ANAMORELIN'S EFFECTS ON APPENDICULAR LEAN BODY MASS IN CANCER PATIENTS WITH CACHEXIA; RESULTS FROM A PHASE II RANDOMIZED, DOUBLE BLIND, MULTICENTER STUDY

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INTRODUCTION

- Cancer cachexia is associated with increased morbidity, and decreased survival independent of the malignancy[1,2].
- Cachectic subjects also have decreased muscle mass/strength and overall lean body mass (LBM) including in the extremities (a.k.a. appendicular LBM or aLBM)
  - Both LBM and handgrip strength (HGS) have been shown to be predictive of survival and quality of life[3-5]
  - aLBM has also been proposed as a surrogate for muscle mass[6,7]
- Anamorelin is a multimodal anticachectic agent with orexigenic and anabolic effects. It is a small molecule, orally active ghrelin receptor agonist that may offer significant therapeutic potential to treat the critical unmet need of anorexia/cachexia associated with cancer.
  - In Phase I studies, anamorelin significantly increased body weight compared to placebo in non-cancer volunteers[8].
  - In Phase II studies, anamorelin increased mean LBM and total body mass (TBM), and improved HGS, in patients with cancer anorexia/cachexia[9].
- The study presented here is a post-hoc analysis on a subset of patients with cancer anorexia/cachexia from a Phase II study[9] that also underwent aLBM assessments, and demonstrates the effect of anamorelin on body composition, HGS and quality of life (QoL).

OBJECTIVES

- To explore **the ability of anamorelin to increase aLBM** in patients with cancer anorexia/cachexia
- To assess the effects of anamorelin on physical strength and QoL measures in patients with cancer anorexia/cachexia, and evaluate correlations with improved aLBM and HGS.

MATERIALS & METHODS

- Phase II study, randomized, placebo-controlled, double-blind
- Multicenter: 17 sites in the US
- Dosage: anamorelin 50 mg once daily or matching placebo for 12 weeks
- Patients were evaluated at baseline, and weeks 4, 8, and 12.
  - 82 patients were included in the Safety Population
  - 74 patients were included in the Intent-to-Treat (ITT) population
  - 72 patients from the ITT population also underwent aLBM assessments and are included in this presentation as the aLBM sub-group.
- Outcome measures included changes in:
  - Body composition parameters (aLBM, total LBM, TBM and fat mass) by DXA central reading;
  - Handgrip strength (HGS);
  - Quality of life (Anderson Symptom Assessment Score [ASAS]).
- Treatment effects were assessed using two repeated measures ANOVA models:
  - Primary analysis model (unstructured covariance matrix) - for key efficacy endpoints only (change from baseline in LBM, HGS of non-dominant hand, and ASAS total score).
  - Confirmatory analysis model for sensitivity analysis (compound symmetry matrix) - for all efficacy endpoints
- Patient were included with:
  - Any histologically proven malignancy;
  - Weight loss≥5% within 6 months prior to enrollment;
  - ECOG performance scores 0-2.
- Patient were excluded for:
  - Inability to consume food (e.g., due to obstructing esophageal lesion);
  - Significant liver disease or diabetes;
  - Significant ascites or edema that could confound assessment of weight;
  - Obesity (BMI>30 kg/m^2);
  - Concomitant medications that could confound study outcome measures (e.g., appetite stimulants, anabolic agents).

RESULTS

Patient Population

- No significant differences were noted between treatment groups at baseline (**Table 1** and **Table 2**).
- Most patients (93%) had solid tumors; no differences between cancer types were discerned between the treatment groups.

Effect on Total Body Mass, Lean Body Mass and Fat Mass

- Mean TBM and LBM were increased from baseline at all evaluations for patients who received anamorelin, while fat mass did not increase (**Table 3**).
  - Mean changes from baseline in TBM and total LBM were significant for anamorelin vs placebo at all evaluations, as well as for the overall treatment difference at Week 12.

