Inappetence in Dogs: What’s New in its Management?

June 10, 2016
ACVIM Forum, Denver, CO

Jessica A. Wofford, DVM, PhD
Speaker Disclosure

Inappetence in Dogs: What’s New in its Management?
Jessica A. Wofford, DVM, PhD

FINANCIAL DISCLOSURE:
Employee of Aratana Therapeutics

UNLABELED/ UNAPPROVED USES DISCLOSURE:
none
Forward-Looking Statement Disclaimer

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements with respect to our ability to bring several innovative products to market; expectations regarding the timing or scope of commercialization of Entyce; and the Company’s plans and opportunities, including without limitation offering innovative therapeutics that fulfill serious unmet needs.

These forward-looking statements are based on management’s current expectations. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, the following: our history of operating losses and our expectation that we will continue to incur losses for the foreseeable future; failure to obtain sufficient capital to fund our operations; risks relating to the impairment of intangible assets AT-004, AT-005, AT-007 and AT-011; unstable market and economic conditions; restrictions on our financial flexibility due to the terms of our credit facility; our substantial dependence upon the success of our product candidates; development of our biologic product candidates is dependent upon relatively novel technologies and uncertain regulatory pathways, and biologics may not be commercially viable; denial or delay of regulatory approval for our existing or future product candidates; failure of our product candidates that receive regulatory approval to obtain market approval or achieve commercial success; failure to realize anticipated benefits of our acquisitions and difficulties associated with integrating the acquired businesses; development of pet therapeutics is a lengthy and expensive process with an uncertain outcome; competition in the pet therapeutics market, including from generic alternatives to our product candidates, and failure to compete effectively; failure to identify, license or acquire, develop and commercialize additional product candidates; failure to attract and retain senior management and key scientific personnel; our reliance on third-party manufacturers, suppliers and partners; regulatory restrictions on the marketing of our product candidates; our small commercial sales organization, and any failure to create a sales force or collaborate with third-parties to commercialize our product candidates; difficulties in managing the growth of our company; significant costs of being a public company; risks related to the restatement of our financial statements for the year ended December 31, 2013, and the identification of a material weakness in our internal control over financial reporting; changes in distribution channels for pet therapeutics; consolidation of our veterinarian customers; limitations on our ability to use our net operating loss carryforwards; impacts of generic products; safety or efficacy concerns with respect to our product candidates; effects of system failures or security breaches; failure to obtain ownership of issued patents covering our product candidates or failure to prosecute or enforce licensed patents; failure to comply with our obligations under our license agreements; effects of patent or other intellectual property lawsuits; failure to protect our intellectual property; changing patent laws and regulations; non-compliance with any legal or regulatory requirements; litigation resulting from the misuse of our confidential information; the uncertainty of the regulatory approval process and the costs associated with government regulation of our product candidates; failure to obtain regulatory approvals in foreign jurisdictions; effects of legislative or regulatory reform with respect to pet therapeutics; the volatility of the price of our common stock; our status as an emerging growth company, which could make our common stock less attractive to investors; dilution of our common stock as a result of future financings; the influence of certain significant stockholders over our business; and provisions in our charter documents and under Delaware law could delay or prevent a change in control. These and other important factors discussed under the caption "Risk Factors" in the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission, or SEC, on March 15, 2016, along with our other reports filed with the SEC could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Any such forward-looking statements represent management’s estimates as of the date of this presentation. While we may elect to update such forward-looking statements at some point in the future, we disclaim any obligation to do so, even if subsequent events cause our views to change. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this presentation.
ENTYCE® (capromorelin oral solution) is for use in dogs only. Do not use in breeding, pregnant or lactating dogs. Use with caution in dogs with hepatic dysfunction or renal insufficiency. Adverse reactions in dogs may include diarrhea, vomiting, polydipsia, and hypersalivation. Should not be used in dogs that have a hypersensitivity to capromorelin. Please see the full Prescribing Information (available at the Aratana Therapeutics booth in the exhibit hall).
Overview

- Mimics the action of ghrelin
- Potent and selective growth hormone secretagogue receptor (GHS-R) agonist
- Orally active small molecule
- Longer half-life compared to ghrelin
ENTYCE™ (Ghrelin Receptor Agonist)

1. Stimulates hypothalamus to increase hunger
2a. Stimulates pituitary gland to release growth hormone (GH)
2b. Via systemic circulation

Ghrelin Receptor Agonist Biology
Safety and Efficacy Studies

- Laboratory Study
- Clinical Field Study
- 12-month Safety Study

A manuscript for each of these studies is currently under peer review for publication.
Capromorelin increases food consumption, body weight, growth hormone and sustained insulin-like growth factor 1 concentrations when administered to healthy adult Beagle dogs.

