlled, double-blind trials in patients with advanced or incurable cancer and weight loss of 5% or more. Patients were stratified by weight loss severity (5–15%, >15%) and randomly allocated (1:1) with a computer-generated randomisation schedule to anamorelin hydrochloride 50 mg or placebo once-daily for 12 weeks. Primary outcome was lean body mass by dual-energy x-ray absorptiometry over the 12 week treatment period in eligible patients who had at least one dose of study drug and post-treatment efficacy assessment. We assessed safety in all patients who received at least one dose of study drug. The trials are registered with ClinicalTrials.gov, numbers NCT00219817 and NCT00267358.

Findings Between June 29, 2005, and Oct 26, 2006, we enrolled 44 patients in the anamorelin group and 38 patients in the placebo group. 74 patients were eligible for the efficacy analyses. Over 12 weeks, lean body mass increased in 38 patients in the anamorelin group by a least-squares mean of 1·89 kg (95% CI 0·84 to 2·95) compared with a decrease of a least-squares mean of –0·20 kg (–1·23 to 0·83) for 36 patients in the placebo group (difference 2·09 kg [0·94–3·25]; p=0·0006). 42 (95%) of 44 patients treated with anamorelin and 33 (87%) of 38 patients treated with placebo had adverse events. The most common grade 3–4 adverse events (treatment-related or not) in the anamorelin group were fatigue, asthenia, atrial fibrillation, and dyspnoea (two [5%] each); in the placebo group, such events were pneumonia (three [8%]) and anaemia, thrombocytopenia, abdominal pain, anxiety, and dyspnoea (two [5%] each).

Interpretation Anamorelin treatment for 12 weeks had a favourable clinical response profile in patients with cancer anorexia-cachexia syndrome. These findings support further investigation in this setting.

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Introduction

Cancer anorexia-cachexia syndrome, a multifactorial syndrome, is characterised by involuntary weight loss. In a 2011 consensus statement, such weight loss was defined as greater than 5% within 6 months or greater than 2% in patients with a body-mass index [BMI] of less than 20 kg/m².[1] Identification and management of cancer anorexia-cachexia syndrome in advanced cancer is an unmet, under-recognised need;[2] the syndrome occurs in more than 50% of patients with various cancers.[2] Moreover, anorexia-cachexia is an adverse prognostic factor associated with poor performance status and quality of life,[2] reduced tolerance or responsiveness to therapy,[1–3] and decreased survival, emphasising the importance of early detection and intervention.[1–4] Hallmarks are decreased muscle mass and strength, overall lean body mass, and lean body mass in the extremities (appendicular lean body mass). Appendicular lean body mass has been proposed as a surrogate for muscle mass.[5] Both lean body mass and muscle strength, as measured by handgrip strength, are predictive of survival and quality of life.[6,7]

Nutritional supplementation alone cannot reverse cancer anorexia-cachexia syndrome,[1,6] and data for present therapies generally show limited efficacy or concerns about tolerability, or are from small studies.[7,8] Available therapies, such as appetite stimulants and serotonin receptor antagonists, have failed to provide clinically meaningful benefits.[8] Hypercaloric feeding has not been shown to increase lean muscle mass,[6] whereas corticosteroids have only modest effects on appetite and food intake.[4] Progestational agents are perhaps the most widely used but increase only fat mass[7] and have potentially clinically important side-effects such as deep vein thrombosis and hypogonadism.[9,10] Other agents in development include anabolic agents, non-steroidal anti-inflammatory drugs, and anti-cytokine approaches.[7] New effective therapies are needed.

Activation of the ghrelin receptor (GRLN receptor, formerly known as GHS-R1a) has anabolic effects and increases food intake and bodyweight.[11] In people without cancer, ghrelin-receptor agonists increase bodyweight and reverse the negative nitrogen balance induced by starvation, independently from their appetite-enhancing

effects. These findings suggest that ghrelin's effects are not entirely mediated through increased appetite and that other mechanisms are involved, such as decreased energy expenditure.[12,13] This effect is relevant because patients with cancer have increased energy expenditure that contributes to cachexia.[14]

Inflammation is thought to play a part in cancer anorexia-cachexia syndrome. Interleukin 6 administration reduces bodyweight in rodents and human beings,[15,16] increases the resting metabolic rate, and suppresses appetite. In animal models of cancer anorexia-cachexia syndrome, ghrelin blunts the anorectic and weight-reducing effect of interleukin 1β, induces increased food intake and bodyweight, and downregulates production of interleukin 6, interleukin 1α, interleukin 1β, and tumour necrosis factor (TNF) α.[17]

Because ghrelin needs parenteral administration and is a peptide with a 30 min half-life, its efficacy in patients is restricted. Ghrelin-receptor agonists could be non-peptidic, orally available, small molecules with a longer half-life allowing for once-daily administration.[18] Anamorelin is an orally available, selective ghrelin-receptor agonist.[19] In phase 1 studies, anamorelin increased bodyweight versus placebo in volunteers who did not have cancer;[11] and in a 3 day crossover period of a phase 2 study, it acutely increased appetite, bodyweight, and quality of life in patients with cancer anorexia-cachexia,[20] but longer term effects of ghrelin-receptor agonists in this setting have not been reported.

