Journal of Veterinary Internal Medicine
Open Access

Standard Article

J Vet Intern Med 2016;30:1851–1857

A Prospective, Randomized, Masked, Placebo-Controlled Clinical Study of Capromorelin in Dogs with Reduced Appetite

B. Zollers, J.A. Wofford, E. Heinen, M. Huebner, and L. Rhodes

Background: Reduced appetite is a common clinical sign in dogs. This study evaluated the effectiveness and safety of capromorelin oral solution, (ENTYCE®, Aratana Therapeutics, Leawood, KS) a new drug that is a ghrelin receptor agonist, for stimulation of appetite in dogs with reduced appetite.

Hypothesis/Objectives: Capromorelin will increase appetite, as measured by the owner's evaluation, over 4 days. An additional objective was to evaluate the safety of capromorelin at the labeled dose.

Animals: A total of 244 client-owned dogs reported by owners to be inappetent for at least 2 days were enrolled, with 177 cases in the effectiveness analysis.

Methods: In this prospective, randomized, masked, placebo-controlled study, dogs were treated daily with capromorelin (3 mg/kg) oral solution (n = 121) or placebo oral solution (n = 56). Owners completed an evaluation of appetite at days 0 and 3 ± 1. Success was defined as improvement in appetite at day 3. Safety was evaluated by physical examination, clinical pathology, and monitoring adverse events and owner observations.

Results: Capromorelin treatment improved appetite compared to placebo (68.6% and 44.6% treatment successes with 95% CI 59.7, 76.3 and 32.2, 57.8, respectively, $P = .008$). Mean body weight in capromorelin-treated dogs increased compared to placebo-treated dogs (1.8% with 95% CI 1.3, 2.3, and 0.1% with 95% CI 0.9, 1.1, respectively, $P < .001$). Adverse reactions occurring in >5% of either group were diarrhea and vomiting.

Conclusions and Clinical Importance: Capromorelin oral solution is an effective treatment for stimulation of appetite in dogs and represents the first ghrelin receptor agonist shown to be effective for this indication.

Key words: Appetite stimulation; Food consumption; Ghrelin receptor agonist; Growth hormone secretagogue; Inappetence.

Growth hormone secretagogues (GHS) are a class of small molecule compounds discovered in the mid-1990s that bind GHS receptors (GHS-R) and stimulate the release of growth hormone (GH). It was subsequently discovered that GHS compounds mimic ghrelin, the hormone that is secreted from endocrine cells in the stomach and stimulates appetite and food intake in humans, rats, and dogs.[1,2] A GHS compound is therefore also called a ghrelin receptor agonist. Compounds in this class could be useful in treatment of anorexia and cachexia,[3] and one compound in this class has been evaluated for its ability to increase body weight and lean muscle mass in human patients with cancer cachexia.[4]

Capromorelin is an orally active small molecule GHS that is a potent and selective ghrelin receptor agonist.[5] (Note: Capromorelin is also referred to as AT-002 and CP-424,391). The compound has been formulated in a flavored solution[a] and approved by the Food and Drug Administration (FDA) for the stimulation of appetite in dogs. We hypothesized that dogs presented at veterinary clinics with a reduced appetite and treated with capromorelin would have increased appetite and, subsequently, body weight. Capromorelin increases food consumption and body weight in laboratory Beagle dogs[6] and appetite and body weight in client-owned dogs with inappetence.[7] The purpose of this study was to examine the appetite-stimulating effect of capromorelin oral solution compared to placebo oral solution in a larger population of client-owned dogs, as well as document the safety of the drug in this population.

Abbreviations:

BUN	blood urea nitrogen
CI	confidence interval
CVM	Center for Veterinary Medicine
FDA	Food and Drug Administration
GH	growth hormone
GHS	growth hormone secretagogue
GHS-R	growth hormone secretagogue receptor
IRIS	International Renal Interest Society
ITT	intention to treat
PPP	per protocol population
SD	standard deviation

Materials and Methods

Study Design

The study was a prospective, multicenter, masked, randomized, placebo-controlled parallel study conducted at 24 veterinary hospitals located across the United States (California, Colorado, Florida, Illinois, Kansas, Michigan, Missouri, Nebraska, New York, Pennsylvania, Tennessee, and Texas). It was conducted according

From Aratana Therapeutics, Leawood, KS (Zollers, Wofford, Heinen, Rhodes); ClinData Services, Fort Collins, CO (Huebner).

