Published in final edited form as:

J Clin Psychiatry. 2018 ; 79(1): . doi:10.4088/JCP.17m11585.

Treatment with a Ghrelin Agonist in Outpatient Women with Anorexia Nervosa: A Randomized Clinical Trial

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Abstract

Objective: To assess the effects of a ghrelin agonist (relamorelin) – an appetite stimulating hormone with effects on gastric emptying on 1) weight gain and 2) gastric emptying in women with anorexia nervosa.

Methods: Using a randomized, double-blind, placebo controlled design, we studied the effects of a ghrelin agonist in twenty-two outpatient women with anorexia nervosa, diagnosed using DSM-5 criteria. The study was conducted at the Massachusetts General Hospital Clinical Research Center between March 11, 2013 and February 26, 2015. Ten participants were randomized to relamorelin (Motus Therapeutics, Boston, MA) 100 mcg subcutaneously daily (mean age $\pm$ SEM: 28.9 ± 2.4 yrs) and 12 were randomized to placebo (28.9 ± 1.9 yrs). We measured changes in weight and gastric emptying time using a gastric emptying breath test (GEBT) in relamorelin versus placebo after four weeks of treatment.

Results: At baseline, subjects did not differ in weight, ghrelin levels or GEBT times. Three subjects randomized to relamorelin stopped use of the study medication due to reported feelings of increased hunger. After four weeks, there was a trend towards an increase in weight in participants randomized to relamorelin (0.86 ± 0.4 kg) compared to placebo (0.04 ± 0.28 kg; $p=0.07$) and gastric emptying time was significantly shorter in relamorelin (median [interquartile range]: 58 [51,78] minutes) compared to placebo (85 [75.8,100.5] minutes; $p=0.03$).

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Previous presentation: Some data in this manuscript were presented as an abstract poster at the Endocrine Society Annual Meeting, Boston, MA on April 3, 2016.

Conclusions: Treatment with a ghrelin agonist in women with anorexia nervosa significantly improves gastric emptying, leads to a trend in weight gain after only four weeks and is well-tolerated. Further study is necessary to determine the long-term safety and efficacy of a ghrelin agonist in the treatment of anorexia nervosa.

Trial Registration: clinicaltrials.gov identifier:

Keywords

Anorexia nervosa; Ghrelin; Clinical trial

Introduction:

Anorexia nervosa (AN), a psychiatric disorder with a lifetime prevalence of up to 2.2% in women¹, is characterized by an extreme fear of weight gain and inappropriately low caloric intake. Nutritional rehabilitation and psychotherapy are first line treatment for AN but relapse rates remain near 40–50% even many years after the initial diagnosis^{2, 3}.

Pharmacological agents including selective serotonin reuptake inhibitors (SSRIs) and atypical antipsychotics have been studied, but definitive benefit has not been demonstrated and there are no approved therapies for AN⁴. As AN has among the highest mortality rates of any psychiatric illness⁵, the need for effective treatments is critical. Importantly, rates of delayed gastric emptying are reported to be as high as 50–80% in this population^{6–8} and associated gastrointestinal symptoms may interfere with eating and impede nutritional recovery.

Ghrelin is an orexigenic hormone produced by the fundal cells of the stomach. Its active form, acylated ghrelin, binds to the growth hormone secretagogue (GHS)1a receptor. In addition to stimulating appetite, ghrelin is a potent stimulator of gastric motility. Despite the fact that total ghrelin levels are elevated in girls and women with AN^{9–11}, women with AN report less hunger than healthy controls¹². This discrepancy may be due to ghrelin resistance in individuals with AN¹³, or to differences in the ratio of the active versus degraded forms of ghrelin in women with AN compared with healthy controls¹⁴. Relamorelin (Motus Therapeutics, formerly Rhythm Pharmaceuticals, Boston, MA) is a potent agonist of the GHS1a receptor. In diabetics with gastroparesis, relamorelin has been shown to accelerate gastric emptying¹⁵. Although prior studies have demonstrated improvements in gastric emptying in AN with prokinetic agents including erythromycin¹⁶ and metoclopramide¹⁷, these agents are not approved for treatment of AN and side-effects may preclude long-term use. Therefore, we hypothesized that in women with AN, treatment with a ghrelin agonist -- a prokinetic agent with the additional potential to stimulate appetite -- would result in 1) weight gain and 2) improved gastric emptying. We investigated this hypothesis in a four week double-blind, randomized, placebo-controlled clinical study.