We aimed to assess the effect of anamorelin hydrochloride treatment for 12 weeks on body composition, physical strength, quality of life, and biochemical markers in cancer anorexia-cachexia syndrome in patients with a diverse range of cancers potentially responsive to anamorelin's postulated mechanisms of action.[17]

Methods

Study design and patients

Two similar randomised, double-blind, placebo-controlled, phase 2 studies were done together at 20 US sites; data were pooled for analysis a priori. Both studies included 12 week, double-blind parallel phases, which were prespecified to be combined for analysis and are reported here. One study contained an initial randomised crossover phase of 3 days of active drug administration versus placebo separated by a 3–7 day washout period (previously published[20]). An additional 3 day placebo run-in period then took place, representing more than five half-lives of anamorelin (about 7 h),[18] before patients were randomly assigned again for the parallel phase. Patients enrolled in the second study were required to have had no previous exposure to anamorelin.

Eligible patients were 18 years or older with advanced or incurable histologically confirmed malignancy, an Eastern Cooperative Oncology Group performance score of 2 or less, an estimated life expectancy of more than 3 months, and cachexia (defined as involuntary weight loss of 5% or more within the previous 6 months).[1] Ineligibility criteria included liver disease (aspartate aminotransferase or alanine aminotransferase more than twice normal concentrations [liver metastases were not specifically excluded]); diabetes; ascites or oedema that could confound weight assessment; inability to eat due to other factors; or BMI of more than 30 kg/m². Concomitant chemotherapy was permitted; however, concomitant medications that could confound study measures, such as appetite stimulants or anabolic agents (including corticosteroids, other than dexamethasone at the time of intravenous chemotherapy administration), CYP3A4 inhibitors, tube feedings, or parenteral nutrition, were not permitted for 1 month before or during the study. Women who were pregnant, breastfeeding, or of childbearing potential and were not using birth control were also ineligible. Patients were free to discontinue at any time, and patients who developed aspartate aminotransferase or alanine aminotransferase concentrations greater than five times the upper limit of normal or fasting glucose greater than 7·0 mmol/L on repeated testing were discontinued. Written informed consent was provided by all patients.

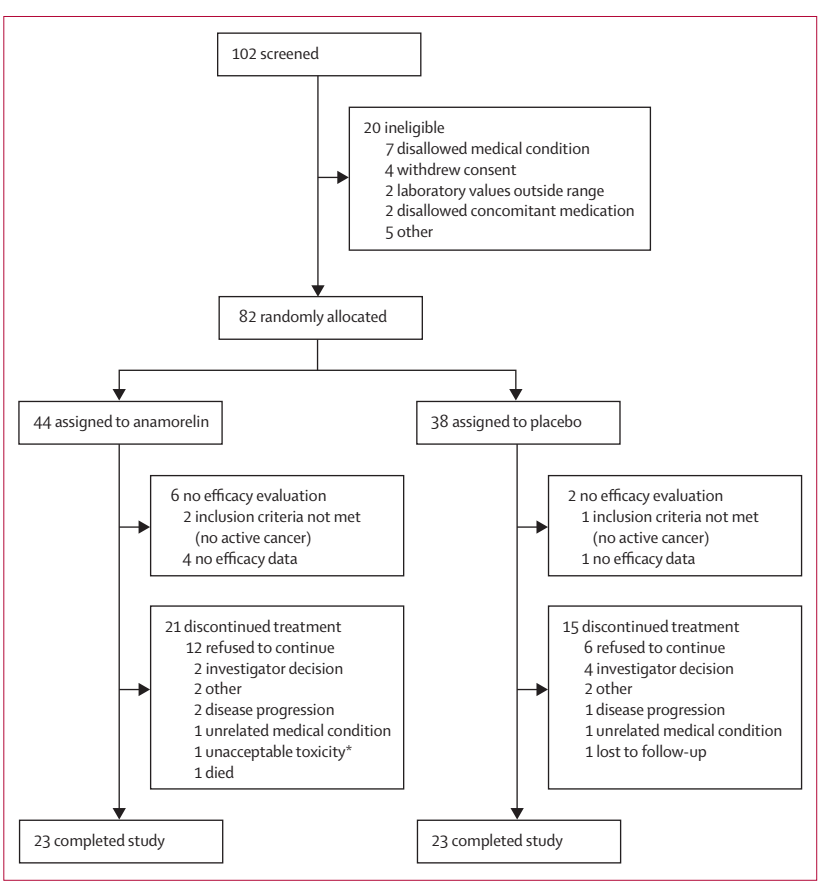

Figure 1: **Trial profile**
*Abdominal pain.

These studies were done in accordance with the Declaration of Helsinki, International Conference on Harmonisation, and Good Clinical Practices. The institutional review board of each study site approved the protocol.

Randomisation and masking

Four digit randomisation codes were computer-generated in blocks of four by the statistical vendor (Scirex Corp, Horsham, PA, USA) and were created separately for each of the two weight-loss strata (5–15% *vs* >15%). Anamorelin or matching placebo tablets were provided to study sites prepackaged to maintain the double-blind design. Investigators assigned randomisation numbers sequentially to eligible patients. The study staff were masked to the interventions throughout the study, confirmed by intact disclosure panels on drug labels.

