Capromorelin increases food consumption, body weight, growth hormone, and sustained insulin-like growth factor 1 concentrations when administered to healthy adult Beagle dogs

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This study's objective was to determine the effects in dogs of oral capromorelin, a ghrelin agonist, at different doses for 7 days on food consumption, body weight and serum concentrations of growth hormone (GH), insulin-like growth factor 1 (IGF-1), and cortisol. Adult Beagles ($n = 6$) were dosed with placebo BID, capromorelin at 3.0 mg/kg SID, 4.5 mg/kg SID, or 3.0 mg/kg BID. Food consumption, body weight, serum capromorelin, GH, IGF-1, and cortisol were measured at intervals on days 1, 4, 7, and 9. Capromorelin increased food consumption and body weight compared to placebo and caused increased serum GH, which returned to the baseline by 8 h postdose. The magnitude of the GH increase was less on days 4 and 7 compared to Day 1. IGF-1 concentrations increased on Day 1 in capromorelin-treated dogs and this increase was sustained through Day 7. Serum cortisol increased postdosing and returned to the baseline concentrations by 8 h. The magnitude of the increase was less on days 4 and 7 compared to Day 1. A dose of 3 mg/kg was chosen for further study in dogs based on this dose causing increased food consumption and sustained IGF-1 serum concentrations that may increase lean muscle mass when administered over extended periods.

INTRODUCTION

Growth hormone secretagogues (GHS) are a class of small molecule compounds discovered in the mid-1990s that stimulate the release of growth hormone (GH) and were developed for the treatment of anorexia and cachexia in people (Smith, 2005a; Garcia *et al.*, 2015). It was subsequently discovered that GHS compounds mimic ghrelin, the hormone that is secreted from endocrine cells in the stomach and that stimulates appetite and food intake in humans (Wren *et al.*, 2001).

Ghrelin is a 28-amino acid peptide with a short half-life (~10 min) produced predominantly in the stomach and is an endogenous ligand of ghrelin receptor, also known as the growth hormone secretagogue receptor (GHS-R) (Kojima *et al.*, 1999). Ghrelin stimulates appetite by central and peripheral pathways and via the vagus nerve. The stomach releases ghrelin during the fasting state. Serum concentrations of the

hormone are increased as the time between meals is prolonged (Cummings, 2006). Ghrelin administration activates neurons in the arcuate nucleus of the hypothalamus directly, and indirectly through the vagus nerve to trigger the sensation of hunger and enhance feeding (Date *et al.*, 2002).

In addition to effects on appetite, ghrelin's ability to activate the GH/IGF-1 axis is important in maintaining normal metabolism of many tissues. The mechanism of action of ghrelin involves binding to GHS-R, a G-protein-coupled receptor that activates protein kinase C and stimulates GH-releasing hormone release from the hypothalamic neurons and GH release from the pituitary gland, resulting in the elevation of circulating GH concentrations (Smith *et al.*, 1997). Increases in GH result in secretion of IGF-1, primarily from the liver. These hormones are involved in the maintenance of appetite, lean body mass, bone mineral density, glucose homeostasis, immune function, and cognitive function (Smith *et al.*, 2005b).

Capromorelin is an orally active small molecule that mimics the action of ghrelin and is a potent and selective GHS-R agonist, which causes appetite stimulation and GH secretion just as ghrelin does. Absorption of capromorelin from the gastrointestinal tract allows it to enter the circulation in the same manner as endogenous ghrelin and naturally mimic the physiology of ghrelin (Fig. 1). Unlike ghrelin, which is a short-acting peptide and requires dosing via injection, capromorelin can be dosed orally and has a longer half-life and therefore more sustained effects. Capromorelin has been approved by the FDA as an appetite stimulant in dogs. A 12-month oral safety study in adult dogs has shown that long-term daily oral administration of capromorelin at a dose approximately 17.5 times that of the expected clinical dose is safe (Zollers et al., 2016).

This study was designed to explore the effects of three capromorelin treatment regimens/doses in dogs on serum GH, IGF-1 and cortisol concentrations over 7 days of administration to help define the dose. In addition, the effect of capromorelin treatment on food consumption and body weight was evaluated.