Corresponding author: Jessica A. Wofford, Aratana Therapeutics, 11400 Tomahawk Creek Pkwy, Suite 340, Leawood, KS 66211; e-mail: jwofford@aratana.com

Submitted March 25, 2016; Revised August 2, 2016; Accepted September 29, 2016.

DOI: 10.1111/jvim.14607

to Good Clinical Practices (Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) Guidance 85; VICH GL 9).

Animals/Subjects

Dogs of any age, breed, or sex were enrolled, but dogs that were pregnant, lactating, or intended for breeding were excluded. Each owner signed a statement of informed consent before the initiation of any study activities.

Inclusion/Exclusion Criteria

Client-owned dogs that were presented by the owner with clinical signs of either a reduced appetite or no appetite for a minimum of 2 days before presentation were candidates for enrollment. The owner was asked to answer the following question as it best described their dog's appetite at screening: "Do you feel that your dog's appetite today compared to when it was at its healthiest adult stage is increased, no change, or decreased?" If the owner's response was "decreased," the dog could be enrolled. Dogs that were in crisis or a moribund state, or dogs with a serious deteriorating condition were excluded, as were dogs that had been hospitalized within the 4 days before presentation. Also excluded were dogs with an active infection that would likely respond to treatment with an antibiotic, and dogs in which food intake was contraindicated such as a suspected foreign body or gastric torsion. Dogs with a regurgitation problem, dental disease severe enough to impair food intake, and any dog with a diagnosis of diabetes mellitus were excluded. Dogs were not enrolled if the owner was unsure if they could reliably evaluate appetite. Medications that might affect appetite or interfere with the study objectives such as anabolic steroids, diazepam, dronabinol, cyproheptadine, mirtazapine, propranolol, progesterone, and systemic corticosteroids (within the last 30 days) were not allowed. Maropitant citrate[b] was allowed during the study if prescribed before study start, and the treatment was stable. No parenteral fluids could be administered within approximately 12 hours of the last study visit on day 3 ± 1, as fluid administration might affect the body weight measurement.

Sample Size Calculation

Based on data from a pilot clinical study[7] in which 70.6% of capromorelin-treated dogs and 38.5% of the placebo-treated dogs were considered a treatment success (increased appetite); a power calculation by PASS 11[c] indicated that a sample size of 100 capromorelin-treated dogs and 50 placebo-treated dogs with evaluable cases would provide more than 97% power (alpha = 0.05, 2-sided) to detect a difference in the proportion of treatment success between groups.

Study Protocol

At screening, owners signed an informed consent form that had been approved by the Center for Veterinary Medicine (CVM) at the FDA. This consent was signed before initiating any study activities. Dogs were screened to see whether they met the inclusion and exclusion criteria, body weight was measured, blood was drawn to evaluate standard serum chemistry and hematology variables, and urine collected for urinalysis. At the screening visit, owners were asked to complete an Owner Appetite Assessment.[d] This questionnaire consisted of 5 questions asking owners about their dog's willingness to eat, hunger and begging behavior, the behavior of their dog when anticipating meal time, the behavior when food was placed in front of their dog, and the amount of food eaten. Each question could be scored from 1 to 5 with 5 indicating the best appetite. Scores for each dog were given as a total score (range of 5–25).

Because assessment of appetite during the study might be confounded by offering the enrolled dogs highly palatable food that was not in their normal diet before the study, owners were asked not to entice or tempt their dog to eat during the study using treats or highly palatable food that they did not normally give their dog. To document this, each owner was asked to record all foods they gave their dogs, including any special foods or treats to encourage eating during the previous 2 days when their dog was experiencing inappetence. This was defined as the base diet. The owner was then instructed to only offer their dog foods on the base diet during the 4 days of the study. Owners were asked to record all the foods that were offered during the study, and the veterinarian reviewed this listing of foods to assure that the owners had not fed foods that deviated from the base diet.

Randomization and Masking

After enrollment, dogs were randomly assigned to the capromorelin or placebo group in a 2 : 1 ratio. The enrollment target was at least 100 capromorelin and 50 placebo-treated evaluable cases per the study randomization schedule across all sites.

Dogs were randomly assigned to 1 of 3 treatment codes based on order of entry into the study, by a randomization table provided by the study statistician. The program used to randomly assign treatments to dogs was SAS® Proc Plan.[e] Each site had a unique randomization schedule. Treatments were labeled as "Treatment A," "Treatment B," or "Treatment C" with 2 of the labeled treatments being capromorelin and 1 of the labeled treatments being placebo to maintain a 2 : 1 ratio. A note to file identifying capromorelin or placebo assignment to treatment codes A, B, and C was created by a contract research group employee not involved in the study and maintained in the central files for the duration of the study. To maintain masking, this note to file was not accessible to any other personnel involved in the study until the database was locked.