Bill Zollers, Linda Rhodes and Roy G. Smith

*Manuscript is undergoing peer review.*
Laboratory Study

- Capromorelin orally for 7 days (n=6/group)

<table>
<thead>
<tr>
<th>Capromorelin Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (placebo)</td>
<td>Twice daily</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>Once daily</td>
</tr>
<tr>
<td>4.5 mg/kg</td>
<td>Once daily</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>Twice daily</td>
</tr>
</tbody>
</table>

- Serum growth hormone (GH), insulin-like growth factor 1 (IGF-1), food consumption and body weights measured
Food Consumption

![Food Consumption Graph](image)

- Placebo
- 3 mg/kg SID
- 4.5 mg/kg SID
- 3 mg/kg BID

* p < 0.005
Change in Body Weight on Day 7

Mean Percent Change in Body Weight ± SD

* p < 0.001

- Placebo
- 3 mg/kg SID
- 4.5 mg/kg SID
- 3 mg/kg BID
Growth Hormone – Day 1

![Graph showing mean growth hormone levels after dosing with different regimens.]

- **Placebo**
- **3 mg/kg SID**
- **4.5 mg/kg SID**
- **3 mg/kg BID**
Growth Hormone – Days 1 and 7

The capromorelin-stimulated GH surge is attenuated after 7 days of dosing as compared to day 1.
IGF-1 – Day 1

Mean IGF-1 ± SD (ng/mL)

Time after dosing (hours)

-1 0 1 2 3 4 5 6 7 8

50 100 150 200 250 300

Placebo
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID
The capromorelin-stimulated IGF-1 increase is similar after 1 or 7 days of dosing.
Conclusions of Laboratory Study

- Treatment with capromorelin resulted in:
  - Transient increase in serum GH
  - Sustained increase in IGF-1

- Capromorelin-treated dogs:
  - Increased food consumption
  - Increased body weight
Clinical Field Study

A prospective, randomized, masked, placebo-controlled clinical study of capromorelin, a ghrelin receptor agonist, in dogs with reduced appetite

Bill Zollers, Jessica A. Wofford, Ernst Heinen and Linda Rhodes

Manuscript is undergoing peer review.
ENTYCE® Clinical Field Study

- Randomized, blinded, placebo-controlled
- 244 client-owned inappetent dogs
  - 3 mg/kg once daily by mouth x 4 days
- Primary Endpoint: Appetite assessment by owner
  - Increase, No change or Decrease
- Secondary Endpoints:
  - Appetite Questionnaire
  - Body Weight
ENTYCE® Clinical Field Study

- Inclusion criteria
  - Reduced appetite for ≥2 days
  - Owner Appetite Assessment score was “decreased”
  - If dog was on medication for chronic condition (OA, hypothyroidism, etc.), the medical condition and treatment regimen were stable
ENTYCE® Clinical Field Study

- Exclusion criteria
  - Dog was pregnant, lactating or intended for breeding
  - Dog in crisis, moribund state, with serious deteriorating condition and/or lab tests indicated condition was serious and/or life-threatening
  - Hospitalized within previous 4 days
  - Had an active infection that would respond to standard of care
  - Food intake was contraindicated
  - Regurgitation problem
  - Dental disease severe enough to impair food intake
  - Diabetes mellitus
  - Owner was unsure s/he could reliably evaluate appetite
ENTRYCE® Clinical Field Study

- Exclusion criteria
  - Dogs on prohibited concomitant medications*:
    - Systemic corticosteroids within 30 days of day 0, unless stabilized on long-term treatment
    - Anabolic steroids or progesterone within 30 days of day 0
    - Mirtazapine, cyproheptadine, diazepam, dronabinol and propranolol within 7 days of day 0
    - Any drug that has an effect on appetite (i.e. increases or decreases appetite) within 7 days of day 0
    - Any other medicine that, in the opinion of the veterinarian, could interfere with the study objectives

* Dogs on maropitant were allowed to enroll if treatment was ongoing and stable
ENTYCE® Clinical Field Study Results: Appetite Assessment Question

- On Day 3±1 or at last study visit (i.e. early removal from study), the Owner answered the following question as it best described their dog's appetite during the study:
  “Do you feel that during the study (over the 4±1 days of treatment) your dog's appetite was increased, no change or decreased?”
- Success = “increased” (primary effectiveness parameter)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ENTYCE®</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite Assessment: Success Rate</td>
<td>68.6%</td>
<td>44.6%</td>
<td>0.0078</td>
</tr>
</tbody>
</table>

Owners reported “increased” appetite in more ENTYCE-treated than placebo-treated dogs
Appetite Questionnaire:
5 questions, each scored 1-5 for total score of 5-25