MATERIALS AND METHODS

Dogs

The study was conducted at Xenometrics, LLC (Stilwell, KS, USA), an AAALAC accredited facility, under a protocol that was approved by their Institutional Animal Care and Use Committee. Twenty-four sexually mature Beagle dogs (12 intact males/12 intact females), some of which had been used in the previous unrelated experiments (i.e., non-naïve), were divided into four treatment groups ($n = 3$ males and 3 females per group). Dogs ranged in age from approximately 1.7–6 years. Body weights ranged from 9–15 kg. At the end of the study, all dogs were returned to the study colony.
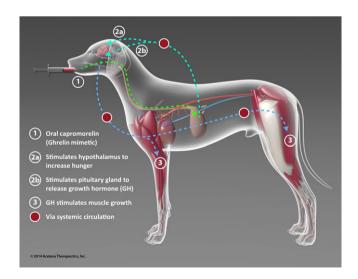

Fig. 1. The pharmacologic mechanism of action of capromorelin.

Housing

Dogs were housed individually in stainless steel cages with controlled temperature (18–29 °C), relative humidity (30–70%), and photoperiod (12 h of light alternating with 12 h of darkness). All dogs were under the care of a licensed veterinarian.

Treatment groups

The study tested three dosage regimes of capromorelin compared to placebo treatment (see Table 1) for 7 days. Group 1 and Group 4 were dosed twice daily at approximately 8 am and 6 pm (10 h ± 30 min apart). The placebo and test drug (31 mg/mL) were flavored liquid solutions (including sweeteners and other flavor enhancers) administered by a syringe placed in the corner of the mouth. The placebo solution was matched to the capromorelin solution but without the active drug. The dose volume administered to the placebo dogs (Group 1) matched the approximate dose volume given to the Group 4 dogs on a mL/kg basis. The first day of dosing was designated as Day 1.

Observations

Dogs were observed at least once a day, and any observations regarding changes in behavior and clinical signs were recorded. Body weights were recorded on days -1, 3, and 7.

Feeding and food consumption measurements

Dogs were fed a 25% protein nutritionally complete and balanced diet[a] once daily. The dogs were placed on a time-restricted feeding period beginning 7 days prior to the start of the study. At approximately 10 am (± 15 min), dogs were offered twice their normal ration (i.e., 800 grams of food) for a total of two hours, at which time any remaining food was removed. Food was weighed prior to and after food offering. Food consumption was recorded daily from Day -7 through Day 7. Water was provided ad libitum.

Table 1. Treatment groups

Treatment group	Treatment	Dose frequency	Number of dogs
1	Placebo	BID	3 male/3 female
2	3.0 mg/kg capromorelin	SID	3 male/3 female
3	4.5 mg/kg capromorelin	SID	3 male/3 female
4	3.0 mg/kg capromorelin	BID	3 male/3 female

[a]Harlan Teklad® Global 25% protein certified dog diet 2025C, Harlan Laboratories Inc.; Indianapolis, IN

Blood collection

Blood was collected on days 1, 4, 7, and 9 for drug and hormone concentration analyses. On days 1, 4, and 7, blood samples (3–4 mL) were collected from the jugular or, if necessary, another accessible vein in a standard serum collection tube with a gel separator and clot activator[b] at approximately 15 min prior to dosing, then at dosing (time 0; just prior to dosing) and 30, 45, 60, 90, 120, 240, 360, and 480 min postdose. On Day 9, one blood sample was collected at time 0 (approximately 8 am). Samples were allowed to clot and then centrifuged within 0.5–2 h postcollection in a refrigerated centrifuge. At that time, 0.5-mL aliquots of serum were transferred to 1-mL cryovials using a plastic pipette. The cryovials of serum were stored frozen (−60 to −80 °C) until packaged on dry ice for shipping to the analytical laboratories. Serum samples were analyzed for capromorelin, GH, IGF-1, and cortisol.