Treatment

Day 0 was the first day of treatment. Each dog was treated once daily for 4 ± 1 days with either placebo or capromorelin dosed orally at 3 mg/kg with a syringe provided with the study drug. Placebo flavored solution was matched to the capromorelin flavored solution, including bottle size and shape, but without the active drug. Owners were instructed to give the dose at approximately the same time each day. Compliance with dosing was evaluated by reconciling the returned study drug with what was dispensed and supported by a daily owner diary indicating administration of the dose.

Outcome Measures

Appetite over the 4 days was evaluated by the owners answering this question on day 3 ± 1: "Do you feel that during the study (over the 4 ± 1 days of treatment), your dog's appetite was increased, no change, or decreased?" If the owner answered that their dog's appetite was increased, the dog was considered a treatment success. To support this assessment of appetite, the owner

also completed the Owner Appetite Assessment they had previously completed at day 0. A comparison of the total scores (range of 5–25) at day 0 and on day 3 ± 1 was made to assess changes in this score over time. In addition, body weights on day 0 and day 3 ± 1 were compared.

Safety

Safety was evaluated by physical examinations (day 0 and day 3 ± 1), clinical pathology tests (day 0 and day 3 ± 1), and monitoring for adverse events and owner observations during the 4 days of dosing. An adverse event was defined as any observation, undesirable experience, or reaction in animals that was unfavorable and unintended and occurred after the use of capromorelin or placebo, whether or not considered to be treatment related. A serious adverse event was defined as any adverse event that resulted in death, was life-threatening, or resulted in persistent or substantial disability/incapacity and occurred after the use of capromorelin or placebo, whether or not considered to be product related.

Statistical Analysis

The primary effectiveness variable was the single owner question on appetite answered on day 3 ± 1. Treatment success was defined as an "increased" appetite as determined by the owner. If the owner reported that the dog's appetite was "no change" or "decreased" on day 3 ± 1 compared to day 0, the dog was classified as a treatment failure.

The primary null hypothesis was there will be no difference in the proportion of treatment success between capromorelin and placebo-treated dogs. For the primary efficacy variable, the number and percentage of success was presented for each site and overall by treatment group. For binary outcomes ("success" rates), the GLIMMIX procedure in SAS® (assuming a binomial distribution and logit link) was used to compare the capromorelin group to the placebo group. The model contained success/failure as the dependent variable, with treatment as a fixed effect and random effects for site and treatment by site interaction. In addition, the scores from the Owner Appetite Assessment were analyzed as follows: Treatment success was defined as an increase in total score of ≥5 points from day 0 to day 3 ± 1. This analysis was also completed excluding dogs with day 0 scores of ≥13 because although owners reported these dogs had exhibited a reduced appetite for 2 days before enrollment, they had only moderate appetite decreases. Finally, mean percent changes in body weight over the treatment period in the 2 groups were compared as well as the percent of dogs which experienced a change in body weight of >0% (defined as a "success" in that they gained weight during the study).

For Owner Appetite Assessment total score and body weight, descriptive statistics (number of subjects, mean, standard deviation, standard error of the mean, 95% confidence intervals, median, minimum and maximum values) were calculated by treatment group for each study day and for the percent change from day 0 to day 3 ± 1. Analysis of variance (ANOVA) modeling was utilized to test for possible differences between treatment groups in the percent change from day 0 by a mixed model (the MIXED procedure in SAS®). The model contained treatment as a fixed term with site and treatment by site interaction as random terms. Assumptions of normality of residuals and homogeneity of variance were investigated before running the model. If it was determined that the distribution could not be approximated by a normal curve, then values were ranked in ascending order with tied values being given a mean rank before running statistical models. For each criterion, the number and percentage of success was presented by treatment group. The method appropriate for binary outcomes (the GLIMMIX procedure in SAS®, assuming a binomial distribution and logit link) was used to compare the capromorelin group to the placebo group. The model contained success/failure as the dependent variable, with treatment as a fixed effect, and random effects for site and treatment by site interaction.

Serum chemistry, hematology and urinalysis data, physical examination data, and adverse event data were summarized and evaluated by treatment group using descriptive statistics.

