Date of Approval: May 16, 2016

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-457

ENTYCE

capromorelin oral solution

Oral Solution

Dogs

For appetite stimulation in dogs

Sponsored by:

Aratana Therapeutics, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-457

B. Sponsor

Aratana Therapeutics, Inc.
11400 Tomahawk Creek Pkwy
Leawood, Kansas 66211

Drug Labeler Code: 086026

C. Proprietary Name

ENTYCE

D. Product Established Name

Capromorelin oral solution

E. Pharmacological Category

Appetite stimulant

F. Dosage Form

Oral solution

G. Amount of Active Ingredient

30 mg/mL flavored oral solution

H. How Supplied

10 mL, 15 mL, and 30 mL bottles with a measuring syringe

I. Dispensing Status

Rx

J. Dosage Regimen

3 mg/kg once daily

K. Route of Administration

Oral

L. Species

Dogs

M. Indication

ENTYCE (capromorelin oral solution) is indicated for appetite stimulation in dogs.

II. EFFECTIVENESS

ENTYCE is also referred to as AT-002 in the studies below.

A. Dosage Characterization

A dose of 3 mg/kg (1.4 mg/lb; capromorelin as the tartrate salt) of ENTYCE administered orally as a flavored solution once daily for appetite stimulation in dogs was selected based on the following two studies.

1. Adult laboratory Beagle dogs were divided into four groups (3/sex/group; n=6/group). Dogs were dosed orally with a flavored solution for 7 consecutive days. The groups were administered vehicle control (solution minus capromorelin) twice daily (BID), 3 mg/kg capromorelin once daily (SID), 4.5 mg/kg capromorelin SID, or 3 mg/kg capromorelin BID. Dogs were offered more than twice the normal amount of food during both the acclimation (Day -7 to Day -1) and in-life feeding phase (Day 1 to Day 7) of the study. Dogs were fasted overnight and then allowed access to food for 2 hours. Following the 2-hour feeding period, the remaining food was removed from the cage, weighed, and recorded. Baseline food consumption was calculated on Day -3 to Day -1. During the in-life feeding phase, dogs were fed approximately 2 hours post-dose. Dogs were weighed prior to feeding on Days -1, 3, and 7.

   Results: Clinical observations included licking, smacking of the mouth/lips, salivation, and/or grimacing in all groups at dosing.

   Table 1: Change in food consumption and body weight by treatment group.

Capromorelin Dose	**Mean Percent Change in Food Consumption from Baseline**	**P-value[a]**	**Mean Percent Change in Body Weight from Baseline**
0 mg/kg BID	-13.5	N/A	-1.17
3 mg/kg SID	57.72	< 0.0001	4.52
4.5 mg/kg SID	37.91	0.0024	3.78
3 mg/kg BID	36.35	0.0033	4.17

[a] P-value for the difference between vehicle control (0 mg/kg) and each treatment group

   Food consumption was statistically significantly increased in all groups administered capromorelin when compared to the vehicle control group. The percent change in body weight was greater in the capromorelin groups compared to the vehicle control group.

2. Adult laboratory Beagle dogs were divided into five groups (3/sex/group; n=6/group). Dogs were dosed orally once daily for 7 consecutive days. The groups were administered vehicle control (solution minus capromorelin), 0.33, 2, 3, or 4 mg/kg capromorelin. The capromorelin test article was the final flavored oral solution formulation proposed for marketing. Dogs were offered more than twice the normal amount of food during both the acclimation (Day -10 to Day -1) and in-life feeding phase (Day 1 to Day 7) of the study. Dogs

were fasted overnight and then allowed access to food for 2 hours. Following the 2-hour feeding period, the remaining food was removed from the cage and weighed. Baseline food consumption was calculated on Day -3 to Day -1. During the in-life feeding phase, dogs were fed approximately 2 hours post-dose. Dogs were weighed prior to feeding on Days -10, -7, -1, 1, and 8. The percent change in food consumption from baseline compared to the treatment period (average of Day 1 through Day 7) was calculated for each dog.

Results: Clinical observations included salivation and head shaking in all groups at dosing.