Serum capromorelin, GH, IGF-1, and cortisol measurements

Serum capromorelin concentrations were analyzed using a validated HPLC–MS/MS method.[c] Capromorelin was measured in serum samples collected on days 1 and 7 at time points 0, 30, 60, 120, 240, and 480 min and on days 4 and 9 at time point 0. Serum GH, IGF-1, and cortisol concentrations were analyzed using validated radioimmunoassay methodologies[d] GH was measured in all serum samples collected for each collection day. IGF-1 was measured in serum samples collected on days 1, 4, and 7 at 15 min prior to dosing and 0, 30, 60, 120, 240, 360, and 480 min postdose and Day 9 (about 48 h after the Day 7 dose). Serum cortisol concentrations were determined in serum samples collected on days 1, 4, and 7 at 15 min prior to dosing and 0, 30, 45, 60, 90, 120, 240, and 480 min postdose and Day 9 (about 48 h after the Day 7 dose).

Statistical analyses

Change in food consumption from the baseline to the end of the treatment phase was determined by comparing the average food consumption on days -3, -2, and -1 to the average daily food consumption over days 1–7. The change in body weight was compared from the baseline (Day -1) to Day 7. For each dog, percent change in food consumption and body weight was determined using the formula [100 (treatment value - baseline value)/baseline value)]. Pearson's correlation coefficient was used to assess the strength of correlation for percent change in food consumption versus the percent change in body weight. Descriptive statistics were presented for percent change from the baseline to treatment phase for each

treatment group. Possible differences between treatment groups were evaluated using analysis of variance modeling with treatment group as effect. Pairwise comparison for each of the groups 2, 3, and 4 to Group 1 (placebo) was derived from this model. Statistical significance was defined as $P \leq 0.05$. All analyses were performed using SAS® version 9.3.[e]

RESULTS

Clinical observations

The capromorelin and placebo oral solutions appeared to be well tolerated. Two dogs each had one observed soft stool on Day 7 (groups 2 and 4). One dog in Group 2 had a soft stool on Day 4. Two dogs in Group 2 displayed some degree of lethargy postdosing on Day 1. A number of dogs across the capromorelin treatment groups and study days exhibited excessive salivation at the time of dosing. One dog in Group 2 displayed excessive salivation at 30 min postdose on days 1, 4, and 7.

Food consumption

In dogs receiving capromorelin oral solution, mean (±standard deviation) food consumption increased compared to the baseline by 57.7 ± 35.1%, 37.9 ± 16.8%, and 36.4 ± 21.4% in groups 2, 3, and 4, respectively (treatment effect $P < 0.005$; Fig. 2). Mean food consumption decreased by 13.5 ± 14.9% in the placebo group. When compared to the placebo group, the difference in food consumption from the baseline to treatment period for each of the groups 2, 3, and 4 was significant ($P < 0.005$).
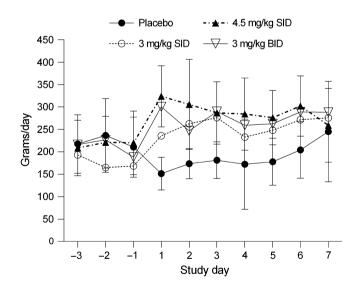
Fig. 2. Mean (± SD) food consumption in dogs (n = 3 males and n = 3 females/group) treated with placebo or capromorelin. Baseline food consumption was measured daily for 3 days prior to dosing and for the 7 days of dosing (Day 1 = first day of dosing).

Body weight

The mean body weight (±standard deviation) in Group 2 was 11.1 ± 1.6 kg on Day -1 and 11.6 ± 1.8 kg on Day 7. The mean body weight for Group 3 was 12.0 ± 1.7 kg on Day -1 and 12.5 ± 1.8 kg on Day 7. The Group 4 mean body weight was 12.5 ± 2.3 kg on Day -1 and 13.1 ± 2.4 kg on Day 7. The mean initial body weight for the placebo group was 11.9 ± 1.7 kg. At the end of the study, the placebo group's mean body weight was 11.8 ± 1.6 kg. Body weight increased in dogs treated with capromorelin by $4.52 \pm 1.67\%$, $3.78 \pm 2.93\%$, and $4.17 \pm 1.35\%$ in groups 2, 3, and 4, respectively (treatment effect $P < 0.001$; Fig. 3). Body weight in placebo dogs decreased by $1.17 \pm 1.51\%$. When compared to the placebo group, the difference in body weight change for each of the groups 2, 3, and 4 was significant ($P < 0.001$). Pearson's correlation coefficient was 0.563 (slope of linear regression = 6.5%, $P = 0.004$) indicates that there is a direct proportionality between the food consumption and body weight changes.

