Date of Approval: January 11, 2021

CORRECTED FREEDOM OF INFORMATION SUMMARY

APPLICATION FOR CONDITIONAL APPROVAL

Application Number 141-526

LAVERDIA™-CA1

verdinexor tablets

Coated Tablet

Dogs

LAVERDIA™-CA1 is indicated for the treatment of lymphoma in dogs.

Sponsored by:

Anivive Lifesciences, Inc.

Executive Summary

LAVERDIA™-CA1 (verdinexor tablets) is conditionally approved for the treatment of lymphoma in dogs. Verdinexor is a selective inhibitor of nuclear export that blocks chromosome region maintenance 1. By inhibiting the export of tumor suppressor proteins and growth regulatory proteins out of a cell's nucleus, verdinexor allows these proteins to continue carrying out their normal functions of controlling cell growth and proliferation. The drug is selectively cytotoxic for cells with genomic damage (i.e., for tumor cells).

Based on a minor use assessment, the rate of occurrence of lymphoma in dogs in the United States (U.S.) was estimated to be below the published "small number" of 70,000 dogs (21 CFR § 516.3) on an annual basis. Therefore, the use of LAVERDIA™-CA1 for the treatment of lymphoma in dogs in the U.S. constitutes a minor use in a major species. Drugs intended for minor uses are eligible for conditional approval.

A conditionally approved animal drug has been shown to be safe and has a reasonable expectation of effectiveness. During the conditional approval period, the sponsor can legally market the drug for the labeled use while making active progress toward demonstration of substantial evidence of effectiveness. The conditional approval is valid for one year. The sponsor can ask FDA to renew the conditional approval annually for up to four more years, for a total of five years of conditional approval. To receive a renewal from FDA, the sponsor must show active progress toward proving substantial evidence of effectiveness for full approval.

Proprietary Name	Established Name	Application Type and Number	Sponsor
LAVERDIA™-CA1	Verdinexor tablets	Conditional Approval Application Number 141-526	Anivive Lifesciences, Inc.

Safety and Reasonable Expectation of Effectiveness

The sponsor conducted a field effectiveness study in 58 client-owned dogs with B- or T-cell type lymphoma. Dogs were either newly diagnosed with lymphoma (naïve) or in their first relapse after completing a single or multi-agent chemotherapy regimen. The study included dogs of varying breeds and weights and both genders (all females were spayed and most males were neutered). A majority of the dogs had lymphoma stage III.

The reasonable expectation of effectiveness of LAVERDIA™-CA1 was evaluated using 4 parameters:

- Time to progression (TTP): the period of time from the first date of treatment to the date that the dog developed clinical or radiographic signs of progressive disease or died from any cause, including euthanasia. Fifty dogs were included in this evaluation, and the median TTP was 29.5 days (range 7 - 244 days). Seventeen dogs had a TTP of at least 56 days, and 3 dogs had a TPP of 182 days or longer.

- Objective response rate (ORR): the number of dogs with a complete response (all lymph nodes returned to a normal, non-pathogenic size) or partial response (≥ 30% decrease in the sum of the longest dimensions of the target lesions compared to pre-treatment), as a percentage of all dogs treated. The ORR for all dogs was 34.5% (20/58 dogs; 1 dog was a complete response and 19 were partial responses).
- Duration of response (DOR): the period of time between the first of 2 evaluations demonstrating an objective response (either a complete or partial response) until the dog developed progressive disease or died. The median DOR was 18 days (range 7 - 187 days).
- Disease control rate (DCR): the number of dogs with a complete response, a partial response, or stable disease (the lymph nodes didn't shrink or increase in size compared to pre-treatment) at 8 weeks, as a percentage of all dogs treated. The DCR at 8 weeks was 29% (17/58 dogs).

All dogs experienced at least one adverse reaction. The most common adverse reactions were anorexia, vomiting, diarrhea, weight loss, lethargy, polydipsia, polyuria, elevated liver enzymes, and thrombocytopenia.

The sponsor conducted a laboratory safety study in 32 young, healthy, intact female and male Beagles. LAVERDIA™-CA1 was given orally at up to 1.17X (1.75 mg/kg) the maximum intended dose 3 times weekly for 13 weeks. The drug is labeled for an initial dose of 1.25 mg/kg administered twice weekly with at least 72 hours between doses. Adverse reactions included vomiting, abnormal feces, inappetence, thin body condition, decreased body weight, excessive shedding, sparse hair, loss of skin elasticity, lacrimation, slight depression, and slight decrease of forelimb strength. Clinical pathology findings included decreases in lymphocytes, eosinophils, monocytes, and chloride; and increases in fibrinogen, albumin, and blood urea nitrogen. Anatomic pathology findings included decreased weight of the testes, thymus, and thyroid/parathyroid gland with histologic lesions in the testes, epididymides, and thymus. LAVERDIA™-CA1 is an anti-neoplastic drug treating a terminal disease; adverse reactions are expected based on how the drug works and the safety profile is acceptable.

The bioavailability of verdinexor in fed dogs is 3- to 5-fold greater than in fasted dogs. Because the drug can cause inappetence and nausea, dogs may have poor food intake, leading to lower drug bioavailability. Dogs in both the field effectiveness and laboratory safety studies were fed before dosing, and the dosing instructions on the drug's labeling states to feed immediately before giving LAVERDIA™-CA1.

User Safety
LAVERDIA™-CA1 is an anti-neoplastic drug with potential safety concerns for people who handle, administer, or are exposed to the drug. The plasma half-life of verdinexor in dogs is approximately 4 to 6 hours, and within 60 hours, the drug typically undergoes 10 half-lives of elimination and less than 0.09% of the initial dose is present. Therefore, the potential risk to people from coming into contact with the bodily fluids of a treated dog (such as feces, urine, vomit, and saliva) is minimal beyond 3 days (72 hours) after dosing. To ensure user safety, a 3-day precautionary period is recommended. The package insert includes detailed user safety information and special instructions for handling and administering the drug. LAVERDIA™-CA1

also comes with a Client Information Sheet for prescribing veterinarians to give to their clients. This sheet is written specifically for dog owners and explains how to safely handle LAVERDIA™-CA1, how to safely clean up after a treated dog, and other important safety information.