Results

Study Population

Out of the 259 dogs screened at the 24 sites, 244 cases were enrolled in the study. A total of 244 dogs were included in the safety population (intention to treat population; ITT) with 171 randomized to treatment with capromorelin and 73 to treatment with placebo. Sixty-seven dogs were considered unevaluable for the purpose of assessing effectiveness. Therefore, the per protocol population (PPP) included a total of 177 dogs with 121 dogs in the capromorelin treatment group and 56 in the placebo treatment group (Fig 1). In the safety population, dogs ranged in age from 4 months to 18 years of age, with the mean age of 8.0 years in the capromorelin group and 8.1 years in the placebo group. The majority of dogs were spayed or castrated, with equal numbers of males and females in the population (122 females, 122 males). Body weights ranged from 1.5 to 76.5 kg with the mean weights in the capromorelin and placebo group of 17.1 and 16.3 kg, respectively (Table 1).

Enrolled dogs had various medical conditions including allergy, arthritis, cardiovascular disease, gastrointestinal disease, renal disease, and others. It was not required that the veterinarian identify the etiology of the inappetence for the dog to be enrolled in the study, and in many dogs, the underlying condition was not specified.

Diet

Dogs enrolled in the study were fed a variety of foods in the base diet, with owners in some cases listing more than 10 foods and treats. Because adding a new or highly palatable food during the study was prohibited, twelve cases were considered unevaluable because dogs were given a food during the 4 days of treatment that was not listed on their base diet. Several cases were considered unevaluable because the dog actively sought out and consumed foods not on their base diet.

Effectiveness

Appetite Assessment. Using the single owner question on day 3 ± 1, where owners could rate their dog's appetite as "increased," "no change" or "decreased," and where only the "increased" answer was defined as treatment success, 68.6% (95% CI, 59.7, 76.3) of dogs in the capromorelin-treated group were classified a treatment success, compared to 44.6% (95% CI, 32.2, 57.8) of the placebo-treated dogs ($P = .008$).

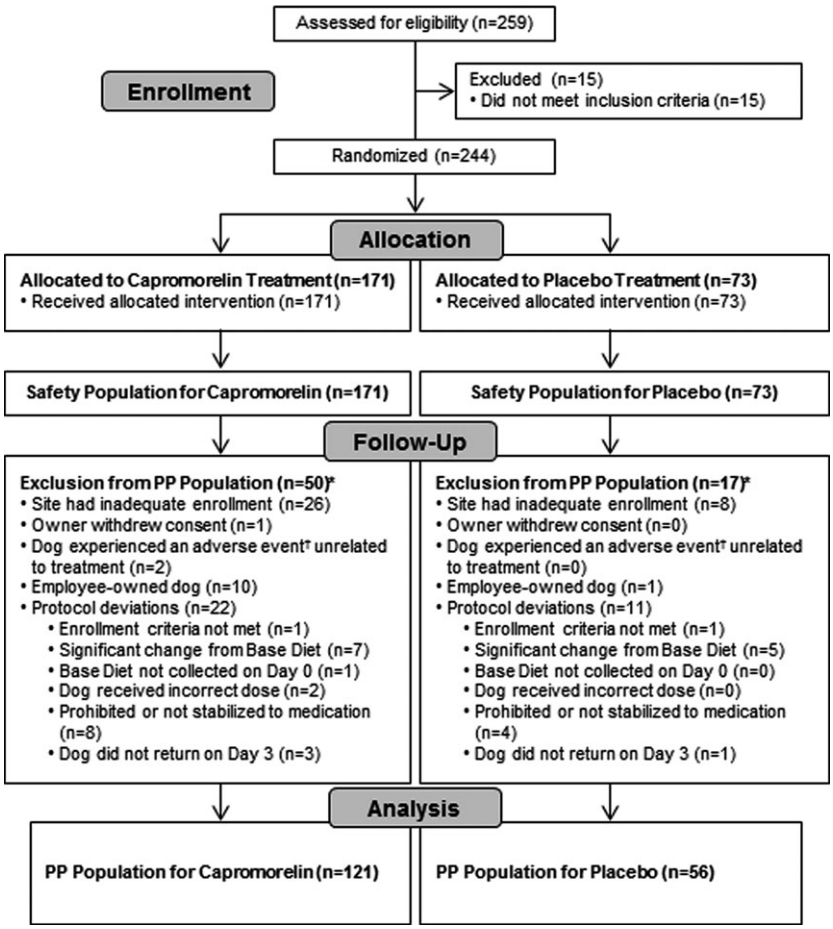

Fig 1. Case flow indicating how the safety (ITT) and PP populations were identified for the capromorelin and placebo treatment groups. *Some dogs were excluded for more than one reason.

Table 1. Population demographics at screening of the intention to treat population.