Capromorelin serum concentrations

The profile of serum capromorelin concentration postdose in groups 2, 3, and 4 showed similar increases followed by a return to nondetectable concentrations by 8 h on Day 1 and Day 7 (Fig. 4). Group 3 had the highest serum concentrations of capromorelin postdose. There was no evidence of serum capromorelin accumulation in groups 2, 3, and 4. As expected, capromorelin was not detected in the placebo group.

GH, IGF-1 and cortisol serum concentrations

Serum GH concentrations increased following the treatment with capromorelin on Day 1. Dogs in groups 2, 3, and 4 exhibited a peak in mean GH concentrations at 30 min postdose. Elevations in serum GH continued for 4–6 h and returned to the baseline by 8 h postdose. On days 4 and 7, mean serum GH was elevated through 2–4 h and returned to the baseline by 6–8 h postdose (Fig. 5). No sustained increase of GH was seen. The
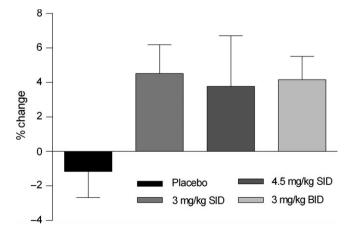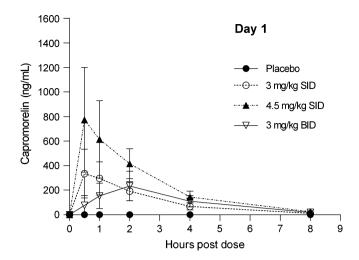
Fig. 3. Mean % change in body weight (± SD) from baseline to Day 7 in dogs treated with placebo or capromorelin.
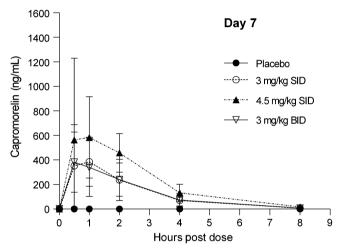
Fig. 4. Mean (±SD) capromorelin serum levels on Day 1 and Day 7 of treatment with capromorelin or placebo. Capromorelin serum levels were not measured on Day 4.

magnitude of GH response was highest in the Day 1 samples and was attenuated in all capromorelin treatment groups on days 4 and 7 when compared to Day 1. Serum GH concentrations were not elevated for any group on Day 9. There was no increase in serum GH at any time point on any day for the placebo group.

Serum concentrations of IGF-1 gradually increased in groups 2, 3, and 4 on Day 1 following capromorelin treatment. Increasing concentrations of IGF-1 were detected in serum in groups 2, 3, and 4 beginning at 2–4 h and reaching maximum concentrations at 8 h postdose (Fig. 6). Elevations in IGF-1 were sustained on Day 4 and Day 7 (Fig. 6) for the capromorelin treatment groups and returned to the baseline on Day 9. There was no increase in serum IGF-1 concentrations at any time point compared to the baseline for the placebo group.