LAVERDIA™-CA1 may cause birth defects and can affect female fertility based on animal studies. Pregnant women, women who may become pregnant, and nursing women should not handle or administer the drug or touch the feces, urine, vomit, or saliva of treated dogs. Children also should not touch LAVERDIA™-CA1 or the feces, urine, vomit, or saliva of treated dogs.

Conclusions
Based on the data submitted by the sponsor for the conditional approval of LAVERDIA™-CA1, FDA determined that the drug is safe and has a reasonable expectation of effectiveness when used according to the label.

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I. GENERAL INFORMATION

A. File Number

Application Number 141-526

B. Sponsor

Anivive Lifesciences, Inc.
3250 Airflite Way
suite 400
Long Beach, CA 90807

Drug Labeler Code: 086121

C. Proprietary Name

LAVERDIA™-CA1

D. Drug Product Established Name

Verdinexor tablets

E. Pharmacological Category

Antineoplastic

F. Dosage Form

Coated tablet

G. Amount of Active Ingredient

Three tablet sizes containing 2.5 mg, 10 mg, or 50 mg of verdinexor per tablet.

H. How Supplied

Each presentation is supplied in a 50-count HDPE bottle with a heat sealed, child-resistant cap and a desiccant included in each bottle.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Dosing Instructions:

1. **Feed the dog immediately before giving LAVERDIA™-CA1.**
2. Wear protective disposable chemotherapy resistant gloves when handling LAVERDIA™-CA1 (see **USER SAFETY WARNINGS**).

3. Administer LAVERDIA™-CA1 at an initial dose of 1.25 mg/kg administered orally twice per week (e.g., Monday and Thursday or Tuesday and Friday) with at least 72 hours between doses (see **Table 1**).
4. If tolerated after 2 weeks, increase the dose of LAVERDIA™-CA1 to 1.5 mg/kg twice per week with at least 72 hours between doses (see **Table 2**).
5. Dose reductions of 0.25 mg/kg to a minimum dose of 1 mg/kg twice per week with at least 72 hours between doses (see **Table 3**) or dose interruptions may be considered as a result of adverse reactions (see **ANIMAL SAFETY WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS**).
6. Do not split or crush tablets.

Dosing Restrictions:

Dogs weighing less than 9 kg may not be accurately dosed or undergo dose adjustments.

LAVERDIA™-CA1 cannot be accurately increased in dose from 1.25 mg/kg to 1.5 mg/kg in dogs weighing 9 to 9.6 kg because the dose administered remains the same.

Dosing Tables:

Table 1. LAVERDIA™-CA1 dose table for the 1.25 mg/kg dose*

		Number of Tablets		
Dog weight (kg)	**Total mg to administer**	**2.5 mg tablets**	**10 mg tablets**	**50 mg tablets**
9 — 11.5	12.5	1	1	-
11.6 — 13.5	15	2	1	-
13.6 — 15.5	17.5	3	1	-
15.6 — 17.5	20	-	2	-
17.6 — 19.5	22.5	1	2	-
19.6 — 21.5	25	2	2	-
21.6 — 23.5	27.5	3	2	-
23.6 — 25.5	30	-	3	-
25.6 — 27.5	32.5	1	3	-
27.6 — 29.5	35	2	3	-
29.6 — 31.5	37.5	3	3	-
31.6 — 33.5	40	-	4	-
33.6 — 35.5	42.5	1	4	-
35.6 — 37.5	45	2	4	-
37.6 — 39.5	47.5	3	4	-
39.6 — 41.5	50	-	-	1
41.6 — 43.5	52.5	1	-	1
43.6 — 45.5	55	2	-	1
45.6 — 47.5	57.5	3	-	1
47.6 — 49.5	60	-	1	1
49.6 — 51.5	62.5	1	1	1
51.6 — 53.5	65	2	1	1
53.6 — 55.5	67.5	3	1	1

		Number of Tablets		
Dog weight (kg)	**Total mg to administer**	**2.5 mg tablets**	**10 mg tablets**	**50 mg tablets**
55.6 — 57.5	70	-	2	1
57.6 — 59.5	72.5	1	2	1
59.6 — 61.5	75	2	2	1

* Use an appropriate combination of tablets to dose dogs over 61.5 kg.

Table 2. LAVERDIA™-CA1 dose table for the 1.5 mg/kg dose**

		Number of Tablets		
Dog weight (kg)	**Total mg to administer**	**2.5 mg tablets**	**10 mg tablets**	**50 mg tablets**
9.7 — 11.3	15	2	1	-
11.4 — 12.9	17.5	3	1	-
13 — 14.6	20	-	2	-
14.7 — 16.3	22.5	1	2	-
16.4 — 17.9	25	2	2	-
18 — 19.6	27.5	3	2	-
19.7 — 21.3	30	-	3	-
21.4 — 22.9	32.5	1	3	-
23 — 24.6	35	2	3	-
24.7 — 26.3	37.5	3	3	-
26.4 — 27.9	40	-	4	-
28 — 29.6	42.5	1	4	-
29.7 — 31.3	45	2	4	-
31.4 — 32.9	47.5	3	4	-
33 — 34.6	50	-	-	1
34.7 — 36.3	52.5	1	-	1
36.4 — 37.9	55	2	-	1
38 — 39.6	57.5	3	-	1
39.7 — 41.3	60	-	1	1
41.4 — 42.9	62.5	1	1	1
43 — 44.6	65	2	1	1
44.7 — 46.3	67.5	3	1	1
46.4 — 47.9	70	-	2	1
48 — 49.6	72.5	1	2	1
49.7 — 51.3	75	2	2	1
51.4 — 52.9	77.5	3	2	1
53 — 54.6	80	-	3	1
54.7 — 56.3	82.5	1	3	1
56.4 — 57.9	85	2	3	1
58 — 59.6	87.5	3	3	1
59.7 — 61.3	90	-	4	1