Procedures

Patients received oral anamorelin hydrochloride 50 mg (University of Iowa Pharmaceuticals [formerly University of Iowa Division of Pharmaceutical Services], Iowa City, IA, USA) or placebo once-daily, about 1 h before breakfast for 12 weeks. This dose was selected based on results from two phase 1 studies in healthy volunteers.[11,21] Outcomes were assessed at baseline and weeks 4, 8, and 12, unless otherwise specified. Blood samples were collected under fasted conditions before dosing at each visit. Dose reductions or interruptions were not permitted per protocols.

Body composition was measured by dual-energy x-ray absorptiometry (DXA) using Hologic (Bedford, MA, USA) or GE Lunar (Wauwatosa, WI, USA) absorptiometers. DXA technologists at each site underwent training for scan acquisition and transfer to the central

	Anamorelin (n=44)	Placebo (n=38)
Sex		
Male	28 (64%)	23 (61%)
Female	16 (36%)	15 (39%)
Age (years)	65·5 (19·0–94·0)	65·0 (37·0–88·0)
Race		
White	35 (80%)	29 (76%)
Black	8 (18%)	7 (18%)
Other	1 (2%)	2 (5%)
Weight (kg)	62·4 (36·2–85·0)	62·6 (35·2–100·4)
Body–mass index (kg/m^2)	21·5 (13·8–30·6)	21·1 (13·8–29·2)
Weight loss stratum		
5–15%	28 (64%)	22 (58%)
>15%	16 (36%)	16 (42%)
Body mass variables*		
Lean body mass (kg)	43·33 (7·76)	43·64 (8·32)
Total body mass (kg)	61·94 (12·04)	62·81 (13·00)
Fat mass (kg)	15·83 (7·26)	16·48 (10·53)
Appendicular lean body mass (kg)	17·53 (3·83)	17·84 (3·79)
Non–dominant handgrip strength (kg)*	26·48 (10·56)	26·86 (10·91)
C–reactive protein (nmol/L)*	388·6 (498·1)	358·1 (548·6)
Interleukin 6 (pg/mL)*	32·00 (41·67)	36·08 (55·78)
Tumour necrosis factor α (pg/mL)*	5·87 (8·58)	7·01 (16·60)
Glucose (mmol/L)*	5·33 (0·85)	5·42 (1·41)
Insulin (pmol/L)*	113·34 (149·53)	101·81 (148·76)
IGF–1 (nmol/L)*	11·97 (7·32)	12·64 (6·32)
IGFBP–3 (μmol/L)*	0·09 (0·03)	0·10 (0·03)
ASAS total score*	69·84 (15·70)	64·89 (17·00)
Time since diagnosis (years)	0·9 (0·1–12·1)	1·1 (0·1–29·8)
ECOG performance score		
0	6 (14%)	5 (13%)
1	27 (61%)	28 (74%)
2	11 (25%)	5 (13%)
(Continued from previous column)		
Karnofsky scale score	80·0 (50·0–100·0)	80·0 (60·0–100·0)
Tumour type		
Breast	6 (14%)	1 (3%)
Colon (colorectal, rectal)	11 (25%)	6 (16%)
Lung	10 (23%)	10 (26%)
Genitourinary (prostate, renal)	8 (18%)	5 (13%)
Other†	9 (20%)	16 (42%)
Concomitant chemotherapy (≥10% in either group)		
Any	35 (80%)	30 (79%)
Bisphosphonates (zoledronic acid)	6 (14%)	0
Pyrimidine analogues (capecitabine, floxuridine, fluorouracil, gemcitabine)	15 (34%)	11 (29%)
Folic acid and derivatives (leucovorin)	6 (14%)	5 (13%)
Platinum compounds (carboplatin, cisplatin, oxaliplatin)	6 (14%)	18 (47%)
Taxanes (docetaxel, paclitaxel, other taxane)	7 (16%)	9 (24%)
Other (bevacizumab‡, erlotinib, imatinib, irinotecan, laetrile)	12 (27%)	8 (21%)

Data are n (%), median (range), or mean (SD). ASAS=Anderson Symptom Assessment Scale. ECOG=Eastern Cooperative Oncology Group. *Intention-to-treat population (anamorelin 50 mg, n=38; placebo, n=36). †Other cancers—in both groups: oesophageal (one anamorelin, two placebo); anamorelin group only: malignant neoplasm or pancreatic (two each), multiple myeloma, medulloblastoma, mantle-cell lymphoma, or fibrous histiocytoma (one each); placebo group only: non-Hodgkin lymphoma or gastric (two each), pharyngeal, myeloid leukaemia, transitional-cell carcinoma, bladder, cystosarcoma phyllodes, gastrointestinal stromal tumour, Kaposi's sarcoma, malignant melanoma, neuroendocrine carcinoma, or not available (one each). ‡Bevacizumab was received by five patients in each group.

Table 1: **Baseline demographic and clinical characteristics (safety population)**

reading facility (Synarc, Herlev, Denmark). The DXA analysis was used to calculate total body mass. Post-hoc assessment of appendicular lean body mass, which is lean body mass of the arms and legs only, was done with prospectively collected DXA data; unlike total lean body mass (which is a composite of striated, cardiac, and smooth muscle, and other non-muscle, non-fat, non-bone tissues such as liver, spleen, and lungs), appendicular lean body mass can be used as a surrogate for muscle mass because most of the lean tissue in the extremities is striated muscle and does not include cardiac and smooth muscle or other organs.