Serum cortisol concentrations increased within 30 min of capromorelin dosing in groups 2, 3, and 4 on Day 1 and returned to the baseline by 8 h postdose (Fig. 7). The cortisol response was similar but attenuated in the capromorelin treatment groups on Day 4 and Day 7 (Fig. 7). Cortisol concentrations returned to the baseline on Day 9. There was no increase in serum cortisol at any time point compared to the baseline for the placebo group.
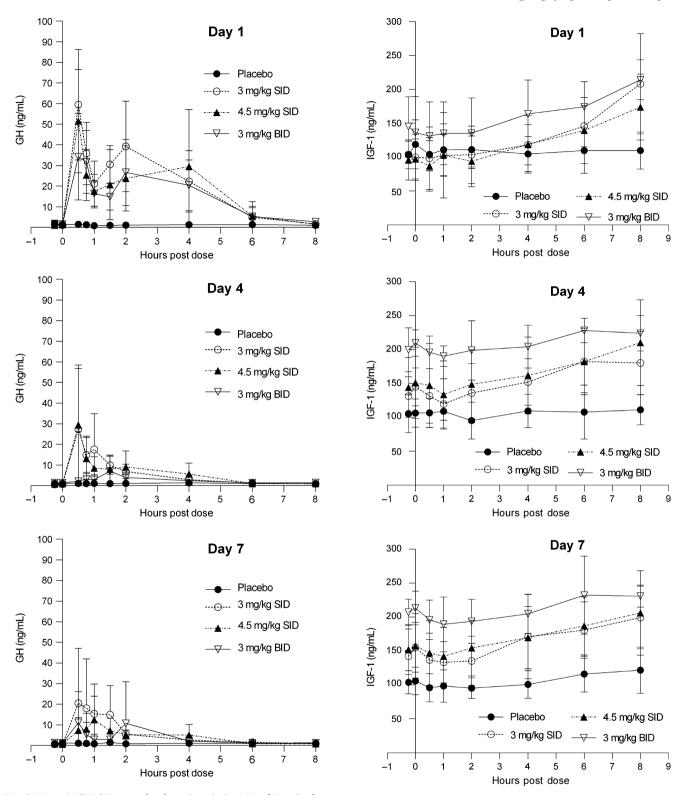
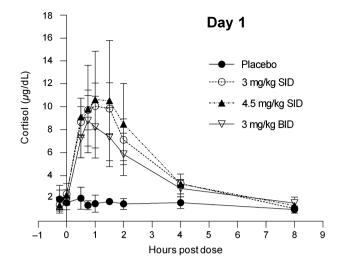**Fig. 5.** Mean (±SD) GH serum levels on Day 1, Day 4 and Day 7 of treatment with capromorelin or placebo.

Fig. 6. Mean (±SD) IGF-1 serum levels on Day 1, Day 4 and Day 7 of treatment with capromorelin or placebo.

DISCUSSION
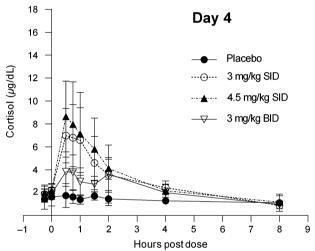
Capromorelin is a potent, selective GHS-R agonist that is orally bioavailable. Capromorelin activates GHS-R expressed on the

hunger centers of the hypothalamus to stimulate appetite and thereby enhancing the food consumption (Cowley *et al.*, 2003).

In this study, orally administered capromorelin in dogs was quickly absorbed from the gastrointestinal tract with peak
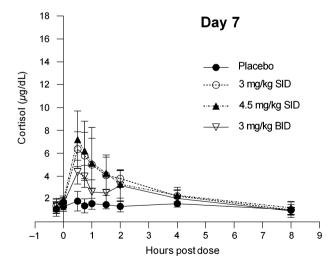
Fig. 7. Mean (±SD) cortisol serum levels on Day 1, Day 4 and Day 7 of treatment with capromorelin or placebo.

the clinical response to the drug, as measured by food consumption and body weight, was similar for all treated groups.

The drug was well tolerated with few clinically observed effects. The lethargy and soft stool observations could be the effects of capromorelin on gastrointestinal motility. However, many factors including the stress of multiple blood draws could result in these observations, which were completed on the days these signs were noted. The excessive salivation seen in dogs treated with capromorelin may be because of the bitter taste of the drug, although flavorings were added to mask any bitterness. Alternatively, salivation may be in response to the sensation of hunger which the dogs may be experiencing as an action of capromorelin. In humans, the ghrelin receptor has been shown to be present in the salivary glands (Gröschl *et al.*, 2005), although this has not been demonstrated in dogs, but if dog salivary glands also have ghrelin receptors, it is possible that capromorelin could have a direct effect on the salivary gland.

Food consumption increased as expected in the groups receiving capromorelin. The percent change in food consumption was highest in dogs receiving 3.0 mg/kg once daily (Group 2), but mean increases were seen in all capromorelin-treated groups. There was a 13.5% decrease in food consumption in the control dogs. It is unknown why the control group experienced a decrease in food consumption, but it could be that the stress of an intensive bleeding schedule on days 1, 4, and 7 affected food consumption. As expected, the change in food consumption was directly related to the change in body weight for all groups, and the amount of weight gained in each capromorelin-treated group was significant.