Method:

Study participants

Study participants were recruited through referrals from local eating disorder providers and on-line advertisements and were enrolled in the study between March 11, 2013 and February

26, 2015. Participants had to meet DSM-5 criteria¹⁸ for AN and have self-reported gastrointestinal symptoms (such as fullness, bloating and constipation). All subjects were outpatients at the time of enrollment and none were receiving hyperalimentation therapy or tube feeds. Inclusion criteria also required subjects to be on a stable medication regimen for at least 2 weeks prior to their baseline visit. Exclusion criteria included pregnancy, diabetes mellitus, peptic ulcer disease, inflammatory bowel disease, Celiac disease, history of gastrointestinal surgery, history of a malignancy, abnormal thyroid function, active substance abuse, evidence of severe depression as measured by a Beck Depression Inventory-2¹⁹ score of ≥ 29 , and use of agents that might affect gastric motility (including metoclopramide, erythromycin, 5HT₃ anti-emetics or opiates) within the 2 weeks prior to the baseline visit.

Study protocol

Subjects who met inclusion criteria after a screening visit presented for a baseline visit at the Massachusetts General Hospital Clinical Research Center (MGH CRC). At the baseline visit, subjects were instructed on how to self-administer the study medication (relamorelin or masked placebo) and after the completion of the baseline visit procedures, they self-administered the first dose. Subjects self-administered the study medication (relamorelin 100mcg subcutaneously or placebo) every morning daily for 4 weeks and returned to the MGH CRC once weekly for a total of 5 weeks. At all of the weekly visits, subjects had a physical exam, they were weighed on an electronic scale while wearing a hospital gown and completed a visual analogue scale (VAS) appetite assessment²⁰ after an overnight fast. At the baseline visit, subjects' height was measured as the average of 3 readings on a single stadiometer and elbow breadth (for estimation of frame size) was measured using calipers and compared to norms based on NHANES-I data. BMI was calculated using the formula [weight (kg)/height (meter)²] and percent of ideal body weight was calculated based on 1983 Metropolitan Life Height and Weight tables²¹. At the baseline and week 4 visits, labs were drawn after an overnight fast, resting energy expenditure was measured using indirect calorimetry (VMAX Encore 29 metabolic cart; Carefusion, San Diego, CA) and a gastric emptying breath test (GEBT) (Advanced Breath Diagnostics, Brentwood, TN) was performed with a meal containing ¹³C-spirulina platensis. Subjects also completed the Beck Depression Inventory-2¹⁹ and the patient assessment of upper gastrointestinal disorders-symptom severity index (PAGI-SYM)²² at baseline, week 2 and week 4.

The study was approved by the Partners Institutional Review Board and complied with the Health Insurance Portability and Accountability Act guidelines. Written informed consent was obtained from all subjects. The study was registered at [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01642550) (identifier: NCT01642550) on July 13, 2012.

Biochemical assessment

Total ghrelin levels were measured by ELISA (EMD Millipore, Billerica, MA) with an intra-assay coefficient of variation (CV) of 1.32% and an inter-assay CV of 6.62%. Plasma was collected in tubes containing phenylmethylsulfonyl fluoride (PMSF)/hydrochloric acid (HCl) in order to measure acylated ghrelin by ELISA (EMD Millipore, Billerica, MA) with an intra-assay CV of 3.09% and an inter-assay CV of 7.56% and desacyl ghrelin by ELISA (Cayman Chemical, Ann Arbor, MI) with an intra-assay CV of 6.93% and an inter-assay CV

of 7.23%. Insulin-like growth factor (IGF)-1 was measured by a luminescent immunoassay analyzer (ISYS Analyzer; Immunodiagnostics Corporation, Woburn, MA). IGF-1 was measured after acid extraction to minimize interference with binding proteins. The intra-assay CV for IGF-1 was 2.2% and the inter-assay CV was 5.1%.

