KindredBio

Best Medicines for Our Best Friends

FORWARD LOOKING STATEMENTS

This presentation contains forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including, but not limited to, statements regarding our expectations about the trials, regulatory approval, manufacturing, distribution and commercialization of our current and future product candidates, and statements regarding our anticipated revenues, expenses, margins, profits and use of cash.

These forward-looking statements are based on our current expectations. These statements are not promises or guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause our actual results to be materially different from any future results expressed or implied by the forward-looking statements. These risks include, but are not limited to, the following: our limited operating history and expectations of losses for the foreseeable future; the absence of significant revenue from Mirataz® (mirtazapine transdermal ointment) and our product candidates for the foreseeable future; the likelihood that our revenue will vary from quarter to quarter; our potential inability to obtain any necessary additional financing; our substantial dependence on the success of Mirataz and our lead product candidates which may not be successfully commercialized even if they are approved for marketing; the effect of competition; our potential inability to obtain regulatory approval for our existing or future product candidates; our dependence on third parties to conduct some of our development activities; our dependence upon third-party manufacturers for supplies of Mirataz and our product candidates; uncertainties regarding the outcomes of trials regarding our product candidates; our potential failure to attract and retain senior management and key scientific personnel; uncertainty about our ability to develop a satisfactory sales organization; our significant costs of operating as a public company; our potential inability to obtain and maintain patent protection and other intellectual property protection for Mirataz and our product candidates; potential claims by third parties alleging our infringement of their patents and other intellectual property rights; our potential failure to comply with regulatory requirements, which are subject to change on an ongoing basis; the potential volatility of our stock price; and the significant control over our business by our principal stockholders and management.

For a further description of these risks and other risks that we face, please see the risk factors described in our filings with the U.S. Securities and Exchange Commission (the SEC), including the risk factors discussed under the caption "Risk Factors" in our Annual Report on Form 10-K and any subsequent updates that may be contained in our Quarterly Reports on Form 10-Q filed with the SEC. As a result of the risks described above and in our filings with the SEC, actual results may differ materially from those indicated by the forward-looking statements made in this press release. Forward-looking statements contained in this press release speak only as of the date of this press release and we undertake no obligation to update or revise these statements, except as may be required by law.

August 1, 2019

WE SPEND GENEROUSLY ON PETS

$72.6 BILLION

We spend $72.6 billion a year on pets

$1.5 BILLION

We spend $1.5 billion a year on knee surgeries for dogs

$700 MILLION

We spend $700 million a year on Valentine’s Day presents for pets

Sources:
APPA National Pet Owners Survey - https://www.americanpetproducts.org/press_industrytrends.asp
Journal of the American Veterinary Medical Association, November 15, 2005, Vol. 227, No. 10, Pages 1604-1607, https://doi.org/10.2460/javma.2005.227.1604
Valentine’s Day Gift Spend: National Retail Foundation—http://consumerist.com/2015/01/28/americans-will-spend-703-million-on-valentines-day-gifts-for-pets
* Figures are with respect to the United States Market

BECAUSE PETS ARE FAMILY

67 PERCENT

67% of pet parents would give up their vacation to pay for pet emergency

35 PERCENT

35% of pet parents would give up their cellphone to pay for pet emergency

71 PERCENT

71% of pets sleep in bed with their pet parents

Sources:
American Institute of Certified Public Accountants-https://www.aicpa.org/content/aicpa/press/pressreleases/2017/survey-explores-financial-sacrifices-americans-make-for-pets.html
2017-2018 APPA National Pet Owners Survey