** Use an appropriate combination of tablets to dose dogs over 61.3 kg.

Table 3. LAVERDIA™-CA1 dose table for the 1 mg/kg dose***

		Number of Tablets		
Dog weight (kg)	**Total mg to administer**	**2.5 mg tablets**	**10 mg tablets**	**50 mg tablets**
9 — 11.9	10	-	1	-
12 — 14.4	12.5	1	1	-
14.5 — 16.9	15	2	1	-
17 — 19.4	17.5	3	1	-
19.5 — 21.9	20	-	2	-
22 — 24.4	22.5	1	2	-
24.5 — 26.9	25	2	2	-
27 — 29.4	27.5	3	2	-
29.5 — 31.9	30	-	3	-
32 — 34.4	32.5	1	3	-
34.5 — 36.9	35	2	3	-
37 — 39.4	37.5	3	3	-
39.5 — 41.9	40	-	4	-
42 — 44.4	42.5	1	4	-
44.5 — 46.9	45	2	4	-
47 — 49.4	47.5	3	4	-
49.5 — 51.9	50	-	-	1
52 — 54.4	52.5	1	-	1
54.5 — 56.9	55	2	-	1
57 — 59.4	57.5	3	-	1
59.5 — 61.9	60	-	1	1

*** Use an appropriate combination of tablets to dose dogs over 61.9 kg.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

LAVERDIA™-CA1 is indicated for the treatment of lymphoma in dogs.

II. EFFECTIVENESS

The conditional dose was selected based on 3 pilot studies. A reasonable expectation of effectiveness was demonstrated in 1 pilot study involving 58 dogs with lymphoma treated with verdinexor.

Conditional Dose: The conditional dose for the indication "for the treatment of lymphoma in dogs" is an initial dose of 1.25 mg/kg administered orally twice per week (e.g., Monday and Thursday or Tuesday and Friday) with at least 72 hours between doses. If tolerated after 2 weeks, increase the dose to 1.5 mg/kg twice per week with at least 72 hours between doses. Dose reductions of 0.25 mg/kg to a

minimum dose of 1 mg/kg twice per week with at least 72 hours between doses, or dose interruptions may be considered as a result of adverse reactions. The safety data and the data to demonstrate a reasonable expectation of effectiveness provide support for this conditional use.

A. Dosage Characterization

The dose of LAVERDIA™-CA1 (verdinexor tablets) administered orally, twice weekly at 1.25 mg/kg with at least 72 hours between doses followed by a dose increase to 1.5 mg/kg after 2 weeks, is based on 3 pilot studies. During development, verdinexor was also referred to as KPT-335.

1. Study Title: Spontaneous Tumors in Dogs. (Study No. KS-50)

A single site, pilot clinical study using verdinexor (not commercial formulation) was conducted to assess safety, dosing schedule, and indications of antitumor activity in dogs with various cancer types. Dogs with lymphoma (n = 6) or metastatic osteosarcoma (n = 1) were treated twice weekly with verdinexor at 1 - 3 mg/kg (average dose 1.5 mg/kg twice per week). Two dogs with lymphoma experienced partial response (PR) to therapy, and another 2 dogs with lymphoma experienced stable disease (SD). Adverse events associated with verdinexor included mild anorexia and diarrhea at doses of 1.75 mg/kg and below, and severe anorexia and liver value elevations at doses of 2 - 3 mg/kg and higher.

2. Study Title: Preclinical Evaluation of the Novel, Orally Bioavailable Selective Inhibitor of Nuclear Export (SINE) KPT-335 in Spontaneous Canine Cancer: A Phase I Study. (Study No. KARYO-1)

A three-center, open label, dose escalating clinical study in 17 dogs with lymphoma or measurable solid tumors was conducted to assess safety and pharmacokinetics of verdinexor (not commercial formulation). The majority of dogs enrolled in the dose escalation portion of the study had lymphoma (14 dogs), and most (12 dogs) had also received prior therapy including surgery, chemotherapy, and/or prednisone. Verdinexor treatment consisted of twice or three-times weekly dosing; dogs received between 1 and 2 mg/kg at each dosing. Dose reductions in incremental levels of 0.25 mg/kg were made for dogs that experienced adverse reactions.

Clinical toxicities included anorexia, weight loss, vomiting, diarrhea, and lethargy. The maximum tolerated dose was established as 1.75 mg/kg administered twice per week (with at least 72 hours between doses). Dose limiting toxicities above 1.75 mg/kg administered twice per week were anorexia, weight loss, and elevated liver enzymes.

Prednisone was administered to 10 dogs during the course of verdinexor treatment. In 8 cases, the dogs entered the study on prednisone and continued to receive prednisone. In 2 cases, the dogs were started on prednisone after the first 28 days of verdinexor treatment to address inappetence issues associated with administration of verdinexor.

The median TTP for all dogs was 35 days (range: 14 - 246 days). Two dogs had a PR for 71 and 246 days, and 8 dogs had SD for a median of 58.5 days (range 28 - 84 days). Of the 3 dogs that received verdinexor at a starting dose of 1.25 mg/kg twice weekly, 1 dog had a PR and 2 dogs had SD and all 3 dogs remained on the study for at least 10 weeks.

A dose expansion cohort of 6 dogs with lymphoma received verdinexor at a dose of 1.5 mg/kg on a 3 times weekly regimen (Monday/Wednesday/Friday). Prednisone was administered to all 6 dogs during the course of verdinexor treatment. In 4 cases, the dogs entered the study on prednisone. In 2 cases, the dogs were started on prednisone after the first 28 days of verdinexor treatment to address inappetence issues associated with administration of verdinexor. Two dogs had a PR for 35 and 354 days, and 2 dogs experienced SD for longer than 28 days (75 and 91 days). The other 2 dogs had progressive disease at day 13.

The most common adverse reactions included anorexia, weight loss, vomiting, and diarrhea. Additional adverse reactions included elevated liver enzymes.

3. Study Title: An Exploratory Study of the Oral Selective Inhibitor of Nuclear Export (SINE) KPT-335 in Dogs with Lymphoma. (Study No. KARYO-2)

The study was an open-label, multi-center, single arm, exploratory clinical field study. Fifty-eight dogs with treatment naïve lymphoma (35 dogs) or first relapse lymphoma (23 dogs) were enrolled. Dogs received verdinexor (not commercial formulation) at either (1) 1.5 mg/kg 3 times weekly, (2) 1.25 mg/kg 3 times weekly, or (3) 1.25 mg/kg 2 times weekly then increased to 1.5 mg/kg 2 times weekly if well-tolerated. Dose modifications in 0.25 mg/kg increments, reductions in dosing frequency, and drug interruptions due to drug intolerance were utilized.