We used a hand-held dynamometer to assess handgrip strength (Jamar Hydraulic Dynamometer; JA Preston Corp, Clifton, NJ, USA). Low handgrip strengths have been shown to be associated with poor outcomes in patients with cancer and other comorbidities.[22] Because the non-dominant hand would be less likely to be affected by training than the dominant hand, the non-dominant hand is expected to be more predictive of a change in total-body muscle strength. For each assessment of handgrip strength, we recorded the highest score of three trials.

We measured biochemical markers, including IGF-1 (normal range 12·31–63·27 nmol/L), IGFBP-3 (0·10–0·25 µmol/L), insulin (41·67–187·52 pmol/L), and glucose (3·89–7·77 mmol/L) (CRL Medinet, Lenexa, KS, USA). IGF-1, IGFBP-3, and insulin along with the inflammatory markers high sensitivity C-reactive protein, interleukin 6, and TNFα were measured by chemiluminescence immunoassay at baseline and each visit (weeks 4, 8, and 12). Serial measurements of growth hormone were not included within the parallel portion of the study to restrict patient burden. IGF-1 concentrations are known to better represent activation of the somatotroph axis because IGF-1 is more stable and has a longer half-life than does growth hormone.

To assess quality of life, we used the Anderson Symptom Assessment Scale (ASAS), which is based on the validated Edmonton Symptom Assessment Scale[23] from 0 (worst imaginable symptoms) to 10 (no symptoms), for patient self-assessment of psychological and physical symptoms.

Safety assessments included adverse events, laboratory tests, electrocardiograms, and vital signs. We coded adverse events according to the Medical Dictionary for Regulatory Activities, version 8.0, and graded them according to the National Cancer Institute Common Toxicity Criteria, version 3.0.

Outcomes

The primary endpoint was change in lean body mass over the 12 week treatment period. Secondary endpoints included handgrip strength, assessment of IGF-1, IGFBP-3, and other biochemical markers, and measures of body composition, ASAS, and safety.

	Anamorelin (n=38)	Placebo (n=36)	Treatment difference
Lean body mass (kg)			
Least-squares mean (SE)	1·89 (0.53)	–0·20 (0·52)	2·09 (0·58)
95% CI	0·84 to 2·95	–1·23 to 0·83	0·94 to 3·25
p value			0·0006
Total body mass (kg)			
Least-squares mean (SE)	0·48 (0·59)	–1·80 (0·59)	2·28 (0·79)
95% CI	–0·70 to 1·66	–2·99 to –0·61	0·69 to 3·87
p value			0·0057
Fat mass (kg)			
Least-squares mean (SE)	–0·89 (0·42)	–1·70 (0·42)	0·81 (0·56)
95% CI	–1·73 to –0·05	–2·53 to –0·86	–0·31 to 1·93
p value			0·15

p value for treatment difference (50 mg *vs* placebo) was estimated from the repeated measures ANOVA model to assess the treatment effects observed during the 12 week treatment period.

Table 2: **Summary of overall treatment effect for dual-energy x-ray absorptiometry body composition variables (intention-to-treat population)**

Statistical analysis

Based on a sample size of 28 patients per treatment group, this analysis would have 80% power to detect a difference of 1·2 kg (SD 1·55) in lean body mass (at α=0·05). Therefore, we planned a sample size of 80 patients, with the objective of 56 patients or more completing 8 weeks. The efficacy analysis included all patients with active cancer and eligible for the study at randomisation who received at least one dose of study medication and completed at least one post-dose efficacy assessment. The safety analysis included all patients who received at least one dose of study drug.

The primary analysis was the treatment comparison between groups and was done using a repeated-measures ANOVA model of change from baseline in terms of treatment, weight loss strata, treatment timepoint, study, and baseline value with an unstructured covariance matrix. Missing data were not imputed for the analysis when repeated measures ANOVA models were used. We did a preplanned sensitivity analysis to confirm the primary analysis with a confirmatory analysis (compound symmetry matrix) that had patient within sequence as a random effect. We used mixed model analysis for treatment comparisons for each variable and derived 95% CIs of the treatment difference from the ANOVA model; we calculated p values for treatment comparison of categorical variables with Fisher's exact test. Results of the sensitivity analysis are only presented when they differ from the primary analysis and also for the treatment comparisons at each visit for lean body mass and handgrip strength. Statistical analyses were done using SAS (release 8.2 or higher) for Windows.

In the prespecified analysis, we made no adjustment for multiplicity. p values for all endpoints other than the primary endpoint are provided based on an exploratory analysis.

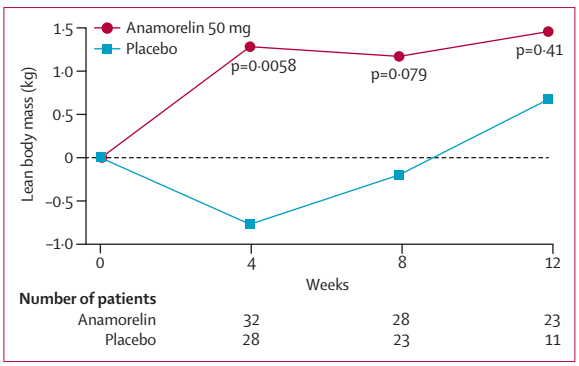

Figure 2: **Changes from baseline in least-squares mean lean body mass**
p value for treatment difference was estimated from the sensitivity analysis of change from baseline to each visit.