Table 2 summarizes the analysis results for food consumption. The 2, 3, and 4 mg/kg capromorelin groups showed statistically significant increased food consumption when compared to the vehicle control group.

Table 2: Change in food consumption by treatment group.

Capromorelin Dose (Once daily)	**Mean Percent Change in Food consumption from Baseline**	**P-value[a]**
0 mg/kg	2.44	N/A
0.33 mg/kg	28.74	0.0879
2 mg/kg	38.92	0.0217
3 mg/kg	33.74	0.0452
4 mg/kg	64.10	0.0004

[a] P-value for the difference between vehicle control (0 mg/kg) and each treatment group

Table 3 summarizes the analysis results for body weight. Body weight increased in females and males in all capromorelin treatment groups.

Table 3: Change in body weight by gender and treatment group.

Capromorelin Dose (Once daily)	**Mean Percent Change in Body Weight from Baseline (in Females, Males)**
0 mg/kg	0.46, -0.37
0.33 mg/kg	2.65, 1.06
2 mg/kg	3.27, 6.63
3 mg/kg	6.25, 4.44
4 mg/kg	2.97, 6.97

B. Substantial Evidence

1. Laboratory Study:

   a. Title: AT-002: Four-day repeat dose food consumption study in Beagle dogs. Study #031805

   b. Study Location: Concord, OH

   c. Study Design:

      (i) Objective: To determine and compare food intake over a 4-day period of daily oral administration of ENTYCE (capromorelin oral solution) and a vehicle control.

      (ii) Study Animals: The study included 24 healthy Beagle dogs, approximately 13-14 months old at first dose administration. The body weights were approximately 6.5 to 9 kg for females and 10 to 12.5 kg for males at the time of randomization.

      (iii) Control and treatment groups:

      Table 4: Treatment groups:

Treatment Group	Dose (mg/kg)	No. and Gender of Dogs
Group 1	0 mg/kg	6 males and 6 females
Group 2	3 mg/kg (1X)	6 males and 6 females

      (iv) Dosage form: The capromorelin was formulated in a flavored oral solution. The vehicle control solution was the identical solution minus active pharmaceutical ingredient.

      (v) Route of administration: Oral

      (vi) Dosage amount, frequency, and duration: ENTYCE or vehicle control was administered once daily for 4 consecutive days. Dogs were fasted at the time of administration. Dosages on all dosing days were calculated for each dog, based on body weights from Day 0 (first day of treatment).

      (vii) Measurements and Observations: Clinical observations, body weight, food consumption, physical examination, complete blood count (CBC), and serum chemistry were performed. Food consumption was measured daily for each dog from Day -14 to Day 3. Dogs were offered more than twice the normal amount of food during both the acclimation (Day -14 to Day -1) and in-life feeding phase (Day 0 to Day 3). Dogs were fasted overnight and then allowed access to food for 3 hours. Following the 3-hour feeding period, the remaining food was removed from the cage, weighed, and recorded. Baseline food consumption was calculated on Day -3 to Day -1. During the in-life phase, dogs were fed approximately 1 hour post-dose.

(viii) Statistical Methods: Percent change from baseline body weight and food consumption was modeled by analysis of variance including treatment, sex, and the treatment-by-sex interaction as fixed effects. If the interaction term was statistically significant then the treatment group comparisons were carried out for each sex separately. Also, within treatment group, comparisons were assessed by the one-sample t-test or Wilcoxon signed rank test, as determined to be appropriate by the Shapiro-Wilk test for normality, to evaluate the percent change from baseline for body weight and food consumption.

d. Results:

Salivation was observed repeatedly in six dogs in the ENTYCE group post-dosing during all treatment days and in two dogs administered vehicle control only one time on Day 0. Emesis was observed in one dog in the ENTYCE group one hour after dosing on Day 1. There were no treatment related findings in the clinical pathology and physical examination results.

The percent change in food consumption was statistically significantly greater ($p<0.001$) in the ENTYCE group (pooled sexes mean = 60.55% change, corresponding to an average 117.6 gram increase in daily consumption) when compared to the vehicle control group (pooled sexes mean = -11.15% change, corresponding to an average 30.4 gram decrease in daily consumption).