KINDREDBIO STORY

One of the **only pet biopharmaceutical companies** in the world

In a high growth, **recession-resistant**, underserved market

Leveraging validated human drugs to **maximize probability of success**

Commercial-stage firm with **rich pipeline**

Industry-leading biologics capabilities – the future of veterinary medicine

OUR STRATEGY:
WE SEEK TO REPURPOSE HUMAN DRUGS FOR PETS

Pursue molecules already known to work in humans

▼

Reduce technical risk

▼

Shorten timelines

Average of $5-8M to develop each drug in 3-6 years

▼

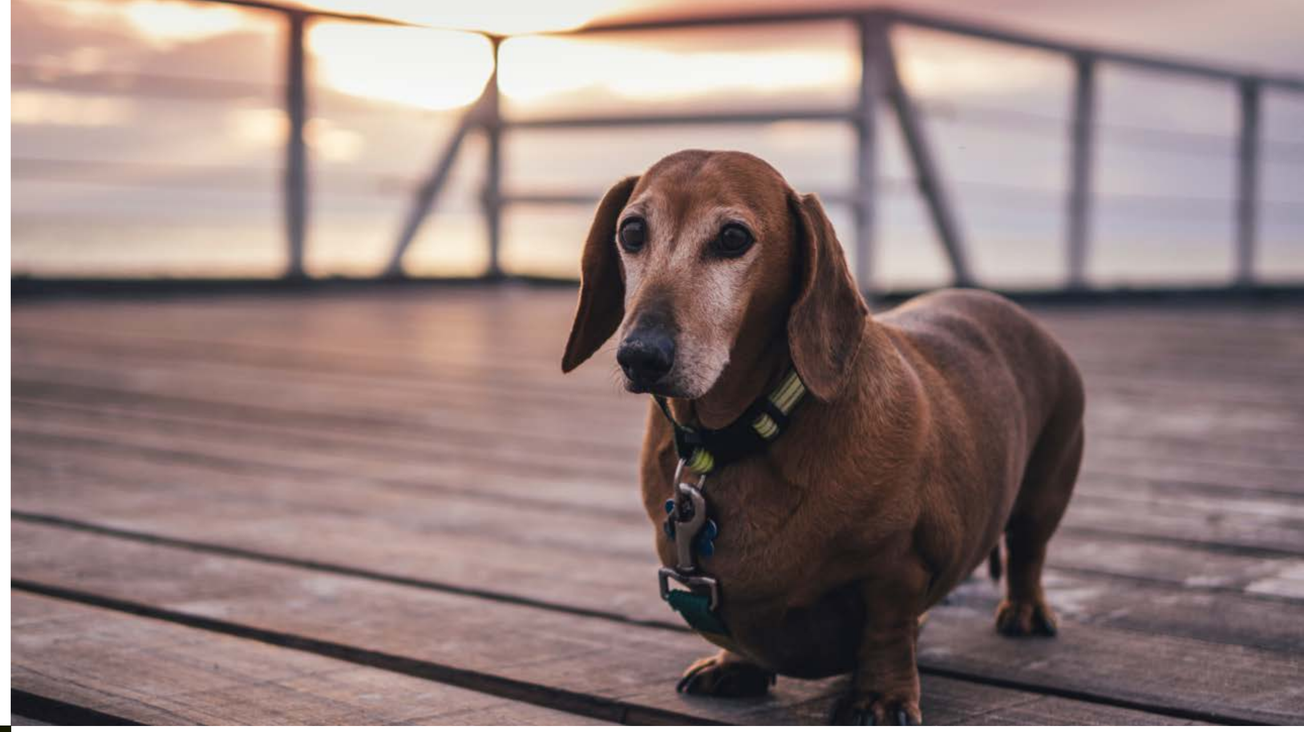
Portfolio approach

▼

Reduce financial risk

COMMERCIAL-STAGE

Industry-leading pipeline of more than 20 drugs in development

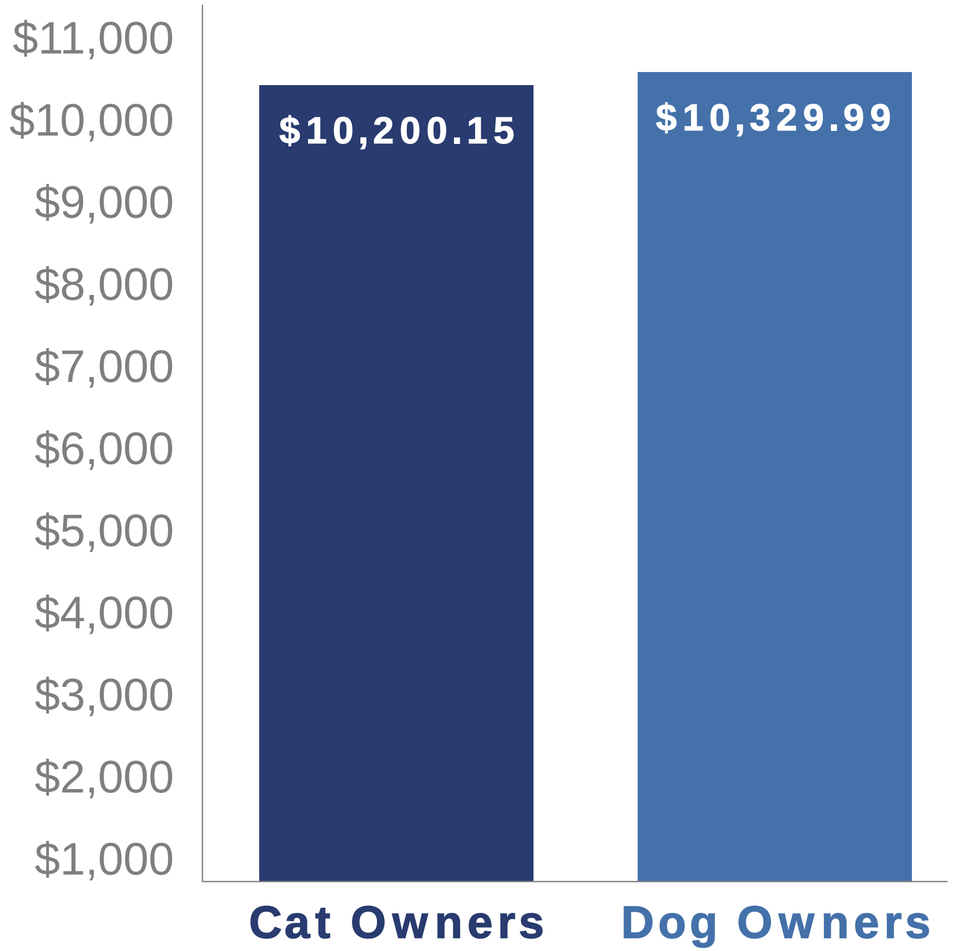


ATTRACTIVE ROI POTENTIAL

Market sizes are 10 times smaller than human markets but the cost of development is **100 times lower**

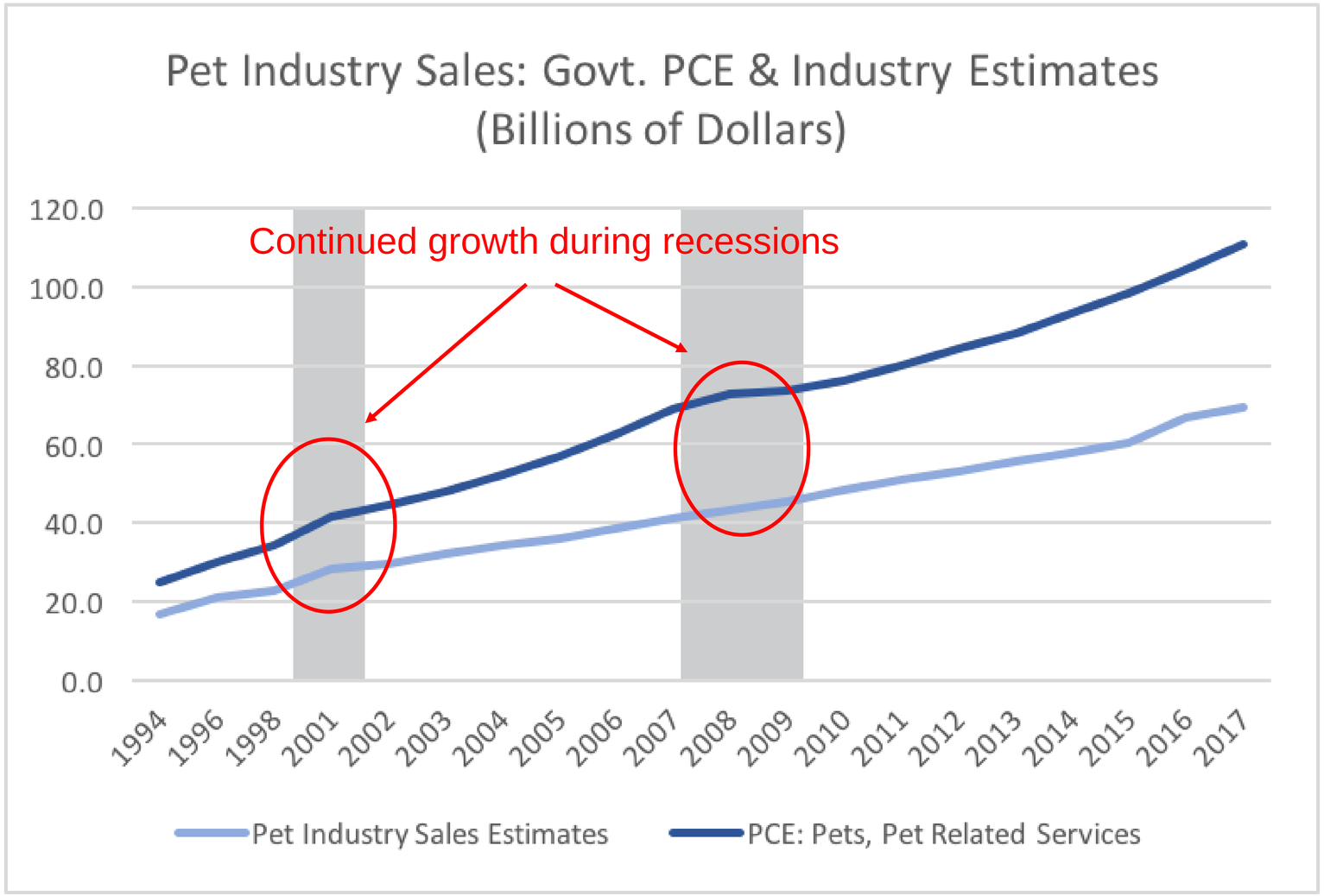
HIGH WILLINGNESS TO PAY

A recent study found that, on average, U.S. pet owners who have both dogs and cats **would spend over $10,000** to save one of their pets from a life-threatening illness or disease



Source:
https://lendedu.com/blog/how-much-are-dog-and-cat-owners-willing-to-spend/

RECESSION-RESISTANT SPEND



Source:
US Bureau of Economic Analysis (2018)
American Pet Products Association (2018)

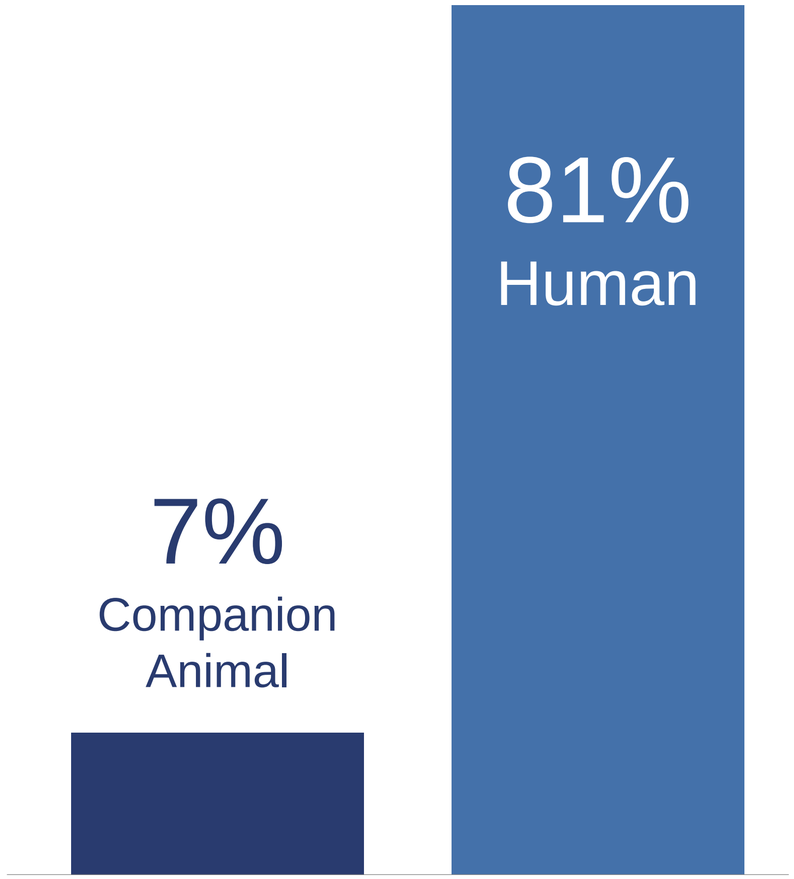
LOW GENERIC PENETRATION

There are very few generic companies, and **no automatic substitution** at the pharmacy