All dogs experienced at least one adverse reaction. Twenty-one dogs (36%) experienced a Veterinary Co-operative Oncology Group (VCOG) Grade 3 (severe), 4 (life-threatening), or 5 (death) adverse reaction.[1] The most common adverse reactions included anorexia, vomiting, diarrhea, weight loss, lethargy, cough/dyspnea, fever, edema/swelling, polyuria, polydipsia, hematuria, proteinuria, low urine specific gravity, urinary tract infection, elevated liver enzymes, elevated blood urea nitrogen, thrombocytopenia, lymphopenia, neutrophilia, leukopenia, and anemia.

For all dogs enrolled, the median TTP was 29 days (range: 7 - 244 days). A subset (17 dogs) of the overall enrolled population had a TTP of at least 56 days.

Conclusion: These 3 studies support a conditional initial dose of 1.25 mg/kg administered orally twice per week with at least 72 hours between doses. If tolerated after 2 weeks, the dose is increased to 1.5 mg/kg twice per week with at least 72 hours between doses.

B. Reasonable Expectation of Effectiveness

1. Field Study

Title: An Exploratory Study of the Oral Selective Inhibitor of Nuclear Export (SINE) KPT-335 in Dogs with Lymphoma. (Study No. KARYO-2)

Study Dates: November 2012 to December 2013

Study Locations:

St. Paul, MN	Washington, DC
Tucson, AZ	Culver, CA
New York, NY	Madison, WI
Columbus, OH	Richmond, VA
Leesburg, VA	College Station, TX

Study Design: An exploratory open-label, single arm, multicenter clinical field study that enrolled 58 dogs with lymphoma either newly diagnosed, or in first relapse following completion of one chemotherapy regimen.

Objective: To determine the safety and antitumor activity of a series of dose regimens of verdinexor in dogs with lymphoma.

Study Animals: A total of 58 client-owned dogs with naïve (35 dogs) or first relapse (23 dogs) lymphoma were enrolled and received at least one treatment in this study. Dogs with first relapse may have received prior treatment with either a single or multi-agent regimen.

For the 35 cases enrolled with naïve lymphoma, 28 dogs had B-cell lymphoma and 7 dogs had T-cell lymphoma. The average weight of the dogs was 31 kg (range: 6 - 85 kg) and the average age was 7 years (range: 3 - 12 year). Twenty males (2 intact) and 15 spayed females were enrolled. Dogs with lymphoma stage III (n = 19) or IV (n = 12) were most common; there was 1 dog with lymphoma stage II and 3 dogs with stage V.

For the 23 cases enrolled with first relapse lymphoma, 14 dogs had B-cell lymphoma and 7 dogs had T-cell lymphoma. Two dogs had phenotypes that were not determined. The average weight was 27 kg (range: 5 - 52 kg) and average age was 8 years (range: 3 - 13 years). Sixteen males (2 were intact) and 7 spayed females were enrolled. All dogs were lymphoma stages III (n = 17) or IV (n = 6).

Experimental Design: Dogs were not randomized, and masking was not used in this study.

The following verdinexor (not commercial formulation) dosing regimens were used:

(1) 1.5 mg/kg 3 times weekly (n = 13);
(2) 1.25 mg/kg 3 times weekly (n = 35); or

(3) 1.25 mg/kg 2 times weekly then increased to 1.5 mg/kg 2 times weekly if well-tolerated (n = 10).

Inclusion Criteria:

- Dog was > 1 year of age.
- Dog had naïve or first relapse lymphoma with cytological or histological diagnosis of either T or B cell type lymphoma.
- Evidence of disease progression on study entry was based on direct tumor measurement.
- At least one peripherally located lymph node measured ≥ 2 cm longest diameter.
- Dog demonstrated adequate organ function as indicated by complete blood count (CBC), chemistry, and urinalysis, including absolute neutrophil count ≥ 1,000/mL and platelet count ≥ 100,000/mL.
- Dog had adequate liver function with total bilirubin ≤ 1.5x the upper limit of normal (ULN), and alanine aminotransferase (ALT) ≤ 2.5x ULN.
- Dog had adequate renal function with serum creatinine ≤ 1.5x ULN.
- Dog received no or only one prior systemic chemotherapy treatment regimen (single agent or multi-agent).
- Dog completed any prior chemotherapy at least 14 days prior to study entry.
- Dog had recovered from any acute toxicities of prior chemotherapy treatment.
- Dog had a Performance Score of 0 or 1 [0 = normal activity; 1 = restricted activity: decreased activity from pre-disease status; 2 = compromised, ambulatory primarily or only for vital activities, consistently defecates and urinates in acceptable areas; 3 = spontaneous tiredness or dyspnea without exertion, often lies on floor; 4 = unable to care for itself, recumbent, 5 = moribund].
- Dog had a life expectancy of ≥ 1 month.
- Owner was able to administer the drug (test article) according to the designated schedule.

Exclusion Criteria:

- Dog weighed < 5 kg.
- Dog had received radiation therapy.
- Dog had evidence of lymphoma involving the central nervous system.
- Dog had significant bulky disease such that clinical deterioration is likely to occur even in the setting of stable disease.
- Dog had any serious medical condition (renal, cardiovascular, hepatic, concurrent malignancy) that may preclude successful treatment outcome.
- Dog showed evidence of diabetes mellitus or other on-going serious endocrine disorder.
- Dog had serum calcium ≥ 13.0 mg/dL.
- Dog was participating in another study or received investigational therapy in the past 7 days.
- Dog was currently using complementary or alternative medicines that in the opinion of the investigator would confound the interpretation of toxicities and/or antitumor activity of the investigational product.
- Dog was pregnant or likely to become pregnant.

- Dog was unavailable for the entire study duration or was felt to be unsuitable by the investigator for any reason.