The percent change in body weight was greater in the ENTYCE group (5.963%; corresponding to an average 0.52 kg gain) compared to the vehicle control group (0.0532% change; corresponding to an average 0.004 kg gain).

e. Conclusions:

This study supports the effectiveness of ENTYCE as an appetite stimulant in dogs. ENTYCE administered orally once a day at a dose of 3 mg/kg/day for 4 consecutive days to approximately 13-14 month old Beagle dogs (6/sex/group) was associated with increased food consumption and body weight.

2. Field Study:

a. Title: Pivotal clinical field study to evaluate the safety and effectiveness of AT-002 on stimulation of appetite in dogs. Study #AT002-CCL-13-003

b. Study Locations:

Riverside, CA	West Palm Beach, FL	Ralston, NE
Los Angeles, CA	Bradenton, FL	Bedford Hills, NY
Fort Collins, CO	Bartonville, IL	Norristown, PA
Denver, CO	Lawrence, KS	Quakertown, PA
Fort Collins, CO	Overland Park, KS	Collierville, TN
Gainesville, FL	Canton, MI	Dallas, TX
Ocala, FL	Grand Rapids, MI	Sequin, TX
West Palm Beach, FL	Springfield, MO	Antioch, TX

c. Study Design:

(i) Objective: To confirm the safety and effectiveness of ENTYCE in dogs under field conditions using a dose of 3 mg/kg administered once daily. The study was conducted according to Good Clinical Practice (GCP).

(ii) Study animals: Two hundred forty-four (244) dogs were enrolled in the study and received at least one treatment. Age of the enrolled dogs ranged from 0.3 to 18.0 years and body weights ranged between 1.5 and 76.6 kilograms at the start of treatment. One hundred twenty-two (122) female dogs were enrolled, 12 of which were intact. One hundred twenty-two (122) males were enrolled, 26 of which were intact. The enrolled dogs had various medical conditions at day 0: arthritis (40); gastrointestinal disease (24); allergy (22); dental disease (22); cardiovascular disease (16); renal disease (13); and others.

(iii) Inclusion criteria:
- Dogs presented with a reduced appetite or no appetite for a minimum of 2 days prior to day 0
- Owner Appetite Assessment score at screening of "Decreased"
- Dogs on medications for certain chronic conditions (such as osteoarthritis, hypothyroidism) were included as long as in the Investigator's/Examining Veterinarian's opinion, the medical condition, treatment regimen and clinical condition was stable

(iv) Exclusion criteria:
- Intended for breeding, or pregnant or lactating female dogs
- Dogs in crisis or moribund
- At the Investigator's discretion, a dog with a serious deteriorating condition and/or preliminary laboratory testing results indicating a condition that was serious and/or life threatening
- Dogs hospitalized within the last 4 days
- Dogs with an active infection (e.g. gastroenteritis) that would respond to standard of care, such as treatment with antibiotics
- Dogs in which food intake was contraindicated (i.e. suspected foreign body, gastric torsion, gastrointestinal surgery)
- Dogs with a regurgitation problem
- Dogs with dental disease severe enough to impair food intake

- Dogs with diabetes
- Any dog where the Owner is unsure that they can reliably evaluate the appetite (e.g. multi-pet household)
- Dogs currently receiving prohibited medications

(v) Treatment and Vehicle Control Groups: Dogs were randomly assigned into two treatment groups in a 2:1 ratio of ENTYCE oral solution or vehicle control (solution minus capromorelin). Veterinarians and owners were masked to treatment group assignment.

Table 5: Treatment groups:

Treatment Group	Dose (mg/kg)	Number of Dogs
ENTYCE oral solution	3 mg/kg	171
Vehicle Control	0 mg/kg	73

(vi) Drug administration: Dogs were administered ENTYCE oral solution at 3 mg/kg or a matched vehicle control oral solution once daily for 4±1 days.

(vii) Measurements and Observations: The primary effectiveness endpoint was an owner appetite assessment at day 3±1. Owners were asked to rate their dog's appetite as "increased", "no change", or "decreased". On day 0 (prior to the first dose), the owner must score their dog as "decreased" to be enrolled on the study. On day 3±1, if the owner scored their dog as "increased" this was considered a treatment success. On day 3±1, if the owner scored their dog as "no change" or "decreased" this was considered a treatment failure.