Many products reach peak sales several years **after patent expiration**

There is **no biosimilar pathway**

Generic Dispensing Rates



Note: Companion Animal dispensing rate within the veterinary clinic.
Source: IMS Health, Putney, BofA Merrill Lynch Global Research

MIRATAZ®
(mirtazapine transdermal ointment)

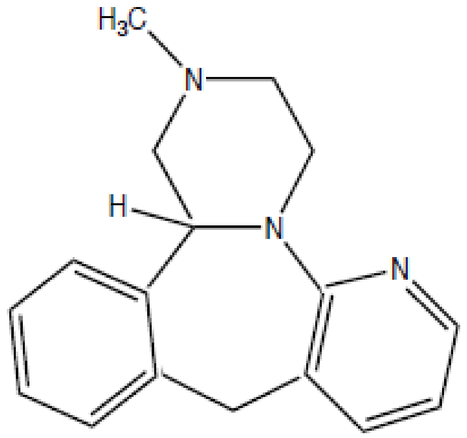
Important Safety Information: Mirataz® (mirtazapine transdermal ointment) is for topical use in cats only under veterinary supervision. Do not use in cats with a known hypersensitivity to mirtazapine or any of the excipients or in cats treated with monoamine oxidase inhibitors (MAOIs). Not for human use. Keep out of reach of children. Wear gloves to apply and wash hands after. Avoid contact with treated cat for 2 hours following application. The most common adverse reactions include application site reactions, behavioral abnormalities (vocalization and hyperactivity) and vomiting. For complete safety information, see the product insert at the end of the presentation.

Mirataz® (mirtazapine transdermal ointment) now available

Mirataz®
(mirtazapine transdermal ointment)

The first and *only* FDA-approved transdermal medication for the management of weight loss in cats

Mirataz is classified pharmacologically as a weight-gain drug



FELINE WEIGHT LOSS CAN BE FATAL

Unintended weight loss is a **leading cause** of feline veterinary visits

Caused by underlying conditions, such as chronic kidney disease, cancer and diabetes

9 million cats are diagnosed with unintended weight loss each year

3 million cats are currently treated for unintended weight loss each year

Sources:
2012 U.S. Pet Ownership & Demographics Sourcebook American Veterinary Medical Association (n=50,000 U.S. Households)
2016 U.S. Veterinarian Mirtazapine Research, Wise Insights May 2016 (n=89 U.S. small animal Veterinarians). Data on file at Kindred Biosciences.
2017 Miratax Pricing Research, Kynetec, September 2017 (n=204 U.S. small animal veterinarians). Data on file at Kindred Biosciences.

COMPLIANCE IS KEY

74% of veterinarians say ease of administration is a **primary factor** in selecting a medication for feline weight loss

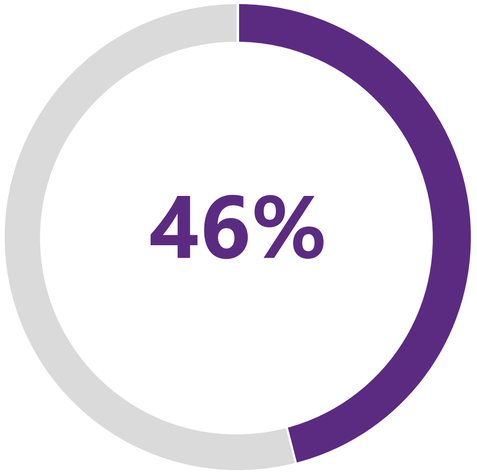
Mirataz® (mirtazapine transdermal ointment) is **applied topically** to the cat's inner ear

Provides **attractive application route versus oral dosing**

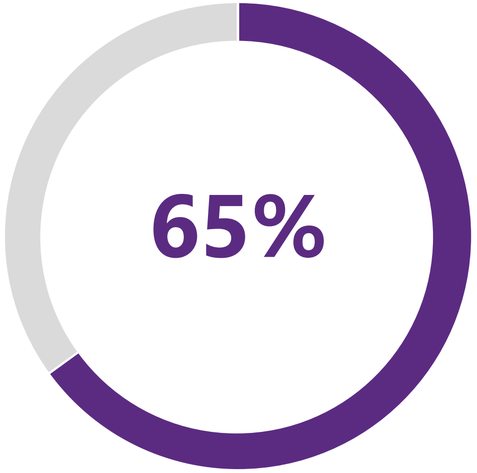
Source:
2016 U.S. Veterinarian Mirtazapine Phase 3 Research, Ipsos, September 2016 (n=201 U.S. small animal Veterinarians). Data on file at Kindred Biosciences.
2017 Mirataz Pricing Research, Kynetec, September 2017 (n=204 U.S. small animal veterinarians). Data on file at Kindred Biosciences.

BROAD UPTAKE THUS FAR

Mirataz® (mirtazapine transdermal ointment) launched in July of 2018



Approximately **46% of veterinary clinics** purchased Mirataz to date



Approximately **65% of veterinary clinics** have re-ordered product so far

The first and only FDA-approved transdermal medication for the management of weight loss in cats

KindredBio

COMMERCIALIZATION

COMPANION ANIMAL COMMERCIALIZATION

25 person direct field sales force, in conjunction with distributors

EQUINE COMMERCIALIZATION

Commercialize with 3-5 person direct sales force, in conjunction with distributors

WORLD-CLASS COMMERCIAL TEAM

15+ YEARS EXPERIENCE

Sales force has average experience of 15.4 years

>10 LAUNCHES

>10 launches per team member on average

LEADING COMPANIES

The team comes from top veterinary companies

Source:
Data on file at Kindred Biosciences.

DEEP PIPELINE

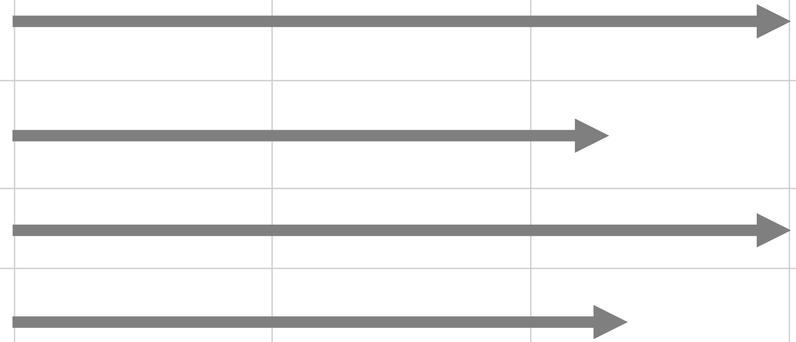
DEEP PRODUCT PIPELINE

Molecule	Proposed Indication	Preclinical	Laboratory Pilot Studies	Field Pilot Studies	Pivotal Study	Approval
KIND-012 (dipyrone injection)	Control of fever in horses					Rolling NADA Filed
KIND-012 (dipyrone oral gel)	Control of fever in horses					Positive Pivotal Study
KIND-510a (feline recombinant epo)	Control of non-regenerative anemia in cats					
IL31 Antibody	Atopic dermatitis in dogs					
IL17 Antibody	Atopic dermatitis in dogs					
IL4/13 SINK	Atopic dermatitis in dogs					
KIND-030	Parvovirus in dogs					

Pipeline Disclaimer: This material is intended to provide investors with information about KindredBio's clinical development pipeline and is not intended for promotional purposes.