Drug Administration: Dogs treated 3 times a week were typically treated on Monday, Wednesday, and Friday. Dogs treated 2 times a week had at least 72 hours between doses. It was recommended that dogs be fed immediately prior to receiving verdinexor. Dogs experiencing adverse events that were perceived to compromise quality-of-life were allowed a drug holiday. Dose increases and decreases, including changes in dosing amount (mg/kg) and dosing frequency (2 versus 3 times per week), were allowed based on drug tolerability and response to treatment. Drug holidays were allowed at the discretion of the investigator.

Measurements and Observations: Determination of antitumor effectiveness was based on VCOG response criteria for peripheral lymphoma in dogs (v1.0).[2]

- Complete response (CR) is defined as the return of all lymph nodes to the normal, non-pathologic size.
- Partial response (PR) is defined as a ≥ 30% decrease in the sum of the longest dimensions of target lesions taking as reference the baseline sum longest dimensions.
- Progressive disease (PD) is defined as a ≥ 20% increase in the sum of the longest dimensions of target lesions taking as reference the smallest sum longest dimensions recorded since the treatment started, or the appearance of 1 or more new lesions.
- Stable disease (SD) is defined as neither sufficient shrinkage to qualify as PR nor sufficient increase to qualify for PD taking as reference the smallest sum longest dimensions recorded since the treatment started. To qualify for SD, 2 or more determinations of SD at least 2 weeks apart must be present.

Exploratory evaluations for effectiveness included TTP, DOR, ORR, and DCR.

- TTP was defined as the period of time from first date of treatment to the date that the dog developed PD because of clinical or radiographic progressive disease or death from any cause, including euthanasia.
- DOR was defined as the period of time between the first of 2 evaluations demonstrating an objective response (defined as patients experiencing CR and PR) until the date of progression or death. DOR is only defined for patients with an objective response.
- ORR was defined as the number of patients with confirmed CR or PR as a percentage of all patients treated.
- DCR was defined as the number of patients with CR, PR, or SD (at 8 weeks), as a percentage of all patients treated.

Safety was monitored through physical examinations, collection of adverse events using Veterinary Cooperative Oncology Group – common terminology criteria for adverse events (VCOG-CTCAE v1.1.[1]; Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = death), and clinical pathology (complete blood count, blood chemistry, and urinalysis).

Statistical Methods: Descriptive summary statistics include median TTP, ORR (best response of PR or better), DCR (best response of SD or better at 8 weeks), and DOR.

Results:

Reasonable Expectation of Effectiveness:

Effectiveness was evaluated in 58 dogs. TTP was evaluated in 50 dogs (8 dogs were removed from the study prior to progression). For the 50 dogs, median TTP was 29.5 days (range 7 - 244 days). The median TTP for the naïve (30/50 dogs) and first relapse (20/50 dogs) cases were 36.5 days (range 7 - 244 days) and 22 days (range 7 - 194 days), respectively.

The ORR for all dogs was 34.5% (20/58 dogs; 1 CR and 19 PRs), distributed proportionately between the naïve (12/35 dogs, 34.3%) and first relapse (8/23 dogs, 34.8%) subgroups.

Among dogs with objective response, the median DOR was 18 days (range 7 - 187 days). A subset (17 dogs) of the overall enrolled population had a TTP of at least 56 days; i.e., the DCR at 8 weeks was 29% (17/58 dogs). Of these 17 dogs, 11 dogs were naïve to treatment and 6 dogs had relapsed lymphoma; 5 dogs had T-cell lymphoma and 12 dogs had B-cell lymphoma. Three dogs, 2 dogs with T-cell lymphoma (1 naïve and 1 relapsed) and 1 dog with B-cell lymphoma naïve to treatment had a TTP of 182 days or longer.

Table II.1 below shows the TTP, dosing regimen, naïve versus relapse lymphoma at enrollment, B versus T-cell lymphoma, timing of prednisone initiation, and prednisone dose for the 17 dogs with a TTP of 56 days or longer.

Table II.1. Dogs with TTP of 56 days or longer

Dog	TTP	Dosing Regimen (duration)[a]	Naïve or Relapse Lymphoma	B or T cell Lymphoma	Prednisone use relative to enrollment	Prednisone dose (mg/kg/day)
06-03	244	1.25 mg/kg, 3x/wk[b] (39 wks)	naïve	T	after[c]	0.5
02-05	194	1.25 mg/kg, 3x/wk (27 wks) 1.25 mg/kg, 2x/wk (9 wks)	relapse	T	prior[d]	0.5
08-05	182	1.25 mg/kg, 3x/wk (28 wks) 1.50 mg/kg, 3x/wk (2 wks)	naïve	B	after	0.3
01-03	114	1.50 mg/kg, 3x/wk (16 wks) 1.75 mg/kg, 3x/wk (1 wk)	naïve	B	none	-
01-13	112	1.25 mg/kg, 3x/wk (6 wks) 1.50 mg/kg, 2x/wk (10 wks)	relapse	B	after	0.6
08-07	112	1.25 mg/kg, 2x/wk (2 wks) 1.50 mg/kg, 2x/wk (14 wks) 1.75 mg/kg, 2x/wk (8 wks) 1.50 mg/kg, 2x/wk (2 wks) 1.75 mg/kg, 2x/wk (5 wks)	relapse	B	prior	0.3
02-01	105	1.25 mg/kg, 3x/wk (15 wks)	naïve	B	prior	0.7
08-06	84	1.25 mg/kg, 2x/wk (6 wks) 1.50 mg/kg, 2x/wk (6 wks)	relapse	B	after	0.3
01-05	73	1.50 mg/kg, 3x/wk (5 wks) 1.25 mg/kg, 3x/wk (2 wks)	naïve	B	after	0.5
01-07	72	1.25 mg/kg, 3x/wk (10 wks)	relapse	T	prior	1.1
01-12	71	1.25 mg/kg, 3x/wk (2 wks) 1.0 mg/kg, 2x/wk (4 wks) 1.25 mg/kg, 3x/wk (2 wks) 1.0 mg/kg, 2x/wk (4 wks) 1.25 mg/kg, 2x/wk (4 wks) 1.50 mg/kg, 2x/wk (2 wks)	naïve	B	after	1.2
03-04	71	1.25 mg/kg, 3x/wk (5 wks) 1.0 mg/kg, 2x/wk (3 wks)	naïve	B	after	0.5
08-01	71	1.25 mg/kg, 3x/wk (9 wks)	naïve	B	after	0.6 (one dose)
01-01	70	1.50 mg/kg, 3x/wk (4 wks) 1.25 mg/kg, 3x/wk (11 wks)	naïve	B	after	0.3
01-06	70	1.50 mg/kg, 3x/wk (3 wks) 1.25 mg/kg, 3x/wk (12 wks) 1.25 mg/kg, 2x/wk (12 wks) 1.50 mg/kg, 2x/wk (1.5 wks)	naïve	B	after	0.6
06-02	62	1.25 mg/kg, 3x/wk (2 wks) 1.0 mg/kg, 2x/wk (14 wks)	naïve	T	after	0.8
01-14	56	1.25 mg/kg, 2x/wk (2 wks) 1.50 mg/kg, 2x/wk (4 wks) 1.38 mg/kg, 2x/wk (2 wks)	relapse	T	after	0.4