A secondary effectiveness variable was an owner appetite assessment questionnaire completed on day 0 (prior to the first dose) and day 3±1. Owners were asked to rate five questions about their dog's appetite. Each question was worth 1 to 5 points for a total score of 5 to 25 points. Treatment success was defined as an "increase in total score of 5 points or more from day 0 to day 3±1". The treatment success was defined as an "increase in total score of 5 points or more from day 0 to day 3±1".

A secondary effectiveness variable was body weight. Treatment success was defined as "more than a zero percent increase in body weight from day 0 to day 3±1".

Safety was assessed through adverse reactions, clinical pathology, and physical examinations.

(viii) Statistical Methods: The analyses of the effectiveness parameters were conducted on a per protocol population, which comprised those dogs without significant protocol violations or missing assessments.

The primary effectiveness variable (owner appetite assessment) was the percent success rate at day 3±1. The primary effectiveness variable (treatment success or failure) was analyzed using a generalized linear mixed model assuming a binomial distribution and

using a logit link. The model included treatment group as a fixed effect, and site and treatment by site interaction as random effects. A 95% confidence interval was calculated for the difference in success rates between active group and vehicle control.

Secondary outcome variables (owner appetite assessment questionnaire and body weight) included success rates and were presented and analyzed as described for the primary outcome variable. Secondary outcome variables also included the percent changes from day 0 to day 3±1. Analysis of variance modeling was employed to assess possible differences between treatment groups. The model contained terms for treatment, site and treatment by site interaction.

d. Results:

(i) Primary effectiveness: Effectiveness was evaluated by owner appetite assessment in 177 dogs; 121 dogs in the ENTYCE oral solution group and 56 dogs in the vehicle control group.

Table 6: Owner Appetite Assessment: Observed success rate on day 3±1 compared to Day 0

Success/Failure	**ENTYCE oral solution (N=121)**	**Vehicle Control (N=56)**
Success	83 (68.6%)	25 (44.6%)
Failure	38 (31.4%)	31 (55.4%)

Based on the statistical model, the estimated success rates are 67.9% and 42.6% for the ENTYCE group and the vehicle control groups, respectively. The difference in success rates is significant at P=0.0078.

(ii) Secondary effectiveness variables:

(a) Owner appetite assessment questionnaire: With success defined as an increase in the total score by 5 points or more from day 0 to day 3±1, a success rate observed in the ENTYCE oral solution group was 56.2% compared to the vehicle control group 26.8%.

Table 7: Owner Appetite Assessment Questionnaire: Observed success rate on day 3±1 compared to day 0

Success/Failure	**ENTYCE oral solution (N=121)**	**Vehicle Control (N=56)**
Success	68 (56.2%)	15 (26.8%)
Failure	53 (43.8%)	41 (73.2%)

(b) Body weight: The mean percent change (±SD) from day 0 to day 3±1 was 1.83% (±2.75) for the ENTYCE oral solution group and 0.11% (±3.61) for the vehicle control group.

Table 8: Body Weight: Percent change in body weight on Day 3±1 compared to day 0

Percent Change in Body Weight	**ENTYCE oral solution (N=121)**	**Vehicle Control (N=56)**
>0%	92 (76.0%)	25 (44.6%)
≤0%	29 (24.0%)	32 (55.4%)

e. Adverse Reactions:

All dogs (n=244; 171 administered ENTYCE, 73 administered vehicle control) enrolled in the study were evaluated for adverse reactions. The enrolled dogs had decreased appetite due to various medical conditions. Some dogs may have experienced more than one of the adverse reactions during the study. The following adverse reactions were observed.