DEEP PRODUCT PIPELINE
OTHER PRODUCTS IN DEVELOPMENT

Molecule	Proposed Indication	Preclinical	Laboratory Pilot Studies	Field Pilot Studies	Pivotal Study	Approval
KIND-014	Equine gastric ulcers					
KIND-015	Metabolic syndrome in horses					
Anti-TNF Antibody	Sick newborn foals					
Anti-TNF Antibody	Inflammatory bowel disease in dogs					
Other products in development (partial list) include KIND-bodies, IgE antibody, CD20 antibody, VEGF antibody, and Checkpoint Inhibitors						



Pipeline Disclaimer: This material is intended to provide investors with information about KindredBio's clinical development pipeline and is not intended for promotional purposes.

DIPYRONE OPPORTUNITY

Dipyrone is designed as an IV and Oral drug intended for the **control of pyrexia (fever)** in horses

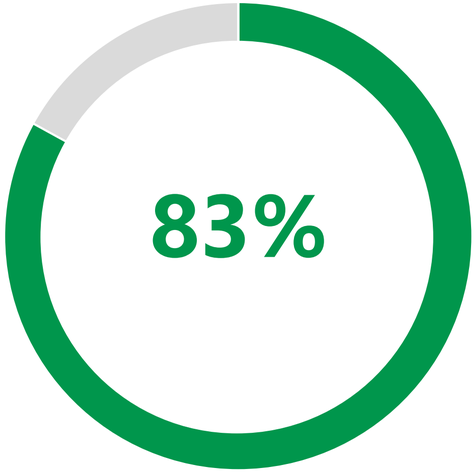
8-9 million horses in the US, and more than **1 million** seen by a veterinarian for fever annually

IV under review at the FDA, Oral pivotal study positive.

Sources:
The Economic Impact of the Horse Industry on the United States, 2005, American Horse Council Foundation (n=18,648 U.S. horse owners/industry suppliers).
Dipyrone Pricing Research, Ipsos Ag & Animal Health, May 2016 (n=160 U.S. equine Veterinarians). Data on file at Kindred Biosciences.
AAEP Industry Partners 2019

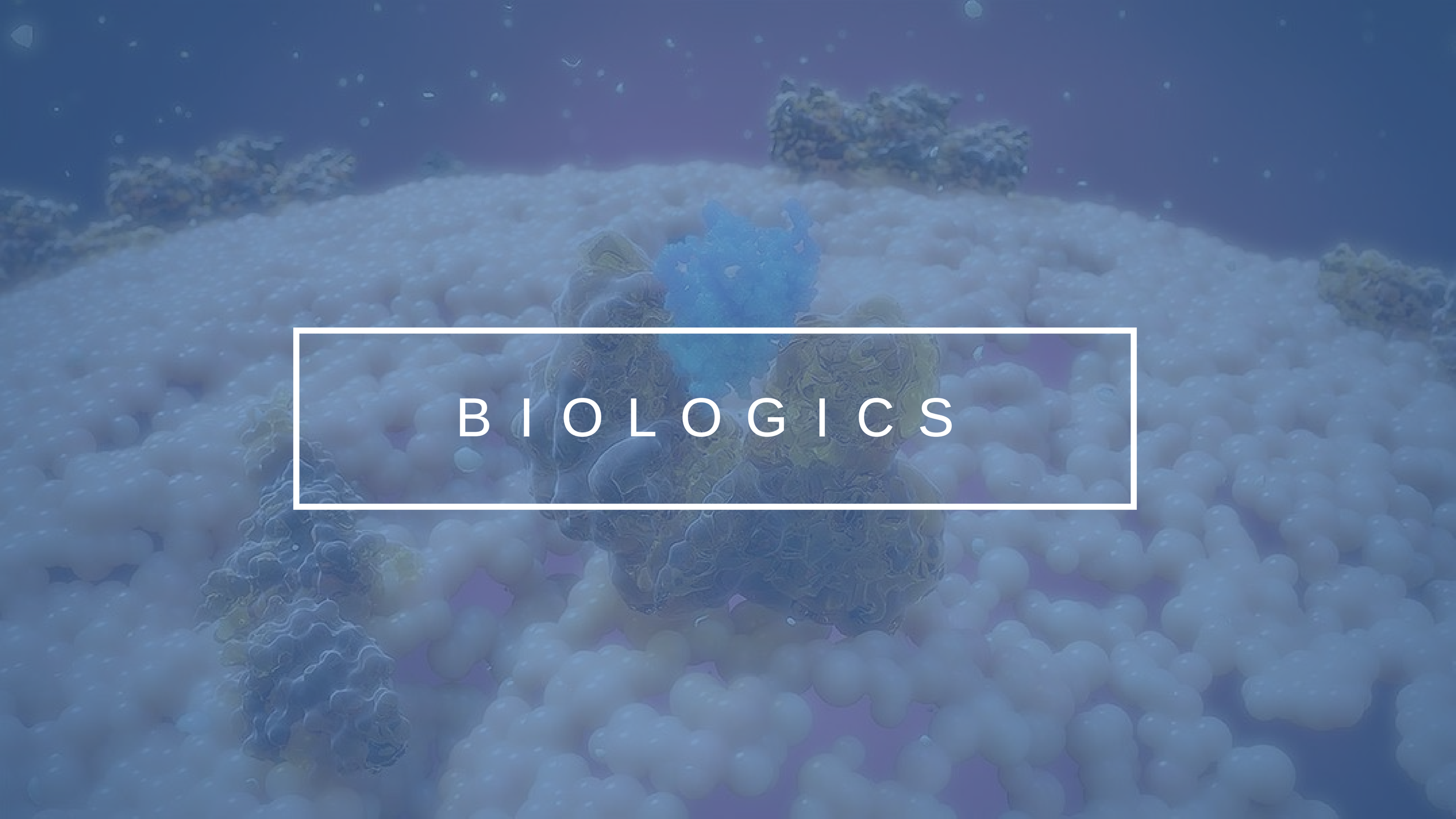
DIPYRONE INJECTION OPPORTUNITY

95% believe that dipyrone would be a good fit for their practice



83% would use dipyrone in the first year

Source:
Dipyrone Pricing Research, Ipsos Ag & Animal Health, May 2016 (n=160 U.S. equine Veterinarians) . Data on file at Kindred Biosciences.


BIOLOGICS

BIOLOGICS: THE FUTURE OF VETERINARY MEDICINE

Veterinary medicine to follow human market, where top drugs are biologics

+

Industry leading biologic programs

+

Highly experienced biologics team responsible for leading human drugs

+

End-to-end capabilities & new technologies (KIND-bodies)