Characteristic		Capromorelin	Placebo
Age (years)	N	171	73
	Mean (SD)	8.0 (4.4)	8.1 (4.4)
	Min, Max	0.3, 16.4	0.9, 18.0
Sex	Female intact	7 (4.1%)	5 (6.8%)
	Female spayed	83 (48.5%)	26 (35.6%)
	Male intact	17 (9.9%)	9 (12.3%)
	Male neutered	64 (37.4%)	32 (43.8%)
Weight (kg)	Mean (SD)	17.1 (1.1)	16.3 (1.5)
	Min, Max	1.7, 76.5	1.5, 52.2

At day 0, no difference in the mean scores of the Owner Appetite Assessment were found between groups. (See Supplemental Information for the distribution of total scores in each group at day 0 and day 3 ± 1.) The mean percent change from day 0 to day 3 ± 1 was 73.3% (SD $\pm$ 75.9; 95% CI, 59.6, 87.0) in the capromorelin treatment group compared to 37.6% (SD $\pm$ 53.9; 95% CI, 23.1, 52.0) in the placebo group ($P = .013$). Defining success as an increase of 5 or more from baseline in the Owner Appetite Assessment, 56.2% (95% CI, 47.2, 64.8) of the capromorelin-treated dogs were defined as success, compared to 26.8% (95% CI, 16.8, 39.9) of the placebo-treated dogs ($P = .007$). Analyzing the scores of the subpopulation of dogs with the worst appetites (Owner Appetite Scores of <13 on day 0; n = 100 capromorelin-treated dogs and n = 48 placebo-treated dogs), capromorelin-treated dogs also showed greater success (an improvement of 5 or more points) than placebo-treated dogs, with 64.0% (95% CI, 54.1, 72.9) compared to 27.1% (95% CI, 16.4, 41.4), respectively ($P = .002$).

Body Weight. Mean body weights in the capromorelin and placebo groups were not different at baseline ($P = .794$). Over the 4 days of treatment, both capromorelin- and placebo-treated dogs gained weight, with capromorelin treatment associated with a mean percentage change significantly greater ($P < .001$) than placebo treatment (1.8% with SD $\pm$ 2.8, CI, 1.3, 2.3 and 0.1% with SD $\pm$ 3.6, CI, 0.9, 1.1, respectively). Additionally, a statistically significantly larger proportion of capromorelin-treated dogs experienced a change in weight of >0% as compared to placebo-treated dogs with 76.0% (95% CI, 67.6, 82.8) and 44.6% (95% CI, 32.2, 57.8) showing weight gain, respectively ($P = .001$).

Safety

The safety (ITT) population consisted of 171 dogs treated with capromorelin and 73 dogs treated with placebo. Capromorelin was generally well tolerated. Nine dogs experienced serious adverse events, 2 in the placebo group and 7 in the capromorelin group. The veterinarians did not attribute any of these serious adverse events to treatment with capromorelin, but instead to a variety of preexisting conditions including heartworm disease, intestinal neoplasia, neurologic disease, hepatic disease, and renal disease.

Frequencies of adverse events potentially related to treatment (adverse reactions) are given in Table 2. There were no adverse events in clinical pathology variables except for values of blood urea nitrogen (BUN), creatinine, and phosphorus (Table 2). These adverse event reports were in separate dogs, except for 1 capromorelin-treated dog which experienced adverse events for both increased BUN and increased phosphorus.

To further explore changes in BUN, creatinine, and phosphorus in dogs in this study, these values were analyzed for the safety population (Table 3). The mean change in BUN was slightly decreased in the capromorelin group and slightly increased in the placebo group, a difference that was statistically significant ($P = .006$), but because these changes were small, they were unlikely to be of clinical relevance. The mean change for creatinine was similar between groups and the mean change in phosphorus was small and positive for both groups, with the placebo group exhibiting a larger mean increase.

Given that increases in BUN, creatinine, and phosphorus can be associated with renal disease, changes in these variables were also evaluated for dogs which at screening satisfied the International Renal Interest Society (IRIS) staging guidelines for chronic kidney disease stage ≥2 (creatinine ≥1.4 mg/dL, regardless of the laboratory's reference interval). Mean changes in BUN from day 0 to day 3 ± 1 were similar between groups (Table 4). The mean changes in creatinine and phosphorus were slightly greater in the capromorelin group as compared to the placebo group, but these differences were not significant.

Table 2. Adverse reactions in dogs treated with either placebo or capromorelin for 4 days (safety population).