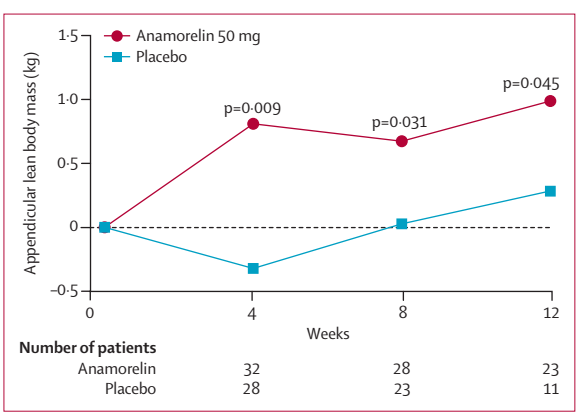

Figure 3: **Changes from baseline in mean appendicular lean body mass (post-hoc analysis)**
p value for treatment difference was estimated with a non-parametric test.

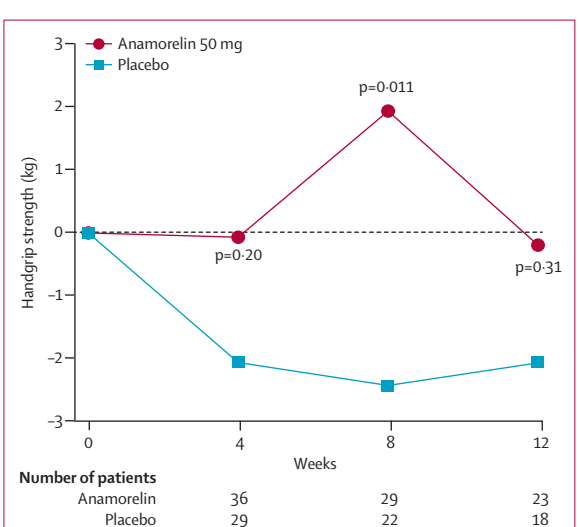

Figure 4: **Changes from baseline in least-squares mean handgrip strength of the non-dominant hand**
p value for treatment difference was estimated from the sensitivity analysis of change from baseline to each visit.

The studies are registered with ClinicalTrials.gov, numbers NCT00219817 and NCT00267358.

Role of the funding source
The study sponsor, Sapphire Therapeutics (now Helsinn Therapeutics [US]), was involved in study design, provision of study materials, data collection, and interpretation, and writing of the report. The corresponding author (JMG) had full access to the data and had final decision to submit for publication.

Results
Study enrolment began on June 29, 2005, and the last patient completed the study on Oct 26, 2006. 82 eligible patients (16 from the study with the preceding crossover period and 66 from the other study) were randomly assigned to anamorelin (n=44) or placebo (n=38; figure 1). The 12 week treatment period was completed by 46 patients (28 patients in the placebo group and 33 in the anamorelin group completed 8 weeks of treatment); treatment discontinuation (figure 1) was mainly due to refusal to continue study participation (18 patients). Efficacy analysis was done in 74 patients (38 patients in the anamorelin group and 36 patients in the placebo group). 76 (93%) of 82 patients had solid tumours (table 1); 62 (76%) had metastases at enrolment and 55 (67%) had stage IV disease at diagnosis. We noted no important differences between treatment groups at baseline (table 1).

Patients receiving anamorelin had an improvement in lean body mass compared with those in the placebo group over 12 weeks (table 2). Figure 2 shows change in lean body mass at week 4, 8, and 12. The post-hoc analysis of appendicular lean body mass showed significant increases among anamorelin-treated patients versus placebo from weeks 4 to 12 (figure 3).

Total body mass increased for patients receiving anamorelin but decreased for patients receiving placebo over 12 weeks (table 2). Fat mass decreased in both groups, although there was no significant difference between groups (table 2). In a post-hoc analysis, increases in lean body mass correlated with changes in total body mass (r^2=0·7249, p=0·0001), suggesting that increases in observed body mass were driven by gains in lean mass.

Over the 12 week treatment period, patients receiving anamorelin improved their non-dominant handgrip strength by a least-squares mean of 2·49 kg (95% CI 0·81–4·17); by contrast, the least-squares mean change in the placebo group was –0·1 kg (–1·71 to 1·51; difference 2·59 kg [SE 1·022], 95% CI 0·54–4·63, p=0·014). Figure 4 shows change in handgrip strength at week 4, 8, and 12. By contrast, mean handgrip strength decreased from baseline at weeks 4, 8, and 12 for the placebo group (figure 4).