[a] Some dogs underwent drug holidays during the study;
[b] wk = week;
[c] Prednisone initiated at Day 0 or after Day 0;
[d] Prednisone initiated prior to and continuing at enrollment

Concomitant Treatments:

The following concomitant medications, listed in decreasing frequency, were administered to > 10% of dogs during the study: prednisone, omeprazole, maropitant, famotidine, metronidazole, ondansetron, metoclopramide, tramadol, mirtazapine, amoxicillin/clavulanic acid, enrofloxacin, s-adenosylmethionine, and loperamide.

Pharmacokinetics:

Plasma verdinexor concentrations were evaluated over a 24-hour period in 8 dogs. Assessments were made on day 14 in all but one dog, the latter being evaluated on day 21. The dogs received verdinexor at a dose of 1.5 mg/kg (n = 4) or 1.25 mg/kg (n = 4) under fed conditions using a Monday/Wednesday/Friday dosing schedule. For all dogs, the average T_{max} occurred at 5.3 hours post-dose, with a $T_{1/2}$ of 5 hours, regardless of dose. The mean C_{max} and AUC for dogs receiving 1.5 mg/kg were slightly higher than that of dogs receiving 1.25 mg/kg. Although the T_{max} for dogs with lymphoma occurred several hours later than did that observed in healthy research dogs (5.3 versus 1.1 hours respectively), the AUC values tended to be similar in both healthy and dogs with lymphoma.

Because bioavailability in fed animals is 3 - 5-fold greater than that observed in fasted dogs, verdinexor induced inappetence and nausea can lead to poor food intake and therefore lower verdinexor bioavailability.

Safety:

Hematology
The most commonly reported hematologic abnormality during the study was thrombocytopenia. A total of 18 dogs were reported with thrombocytopenia during the study. Seven dogs were reported with Grade 2 thrombocytopenia; the remaining dogs were reported with Grade 1 thrombocytopenia. Reports of bruising (2 dogs; both had Grade 1 thrombocytopenia), epistaxis (1 dog; Grade 2 thrombocytopenia), and hematuria (6 dogs; 2 had Grade 1 and 4 had Grade 2 thrombocytopenia) were reported within 2 weeks of the reported thrombocytopenia. Table II.2 shows select reported hematologic toxicities during the study.

Table II.2. Select hematologic toxicities in verdinexor treated dogs

Hematology Variable	Number of dogs	Grades[a]			
		1	2	3	4
Thrombocytopenia	18	11	7	-	-
Lymphopenia	17	17	-	-	-
Neutrophilia	15	12	1	2	-
Anemia	13	10	3	-	-
Leukopenia	12	11	-	-	1
Neutropenia	9	8	-	-	1
Monocytosis	9	9	-	-	-

Hematology Variable	Number of dogs	Grades[a]			
		1	2	3	4
Eosinopenia	9	9	-	-	-
Prolonged PTT[b]	8	8	-	-	-
Leukocytosis	5	5	-	-	-
Prolonged PT[c]	2	2	-	-	-

[a] Highest Grade reported for each dog. (Some dogs were reported with a toxicity on more than one occasion, but are only presented once in the table above for each affected variable)
[b] PTT = Partial thromboplastin time
[c] PT = Prothrombin time

Serum Chemistry
The most commonly reported serum chemistry abnormalities during the study were elevations of the liver enzymes. A total of 33 dogs were reported with adverse events (AEs) involving increased liver enzymes (increased alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], or bilirubin). Most of the dogs with elevated liver enzymes had elevations in multiple liver enzymes. Table II.3 below shows select reported serum chemistry toxicities during the study.

Table II.3. Select reported serum chemistry toxicities in verdinexor treated dogs

Serum Chemistry Variable	Number of dogs	Grades[a]			
		1	2	3	4
Increased ALP	28	15	6	6	1
Increased ALT	21	11	5	3	2
Increased blood urea nitrogen	15	14	1	-	-
Hypercalcemia	10	7	-	2	1
Hypochloremia	8	8	-	-	-
Hyperphosphatemia	7	7	-	-	-
Hypoglobulinemia	7	7	-	-	-
Increased AST	6	4	1	1	-
Hypoproteinemia	6	6	-	-	-
Hypoalbuminemia	5	5	-	-	-
Hypocholesterolemia	5	5	-	-	-
Increased bilirubin	4	2	1	-	1
Hypercholesterolemia	4	4	-	-	-
Hyperkalemia	3	3	-	-	-
Hypokalemia	3	3	-	-	-
Increased creatinine	2	2	-	-	-
Hypophosphatemia	2	2	-	-	-

[a] Highest Grade reported for each dog. (Some dogs were reported with a toxicity on more than one occasion, but are only presented once in the table above for each affected variable)

Urinalysis
Table II.4 below shows select reported urinalysis abnormalities during the study.