Adverse reactions*	Capromorelin (N = 171) N (%)	Placebo (N = 73) N (%)
Diarrhea	12 (7.0%)	5 (6.8%)
Vomiting	11 (6.4%)	4 (5.5%)
Increased blood urea nitrogen	7 (4.1%)	2 (2.7%)
Polydipsia	7 (4.1%)	1 (1.4%)
Increased phosphorus	4 (2.3%)	1 (1.4%)
Hypersalivation	4 (2.3%)	0 (0.0%)
Abdominal discomfort	2 (1.2%)	0 (0.0%)
Flatulence	2 (1.2%)	0 (0.0%)
Lethargy/depression	2 (1.2%)	0 (0.0%)
Nausea	2 (1.2%)	0 (0.0%)
Increased creatinine	1 (0.6%)	1 (1.4%)

*Dogs might have experienced more than one type or occurrence during the study.

Discussion

This study indicates that a ghrelin receptor agonist, capromorelin, can stimulate appetite and increase body weight when given to a large population of dogs with reduced appetite of varying etiologies. The results establish that owners can evaluate relative changes in their dog's appetite, using either a single simple question or an assessment questionnaire of the dog's behavior. Increased appetite (hunger) is reflected in behaviors that owners can observe, which can be broadly defined as how much a dog eats, how rapidly a dog eats, and how aggressively a dog seeks out food. The 5 questions on the Owner Appetite Assessment were designed to help owners rate these behaviors. Although shown to be useful in distinguishing between placebo- and capromorelin-treated dogs in this study, additional work is required to formally validate this questionnaire.

As in other measurements where owners are asked to assess a clinical condition in their dogs, such as pain assessed by the Canine Brief Pain Inventory,[8] This study demonstrates a large placebo effect, with over 44% of owners saying their placebo-treated dog had an increased appetite using the single question and 37.6% when using the Owner Appetite Assessment questionnaire. Some of these placebo-treated dogs might have legitimately had an increased appetite due to spontaneous improvement in the underlying cause of inappetence, but it is not unexpected to see a large placebo effect in an owner assessment in studies with client-owned dogs. The single question did not seem to be as robust (success difference of 24% between groups) in assessing appetite changes as the Owner Appetite Assessment, which gave owners a more nuanced set of questions to answer (success difference of 35.7% between groups).

Given the short duration of this study, changes in body weight were expected to be small. Even in such a short period of time, the capromorelin-treated group experienced a larger increase in body weight as compared to the placebo-treated group. Additionally, a larger proportion of dogs in the capromorelin-treated group exhibited a change in body weight of >0%. These results are consistent with capromorelin stimulation of appetite resulting in increased contents of the gastrointestinal tract, both food and water. One of the actions of capromorelin is to stimulate an increase in GH,[6] which can result in an increase in lean muscle mass, but it is unlikely that dogs gained muscle mass during such a short study. Future studies will be needed to investigate the effects of long-term administration of capromorelin oral solution on body weight and lean muscle mass in client-owned dogs.

Care was taken in the study to not confound the results by offering or enticing the dogs with particularly palatable food, which would make assessing the appetite difficult. If foods were consumed that were not listed on the base diet, then those cases were considered to be

Table 3. Mean (SD) BUN, creatinine, and phosphorous values at day 0 and day 3 ± 1 and mean (SD) change in each variable from day 0 to day 3 ± 1 in the safety population.

		BUN (mg/dL)		Creatinine (mg/dL)		Phosphorus (mg/dL)	
Study day		Capromorelin N = 164	Placebo N = 72	Capromorelin N = 164	Placebo N = 72	Capromorelin N = 164	Placebo N = 72
Day 0	Mean (SD)	22.6 (20.0)	22.5 (15.2)	1.18 (0.69)	1.16 (0.47)	4.03 (1.23)	4.08 (0.94)
Day 3 ± 1	Mean (SD)	21.5 (22.3)	23.0 (15.4)	1.18 (0.79)	1.16 (0.45)	4.30 (1.33)	4.56 (1.90)
Change	Mean (SD)	−1.08 (8.59)	0.53 (6.21)	0.01 (0.31)	0.01 (0.14)	0.27 (1.04)	0.48 (1.78)
	P-value	.006		.113		.464	

Only dogs in the safety population with both pretreatment and posttreatment values are included.

Table 4. Mean (SD) BUN, creatinine, and phosphorous values at day 0 and day 3 ± 1 and mean (SD) change in each variable from day 0 to day 3 ± 1 in dogs with IRIS Stage ≥2 CKD (creatinine ≥1.4 mg/dL) at screening.