For quality of life, patients in the anamorelin group had an improvement over the 12 week treatment period in adjusted ASAS total score of least-squares mean 1·52 points (95% CI –3·40 to 6·45) compared with

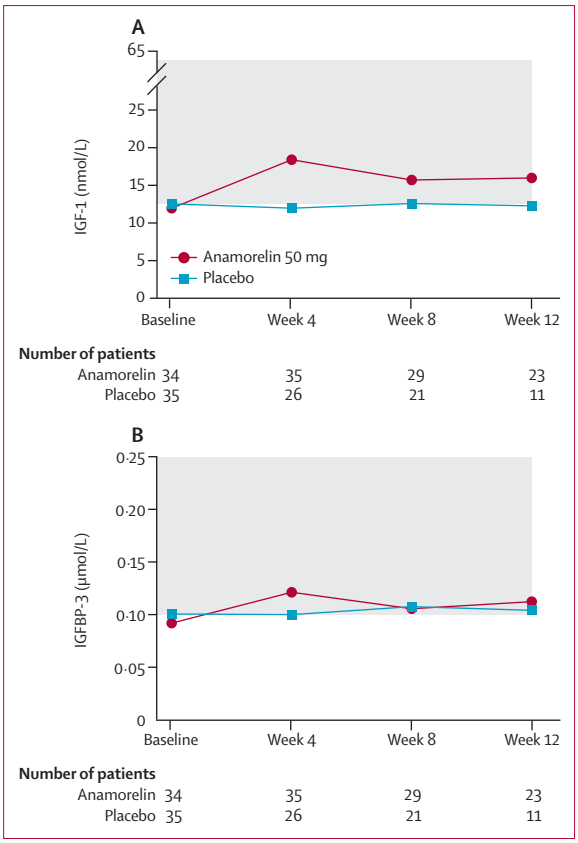

Figure 5: **Mean absolute concentrations of (A) insulin-like growth factor (IGF)-1 and (B) IGF-binding protein 3 (IGFBP-3) and lowest defined normal ranges**
(A) Normal range 12·31–63·27 nmol/L. (B) Normal range 0·10–0·25 µmol/L.

–5·13 points (–9·99 to –0·27) for patients in the placebo group (difference 6·66 points [SE 2·97], 0·72–12·59, p=0·029). Moreover, improvements were also noted for individual ASAS items (drowsy, feeling of well-being, nausea, and sleep) in patients in the anamorelin group compared with those in the placebo group (appendix). However, adjusted ASAS total scores did not differ between groups in the confirmatory sensitivity analysis (difference of 6·28 points [SE 3·431], –0·60 to 13·16, p=0·073).

Over 12 weeks, least-squares mean change from baseline in IGF-1 concentrations were 5·46 nmol/L (95% CI 3·36 to 7·56) compared with 0·45 nmol/L (–2·00 to 2·09) for patients in the placebo group (difference 5·41 nmol/L [SE 1·31], 95% CI 2·79–8·04, p=0·0001). At 12 weeks, IGFB-3 least-squares mean change from baseline concentrations were 0·025 µmol/L (95% CI 0·014 to 0·035) compared with –0·001 µmol/L (–0·011 to 0·009) for patients in the placebo group (difference 0·026 µmol/L [SE 0·007], 95% CI 0·013 to 0·039, p=0·0002). Compared with placebo, increases were observed at all timepoints for IGF-1 and at weeks 4 and 12 for IGFBP-3 (figure 5). All concentrations remained within the normal ranges. Mean values of C-reactive protein, interleukin 6, and TNFα did not differ significantly between groups (appendix).

Dosing was maintained unchanged throughout the study, except that one patient in the anamorelin group had an interruption of 1 week; the patient discontinued 1 month later. 42 (95%) of 44 patients treated with anamorelin and 33 (87%) of 38 patients treated with placebo had adverse events (table 3); serious adverse events were present in 14 (32%) patients receiving anamorelin and nine (24%) patients receiving placebo. Types of adverse events, including tumour progression, were similar between the treatments (table 3). The most common grade 3–4 adverse events (treatment-related or not) in the anamorelin group were fatigue, asthenia, atrial fibrillation, and dyspnoea (two [5%] each); in the placebo group, such events were pneumonia (three [8%]) and anaemia, thrombocytopenia, abdominal pain, anxiety, and dyspnoea (two [5%] each). No deaths related to treatment occurred. Mean change from baseline over the treatment period in glucose and insulin concentrations were increased with anamorelin versus placebo (treatment differences of 0·95 mmol/L for glucose [p=0·0002] and 77·92 pmol/L for insulin [p=0·0031]).

Discussion

Our study shows that 3 months of anamorelin treatment for patients with cancer anorexia-cachexia syndrome led to increased lean body mass versus placebo, with improvements noted in muscle strength and quality of life. These findings expand upon the previously reported 3 day course of anamorelin, in which increases in bodyweight, appetite, and quality of life were reported (panel).[20]

Cancer anorexia-cachexia syndrome is a multifactorial syndrome. Based on the international consensus from Fearon and colleagues,[1] the diagnosis is dependent on bodyweight. More recent work validating diagnostic criteria have also begun to take into account other aspects (eg, appetite loss, reduced food intake, or inflammatory markers),[24] but these other definitions have not yet been used in cachexia trials. Notably, the weight-based diagnostic criteria were proposed in 2011 and this study took place between 2005 and 2006. The study, including post-hoc analyses, were presented at several congresses between 2007 and 2013.[6]

See Online for appendix

Low lean body mass has been associated with poor survival and might also predict treatment toxic effects.[25] Appendicular lean body mass is also a useful surrogate for muscle mass because most of the lean tissue in the extremities is striated muscle. Trunk lean body mass includes a large amount of tissue that is not striated muscle, which might explain why only appendicular lean body mass differs between patients with cancer-related cachexia and those without cachexia or matched controls without cancer.[4] In this study, anamorelin increased appendicular lean body mass and had other anabolic and

anti-catabolic effects as early as 4 weeks, and these effects seemed to be sustained throughout the study. Although this study was not designed to determine the specific mechanisms mediating these changes, that the effects plateau after a certain time is unsurprising, because such an effect has been reported before with other drugs in this class[26] and with other anabolic agents.[27] Further studies will be needed to establish the mechanisms responsible for these changes.