Effect on Appendicular Lean Body Mass

- Placebo-treated patients lost a significant amount of LBM in the arms, while aLBM in the legs was more stable with slight gains at Weeks 8 and 12. Anamorelin-treated patients gained LBM in both the arms and legs beginning at Week 4 and maintained during the study.
- Total aLBM (arms + legs) was significantly increased in anamorelin-treated patients compared to placebo (**Figure 1**).
  - At all time points measured, the change from baseline of aLBM in arms+legs was significant between the anamorelin and placebo groups (p=0.009 at Week 4; p=0.0308 at Week 8; p=0.0445 at Week 12)
  - At Week 12, the percentage change from baseline of aLBM in arms+legs was 5.8% in the anamorelin-treated patients compared to 1.5% in the placebo-treated patients.

Table 1: Demographic and Baseline Characteristics - Safety Population

	ANAM 50 mg n = 44	Placebo n = 38
Gender, n (%)		
Men	28 (63.6%)	23 (60.5%)
Women	16 (36.4%)	15 (39.5%)
Age (yrs); Mean (SD)	64.4 (14.70)	65.3 (12.08)
Race, n (%)		
Caucasian	35 (79.5%)	29 (76.3%)
Black	8 (18.2%)	7 (18.4%)
Other	1 (2.3%)	2 (5.3%)
Weight (kg); Mean (SD)	62.3 (11.70)	64.0 (14.37)
BMI (kg/m^2); Mean (SD)	21.7 (3.50)	22.1 (4.13)
Weight loss stratum (%)		
5% - 15%	28 (63.6%)	22 (57.9%)
> 15%	16 (36.4%)	16 (42.1%)
Time since diagnosis (yrs); Mean (SD)	2.3 (3.01)	3.4 (6.58)
ECOG performance score, n (%)		
0	6 (13.6%)	5 (13.2%)
1	27 (61.4%)	28 (73.7%)
2	11 (25.0%)	5 (13.2%)
Karnofsky scale score, Mean (SD)	79.9 (12.87)	81.8 (10.36)

BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; SD: standard deviation.
The 72 patients in the aLBM sub-group had similar demographic and clinical characteristics compared to the patients in the Safety Population. No statistical difference was observed between the two groups.

Table 2: Baseline Body Composition Characteristics - ITT Population

	ANAM 50 mg n = 38	Placebo n = 36
Total Body Mass (kg); Mean (SD)	61.94 (12.04)	62.81 (13.00)
Lean Body Mass (kg); Mean (SD)	43.33 (7.76)	43.64 (8.32)
Fat Mass (kg); Mean (SD)	15.83 (7.26)	16.48 (10.53)
Appendicular Lean Body Mass (kg);		
Mean (SD)[1]		
Arms	4.57 (1.17)	4.57 (1.28)
Legs	12.95 (2.70)	13.27 (2.68)
Arms+Legs	17.53 (3.83)	17.84 (3.79)

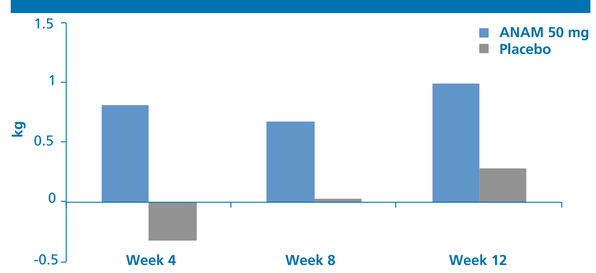
[1]For appendicular lean body mass, the sample size was n = 38 for ANAM 50 mg and n = 34 for Placebo.
The 72 patients in the aLBM sub-group had similar baseline body composition characteristics compared to the patients in the ITT Population. No significant difference was observed between the two groups

Table 3: Changes from Baseline in Body Composition Parameters - ITT Population

	Week 4		Week 8		Week12		p-value
	ANAM 50mg n = 38	Placebo n = 36	ANAM 50mg n = 38	Placebo n = 36	ANAM 50mg n = 38	Placebo n = 36	for Overall Treatment Dif.[1]
Lean Body Mass (kg)	1.85 (2.38)	-0.42 (2.59)	1.84 (2.74)	0.37 (3.77)	2.08 (2.96)	0.94 (2.56)	**0.0006**
Total Body Mass (kg)	1.32 (2.74)	-1.52 (3.08)	0.98 (3.25)	-1.57 (4.06)	1.22 (4.28)	-0.46 (3.06)	**0.0057**
Fat Mass (kg)	-0.51 (1.47)	-1.08 (1.54)	-0.83 (2.40)	-1.91 (2.69)	-0.84 (3.68)	-1.36 (3.29)	0.1532

Data are presented as mean (SD).
[1]p-value for treatment difference (50 mg vs Placebo) was estimated from the repeated measures ANOVA model (LBM - unstructured covariance model; TBM and Fat Mass - compound symmetry covariance structure).