Table II.4. Select reported urinalysis abnormalities in verdinexor treated dogs

Urinalysis Variable	Number of dogs	Grades[a]			
		1	2	3	4
Hematuria	16	16	-	-	-
Urinary tract infection	12	11	1	-	-
Hyposthenuria/Isosthenuria/Low urine specific gravity	11	11	-	-	-
Proteinuria	9	7	1	1	-
Alkaline urine	7	6	-	1	-
Bilirubinuria	6	6	-	-	-

[a] Highest Grade reported for each dog. (Some dogs were reported with a toxicity on more than one occasion, but are only presented once in the table above for each affected variable)

Adverse Reactions: All dogs experienced at least one adverse reaction. Twenty-one dogs (36%) experienced a VCOG-CTCAE v1.1 Grade 3, 4, or 5 adverse reaction. Table II.5 below shows the non-clinical pathology adverse reactions during the study.

Table II.5. Non-clinical pathology adverse reactions in verdinexor treated dogs

Adverse Reaction	Number of Dogs	Grades[a]				
		1	2	3	4	5
Anorexia	43	26	14	3	-	-
Vomiting	34	28	6	-	-	-
Diarrhea	30	20	10	-	-	-
Weight loss	28	18	9	1	-	-
Lethargy	24	21	3	-	-	-
Polydipsia	19	17	2	-	-	-
Polyuria	18	16	2	-	-	-
Cough/Dyspnea/Harsh lungs sounds	12	10	2	-	-	-
Fever	9	6	3	-	-	-
Edema, subcutaneous swelling/periocular swelling	8	5	3	-	-	-
Weakness	7	5	1	-	1	-
Generalized pain	7	3	1	3	-	-
Increased panting	7	7	-	-	-	-
Pyoderma/ Seborrhea	6	5	1	-	-	-
Seizure/Tremor	4	4	-	-	-	-
Lameness	3	1	1	1	-	-
Hepatomegaly	3	2	1	-	-	-
Arrhythmia, Heart block, Heart murmur	3	3	-	-	-	-
Bruising	3	3	-	-	-	-
Muscle atrophy	3	3	-	-	-	-
Nasal discharge	3	3	-	-	-	-
Urinary incontinence	3	3	-	-	-	-
Ataxia	2	1	-	1	-	-
Abdominal discomfort	2	2	-	-	-	-

Adverse Reaction	Number of Dogs	Grades[a]				
		1	2	3	4	5
Alopecia	2	2	-	-	-	-
Cachexia	2	2	-	-	-	-
Tumors	2	2	-	-	-	-
Erythema	2	2	-	-	-	-
Paresis/intervertebral disk disease	1	-	-	-	-	1
Protein Losing Nephropathy	1	-	-	1	-	-
Epistaxis	1	-	1	-	-	-
Blocked nasal airflow	1	-	1	-	-	-
Lymph node abscess	1	-	1	-	-	-
Obtunded	1	-	1	-	-	-
Ascites	1	1	-	-	-	-
Corneal opacity	1	1	-	-	-	-
Disorientation	1	1	-	-	-	-
Gastrointestinal ulceration	1	1	-	-	-	-
Oral ulceration	1	1	-	-	-	-
Uveitis	1	1	-	-	-	-

[a] Highest Grade reported for each dog. (Some dogs were reported with a toxicity on more than one occasion, but are only presented once in the table above for each reported adverse reaction)

Protein losing nephropathy
One dog was reported with a protein losing nephropathy (PLN). Two additional dogs, though not reported, may have had a PLN. One dog was reported with hypoalbuminemia and proteinuria on day 21 which progressed until study end (day 194). Another dog was reported with proteinuria at day 7 which persisted (and worsened) until study end (day 105). At the start of the study the dog had hyperalbuminemia; by day 105 the dog had hypoalbuminemia.

Conclusions: The study results support a reasonable expectation of effectiveness for the use of LAVERDIA™-CA1 (verdinexor tablets) administered at 1.25 mg/kg twice a week and, if tolerated after 2 weeks, increased to 1.5 mg/kg for the treatment of lymphoma in dogs. The most frequent adverse reactions were anorexia, vomiting, diarrhea, weight loss, lethargy, polydipsia, polyuria, elevated liver enzymes, and thrombocytopenia.

III. TARGET ANIMAL SAFETY

The safety of LAVERDIA™-CA1 (verdinexor tablets) for the treatment of lymphoma in dogs was demonstrated in the laboratory study (ANIV-126b-901) described below. The study demonstrated that LAVERDIA™-CA1 has an adequate margin of safety for the treatment of lymphoma when administered at an initial dose of 1.25 mg/kg administered orally twice per week with at least 72 hours between doses, with an increase to 1.5 mg/kg after two weeks. Clinical observation/examination findings related to administration of LAVERDIA™-CA1 included vomiting, abnormal feces, inappetence, thin body condition, decreased body weight, excessive shedding, sparse hair, loss of skin elasticity, lacrimation, slight depression, and slight decrease of forelimb strength. Clinical pathology findings related to administration of

LAVERDIA™-CA1 included decreases in lymphocytes, eosinophils, monocytes, and chloride; and increases in fibrinogen, albumin, and blood urea nitrogen. Anatomic pathology findings included lower testes, thymus, and thyroid/parathyroid gland weights with histologic lesions in the testes, epididymides, and thymus.

A. Target Animal Safety Study

Title: A 13-Week (13-cycle) Oral Tablet Target Animal Safety Study of Verdinexor in Dogs. (Study No. ANIV-126b-901)

Study Dates: February 26, 2018 to May 30, 2019

Study Location: Mattawan, Michigan

Study Design:

Objective: This study was conducted to evaluate the safety of LAVERDIA™-CA1 (verdinexor tablets), when administered orally at up to 1.17X (1.75 mg/kg) the maximum intended clinical dose 3 times weekly for 13 weeks to healthy Beagle dogs.

Study Animals: Sixteen male and 16 female Beagle dogs were selected. The dogs were approximately 7 months old at the initiation of dose administration. Body weights ranged from 7.1 kg to 10.8 kg for the males and 4.9 kg to 7.2 kg for the females at the initiation of dosing.