Table 9: Adverse Reactions reported in dogs administered ENTYCE oral solution compared to Vehicle Control

Organ System	**Adverse Reaction**	**ENTYCE oral solution (N=171) n (%)**	**Vehicle Control (N=73) n (%)**
Gastrointestinal	Diarrhea	12 (7.0 %)	5 (6.8 %)
	Vomiting	11 (6.4 %)	4 (5.5 %)
	Hypersalivation	4 (2.3 %)	0 (0.0 %)
	Abdominal discomfort	2 (1.2 %)	0 (0.0 %)
	Flatulence	2 (1.2 %)	0 (0.0 %)
	Nausea	2 (1.2 %)	0 (0.0 %)
Clinical Pathology	Elevated blood urea nitrogen	7 (4.1 %)	2 (2.7 %)
	Elevated phosphorus	4 (2.3 %)	1 (1.4 %)
	Elevated creatinine	1 (0.6 %)	1 (1.4 %)
Other	Polydipsia	7 (4.1 %)	1 (1.4 %)
	Lethargy/depression	2 (1.2 %)	0 (0.0 %)

The following adverse reactions were reported in <1% of dogs administered ENTYCE: hyperactivity, increase fecal volume, increase gut sounds, and polyuria.

f. Conclusions: Administration of ENTYCE oral solution at a dose of 3 mg/kg once daily for 4 days was safe and effective for appetite stimulation in dogs.

III. TARGET ANIMAL SAFETY

A. Safety Study:

1. Title: CP-424,391-18 – 1 Year Oral Toxicity Study in Beagle Dogs. Study #96-1340-13.

2. Study Location: Groton, CT

3. Study Design:

   a. Objective: To investigate the potential toxicity of CP-424,391-18 (also known as capromorelin) in Beagle dogs following oral administration, once daily, for 12-months at 0 (placebo), 0.3, 7, and 40 mg/kg/day.

   b. Study Animals: Thirty-two healthy Beagle dogs, approximately 11-12 months old at first dose administration, weighing 9-13.6 kg.

   c. Control and treatment groups:

   Table 10: Treatment groups:

Tx Group	Dose (mg/kg)	Number and Gender of Dogs
Group 1	0 mg/kg	4 males and 4 females
Group 2	0.3 mg/kg (0.13X)	4 males and 4 females
Group 3	7 mg/kg (3.07X)	4 males and 4 females
Group 4	40 mg/kg (17.5 X)	4 males and 4 females

   Note: The 0.3, 7, and 40 mg/kg doses are based on capromorelin base. The equivalent doses based on capromorelin tartrate were 0.39, 9.2 and 52.4 mg/kg. The therapeutic dose is 3 mg/kg based on capromorelin tartrate.

   d. Dosage form: The active pharmaceutical ingredient was dissolved in deionized water. This formulation was not the final market formulation.

   e. Route of administration: Oral gavage

   f. Dosage amount, frequency, and duration: Capromorelin was administered once daily for 12 consecutive months. Dogs were fasted at the time of administration.

   g. Measurements and Observations: Clinical observations, body weight, food consumption, physical examination/vital signs, electrocardiogram, blood pressure, ophthalmology examination, complete blood count (CBC) and serum chemistry, urinalysis, capromorelin plasma concentration, growth hormone (GH) and insulin-like growth factor-1 plasma concentrations, gross pathology, organ weights, and histopathology were performed.

h. Statistical Methods: Models included treatment, sex, and the treatment-by-sex interaction as fixed effects. For variables measured more than once throughout the study, the following fixed effects were also included: time and the interactions treatment-by-time, sex-by-time, and treatment-by-sex-by-time. If pre-treatment values existed, the value closest to the first treatment administration was included as a covariate.

4. Results:

   Administration of capromorelin was associated with increased salivation and reddening/swollen paws. No treatment related clinical effects were noted on vital signs. No treatment related effects were noted on ophthalmology examinations. Electrocardiograms noted an increase in the PRQ interval at 1 to 2 hours post-dose in the 7 mg/kg/day and 40 mg/kg/day groups. No histological lesions were observed in the heart. There were treatment related decreases in red blood cell count, hemoglobin, and hematocrit in the 40 mg/kg group. Pale skin, pale gums, and decreased red blood cell count, hemoglobin and hematocrit were observed in one dog administered 40 mg/kg/day. Increases were noted in cholesterol, high density lipoproteins, and the liver specific isozyme of serum alkaline phosphatase (ALP) in the 40 mg/kg group. Growth hormone and insulin like growth factor-1 (IGF-1) plasma levels were increased in all groups administered capromorelin. Liver weights were increased in the 7 mg/kg/day and 40 mg/kg/day groups. An increase in hepatocellular cytoplasmic vacuolation was observed in all groups. There were no effects noted on gross necropsy. Capromorelin levels were similar in plasma collected on days 90, 181, and 349 indicating no accumulation of the drug.