STATE-OF-THE-ART MANUFACTURING PLANT

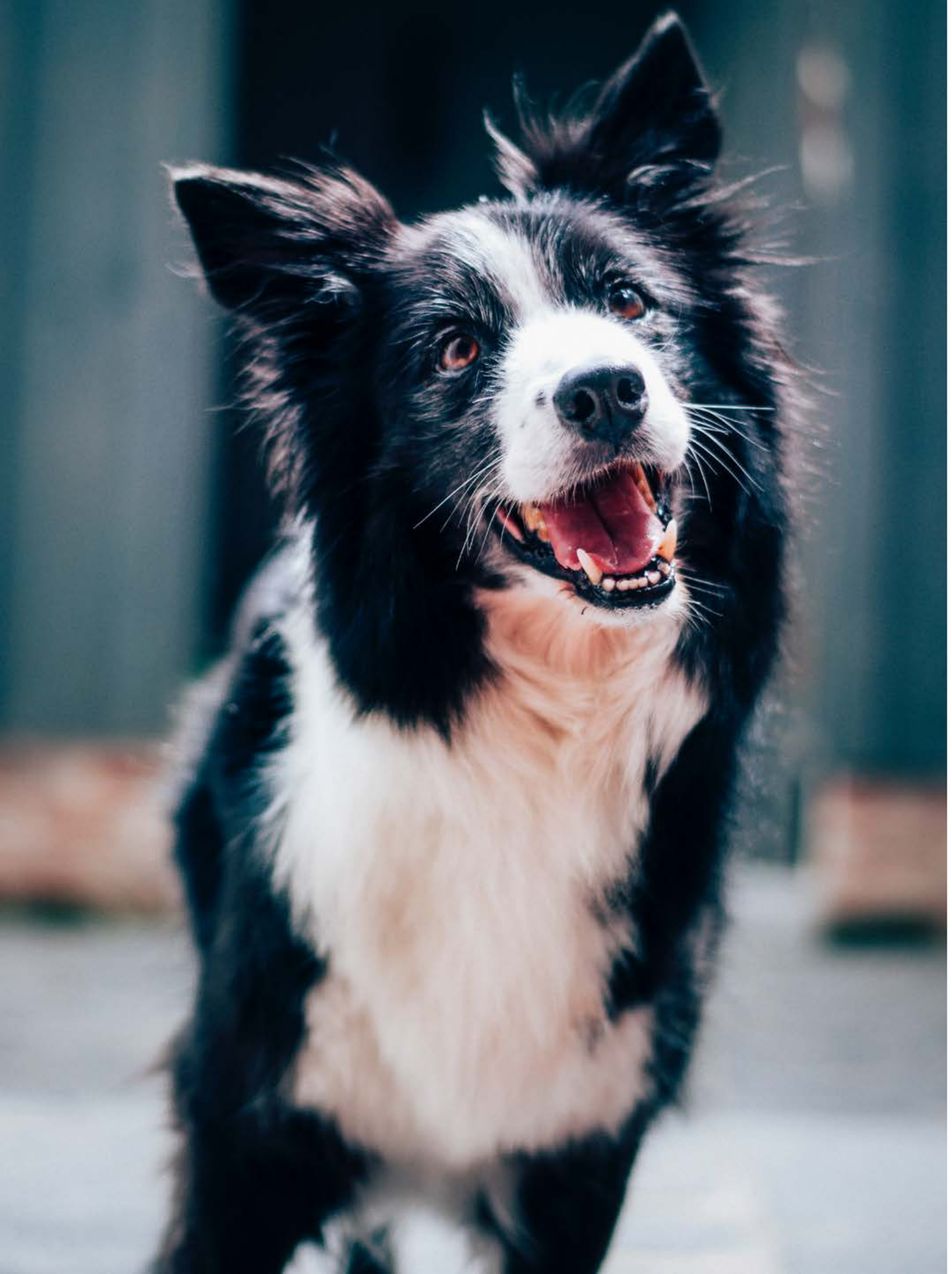
Elwood, KS facility includes approx. **180,000 ft²** for biologics & small molecule manufacturing

One of the **only biologics manufacturing facilities** in animal health

Plant to **manage COGS** and remove need for contract manufacturers

Construction to support initial production lines completed mid-2019

Burlingame, CA facility to manufacture feline recombinant erythropoietin, small molecules and clinical trial batches



CANINE DERMATITIS

10-15% of dogs have atopic dermatitis, an allergic skin disease

It is the **primary reason** owners take their dog to the veterinarian

Two recent drugs are selling over **$600M a year** (combined) and growing

Millions of dogs have atopic dermatitis

Source:
Hillier, A. and C.E. Griffin, The ACVD task force on canine atopic dermatitis (I): incidence and prevalence. Vet Immunol Immunopathol, 2001. 81(3-4): p. 147-51.
Website, N.P.I. Top 10 Medical Conditions of 2016. Available from: https://press8.petinsurance.com/articles/2017/march/nationwide%C2%AE-data-reveals-most-common-medical-conditions-for-dogs-and-cats.

CANINE IL31 ANTIBODY

Second generation, fully caninized, high-affinity antibody that blocks IL31, a mediator of itching

Positive topline results from pilot field effectiveness study - rapid and dramatic reduction in pruritus (itch) and CADESI score versus placebo

Pivotal study to commence by year-end 2019

IL4/IL13 SINK

IL4/IL13 SINK **blocks inflammation**

Analogous to dupilumab, which was recently approved in human atopic dermatitis

Pilot safety study has been completed and the molecule was **well tolerated**

OTHER DERMATITIS CANDIDATES

Initial pilot study of IL17 antibody has also been completed and the molecule was **well-tolerated**

KindredBio has **multiple other preclinical candidates** for atopic dermatitis

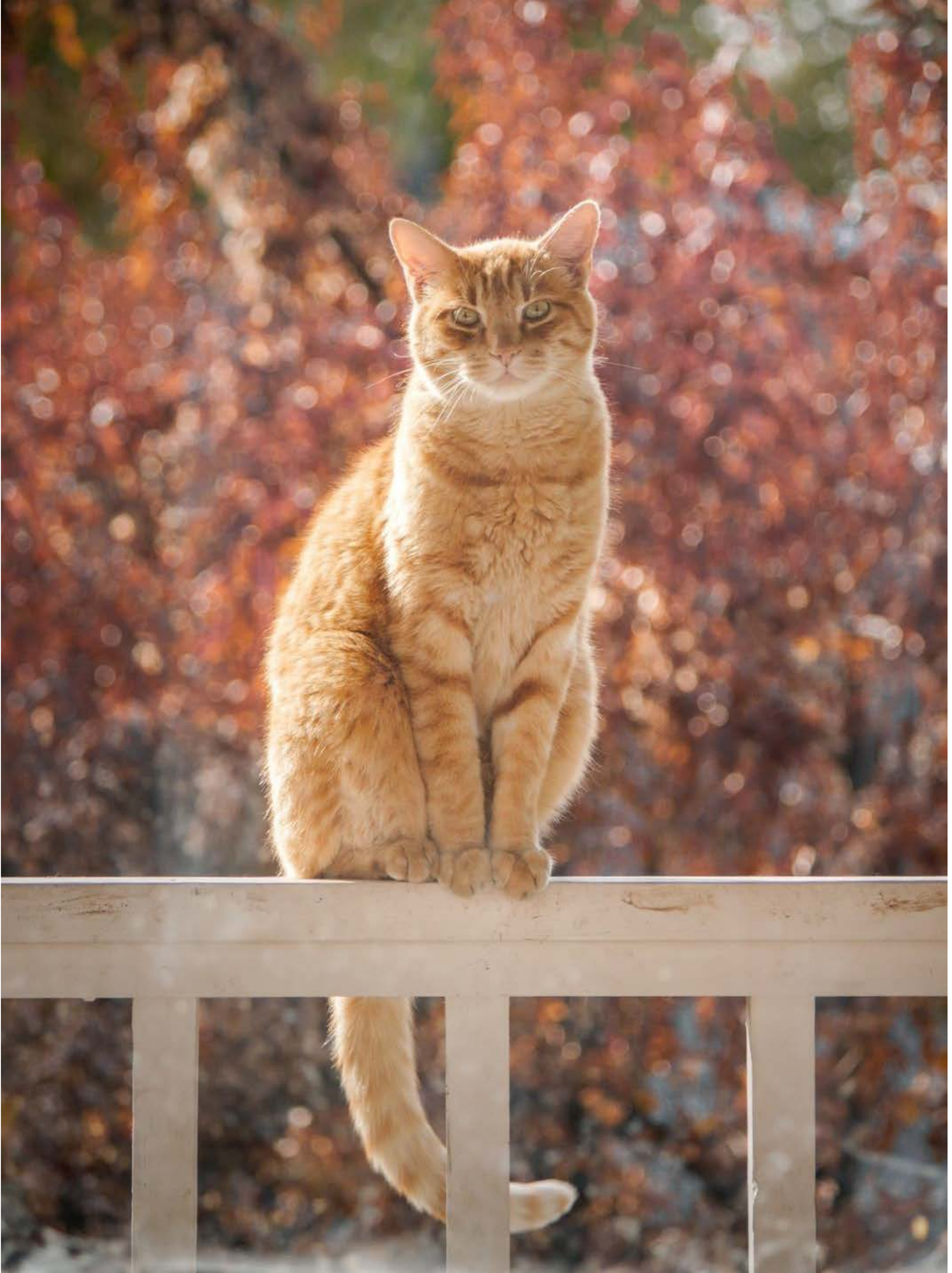
CANINE PARVOVIRUS

Highly contagious disease affecting mostly puppies, with **no current therapies**

Even with supportive therapy, which can cost thousands, **mortality remains high**

Positive results from pilot efficacy study – mortality benefit seen in both prophylaxis and treatment of parvovirus infection

Approval expected by late 2020, or early 2021



FELINE ANEMIA

About 50% of all cats develop kidney disease when they get old, which often causes anemia