Animal studies have shown that fat metabolism is severely affected in this setting and that targeting of this pathway has therapeutic potential.[28] In this study, fat mass, which might partially reflect energy balance, decreased more in patients who received placebo than in those who received anamorelin, although the difference was not significant.

Overall quality of life was improved with anamorelin compared with placebo, mainly driven by improvements in sense of well-being, sleep, nausea, and ASAS drowsiness scores. No gold standard exists to assess quality of life in this population, although several methods have been used, including generic cancer instruments (eg, EORTC QLQ C30, FACT-G, and ASAS) and cachexia-specific instruments (eg, FAACT). Although appetite improves acutely with ghrelin and anamorelin,[18,19] changes in appetite scores were not different from placebo in this analysis. Further studies will be needed to validate visual-scale rated appetite (eg, the ASAS) as a construct for food intake and establish whether the present study's findings show a lack of power or if effects on appetite are more pronounced in acute settings.

Several mechanisms have been postulated for anamorelin's effects on muscle mass and strength.[29] Activation of the ghrelin receptor by ghrelin or ghrelin-receptor agonists, such as anamorelin, is expected to induce growth hormone secretion, thereby increasing IGF-1 concentrations.[19] In turn, growth hormone and IGF-1 affect muscle growth through a direct effect on muscle and indirect effects through the production of

	Anamorelin (n=44)				Placebo (n=38)			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Related adverse event (SOC or PT)								
Any event*	11 (25%)	2 (5%)	0	0	9 (24%)	0	0	0
Gastrointestinal disorders*	2 (5%)	1 (2%)	0	0	5 (13%)	0	0	0
Diarrhoea	0	1 (2%)	0	0	2 (5%)	0	0	0
General disorders and administration site condition*	1 (2%)	1 (2%)	0	0	1 (3%)	0	0	0
Fatigue	1 (2%)	1 (2%)	0	0	0	0	0	0
Non-related adverse event (SOC or PT)								
Any event	11 (25%)	12 (27%)	1 (2%)	5 (11%)	7 (18%)	13 (34%)	2 (5%)	2 (5%)
Blood and lymphatic system disorders	5 (11%)	2 (5%)	0	0	7 (18%)	3 (8%)	0	0
Cardiac disorders	0	2 (5%)	1 (2%)	1 (2%)	1 (3%)	0	0	0
Gastrointestinal disorders	21 (48%)	2 (5%)	0	0	11 (29%)	3 (8%)	1 (3%)	0
Diarrhoea	6 (14%)	0	0	0	3 (8%)	0	0	0
General disorders and administration site condition	19 (43%)	3 (7%)	0	1 (2%)	12 (32%)	3 (8%)	1 (3%)	0
Fatigue	3 (7%)	1 (2%)	0	0	6 (16%)	0	0	0
Hepatobiliary disorders	0	1 (2%)	0	0	2 (5%)	0	0	0
Infections and infestations	11 (25%)	1 (2%)	0	1 (2%)	12 (32%)	3 (8%)	0	0
Injury, poisoning, and procedural complications	6 (14%)	0	0	0	5 (13%)	0	0	0
Investigations	6 (14%)	2 (5%)	0	0	7 (18%)	1 (3%)	1 (3%)	0
Metabolism and nutrition disorders	7 (16%)	2 (5%)	1 (2%)	0	9 (24%)	1 (3%)	0	1 (3%)
Muscoskeletal and connective tissue disorders	8 (18%)	2 (5%)	0	0	9 (24%)	1 (3%)	0	0
Neoplasm benign, malignant, and unspecified	2 (5%)	3 (7%)	0	1 (2%)	3 (8%)	2 (5%)	0	1 (3%)
Nervous system disorders	8 (18%)	1 (2%)	0	0	4 (11%)	5 (13%)	0	0
Psychiatric disorders	8 (18%)	1 (2%)	0	0	5 (13%)	2 (5%)	0	0
Renal and urinary disorders	4 (9%)	1 (2%)	0	0	2 (5%)	0	0	0
Reproductive system and breast disorders	2 (5%)	0	0	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders	12 (27%)	2 (5%)	2 (5%)	1 (2%)	8 (21%)	3 (8%)	0	0
Skin and subcutaneous tissue disorders	10 (23%)	0	0	0	10 (26%)	0	0	0
Vascular disorders	5 (11%)	2 (5%)	0	0	3 (8%)	0	0	0

Data are n (%). Adverse events were assessed with Medical Dictionary for Regulatory Activities (version 8.0) and graded according to Common Terminology Criteria for Adverse Events (version 3.0). SOC=system organ class. PT=preferred term. *Other related adverse events were of grades 1–2 and occurred in less than 10% of patients.