Statistical analysis

A sample size of 20 participants was planned using a standard deviation for a four-week change in weight of 1kg. Statistical analysis was performed using JMP Pro 11.0 (SAS Institute, Cary, NC) software. Means and standard error of the mean (SEM) measurements are reported and compared using the Student's t-test unless the data were non-normally distributed, in which case the Wilcoxon's Rank Sum test was used. Percentages were compared using the Fisher's exact test. One acylated ghrelin level at baseline and three acylated ghrelin values (two from the relamorelin group and one from the placebo group) at the week 4 time-point were below the detection limit of the assay. Since the mean and median acylated ghrelin levels at week 4 for the relamorelin group were lower than that of the placebo group, these samples were left out of the analysis (for acylated ghrelin only), rather than substituting a value less than the detection limit, in order to minimize bias. A longitudinal general linear mixed effects model was used to detect a between group difference of the longitudinal mean changes by testing the group $\times$ time interaction for endpoints in which more than two time-points were measured. Multivariable analyses were performed using least-squares linear regression in order to control for confounders. A p -value of < 0.05 on a two-tailed test was used to indicate statistical significance and data were analyzed using an intention-to-treat analysis.

Results:

Study participants

Forty-nine individuals screened for the study and a total of 29 were found to be eligible (Figure 1). Reasons for ineligibility included not meeting DSM-5 criteria for anorexia nervosa ($n=9$), abnormal screening labs ($n=3$), Beck Depression Inventory-2 score of ≥ 29 ($n=5$), history of a malignancy ($n=1$), history of intestinal surgery ($n=1$), and participation in another clinical trial within the last 30 days ($n=1$). Twenty-two subjects enrolled in the study and seven eligible subjects chose not to enroll. Reasons for not participating included the inability to commit the time required for the study ($n=2$), not interested in participating ($n=4$), subject was not able to start the study before study closure ($n=1$).

Baseline characteristics of the study participants are listed in Table 1. Study subjects in both groups were of similar % ideal body weight (relamorelin: $79.9 \pm 1.5\%$ versus placebo: $81.0 \pm 2.1\%$; $p=0.67$) and had similar baseline gastric emptying times (median [interquartile range]: relamorelin: 89 [69.5, 110.8] minutes versus placebo: 85.5 [74, 125.8] minutes; $p=0.60$). Participants in the relamorelin group had a higher baseline score for the VAS hunger assessment (relamorelin: 6.3 [2.2, 8.1] cm versus placebo: 3.0 [1.0, 5.5] cm but this difference was not statistically significant ($p=0.15$). Nine subjects (75%) randomized to placebo and all ten subjects (100%) randomized to relamorelin ($p=0.22$) were receiving long-term outpatient therapy, which continued during the course of the study. None of the

subjects were transitioned to inpatient therapy or a higher level of care during the course of the study. None of the subjects had any changes to their treatment during the study except that one subject randomized to relamorelin and one subject randomized to placebo each had a dose increase in medications (escitalopram and duloxetine, respectively) during the course of the study. There was a mean of 31.3 ± 4.5 days between the screening visit and the baseline visit for subjects in the study. During this month prior to the initiation of study drug (which occurred at the baseline visit), the mean change in weight was similar in both groups (relamorelin: -0.25 ± 0.4 kg and placebo: -0.2 ± 0.4 kg; $p=0.93$).

Change in weight

Participants randomized to relamorelin gained more weight (0.86 ± 0.4 kg; range: -0.3 kg to 2.8 kg) as compared to participants in the placebo group (0.04 ± 0.3 kg; range: -1.6 kg to 2.1 kg), although there was only a trend towards statistical significance ($p<0.07$) (Figure 2). The results were similar ($p=0.06$) when controlling for baseline VAS hunger score. Of the twenty subjects for whom we have follow-up data, seven out of eight of the subjects (87.5%) randomized to relamorelin gained weight between baseline and week 4 whereas only six out of 12 of the subjects (50%) randomized to placebo gained weight.

Change in gastric emptying time

After four weeks of treatment, participants randomized to relamorelin had a significantly shorter gastric emptying time as compared to those randomized to placebo (relamorelin: $58.0 [51.0, 78.0]$ minutes versus placebo: $85.0 [75.8, 100.5]$ minutes; $p=0.03$) (Figure 3). The percent decrease in gastric emptying time was also significantly greater in the relamorelin group (-24.3 ± 3.9 %) as compared to placebo (-5.1 ± 7.3 %; $p=0.03$).