		BUN (mg/dL)		Creatinine (mg/dL)		Phosphorus (mg/dL)	
Study day		Capromorelin N = 28	Placebo N = 17	Capromorelin N = 28	Placebo N = 17	Capromorelin N = 28	Placebo N = 17
Day 0	Mean (SD)	49.7 (35.9)	37.5 (20.8)	2.32 (1.01)	1.84 (0.42)	4.51 (1.76)	4.45 (1.31)
Day 3 ± 1	Mean (SD)	50.5 (39.9)	38.4 (22.4)	2.48 (1.17)	1.78 (0.45)	5.02 (1.71)	4.65 (1.75)
Change	Mean (SD)	0.82 (16.86)	0.82 (9.13)	0.16 (0.61)	−0.06 (0.19)	0.51 (1.19)	0.20 (1.08)
	P-value	.321		.184		.309	

unevaluable. There were, however, certain cases where some judgment was used and the appetite behavior of the dog could be interpreted in different ways. For example, 1 dog treated with capromorelin jumped on the counter and consumed several crescent rolls, a food not listed on the base diet. Because this demonstration of an increased appetite could be attributed either to the treatment (masked to the owner) or to the extra palatability of the rolls, this dog was not considered as an evaluable case during a blinded review of protocol deviations.

Another possible method to assess appetite would be to measure actual food intake. Inappetent, client-owned dogs are fed a large variety of foods and asking owners to weigh food or estimate volume, as well as account for feeding of treats and other foods by family members outside of normal meals, and record all food actually eaten was considered impractical and likely to impede owners' consenting to participate in the study. Instead, food intake in capromorelin-treated dogs was evaluated in 2 studies in laboratory Beagles, where food intake can be carefully measured by weighing a single type of food. Capromorelin treatment resulted in increased food intake which was significant compared to a placebo-treated group[6] (and B Zollers, L Rhodes, manuscript submitted). Therefore, it is highly likely that the owner's assessment of capromorelin treatment increasing appetite when compared to placebo treatment is an accurate assessment of the appetite stimulation effect.

Capromorelin generally was well tolerated in this study. Per the protocol inclusion criteria, enrolled dogs were required to have a reduced appetite for at least 2 days before enrollment. Reduced appetite is a common, albeit nonspecific, clinical sign, and thus, this enrollment criterion selected for a population of dogs with a variety of medical conditions. Thus, it was not unexpected that for some dogs, the preexisting clinical condition did not improve during the 4 days of the study and the dog experienced continued clinical decline, as evidenced in some dogs by the serious adverse events reported during the study. The most common adverse reactions potentially related to treatment were diarrhea and vomiting, which occurred with similar frequencies in both treatment groups. Polydipsia and hypersalivation were reported in multiple capromorelin-treated dogs[7] (polydipsia and 4 hypersalivation), as compared to only 1 placebo-treated dog (polydipsia only), which is consistent with capromorelin's mechanism of action to increase appetite: An increase in water consumption is expected when a previously inappetent dog increases its food consumption and salivation is a common precursor to eating. Abdominal discomfort, flatulence, nausea, and lethargy or depression were reported in 2 dogs each, and thus, their clinical relevance is unclear, although these signs could be sequelae to increased food intake. The clinical relevance of elevations in BUN, creatinine, and phosphorus is unclear. Based on results in both the safety population and the subpopulation of dogs with creatinine indicating IRIS stage ≥2, no clinically relevant changes were observed in either treatment group.

A limitation of this study was that it did not evaluate the effectiveness and safety of capromorelin for >4 days. In a pilot study, using a higher dose of capromorelin (4.5 mg/kg) over 7 days of treatment, capromorelin was shown to be effective in increasing appetite.[7] Longer term safety data were collected in a safety study conducted in laboratory Beagle dogs treated once daily for 12 months with doses up to 17.5 times the dose used in this study

(3 mg/kg). The drug was well tolerated, and no drug accumulation was seen with daily dosing.[9] Longer term studies will be required to demonstrate continued effectiveness over time. Another limitation of this study was that given the study population size, it is unlikely that rare adverse events would have been detected. The sample size was calculated to detect a treatment effect on appetite stimulation, not based on differences in safety variables. Wider clinical use is required to fully evaluate the risk/benefit of any new therapeutic agent.