Human epo is **immunogenic** in most cats

High unmet medical need, with **millions of patients**

FELINE RECOMBINANT ERYTHROPOIETIN

Intended for **non-regenerative anemia** in cats

Positive results from pilot field effectiveness study – statistically significant improvement in hematocrit

Successful completion of first cGMP drug substance manufacturing runs at plant in 2Q 2019

Pivotal study expected to commence in 2019

CORPORATE INFO

SELECT SUMMARY FINANCIALS

	June 30, 2019	
	Quarter	Year-to-Date
Net product revenues	$1.2	$1.8
Operating costs and expenses		
Cost of Product Revenues	$0.2	$0.3
Research and Development	$6.7	$13.9
Selling, General and Administrative	$9.1	$18.9
Total cash operating costs and expenses (excluding stock-based compensation)	$14.1	$29.4
Total operating costs and expenses (including stock-based compensation)	$16.0	$33.1
Total cash, cash equivalents, and investments	$79.6	$79.6

CAPITAL STRUCTURE AND ANALYST COVERAGE

Shares outstanding[1]	**39.1M**
Options[2]	**6.5M**
Market Cap[3]	**US$266.4M**

Analyst Coverage

Aegis Capital Corp. • Nathan Weinstein • nweinstein@aegiscap.com

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Stifel • Jonathan Block • blockj@stifel.com

[1] As of July 31, 2019
[2] As of June 30, 2019; avg. $7.90
[3] As of close of market July 31, 2019

2019 EXPECTED NEWS FLOW

IL4/IL13 – Pilot effectiveness results

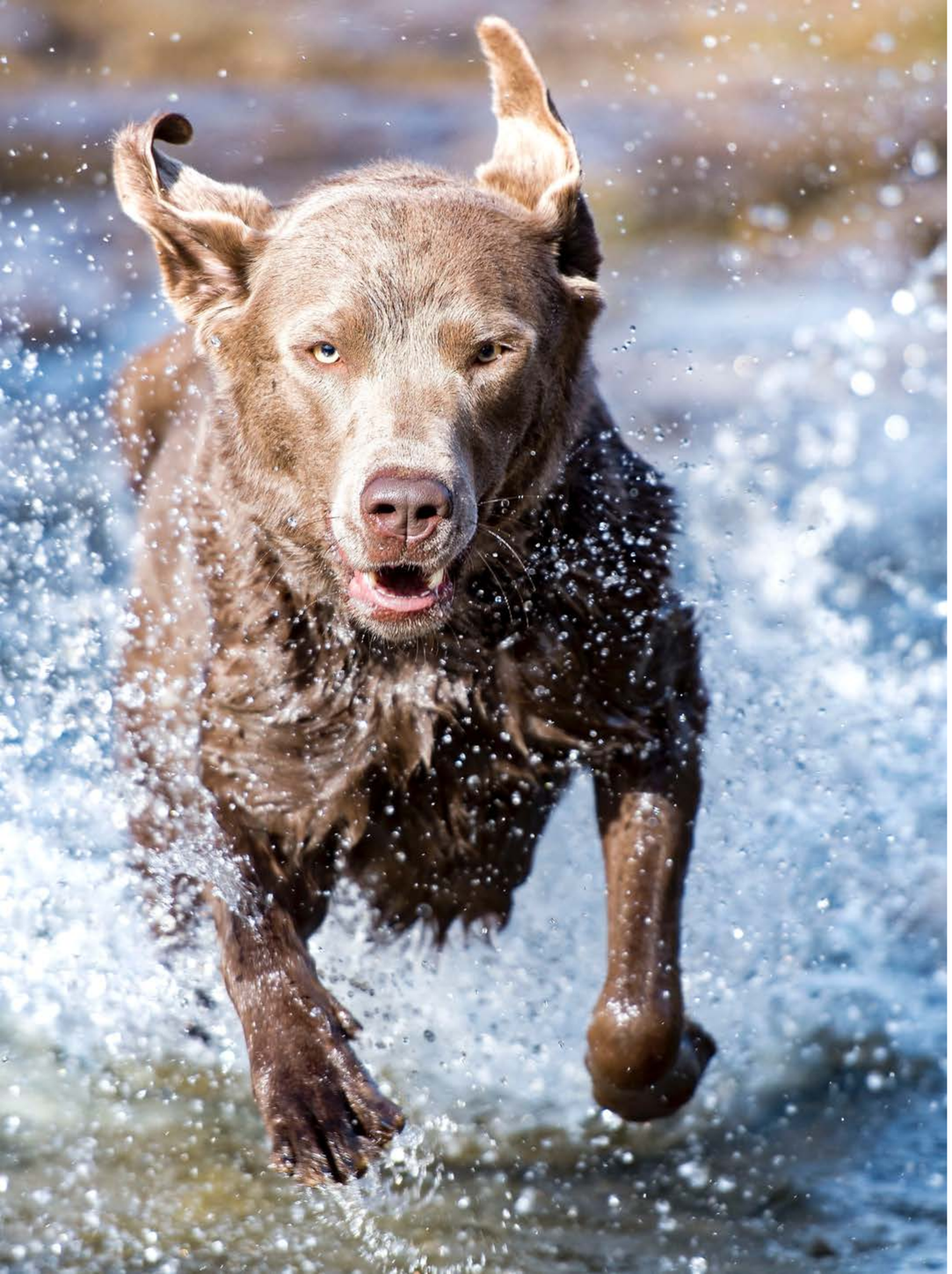
IBD – Pilot effectiveness results

Feline Recombinant Erythropoietin – Initiation of pivotal study

IL31 – Initiation of pivotal study

Equine Ulcer – Initiation of pivotal study

SUMMARY



SUMMARY

KindredBio develops innovative therapies for companion animals by **leveraging validated human drugs.** The markets are ten times smaller than human markets, but the cost of development is a **hundred times lower**, providing **attractive ROI potential.**

KindredBio

Best Medicines for Our Best Friends

Prescribing Information

Mirataz®
(mirtazapine transdermal ointment)

Mirataz™
(mirtazapine transdermal ointment)

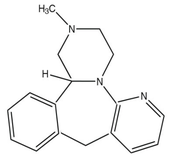
Each 1 g of Mirataz™ contains 20 mg mirtazapine (2%). Each 5 g tube contains 100 mg (0.1 g) of mirtazapine.

For topical application in cats only. Not for oral or ophthalmic use.

CAUTION:
Federal law (USA) restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:
Mirataz™ (mirtazapine transdermal ointment) is a white to off-white ointment containing 2% (w/w) of mirtazapine suitable for transdermal (topical) administration. Mirataz™ contains the following inactive ingredients: Polyethylene Glycol (PEG) 400, PEG 3350, Diethylene Glycol Monoethyl Ether, PEG-8 Caprylic/Capric Glycerides, Oleyl Alcohol, Butylated Hydroxytoluene, Dimethicone, and Dry Flo TS.

The structural formula of mirtazapine is:



Molecular Formula: $C_{17}H_{19}N_3$ Molecular Weight: 265.35

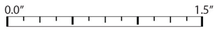
INDICATION:
Mirataz™ is indicated for the management of weight loss in cats.

DOSAGE AND ADMINISTRATION:
Administer topically by applying a 1.5-inch ribbon of ointment (approximately 2 mg/cat) on the inner pinna of the cat's ear once daily for 14 days (see Diagrams below).

Wear disposable gloves when applying Mirataz™. Dispose of used gloves after each application.

Alternate the daily application of Mirataz™ between the left and right inner pinna of the ears. Do not administer into the external ear canal. If desired, the inner pinna of the cat's ear may be cleaned by wiping with a dry tissue or cloth immediately prior to the next scheduled dose. If a dose is missed, apply Mirataz™ the following day and resume daily dosing.

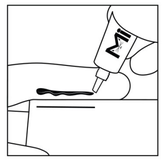
To demonstrate the method of administering the dose, the veterinarian or trained personnel at the clinic should apply the first dose in the presence of the owner.



This ruler measures 1.5 inches. Use this ruler to measure the 1.5 inch ribbon of ointment to be applied.

To apply Mirataz™:

Step 1: Wear disposable gloves. Twist cap on tube counterclockwise to open.