Change in VAS hunger score, self-reported gastrointestinal symptoms and resting energy expenditure

Change in VAS hunger score was similar in both groups after four weeks of treatment (relamorelin: -0.48 ± 0.77 cm versus placebo: 0.63 ± 0.51 cm; $p=0.26$), as was change in self-reported gastrointestinal symptoms (relamorelin: $-0.52 [-0.91, 0.06]$ versus placebo: $-0.23 [-0.71, 0.06]$; $p=0.65$). On repeated measures analysis, there was no significant group $\times$ time interaction with respect to VAS hunger score ($p=0.35$) or gastrointestinal symptoms ($p=0.61$). Resting energy expenditure, as measured by indirect calorimetry, was similar in both groups at week 4 (relamorelin: 1098 ± 39 kcals/day versus placebo: 1063 ± 49 kcals/day; $p=0.59$), as was percent change in resting energy expenditure after four weeks of treatment (relamorelin: $0.3 [-4.7, 11.7]$ % versus placebo: $-0.8 [-8.2, 7.4]$ %; $p=0.46$).

Change in hormone levels

Total, desacyl and acylated ghrelin—After four weeks of treatment, acylated ghrelin levels decreased in the relamorelin group ($-47.3 [-91.7, 5.8]$ %) as compared to placebo ($114.7 [-36.8, 329.3]$ %) and this difference was statistically significant ($p=0.04$). In contrast, the percent change in total ghrelin (relamorelin: -7.5 ± 8.0 % versus placebo: 4.4 ± 5.7 %) and desacyl ghrelin (relamorelin: -5.5 ± 13.5 % versus placebo: 2.1 ± 9.5 %) was similar in both groups ($p=0.25$ and $p=0.65$, respectively).

Growth hormone axis—IGF-1 levels increased significantly in the relamorelin group as compared to placebo after four weeks of treatment. IGF-1 levels increased by a mean of 28.8 ± 9.9 ng/ml in the relamorelin group as compared to decreasing by 11.3 ± 5.8 ng/ml in the placebo group ($p < 0.01$). This corresponds to a percent change in IGF-1 levels of $18 \pm 6.1\%$ after four weeks of relamorelin as compared to $-5.8 \pm 2.9\%$ after four weeks of placebo ($p < 0.01$). These differences remained significant after controlling for change in weight ($p < 0.01$ for both).

Adverse events and tolerability

The study drug was well tolerated during this 4 week study. Mean depression severity scores (BDI-2) decreased similarly in both groups after four weeks of treatment (relamorelin: -1.5 ± 1.3 versus placebo: -1.1 ± 1.5 ; $p = 0.84$). Two participants, both randomized to relamorelin, dropped out of the study. One dropped out after four days of using relamorelin and the second dropped out after 12 days. Both reported that they were discontinuing the study medication due to a significant increase in hunger. A third participant, also randomized to relamorelin, remained in the study but stopped using the study drug after 14 days due to experiencing hunger and weight gain (weight increased 1.6 kg during the 14 days on which she was on the study medication). The remaining 19 study subjects completed the study.

Adverse events are reported in Table 2. Four subjects in each group experienced minor injection site reactions (bruising, ecchymoses and/or erythema) and all reactions resolved spontaneously. One participant, randomized to relamorelin, developed abdominal cramping and became diaphoretic 20 minutes after her initial dose of relamorelin but did not have a recurrence of these symptoms on continuing treatment and successfully completed the study. Two subjects who completed the study and were randomized to relamorelin had triglyceride levels > 150 mg/dl during the study (one peaked at 199 mg/dl and the other at 153 mg/dl) but by the week 4 visit, both subjects had triglyceride levels < 100 mg/dl. On repeated measures analysis, there was no significant group $\times$ time interaction with respect to triglyceride levels ($p = 0.25$).

Of the seventeen subjects who did not report dizziness at baseline, no subjects in the placebo group (0 out of 11) and three of six (50%) in the relamorelin group reported experiencing dizziness during the study ($p = 0.03$).

Discussion:

We have shown that in women with AN, treatment with a ghrelin agonist significantly decreases gastric emptying time. Although we did not find significant differences in VAS hunger score in the relamorelin group as compared to the placebo group after four weeks of treatment, three participants stopped use of relamorelin due to symptoms of increased hunger and two dropped out of the study for that reason. We also found that the relamorelin group gained more weight than the placebo group, although there was only a trend towards significance for this outcome.