5. Conclusions:

   This study supports the safe use of capromorelin administered orally at 3 mg/kg/day. Oral administration of capromorelin via oral gavage to approximately 11-12 month old Beagle dogs (4/sex/dose) at doses of 0, 0.3, 7, and 40 mg/kg/day for 12 consecutive months was associated with increased salivation, reddening/swollen paws, increased liver weights, and hepatocellular cytoplasmic vacuolation. Other findings considered to be related to the oral administration of capromorelin at the 40 mg/kg group include decreased red blood cell count, hemoglobin, and hematocrit; and increased ALP, cholesterol, high density lipoproteins, GH, and IGF-1.

B. Pharmacokinetic Study:

1. Title: AT-002: Pharmacokinetic comparison of two formulations in a cross-over design in Beagle dogs for two dose levels. Study #031599

2. Study Location: Concord, OH

3. Study Design:

   a. Objective: To investigate and compare the pharmacokinetic (PK) parameters of capromorelin after a single oral administration of ENTYCE (capromorelin oral solution) and a deionized water formulation, at two dose levels (3 mg/kg and 52.4 mg/kg), in a crossover study design in Beagle dogs.

   b. Study Animals: The study included 24 healthy Beagle dogs, approximately 12 months old at first dose administration, weighing between 6.2 and 12.3 kg. To control for bias, animals were randomly assigned to Groups 1A-2B, using a computer-generated randomization procedure based on body weight.

   c. Treatment Groups:

Table 11: Treatment groups:

Tx Group	Dose (mg/kg)	Animal Cohort	Day 0 Formulation	Day 7 Formulation	Number and Gender of Animals
Group 1	3	A	ENTYCE	Deionized	3 males and 3 females
	3	B	Deionized	ENTYCE	3 males and 3 females
Group 2	52.4	A	ENTYCE	Deionized	3 males and 3 females
	52.4	B	Deionized	ENTYCE	3 males and 3 females

   d. Dosage form: The study evaluated two different formulations. In the "deionized" formulation, the active pharmaceutical ingredient (API) was dissolved in deionized water. In the "flavored" formulation, the active pharmaceutical ingredient was in an oral flavored solution. This flavored solution is the final market formulation (ENTYCE).

   e. Route of administration: Oral gavage

   f. Dosage amount, frequency, and duration: Dogs received a single dose of each formulation of capromorelin with a 7-day washout period between dose administrations. Dosing occurred following an overnight fast. Food was offered approximately 4 hours post-dose.

   g. Measurements and Observations: Clinical observations, physical examination, hematology, serum chemistry, body weight measurement, and capromorelin serum concentration were performed.

h. Following dosing on Days 0 and 7, blood samples were collected in tubes without anticoagulant from all animals pre-dose and at 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours post-dose. Serum was harvested for analysis of capromorelin concentration. Non-compartmental PK parameters as defined below were calculated.

- $AUC_{(0\text{-}t)}$ =Area under the time vs. capromorelin serum concentration curve from time 0 to last measurable concentrations (t_{last})
- C_{max}=Peak capromorelin serum concentration
- T_{max}=Time to reach peak capromorelin serum concentration
- $T_{1/2}$ = Terminal elimination half–life
- $AUC_{(0\text{-}inf)}$ = Area under the time vs. capromorelin serum concentration curve from time 0 to infinity calculated as sum of $AUC_{(0\text{-}t)}$ and (t_{last}/terminal elimination rate constant).

i. Statistical Methods: An analysis of variance (ANOVA) was conducted to assess formulation differences for each dose of C_{max}, T_{max}, and $AUC_{(0\text{-}t)}$ and to determine the intrasubject coefficient of variation. For each dose, the PK parameters were natural log-transformed, and the ANOVA model included sequence, formulation and period as fixed effects, with the subject nested within sequence as a random effect. Each ANOVA included calculation of least square mean (LSM), the difference between formulation LSM, and the standard error associated with the difference for each dose. Ratios of LSM were calculated for each dose using C_{max}, T_{max}, and $AUC_{(0\text{-}t)}$. For each dose, these ratios were expressed as a percentage relative to the reference formulation (deionized water). Ninety percent confidence intervals for the ratios were derived for each dose. If a dog vomited within the first hour of dosing on any dose day, the statistical analysis for that day was performed with and without that dog.