Step 2: Apply even pressure on tube and squeeze a 1.5-inch line of ointment onto your gloved finger using the measured line on the carton or in this package insert.

Step 3: Using your gloved finger, gently rub ribbon of ointment on inside pinna of the cat's ear spreading it evenly over the surface. Dispose of used gloves after each application. If contact with your skin occurs wash thoroughly with soap and warm water.

CONTRAINDICATIONS:
Mirataz™ is contraindicated in cats with a known hypersensitivity to mirtazapine or to any of the excipients.

Mirataz™ should not be given in combination, or within 14 days before or after treatment with a monoamine oxidase inhibitor (MAOI) [e.g. selegiline hydrochloride (L-deprenyl), amitraz], as there may be an increased risk of serotonin syndrome.

HUMAN WARNINGS:
Not for human use. Keep out of reach of children.

Wear disposable gloves when handling or applying Mirataz™ to prevent accidental topical exposure. After application, dispose of used gloves and wash hands with soap and water. After application, care should be taken that people or other animals in the household do not come in contact with the treated cat for 2 hours because mirtazapine can be absorbed transdermally and orally. However, negligible residues are present at the application site and the body of the cat at 2 hours after dosing.

In case of accidental skin exposure, wash thoroughly with soap and warm water. In case of accidental eye exposure, flush eyes with water. If skin or eye irritation occurs seek medical attention.

In case of accidental ingestion, or if skin or eye irritation occurs, seek medical attention.

PRECAUTIONS:
Do not administer orally or to the eye.

Use with caution in cats with hepatic disease. Mirtazapine may cause elevated serum liver enzymes (See Animal Safety).

Use with caution in cats with kidney disease. Kidney disease may cause reduced clearance of mirtazapine which may result in higher drug exposure.

Upon discontinuation of Mirataz™, it is important to monitor the cat's food intake. Food intake may lessen after discontinuation of mirtazapine transdermal ointment. If food intake diminishes dramatically (>75%) for several days, or if the cat stops eating for more than 48 hours, reevaluate the cat.

Mirataz™ has not been evaluated in cats < 2 kg or less than 6 months of age.
The safe use of Mirataz™ has not been evaluated in cats that are intended for for breeding, pregnant, or lactating cats.

ADVERSE REACTIONS:
In a randomized, double-masked, vehicle-controlled field study to assess the effectiveness and safety of mirtazapine for the management of weight loss in cats, 115 cats treated with Mirataz™ and 115 cats treated with vehicle control were evaluated for safety. The vehicle control was an ointment containing the same inert ingredients as Mirataz™ without mirtazapine. The most common adverse reactions included application site reactions, behavioral abnormalities (vocalization and hyperactivity), and vomiting. The adverse reactions observed in the study and number of cats experiencing each adverse reaction is summarized in Table 1 below.

Table 1. Adverse Reactions Reported During the Field Study

Adverse Reaction	Mirataz™ N=115 (%)	Vehicle Control N=115 (%)
Application site (Ear pinna)		
Erythema	12 (10.4%)	20 (17.4%)
Crust/Scab	3 (2.6%)	6 (5.2%)
Residue	3 (2.6%)	8 (7.0%)
Scaling/Dryness	3 (2.6%)	3 (2.6%)
Dermatitis or irritation	1 (0.9%)	9 (7.8%)
Alopecia	1 (0.9%)	2 (1.7%)
Pruritus	1 (0.9%)	4 (3.5%)
Behavioral		
Vocalization	13 (11.3%)	2 (1.7%)
Hyperactivity	8 (7.0%)	1 (0.9%)
Disoriented state or ataxia	4 (3.5%)	2 (1.7%)
Lethargy/weakness	4 (3.5%)	9 (7.8%)
Attention Seeking	3 (2.6%)	0
Aggression	2 (1.7%)	0
Physical Examination or Observational		
Vomiting	13 (11.3%)	15 (13.0%)
Dehydration	6 (5.2%)	5 (4.3%)
Diarrhea or soft stool	6 (5.2%)	7 (6.1%)
Heart murmur	5 (4.3%)	7 (6.1%)
Inappetence	5 (4.3%)	5 (4.3%)
Renal insufficiency*	4 (3.5%)	0
Ear infection	3 (2.6%)	0
Urinary tract infection	3 (2.6%)	0
Clinical Pathology		
Hematuria	7 (6.1%)	1 (0.9%)
Elevated BUN (without creatinine)**	6 (5.2%)	0
Elevated creatinine and BUN	5 (4.3%)	1 (0.9%)
Hyperphosphatemia	5 (4.3%)	0
Hypokalemia	5 (4.3%)	2 (1.7%)
Pyuria	5 (4.3%)	0
Anemia	3 (2.6%)	8 (7.0%)
Low urine specific gravity	3 (2.6%)	1 (0.9%)
Monocytosis	3 (2.6%)	2 (1.7%)
Neutrophilia	3 (2.6%)	2 (1.7%)

* One cat with renal insufficiency was reported with a serious adverse reaction of acute renal failure, hematuria, and pyuria at the Week 2 visit. The cat was enrolled with a history of chronic kidney disease. Euthanasia was elected and necropsy revealed hypertrophic cardiomyopathy, bilateral parathyroid hyperplasia, and mild to moderate renal disease.
** At Week 2, blood urea nitrogen (BUN) values were significantly higher in the Mirataz™ group compared to the vehicle control group ($p<0.10$). The BUN in the Mirataz™ group was 43.60 mg/dL (reference range 16-37 mg/dL) compared to 36.05 mg/dL in the vehicle control group.

Prescribing Information

Mirataz®
(mirtazapine transdermal ointment)

Post study, follow-up was done in 199 cats (103 in the Mirataz™ (mirtazapine transdermal ointment) group and 96 in the vehicle control group). Following cessation of Mirataz™, four cats were reported as being less social or less restless, one cat was reported as more active, and one cat was reported with increased hissing and urinating out of the litter box.

To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Kindred Biosciences, Inc. at 888-608-2542.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVeterinary/SafetyHealth

INFORMATION FOR CAT OWNERS:
Upon discontinuation of Mirataz™, it is important to monitor your cat's food intake. Your cat's food intake may lessen after discontinuation of mirtazapine transdermal ointment. If food intake diminishes dramatically (>75%) for several days or if your cat stops eating for more than 48 hours, contact your veterinarian.

CLINICAL PHARMACOLOGY:

Mechanism of Action:
The exact mechanism by which mirtazapine induces weight gain has not been clearly elucidated but appears to be multifactorial.[1] Mirtazapine is an α2-adrenergic receptor antagonist nor-adrenergic and serotonergic antidepressant drug. Mirtazapine is known to be a potent antagonist of 5-HT2 and 5-HT3 serotonin receptors in the central nervous system (CNS), and a potent inhibitor of histamine H1 receptors. Because mirtazapine blocks 5-HT2 and 5-HT3 receptors, only 5-HT1A- mediated serotonergic transmission is enhanced. Inhibition of 5-HT2 receptors may account for the orexigenic effects of mirtazapine. Another hypothesis is that mirtazapine induced weight gain may be secondary to changes in leptin and the tumor necrosis factor α(TNF-α) cytokine system.[2] A study by Fernstorm (1995) demonstrated a reduction of the basal metabolic rate in patients treated with antidepressants in general.[3]

Pharmacokinetics:
In a crossover study in eight cats to determine the relative bioavailability of oral and transdermal 2% mirtazapine, the mean half-life (26.8 hours) with topical administration was over 2X longer than the mean half-life (10.1 hours) with oral administration.

The doses used in the target animal safety study were higher (2.8 to 5.4 mg) than the label dose. Based on dose proportionality in $AUC_{0\text{-}24hr}$ and C_{max} observed in this study, these pharmacokinetic parameters were extrapolated for the 2 mg/cat label dose administered once per day for 35 days (see Table 2).

Steady state was achieved within 14 days. The median accumulation between first and 35th dose was 3.71X (based on AUC ratio) and 3.90X (based on C_{max} ratio).