Desacyl ghrelin constitutes the majority of circulating levels of ghrelin and does not bind to the GHS1a receptor. Desacyl ghrelin was thought to be an inactive form of ghrelin, although

recently it has been shown to have potential anti-ghrelin effects including blocking ghrelin's appetite-stimulatory effects²³. Since desacyl ghrelin levels are higher in women with AN as compared to healthy controls¹⁴, this may explain why women with AN report lower levels of hunger when compared to normal-weight controls¹² despite the fact that they have higher total ghrelin levels. In AN, levels of acylated ghrelin -- the orexigenic form of ghrelin -- have been reported in a number of studies to be lower than or similar to normal-weight controls^{14, 24}, and therefore treatment with acylated ghrelin or a GHS1a receptor agonist may be useful for stimulating hunger in AN.

Gastrointestinal symptoms are common in individuals with AN²⁵. Frequently reported symptoms, including postprandial fullness and abdominal distention²⁶, may impede recovery by making it difficult for individuals with AN to consume an adequate number of calories. Some of the gastrointestinal symptoms reported in AN may be due to delayed gastric emptying, which is reported in as many as 50–80% of individuals with AN^{6–8}. Therefore treatment with an agent that improves gastric emptying, such as a ghrelin agonist, could potentially aid in the nutritional rehabilitation of individuals with AN. In fact, prior studies involving prokinetic agents have demonstrated improvements in gastric emptying and weight gain in AN^{16, 17}, yet these agents are not approved for use in the treatment of AN likely because of the side effects associated with long-term use of medications such as metoclopramide.

Ghrelin has been used as a potential appetite stimulant in a number of patient populations²⁷, including women with AN. A prior study investigating the effects of a human ghrelin infusion in five individuals with AN demonstrated an increase in food intake during and after the infusion period as compared to the pre-treatment period²⁸. But because there was no control group – all five participants received ghrelin – and because all of the participants were hospitalized for hyperalimentation therapy, the benefit of ghrelin independent of hyperalimentation therapy is difficult to discern²⁸. As most individuals with AN are treated as outpatients and not hospitalized, the results of our study are generalizable to a slightly broader population of individuals with AN, as all of our participants were outpatients and none received hyperalimentation therapy during the course of the study. Yet importantly, all three subjects who discontinued study drug during the course of the study were randomized to relamorelin, which suggests that this treatment may not be tolerated by all individuals with anorexia nervosa; therefore further study will be necessary to carefully determine which patients may best benefit from this potential treatment.

Acylated ghrelin, the form that is able to bind to the GHS1a receptor, not only stimulates appetite and gastric motility, but it is also a potent activator of the growth hormone-IGF-1 axis. In this four-week study, we also found a significant increase in IGF-1 in the relamorelin group as compared to the placebo group, even after controlling for change in weight. Given the fact that the GHS1a receptor is a stimulator of growth hormone secretion, this would not be surprising but for the fact that women with AN are growth hormone resistant – their GH levels are normal or elevated in the setting of low IGF-1 levels^{29–31}. This resistance state allows for growth hormone to stimulate lipolysis and fat mobilization³² to provide critical nutrients for survival in this state of chronic undernutrition, while the low IGF-1 levels allow for minimization of energy expenditure on growth. We have previously shown that treatment

with supraphysiologic doses of recombinant human growth hormone does not increase IGF-1 levels in AN³³ and therefore the mechanism of this rise in IGF-1 levels is unclear and warrants further study. But importantly, IGF-1 levels have been positively associated with bone mineral density in AN³⁴, and treatment with recombinant human IGF-1 in combination with estrogen leads to gains in BMD³⁵ in women with AN, suggesting that a GHS1a receptor agonist may have additional potential benefits in women with AN beyond weight gain alone.

Limitations of our study include its small sample size and short follow-up period. As this was a pilot study and the first use of a ghrelin agonist in women with anorexia nervosa, we designed a short-term study to minimize the potential changes in weight that may be observed if a participant was hospitalized or entered into a treatment facility. The short-term nature of the study allowed us to observe changes that are most likely attributable to the study drug rather than to changes in the treatment status of our participants, although it limits our ability to project the long-term benefits of this therapy.

In conclusion, we have shown that treatment with a ghrelin agonist significantly improves gastric motility and may be a stimulator of weight gain in women with AN. As there are no currently approved medical therapies for the treatment of this chronic disease characterized by significant morbidity and mortality, further study is necessary to determine the long-term efficacy and safety of a ghrelin agonist as a potential therapeutic option for individuals with AN.

Acknowledgements:

We would like to thank the nurses and bionutritionists of the MGH Clinical Research Center for their expert care.