Willingness to eat:
1. Always have to coax to eat or refuses food
2. Often have to coax to eat
3. Sometimes have to coax to eat
4. Never have to coax to eat
5. Never coax as dog always eats with enthusiasm
Appetite Questionnaire:
5 questions, each scored 1-5 for total score of 5-25

Anticipating meal time:
1. Avoids or hides when food bowl is filled
2. Little interest in meal time
3. Comes to eat when called
4. Anticipates meal time
5. Runs to the food bowl
Appetite Questionnaire:
5 questions, each scored 1-5 for total score of 5-25

Hunger/begging behavior:
1. Never seeks food, never begs
2. Rarely seeks or begs for food
3. Sometimes seeks or begs for food when sees, smells or hears food
4. Always seeks food when sees, smells or hears food
5. Actively seeks food even when your pet does not see, smell or hear food
Appetite Questionnaire:
5 questions, each scored 1-5 for total score of 5-25

When food placed in front of dog:
1. Avoids or refuses food
2. Slow to eat food
3. Eats food offered in reasonable time
4. Eats food offered quickly
5. Eats food offered rapidly, with enthusiasm
Appetite Questionnaire:
5 questions, each scored 1-5 for total score of 5-25

Your dog:
1. Eats no food without being force fed
2. Eats half or less of food offered
3. Eats most food offered
4. Eats all food offered
5. Eats all food offered and begs for more
### ENTYCE® Clinical Field Study Results: Appetite Questionnaire

- Questionnaire composed of 5 questions of 5 points each
  - Total score 5-25
  - Higher score = better appetite

- Success = Total score improved by at least 5 points

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ENTYCE®</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite Questionnaire: Success Rates</td>
<td>56.2%</td>
<td>26.8%</td>
<td>0.0071</td>
</tr>
</tbody>
</table>

ENTYCE-treated dogs had more “successes” in appetite-related behaviors, as compared to placebo-treated dogs.
## ENTYCE® Clinical Field Study Results: Body Weight

- **Percent change in total body weight:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ENTYCE® (N=121)</th>
<th>Placebo (N=56)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean percent change in body weight (±SD)</td>
<td>1.83% (±2.75)</td>
<td>0.11% (±3.61)</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

- **Percent of dogs in which total body weight increased:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ENTYCE® (N=121)</th>
<th>Placebo (N=56)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent change in body weight &gt;0%</td>
<td>92 (76.0%)</td>
<td>25 (44.6%)</td>
<td>0.0012</td>
</tr>
</tbody>
</table>

**ENTYCE-treated dogs’ increased body weight attributable to increased food consumption**
## ENTYCE® Clinical Field Study Results: Safety – Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reactions*</th>
<th>ENTYCE (N=171) N (%)</th>
<th>Placebo (N=73) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>12 (7.0 %)</td>
<td>5 (6.8 %)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (6.4 %)</td>
<td>4 (5.5 %)</td>
</tr>
<tr>
<td>Elevated blood urea nitrogen (BUN)</td>
<td>7 (4.1 %)</td>
<td>2 (2.7 %)</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>7 (4.1 %)</td>
<td>1 (1.4 %)</td>
</tr>
<tr>
<td>Elevated phosphorus</td>
<td>4 (2.3 %)</td>
<td>1 (1.4 %)</td>
</tr>
<tr>
<td>Hypersalivation</td>
<td>4 (2.3 %)</td>
<td>0 (0.0 %)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2 (1.2 %)</td>
<td>0 (0.0 %)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2 (1.2 %)</td>
<td>0 (0.0 %)</td>
</tr>
<tr>
<td>Lethargy/depression</td>
<td>2 (1.2 %)</td>
<td>0 (0.0 %)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (1.2 %)</td>
<td>0 (0.0 %)</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>1 (0.6 %)</td>
<td>1 (1.4 %)</td>
</tr>
</tbody>
</table>

*Dogs may have experienced more than one type or occurrence during the study.*
ENTYCE® Clinical Field Study Results: Safety Population

<table>
<thead>
<tr>
<th>Study Day</th>
<th>BUN (mg/dL)</th>
<th>Creatinine (mg/dL)</th>
<th>Phosphorus (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ENTYCE N=164</td>
<td>Placebo N=72</td>
<td>ENTYCE N=164</td>
</tr>
<tr>
<td>Day 0</td>
<td>Mean ±SD</td>
<td>22.58 ±20.02</td>
<td>22.51 ±15.21</td>
</tr>
<tr>
<td>Day 3 ±1</td>
<td>Mean ±SD</td>
<td>21.50 ±22.27</td>
<td>23.04 ±15.38</td>
</tr>
<tr>
<td>Change</td>
<td>Mean ±SD</td>
<td>-1.08 ±8.59</td>
<td>0.53 ±6.21</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>0.0055</td>
<td>0.1130</td>
</tr>
</tbody>
</table>