4. Results:

A relative bioavailability analysis was performed using data from all dogs (n=12) administered 3 mg capromorelin/kg bodyweight. Dogs administered 3 mg/kg of ENTYCE had a lower capromorelin exposure than the dogs administered 3 mg/kg of the API in deionized water (relative bioavailability based on geometric mean $AUC_{(0\text{-}t)}$ ratio of 74.4% with 90% CI: 61.12 to 90.57). Further, the capromorelin C_{max} was lower following administration of ENTYCE compared to following administration of the API in deionized water (geometric mean C_{max} ratio of 83.07% with 90% CI: 64.20 to 107.5). At the 3 mg/kg dose, the median T_{max} and mean terminal half-life following both the formulations was similar (0.5 hr and ~1 hr respectively).

Table 12: Summary of Statistical Analysis Including All Dogs (Dose = 3 mg/kg)

Parameter	Geometric Mean (Deionized)	Geometric Mean (ENTYCE)	Ratio% (ENTYCE/Deionized)	90% CI	P-value
$AUC_{(0-t)}$ (hr*ng/mL)	793.88	590.68	74.40	(61.12, 90.57)	0.0214
C_{max} (ng/mL)	360.96	299.84	83.07	(64.20, 107.5)	0.2212
T_{max} (hr)	0.67	0.71	105.9	(68.12, 164.8)	0.8174

$AUC_{(0-t)}$ =Area under the time vs. capromorelin serum concentration curve from time 0 to last measurable concentrations
C_{max}=Peak capromorelin serum concentration
T_{max}=Time to reach peak capromorelin serum concentration
CI= Confidence intervals

At the 52.4 mg/kg dose level, there were a number of dogs in both groups (9 dogs in the Deionized group and 6 dogs in ENTYCE group) that had episodes of emesis within 0.5 hr after dose administration. The observed median T_{max} at the 52.4 mg/kg dose was within 0.5 hr (range 0.5-2 hr). Because one or more emetic events occurred prior to C_{max}, the dogs could be considered to have missed the dose. Although a small number of dogs (3 dogs in Deionized group and 6 dogs in ENTYCE group) provided evaluable PK data at 52.4 mg/kg dose, the relative bioavailability for the 52.4 mg/kg dose was not calculated as there were not sufficient dogs without emesis to perform any inferential ANOVA analysis.

5. Conclusions:

This PK study adequately bridges the exposure of ENTYCE to the exposure of capromorelin in deionized water, as was used in the 1-Year Oral Toxicity Study in Beagle Dogs (#96-1340-13), for the purpose of assessing target animal safety. This PK study showed that a 3 mg/kg dose of ENTYCE results in lower capromorelin exposure than that of capromorelin in deionized water. Further, the capromorelin C_{max} was lower following administration of ENTYCE compared to capromorelin in deionized water (geometric mean C_{max} ratio of 83.07% with 90% CI: 64.20 to 107.5). Therefore drug exposure in the 1-Year Oral Toxicity Study in Beagle Dogs is representative for evaluating the margin of safety for the flavored oral solution formulation.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to ENTYCE:

> "Not for use in humans. Keep this and all medications out of reach of children and pets. Consult a physician in case of accidental ingestion by humans. **For use in dogs only."**

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that ENTYCE, when used according to the label, is safe and effective for appetite stimulation in dogs.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is needed to diagnose and manage decreased appetite in dogs. Furthermore, the veterinarians' expertise is needed to monitor patients for possible adverse effects of the drug.

B. Exclusivity

ENTYCE as approved in our approval letter qualifies for FIVE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the FD&C Act because this is the first time we are approving this active ingredient in a new animal drug application submitted under section 512(b)(1) of the FD&C Act.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.