Figure 1: Changes from Baseline in Mean Appendicular LBM - aLBM Sub-group



Effect on Hand Grip Strength of the Non-Dominant Hand

- Mean HGS decreased from baseline at 4 weeks and 8 weeks for patients who received placebo, with a modest increase at 12 weeks (Figure 2).
- HGS change from baseline improved in anamorelin-treated patients vs placebo (**Figure 2**).
  - Over the 12-week treatment period, patients treated with anamorelin improved their non-dominant HGS by 2.59 kg (95% CI: 0.54 to 4.63 kg) compared to patients treated with placebo (p=0.0140).
- The correlation between HGS and aLBM was statistically significant at all time points evaluated, as listed below. The fitted linear models for HGS vs aLBM at Week 12 are presented in **Figure 3**, and demonstrate that changes in aLBM induced by anamorelin are associated with changes in HGS.
  - Week 4: Pearson correlation was 0.6581 (p=0.009) for the anamorelin group, and was 0.6466 (p=0.0125) for the placebo group
  - Week 8: Pearson correlation was 0.7576 (p<0.0001) for the anamorelin group, and was 0.6379 (p=0.0141) for the placebo group
  - Week 12: Pearson correlation was 0.7351 (p<0.0001) for the anamorelin group, and was 0.6130 (p=0.0197) for the placebo group

Figure 2: Change from Baseline in Mean HGS of the Non-Dominant Hand- ITT Population

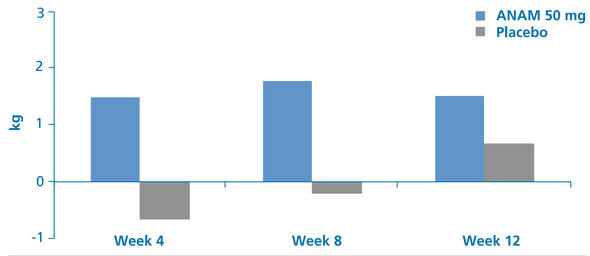
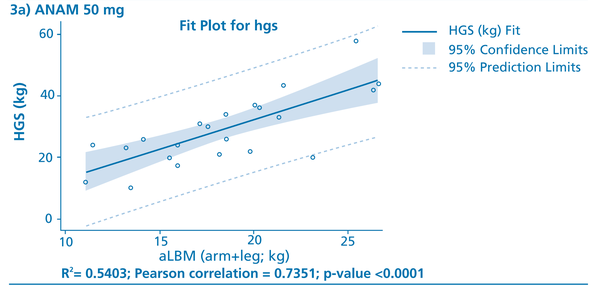


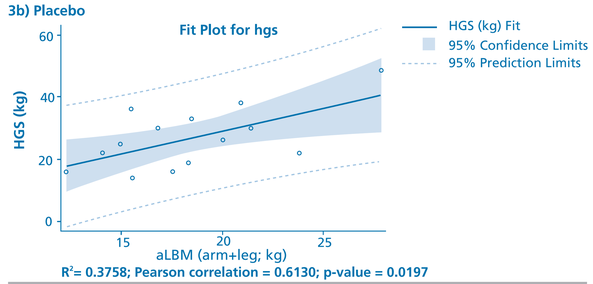
Figure 3: HGS vs aLBM at Week 12 by General Linear Model - aLBM Sub-group