Only dogs in the safety population with both pre- and post-treatment values are included.
# ENTYCE® Clinical Field Study Results: Safety – Azotemic* Population

## Safety – Azotemic* Population

<table>
<thead>
<tr>
<th>Study Day</th>
<th>BUN (mg/dL)</th>
<th>Creatinine (mg/dL)</th>
<th>Phosphorus (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ENTYCE N=28</td>
<td>Placebo N=17</td>
<td>ENTYCE N=28</td>
</tr>
<tr>
<td>Day 0</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
</tr>
<tr>
<td></td>
<td>49.71 ±35.87</td>
<td>37.53 ±20.79</td>
<td>2.32 ±1.01</td>
</tr>
<tr>
<td>Day 3 ±1</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
</tr>
<tr>
<td></td>
<td>50.54 ±39.88</td>
<td>38.35 ±22.44</td>
<td>2.48 ±1.17</td>
</tr>
<tr>
<td>Change</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
</tr>
<tr>
<td></td>
<td><strong>0.82 ±16.86</strong></td>
<td><strong>0.82 ±9.13</strong></td>
<td><strong>0.16 ±0.61</strong></td>
</tr>
</tbody>
</table>

| p-value   | 0.3212     | 0.1835             | 0.3087             |

* Baseline azotemia was defined based on the IRIS Stage ≥2 CKD criterion for creatinine ≥1.4 mg/dL
ENTYCE® Clinical Field Study: Conclusions

- ENTYCE, a ghrelin receptor agonist, when administered to clinically inappetent dogs, resulted in an increase in appetite in this study.

- ENTYCE was well-tolerated in this study.

ENTYCE® (capromorelin oral solution) is for use in dogs only. Do not use in breeding, pregnant or lactating dogs. Use with caution in dogs with hepatic dysfunction or renal insufficiency. Adverse reactions in dogs may include diarrhea, vomiting, polydipsia, and hypersalivation. Should not be used in dogs that have a hypersensitivity to capromorelin. Please see the full Prescribing Information (available at the Aratana Therapeutics booth in the exhibit hall) for more details.
12-Month Safety Study

Evaluation of the safety in dogs of long-term, daily oral administration of capromorelin, a novel drug for stimulation of appetite.

Bill Zollers, Margie Huebner, Glenda Armintrout, Lesley C. Rausch-Derra and Linda Rhodes

Manuscript is undergoing peer review.
12-Month Safety Study

- Capromorelin orally once daily for 12 months (n=4/sex/group)

<table>
<thead>
<tr>
<th>Capromorelin base dose</th>
<th>Capromorelin tartrate equivalent dose</th>
<th>Relative to therapeutic dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (placebo)</td>
<td>0 (placebo)</td>
<td>0X</td>
</tr>
<tr>
<td>0.3 mg/kg</td>
<td>0.39 mg/kg</td>
<td>0.13X</td>
</tr>
<tr>
<td>7 mg/kg</td>
<td>9.2 mg/kg</td>
<td>3.07X</td>
</tr>
<tr>
<td>40 mg/kg</td>
<td>52.4 mg/kg</td>
<td>17.5X</td>
</tr>
</tbody>
</table>

- Clinical signs, food consumption, body weight, CBC, chemistry, UA, ophthalmology, EKG and vital signs
- Capromorelin, GH and IGF-1 blood levels
12-Month Safety Study: Results

- Body weight increased in all capromorelin-treated groups
- GH and IGF-1 were increased in all capromorelin-treated groups
- Capromorelin levels were similar throughout the study, indicating no drug accumulation
- Well-tolerated overall
12-Month Safety Study: Results

- Observed to some extent in capromorelin groups:
  - Increased salivation
  - Reddened/swollen paws
  - Increase in hepatocellular cytoplasmic vacuolation

- Observed in 9.2 (3.03X) and 52.4 (17.5X) mg/kg groups:
  - Increased liver weights, proportional to total body weight
  - Slight increase in PRQ interval 1-2 hours after dosing (no histological lesions observed in the heart)

- Observed only in 52.4 mg/kg (17.5X) group:
  - Decreases in RBCs, Hb and Hct
  - Increases in cholesterol, HDL and liver-specific isoenzyme of ALP
12-Month Safety Study: Conclusions

- Capromorelin at up to 17.5 times the labeled dose resulted in:
  - Increased body weight, GH and IGF-1, consistent with activity of the drug
  - Minimal toxicity, as outlined on the previous slide
Product Overview

- For appetite stimulation in dogs
- Flavored oral solution (30 mg/mL)
- Administered once daily, by mouth at 3 mg/kg
- FDA-approved May 16, 2016
- Expected commercial availability in conjunction with NAVC in February 2017