Table 3: **Adverse events grades 1–2 with an incidence of more than 10% in either group plus any grades 3–5 (safety population)**

both muscle-restricted IGF-1 and anti-cachectic cytokines. Additionally, the known orexigenic effects of ghrelin or anamorelin[18] and their reported anti-inflammatory effects probably play a part in muscle-mass preservation independently of growth hormone. Although differences in cytokine measurements were not significant, circulating concentrations might not be a true reflection of cytokine tissue concentration or action, and other cytokines not measured in our study could also play a part.

Because of anamorelin's mechanism of action, IGF-1 and IGFBP-3 concentrations increased; the increases were sustained, but remained within normal ranges. Decreased IGF-1 concentrations probably contribute to cancer cachexia and muscle dysfunction.[30] Preclinical and retrospective studies suggest that increased IGF-1 might promote tumour progression;[31] however, IGFBP-3 could provide a counterbalance by binding to IGF-1 or by direct IGF-independent mechanisms.[31,32] In our studies, the increases in IGFBP-3 were far greater than the increases in IGF-1 on a molar basis. Whole animal studies increasing growth hormone or ghrelin tone, and human studies of ghrelin or ghrelin-receptor agonists, have not shown an effect of ghrelin on tumour growth.[17,33] Individuals with oesophageal cancers receiving ghrelin and chemotherapy had improved tolerance to therapy and no effect on tumour response to treatment.[34] In a non-small-cell lung cancer cachexia animal model, administration of anamorelin or ghrelin for 28 days increased mean bodyweight but did not promote tumour growth.[35] Moreover, in this clinical study, no treatment-related deaths occurred and no difference in incidence of tumour progression adverse events occurred between the anamorelin and placebo groups. Future long-term studies with large, homogeneous populations will further assess this question.

As expected in a population with advanced cancer, adverse events and discontinuations were common. Discontinuations were anticipated and accounted for a priori in the study design and power calculations. However, the dropout rate was balanced between groups and not due to toxic effects. Glucose and insulin concentrations rose slightly, although they remained mostly within the normal range, and the rate of hyperglycaemia was similar between groups. This finding might show direct activation of the ghrelin axis on glucose metabolism or a possible effect of the reversal of cancer anorexia-cachexia syndrome. Patients with diabetes or obesity were excluded from the studies; hence, changes in glucose in these settings remain unknown.

The study enrolled patients with diverse tumour types to potentially identify patients who would respond to treatment. However, study limitations include the small sample size and subsequent lack of stratification of results by heterogeneity of tumour type, chemotherapy, performance status, and staging. Therefore, whether our findings were driven by specific subpopulations or are generalisable to a broad population of patients with cancer anorexia-cachexia syndrome is unknown. Muscle function was assessed by handgrip strength, which measures upper-extremity strength only and might not indicate overall physical performance or spontaneous activity. No validated standard exists to assess muscle strength, and sparse data are available on the usefulness of handgrip strength as a marker of treatment effect.

On the basis of these results, further testing of anamorelin on a larger scale is warranted. Anamorelin is now being assessed in phase 3 studies (NCT01387269, NCT01387282, and NCT01395914) investigating efficacy and safety in patients with non-small-cell lung cancer and cancer anorexia-cachexia syndrome.[36]

***Panel:* Research in context**

Systematic review

Two recent systematic reviews of the literature for "cancer," "cachexia", and other terms associated with involuntary weight loss in cancer identified few potentially relevant studies, and none that showed clear therapeutic efficacy on relevant endpoints including skeletal muscle, lean body mass, metabolic processes, and functional capacity.[1,10] We did similar systematic searches of PubMed and Medline with the search terms "cancer" AND "cachexia" AND "clinical trial" AND "placebo" from Jan 1, 2006, to Aug 15, 2014, and ClinicalTrials.gov. All such studies were reviewed for interventional agent, phase of development, placebo control, and significance of results. As with the earlier reviews, we identified no agents that had been proven to offer clinically meaningful efficacy in a rigorous phase 3 trial. Thus, treatment of cancer anorexia-cachexia syndrome remains an unmet medical need.

Interpretation

Our study suggests that anamorelin has a favourable clinical response profile in cancer anorexia-cachexia syndrome, specifically, sustained increases in lean body mass and appendicular lean body mass (a surrogate of muscle mass) and measures of muscle strength and quality of life. These findings warrant further investigation.

Contributors

JMG, RVB, CDG, and SA were responsible for the study conception and design. JMG, RVB, CDG, and SA contributed to the provision of study materials or patients. JMG, RVB, CDG, YY, SA, and JF were involved in the collection and assembly of data. JMG wrote the first draft of the manuscript. All authors participated in the study data analysis and interpretation and manuscript writing, and provided their final approval of this manuscript.

Declaration of interests

YY, EMD, SA, and JF are employees at Helsinn Therapeutics (US). JMG has received consulting or advisory role's fees from Aeterna Zentaris and Helsinn Therapeutics (US), and research grants from the Department of Veterans Affairs (MERIT grants I01-BX000507 and I01 CX000174, and the NIA T32AG000183 and AG040583), Aeterna Zentaris, and Helsinn Therapeutics (US). RVB and CDG declare no competing interests.

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