3a) ANAM 50 mg



R^2= 0.5403; Pearson correlation = 0.7351; p-value <0.0001

3b) Placebo

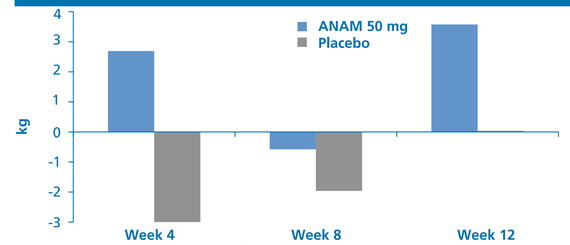


R^2= 0.3758; Pearson correlation = 0.6130; p-value = 0.0197

Effect on Quality of Life

- Positive improvements in ASAS total scores were shown in anamorelin-treated patients compared to placebo-treated patients (**Figure 4**).
- Over the 12-week treatment period, a statistically significant improvement in ASAS total score was seen in anamorelin-treated patients compared to placebo patients (mean total score increased by 6.66; 95% CI was 0.72 to 12.59; p=0.0287), although this difference did not reach statistical significance on the confirmatory sensitivity analysis (0=0.0729).
- Statistically significant improvements were also noted for individual ASAS items (drowsy, feeling of well-being, nausea, and sleep) in anamorelin-treated patients compared to placebo-treated patients (**Table 5**), with positive trends for the majority of other individual items.

Figure 4: Change from Baseline in Mean Adjusted ASAS Total Score - ITT Population



The adjusted ASAS scores are the inverted original ASAS scores. eg, the adjusted score of 0 indicates worst imaginable symptoms and 10 indicates no symptoms. Positive changes from baseline indicate improvement, while negative changes from baseline indicate worsening.

Table 5: Changes from Baseline in Mean Adjusted ASAS Score - ITT Population

	Week 12		
	ANAM 50 mg n = 38	Placebo n = 36	p value for treatment difference[1]
Total Score	1.52 (2.46)	-5.13 (2.43)	**0.0287**
Individual Items:			
Anxiety	0.01 (0.36)	-0.38 (0.35)	0.4105
Appetite	1.54 (0.40)	1.06 (0.40)	0.3570
Depression	0.11 (0.37)	-0.33 (0.37)	0.3436
Drowsy	0.06 (0.40)	-0.97 (0.39)	**0.0418**
Fatigue	0.26 (0.39)	-0.49 (0.38)	0.1279
Feeling of Well-being	0.25 (0.30)	-0.65 (0.30)	**0.0212**
Nausea	0.16 (0.38)	-1.30 (0.38)	**0.0046**
Pain	-0.53 (0.45)	-0.80 (0.44)	0.6370
Shortness of Breath	-0.25 (0.32)	-0.85 (0.32)	0.1394
Sleep	0.41 (0.34)	-0.62 (0.34)	**0.0224**

Data are presented as observed overall LS mean (SE).
The adjusted ASAS scores are the inverted original ASAS scores. e.g: the adjusted score of 0 indicates worst imaginable symptoms and 10 indicates no symptoms.
[1]p-value for treatment difference (50 mg vs Placebo) was estimated from a repeated measures ANCOVA model (unstructured covariance).

Safety

- Anamorelin was well-tolerated:
  - Any adverse event: 96% anamorelin; 87% placebo;
  - Serious adverse event: 32% anamorelin; 26% placebo.
- Types of adverse events were similar between the treatments[9]

DISCUSSION AND CONCLUSIONS

- LBM loss is a negative and independent prognostic factor in patients with cancer cachexia. Moreover, decreased grip strength is associated with poor survival in this population.
- LBM in the extremities (aLBM) may be a good surrogate for muscle mass, given that most of the lean tissue in this area is striated muscle. Trunk lean body mass includes a large amount of tissue that is not striated muscle, which could explain why only aLBM are different between cancer-cachectic patients and cancer patients without cachexia or matched non-cancer controls[6,10].
- Results of this Phase II study with anamorelin demonstrated:
  - Increased mean LBM, aLBM and TBM, with significant differences compared to placebo that were evident at 4 weeks and maintained for the duration of the study (12 weeks);
  - Improved handgrip strength and QoL changes, that were also maintained during the 12-week study;
  - Significant correlations between aLBM and HGS suggest that improvements in aLBM are clinically relevant as they correlate with HGS and thus muscle function; these data also provide support that this simple clinical test (HGS) may be a surrogate for muscle mass and function.
- Anamorelin was well-tolerated and no dose-limiting toxicity was observed.
- Anamorelin may offer significant potential to treat cancer anorexia/cachexia via its ghrelin mimetic activity. Continued investigation in Phase III studies is currently ongoing in cachectic patients with advanced non-small cell lung cancer (NCT01387269 and NCT01387282).

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