This study indicates that the ghrelin receptor agonist, capromorelin, when given orally once daily at 3 mg/kg for 4 days to dogs with a reduced appetite, results in increased appetite and body weight when compared to placebo. Furthermore, in dogs of varying ages and breeds with concomitant medications and clinical conditions, capromorelin-related adverse events were mild and some of the adverse events were consistent with a restored appetite. Although serious adverse events were documented, none were attributed to capromorelin treatment and were not unexpected in the population of sick, inappetent dogs enrolled in this study. These data support the conclusion that capromorelin represents a promising new treatment modality for appetite stimulation in dogs. The FDA approval of capromorelin oral solution (ENTYCE®)[a] represents the first regulatory approval, either veterinary or human, of a drug with this mechanism of action, that is, a ghrelin receptor agonist.

Acknowledgments

The authors acknowledge Georgiana Syby, Jonathan Hopper, and the staff at AlcheraBio in Edison, NJ for assistance in conducting the study, and the following investigators: A. Cistola, B. Harris, B. Witzel, D. Bain, D. Knaak, D. Menard, E. Jezbera, H. Robinson, J. Bruening, J. DeBiasio, J. Steen, J. Teeter, K. Rowland, M. Girone, M. Petty, R. Carpenter, R. Sifferman, M. Wiest, S. Baker, S. Geller, S. Kingsley, S. Yoshimoto, T. Clekis, T. Newcomer, and V. Manoharan.

Conflict of Interest Declaration: This clinical study was conducted at 24 veterinary hospitals throughout the United States and was funded by Aratana Therapeutics in support of FDA approval of ENTYCE® (capromorelin oral solution). J.A. Wofford and E. Heinen are current employees of Aratana Therapeutics, and B. Zollers and L. Rhodes are former employees of Aratana Therapeutics; all of these authors have stock, stock options, or both in the company.

An independent contract research organization was employed to manage study conduct on behalf of the company. As the sponsor of the study, Aratana's employees were blinded to treatment group until the study database were locked at the end of the study. E. Heinen, B. Zollers, and L. Rhodes are on patents for capromorelin. L. Rhodes has retired and now serves as a consultant to Aratana. M. Huebner works as an independent contractor for Aratana and was also blinded until the study database were locked.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

Footnotes

[a] ENTYCE®, Aratana Therapeutics, Leawood, KS
[b] Cerenia™, Zoetis, Kalamazoo, MI
[c] PASS 11, NCSS, LLC, Kaysville, UT
[d] Owner Appetite Assessment questionnaire ©2016, available at www.aratana.com
[e] SAS®, Version 9.3.1, SAS Institute, Inc., Cary, NC

References

1. Smith RG. Development of growth hormone secretagogues. Endoc Rev 2005;26:346–360.

2. Wren AM, Seal LJ, Cohen MA, et al. Ghrelin enhances appetite and increases food intake in humans. J Clin Endocrinol Metbol 2001;86:5992–5996.

3. Yokoyama M, Nakahara K, Kojima M, et al. Influencing the between-feeding and endocrine responses of plasma ghrelin in healthy dogs. Eur J Endocrin 2005;152:155–160.

4. Garcia JM, Boccia RV, Graham CD, et al. Anamorelin for patients with cancer cachexia: An integrated analysis of two phase 2, randomised, placebo-controlled, double-blind trials. Lancet Oncol 2015;16:108–116.

5. Carpino PA, Lefker B, Toler SM, et al. Pyrazolinone-piperidine dipeptide growth hormone secretagogues (GHS): Discovery of capromorelin. Bioorg Med Chem 2008;11:581–590.

6. Zollers B, Rhodes L, Smith RG. Capromorelin increases food consumption, body weight, growth hormone and sustained insulin-like growth factor-1 concentrations when administered to healthy adult Beagle dogs. J Vet Pharm Ther 2016 doi:10.1111/jvp.12344.

7. Zollers B, Rhodes L. Capromorelin, an orally active ghrelin agonist, stimulates appetite and weight gain in inappetent dogs in a multi-site field study. J Vet Intern Med 2014;28:1032.

8. Brown DC, Bell M, Rhodes L. Power of treatment success definitions when the Canine Brief Pain Inventory is used to evaluate carprofen treatment for control of pain and inflammation in dogs with osteoarthritis. Am J Vet Res 2013;74:1467–1473.

9. Zollers B, Huebner M, Armintrout G, et al. Evaluation of safety in dogs of long-term, daily oral administration of capromorelin, a novel drug for stimulation of appetite. J Vet Pharm Ther 2016 doi:10.1111/jvp.12358.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Fig S1. Distribution of Total Scores on the Owner Appetite Assessment questionnaire for the capromorelin- (n = 121) and placebo-treated (n = 56) groups on day 0 and day 3 ±1.

Data S1. Dog Owner Appetite Assessment.