Table 2. Plasma pharmacokinetic parameters at steady state after 2 mg/cat dose of mirtazapine 2.0% transdermal ointment in healthy cats

Parameter	Unit	Mean (SD)
C_{max}	ng/mL	32.1 (19.9)
T_{max}	hr	6 (2-6)[a]
$AUC_{0\text{-}24hr}$	hr*ng/mL	410.3 (213.5)
Half-life[b]	hr	11.2 (2.98)

C_{max} = extrapolated maximum plasma concentration
[a]T_{max} = time to maximum plasma concentration (reported as median and range)
$AUC_{0\text{-}24hr}$ = extrapolated area under the plasma time vs. concentration curve
[b]The half-life value is reflective of both topical and oral exposure. In another study where cats wore Elizabethan collar to restrict access to their ears and consequent oral exposure, a longer half-life (Mean= 20.7 hr) was observed

EFFECTIVENESS:
The effectiveness of Mirataz™ (mirtazapine transdermal ointment) was demonstrated in a randomized, double-masked, vehicle-controlled, multi-site field study involving client-owned cats of various breeds.

Enrolled cats were ≥ 1 year of age and had existing documented medical history of ≥ 5% weight loss deemed clinically significant. The most common pre-existing conditions included renal insufficiency, vomiting, and hyperthyroidism. Some cats had more than one pre-existing condition. Cats were randomized to treatment groups in a 1:1 ratio of Mirataz™ to vehicle control. A total of 230 cats were enrolled and received either Mirataz™ (115 cats) or a vehicle control (115 cats) containing the same inert ingredients without mirtazapine. The cats were 2.8-24.6 years of age and weighed 2.1-9.2 kg. The dosage was a 1.5-inch ribbon (approximately 2 mg/cat) mirtazapine or vehicle ointment administered topically to the inner pinna of the cat's ear.

A total of 177 cats were determined to be eligible for the effectiveness analysis; 83 cats were in the Mirataz™ group and 94 cats were in the vehicle control group. The primary effectiveness endpoint was the mean percent change in body weight from Day 1 to the Week 2 Visit.

At Week 2, the mean percent increase in body weight from Day 1 was 3.94% in the mirtazapine group and 0.41% in the vehicle control group. The difference between the two groups was significant ($p<0.0001$) based on a two-sample t-test assuming equal variances. A 95% confidence interval on the mean percent change in body weight for the Mirataz™ group is (2.77, 5.11), demonstrating that the mean percent change is statistically different from and greater than 0.

ANIMAL SAFETY:
The margin of safety of mirtazapine was evaluated in one laboratory study, a comprehensive review of six pilot studies (five laboratory and one clinical) utilizing the final market formulation, and one laboratory study that was not final market formulation.

Laboratory Safety Study:
In a 6-week laboratory safety study, 48 healthy cats aged 7-10 months were dosed topically with mirtazapine once daily at 0 mg/kg (vehicle control), 1.1 mg/kg (1.4 to 2.7X), 3.2 mg/kg (4.3-7.5X), and 5.3 mg/kg (7.1-12.2X) body weight. Four cats/sex/group in the 1.1 and 3.2 mg/kg groups were dosed topically to the inner pinna of the ear, alternating between right and left ears. Eight cats/sex/group in the 0 and 5.3 mg/kg groups were dosed topically to the inner pinna of the ear, splitting the dose between both ears. Four cats/sex/group in the 0 and 5.3 mg/kg groups were maintained and monitored during a 4-week recovery period.

6 Week Dosing Period
Application of mirtazapine and vehicle control was associated with ear flicking, head shaking, pulling away/flinching and infrequently with struggling/fractious behavior, and hypersalivation. Inner and outer pinna erythema, flaking, alopecia, and thickening were observed in all cats in all groups. Erythema, crusting, alopecia, and scabbing of the skin, mostly around the head and neck, was frequently observed in all groups and occasionally affected the tail, tarsi or carpi, likely due to spread of the ointment to these areas by self-grooming.

Mirtazapine administration resulted in increased vocalization, hyperactivity, attention-seeking behaviors, and tremors in all mirtazapine dose groups. Frank blood in the stool was infrequently observed in the vehicle control, 3.2, and 5.3 mg/kg groups. Polyuria was observed in all groups. Polydipsia was observed in one cat in the 5.3 mg/kg group. Three cats (one from each mirtazapine dose group) were isosthenuric. Eight cats developed cystitis with or without urethral obstruction throughout the study in all groups. One cat each from the vehicle control and 3.2 mg/kg group were euthanized early on Day 35 due to urethral obstruction.

Two cats from the 1.1 mg/kg group had either ventricular premature contractions (VPC) or tall R waves, and one cat from the 5.3 mg/kg group had both VPC and a right axis deviation.

Eosinophilia was noted sporadically in the vehicle control, 1.1, and 5.3 mg/kg groups. Mild elevations in ALT values were noted sporadically in vehicle control, 3.2, and 5.3 mg/kg groups. On Day 15, one cat in the 3.2 mg/kg group demonstrated a marked ALT elevation of 3397 U/L, with concurrent elevations in AST and GGT. By Day 42, the ALT declined to 109 U/L and the AST and GGT returned to within normal limits.

Gross pathology findings, confirmed with histopathology, were hyperplastic dermatitis (alopecia, hyperkeratosis, thickening, and ceruminous gland secretion) of the pinnae in all cats and findings consistent with cystitis (mucosal urinary bladder hemorrhage, mottled-dark red appearance, and irregular contour) in four male cats (two vehicle control, one 3.2 mg/kg and one 5.3 mg/kg). Additional histopathologic findings included pyelonephritis (two vehicle control and one 5.3 mg/kg), nephrocalcinosis (three vehicle control, one 1.1 mg/kg, three 3.2 mg/kg, and one 5.3 mg/kg), necrosis of the kidneys (one vehicle control and one 3.2 mg/kg), unilateral hypoplasia of the thyroid gland (two 5.3 mg/kg), and unilateral hypertrophy of the thyroid gland (one 5.3 mg/kg).

4 Week Recovery Period
Following a 4-week recovery period, ALT elevations resolved. Polyuria was reduced and only occurred in two cats in the 5.3 mg/kg group. Pinnal lesions (erythema and flaking) completely resolved in the vehicle control and improved in the 5.3 mg/kg groups. Ear thickening improved in both groups.

Pilot Safety Studies:
In six pilot studies (five laboratory and one clinical study) utilizing the final market formulation of Mirataz™, and one laboratory study that utilized non-final market formulation, a total of 76 cats were administered mirtazapine. Five studies administered mirtazapine ointment topically (0.5-5.3 mg/kg), one study administered mirtazapine topically and orally (0.5 mg/kg), and one study administered mirtazapine orally (10.6 mg/cat).

The most common observations were ear pinnae reactions (erythema with or without blood and flaking), mild behavioral observations (vocalization and tremors), vomiting, and diarrhea.

One study reported six cats with blood in the stool. Two studies reported one cat each showing aggression. One study reported polyuria in one cat; another study reported stranguria and possible urinary tract infection in one cat. Two studies reported cardiac abnormalities, including sinus tachycardia not present at baseline, development of a grade 3/6 heart murmur, tall QRS complexes, and left or right axis deviation. One study reported one cat with ataxia. In the studies that administered mirtazapine orally, salivation and lip licking were frequently observed.

In the terminal study administering 5.3 mg/kg mirtazapine topically, histopathology showed chronic hyperplastic dermatitis at the application site.

STORAGE:
Store below 25°C (77°F). Multi-use tube. Discard within 30 days of first use.

HOW SUPPLIED:
Mirataz™ is supplied in a 5 gram aluminum tube.

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1. Laimer, M., Kramer-Reinstadler, K., Rauchenzauner, M., Lechner-Schoner, T., Strauss, R., Engl, J., & Ebenbichler, C. F. (2006). Effect of mirtazapine treatment on body composition and metabolism. The Journal of clinical psychiatry, 67(3), 421-424.
2. Kraus, T., Haack, M., Schuld, A., Hinze-Selch, D., Koethe, D., & Pollmächer, T. (2002). Body weight, the tumor necrosis factor system, and leptin production during treatment with mirtazapine or venlafaxine. Pharmacopsychiatry, 35(06), 220-225.
3. Fernstrom, M. H. (1995). Drugs that cause weight gain. Obesity research, 3(S4), 435S-439S.

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