There was no significant difference in the clinical response to capromorelin dosed twice daily versus once daily or when using 3.0 mg/kg once daily versus 4.5 mg/kg once daily. Similarly, in a masked, placebo-controlled, randomized clinical pilot study of dogs with reduced appetite from a number of clinical conditions (Zollers & Rhodes, 2014), it was shown that capromorelin given at 4.5 mg/kg once-a-day improved owner assessment of appetite and increased body weight over a 7-days treatment period.

After the first dose of capromorelin, the expected high peak of GH was seen very quickly. This GH releasing action is expected from a drug that binds the GHS receptor. It would not be desirable to stimulate the release of such a super-physiological amount of GH chronically, and therefore, it is important that over the 8 h after the first dose of capromorelin, the concentrations of IGF-1 increase. This IGF-1 increase serves as negative feedback, suppressing GH release. Clearly, by days 4 through 7 of dosing, the sustained elevation in IGF-1 concentrations seen in the capromorelin-treated dogs result in an attenuation of the GH spike observed after the dose of capromorelin is administered.

To maintain this negative feedback suppression of the GH release, IGF-1 serum concentrations need to remain elevated in capromorelin-treated dogs. This study evaluated whether capromorelin needed to be dosed once or twice a day to maintain elevated serum IGF-1 concentrations, and the data clearly show that once-a-day dosing is sufficient. Further, there was no difference between dogs dosed at 3 mg/kg or 4.5 mg/kg once a day, indicating that the 3 mg/kg dose is sufficient to keep IGF-1 serum concentrations high enough to attenuate the GH peak and also to

serum drug concentrations generally achieved within 30 min of administration. Although serum capromorelin concentrations were highest in the 4.5 mg/kg capromorelin SID group,

stimulate food consumption. Further, in a 12-month study in normal laboratory dogs, daily doses up to 17.5 times the proposed 3 mg/kg were shown to be well tolerated (Zollers *et al.*, 2016).

The GH and IGF-1 effects seen with capromorelin treatment in this study are similar to the GH and IGF-1 secretion patterns observed following repeat administration of MK-0677, another small molecule GHS, in Beagle dogs (Hickey *et al.*, 1997). Other studies conducted in elderly human subjects with low GH and IGF-1 concentrations have shown that the treatment with ghrelin receptor agonists will increase GH and IGF-1 concentrations to those of young adults, but will not exceed those concentrations (Chapman *et al.*, 1996; Smith *et al.*, 1997).

Cortisol release is also seen in capromorelin-treated dogs, with peak stimulation within about 1 h after dosing. Similar to GH, cortisol stimulation appears to be attenuated on days 4 and 7 of treatment, with concentrations decreasing to the baseline by around 4 h after dosing. The mechanism for this negative feedback may be through suppression of ACTH release, but this was not measured in this study.

We hypothesize that the increase in serum GH and IGF-1 demonstrated in this study may result in positive effects on lean muscle mass over a longer-term treatment, as has been shown in dogs treated with GH (Molon-Noblot *et al.*, 1998). To demonstrate the hypothesized effect on body composition, a study using advanced imaging techniques to assess the effects of capromorelin on lean body mass and body fat would be necessary. The results of the present study are consistent with the action of this class of drugs, which has been demonstrated to be beneficial in various human clinical conditions, such as elderly people recovering from hip fracture (Adunsky *et al.*, 2011), and also in older adults with declining strength (White *et al.*, 2009).

In conclusion, capromorelin, a ghrelin agonist drug approved by the FDA (Entyce®) for appetite stimulation in inappetent dogs, was shown to increase food consumption and body weight through a well-defined endocrine mechanism. The increases in serum GH and IGF-1 observed following capromorelin treatment are an expected result of a ghrelin agonist. Once-a-day administration is sufficient to elevate serum concentrations of IGF-1, which allows attenuation of the GH stimulation effect of the drug; 3 mg/kg once-a-day dose is sufficient to increase food consumption and body weight. The 3 mg/kg dose is the dose approved by the FDA to stimulate appetite in dogs.

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