Sources of support: This project was supported by an investigator initiated grant from Motus Therapeutics, formerly Rhythm Pharmaceuticals (Boston, MA). Dr. Fiedorek holds an equity interest in Motus Therapeutics. No other authors report any financial disclosures. Dr. Fazeli had full access to the data and takes responsibility for the integrity of the data and accuracy of the data analysis. The funding source did not have a role in the collection, management, analysis or interpretation of the data or the decision to submit the manuscript for publication and approval of the manuscript was not required prior to submission. The project described was also supported by grant number 8 UL1 TR000170, Harvard Clinical and Translational Science Center, from the National Center for Advancing Translational Science and grant number 1UL1TR001102. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources, the National Center for Advancing Translational Science, or the National Institutes of Health.

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Clinical Points:

- Anorexia nervosa has a high relapse rate and there are no approved medical therapies for this disorder
- Ghrelin is an appetite stimulating hormone with effects on gastric emptying
- Treatment with a ghrelin agonist may lead to improved gastric emptying and weight gain in a subset of women with anorexia nervosa

Figure 1:
CONSORT diagram

Figure 2:

After four weeks of treatment, mean weight gain was greater in women with AN randomized to relamorelin as compared to placebo ($p < 0.07$). Mean (SEM).

Figure 3:

After four weeks of treatment, gastric emptying time was significantly shorter in women randomized to relamorelin as compared to placebo ($p=0.03$). Box and whisker plot representing maximum and minimum values as well as medians and interquartile ranges.

Table 1:

Baseline clinical characteristics of the study participants

	Relamorelin (n=10)	Placebo (n=12)	<i>p-value</i>
Age (years)	28.9 ± 2.4	28.9 ± 1.9	0.99
% Ideal body weight	79.9 ± 1.5	81.0 ± 2.1	0.67
Weight (kg)	48.1 ± 1.5	48.9 ± 1.8	0.73
Height (cm)	165.2 ± 2.3	165.3 ± 1.9	0.97
BMI (kg/m ²)	17.6 ± 0.4	17.8 ± 0.4	0.58
Duration of anorexia nervosa (years)	13.2 ± 2.2	14.8 ± 2.2	0.60
Gastric emptying time (minutes) *	89 [69.5, 110.8]	85.5 [74.0, 125.8]	0.60
Resting energy expenditure (kcal/day)	1040 ± 40	1055 ± 53	0.83
Beck Depression Inventory-2 score	15.2 ± 2.8	12.3 ± 2.1	0.41
Visual Analog Scale – Hungry *	6.3 [2.2, 8.1]	3.0 [1.0, 5.5]	0.15
Total ghrelin (pg/ml) *	878 [722, 1191]	1131 [825, 1263]	0.34
Acylated ghrelin (pg/ml) *	162 [118, 293]	140 [52, 366]	0.65
Desacyl ghrelin (pg/ml) *	422 [225, 678]	444 [318, 599]	0.87
IGF-1 (ng/ml)	156 ± 10	171 ± 14	0.39
Serum glucose (mg/dL)	77.8 ± 2.3	83.1 ± 2.4	0.13

Mean ± SEM

*
median [interquartile range]

Table 2:

Adverse effects experienced by study participants

	Relamorelin (n=8)	Placebo (n=12)	p-value
Injection site ecchymoses, bruising, erythema	4 participants (50%)	4 participants (33.3%)	0.65
Electrolyte abnormalities	2 participants (25%)	4 participants (33.3%)	0.99
Dizziness			
-All participants	5 participants (62.5%)	1 participant (8.3%)	0.02
-Participants not reporting symptom at baseline	3 participants (50%)	0 participants (0%)	0.03
Fatigue			
-All participants	7 participants (87.5%)	5 participants (41.7%)	0.07
-Participants not reporting symptom at baseline	2 participants (66.7%)	2 participants (25%)	0.49
Abdominal pain/cramping			
-All participants	7 participants (87.5%)	9 participants (75%)	0.62
-Participants not reporting symptom at baseline	1 participant (50%)	3 participants (60%)	0.99
Muscle weakness			
-All participants	1 participant (12.5%)	2 participants (16.7%)	0.99
-Participants not reporting symptom at baseline	1 participant (12.5%)	1 participant (9.1%)	0.99
Hyperhidrosis			
-All participants	2 participants (25%)	1 participant (8.3%)	0.54
-Participants not reporting symptom at baseline	1 participant (14.3%)	0 participants (0%)	0.41