Experimental Design: This was a masked, randomized, sham (untreated) controlled laboratory study. The thirty-two dogs were randomly assigned to 4 treatment groups of 8 dogs each (4 males and 4 females). Masking was maintained by separation of function. Persons performing masked observations or duties did not perform unmasked duties (dose administration). Masked observations and procedures included body weight and food consumption measurements, clinical observations, clinical pathological analyses, ophthalmological examinations, physical examinations including neurological assessment, necropsies, and gross pathology evaluation. This laboratory study was conducted in accordance with Good Laboratory Practice (GLP) regulations.

Drug Administration: Dogs in the LAVERDIA™-CA1 treatment groups were administered a combination of 2.5 and/or 10 mg LAVERDIA™-CA1 tablets 3 times weekly (every Monday, Wednesday, and Friday) for 13 weeks. The control group was sham dosed by simulating the dosing procedure in the same manner as the LAVERDIA™-CA1 treatment groups. Dogs were fed prior to dosing.

Table III.1. Treatment Groups for Target Animal Safety Study

Treatment Group	Treatment	Dosage Level (mg/kg)	Number and Sex of Animals
1	Sham	0	4M, 4F
2	LAVERDIA™-CA1	1.0	4M, 4F
3	LAVERDIA™-CA1	1.5	4M, 4F
4	LAVERDIA™-CA1	1.75	4M, 4F

Measurements and Observations: Clinical observations were performed once daily pre-study and twice daily throughout the study period, and at 2 - 3 hours following dose administration. In addition, all dogs were observed 15- and 60-minutes following dose administration. A veterinarian conducted physical examinations pre-study, and on study days 1 (pre-dose), 15, 29, 43, 57, 71, 85, and 92. Individual body weights were recorded pre-study and weekly throughout the study. Individual food weights were recorded once daily pre-study and through the end of the study. Heart rates were recorded on study days 1 (pre-dose) and 84. Respiratory rates were recorded pre-study, and on study days 1 (pre-dose), 15, 29, 43, 57, 71, 85, and 92. Indirect blood pressures were recorded on study days 1 (pre-dose), 29, 57, and 84. Neurobehavioral assessments to examine motor, sensory, and autonomic pathways were conducted once pre-study and on study day 89. Blood and urine samples for clinical pathology evaluations (hematology, coagulation, serum chemistry, and urinalysis) were collected twice pre-study, and on study days 4, 32, 60, and 91. Ophthalmoscopic examinations were conducted pre-study and study day 89. A complete set of tissues were collected for gross pathology and histopathology evaluations on study day 92. Selected organs were weighed.

Statistical Methods: The experimental unit used for this study was the individual animal. The analysis of variance (ANOVA) model included 'treatment', 'sex', and 'treatment by sex' as fixed effects. The analysis of covariance (ANCOVA) included 'treatment', 'sex', 'treatment by sex' as fixed effects and the pretreatment measurement as a covariate. The repeated analysis of covariance (RMANCOVA) model included treatment, sex, time, treatment by sex, sex by time, treatment by time, and treatment by sex by time terms as fixed effects, and animal identified as the subject in the repeated statement of the GLIMMIX procedure in SAS. Pretreatment values (prior to the first dose) was used as a covariate. The three-way interaction (treatment by sex by time) was performed at the 0.05 level of significance. All statistical comparisons of main effects (treatment, time, sex), and two-way interactions (treatment by time, treatment by sex, time by sex) were performed at the 0.10 level of significance.

Results:

Mortality

All animals survived to the scheduled necropsy.

Clinical Observations and Physical Examinations

There were 5 instances of vomiting post-dosing in a total of 4 dogs administered LAVERDIA™-CA1. Two dogs at 1 mg/kg and 1 dog at 1.5 mg/kg vomited 15 minutes post-dosing. Tablets or partial tablets were present in the vomit; therefore, these dogs were re-dosed. One dog at 1.75 mg/kg vomited 15 minutes post-dosing and 1-hour post-dosing on different days. No tablets were seen in the vomit; therefore, the dog was not re-dosed.

Dose-dependent LAVERDIA™-CA1-related findings included vomiting, inappetence, decreased body condition, decreased body weight, loss of skin elasticity, and lacrimation. Non-dose-dependent LAVERDIA™-CA1-related findings included abnormal feces (soft, watery, or mucoid feces), excessive shedding, and sparse hair.

There were no LAVERDIA™-CA1 related effects on heart rate, respiration, or body temperature.

Neurobehavioral Assessment

On study day 89, slight depression was observed in 2 dogs administered 1.75 mg/kg LAVERDIA™-CA1 and slight decrease of forelimb strength was observed in 2 dogs, 1 dog administered 1.5 mg/kg and 1 dog administered 1.75 mg/kg LAVERDIA™-CA1.

Body Weights

Compared to sham control dogs, dogs in the 1.0 mg/kg group starting on study day 28 and dogs in the 1.5 and 1.75 mg/kg groups starting on study day 21 had lower body weight values that continued to the end of the study.

Individually, 1 dog in the sham control, 7 dogs in the 1.0 mg/kg group, 8 dogs in the 1.5 mg/kg group, and 4 dogs in the 1.75 mg/kg group lost weight during the study (i.e. weighed less on study day 91 compared to study day -1).

Food Consumption

There were no statistically significant effects on the mean dry food consumption. However, in general, there was a decrease in dry food consumption values in dogs administered LAVERDIA™-CA1 that lost body weight.

Four dogs in the sham control, 5 dogs in the 1.0 mg/kg group, 4 dogs in the 1.5 mg/kg group, and 7 dogs in the 1.75 mg/kg group received supplemental food at the direction of the attending veterinarian due to test article-related effects of body weight loss, thin body condition, and abnormal feces.

Indirect Blood Pressures

There were no LAVERDIA™-CA1 related effects on blood pressure.

Ophthalmoscopic Examination

There were no LAVERDIA™-CA1 related findings on ophthalmoscopic examination.

Clinical Pathology

Hematology: Mean lymphocyte counts were lower in dogs in the 1.5 mg/kg group on study day 60 and in a non-dose-dependent manner in all LAVERDIA™-CA1 groups on study day 91.

Individually, there were 16 dogs with lymphocyte counts < 1.95 k/uL (reference range low 1.95 k/uL for males; 1.88 k/uL for female) at various timepoints throughout the study. Decreased lymphocytes counts were observed in 1 dog in the sham control, 4 dogs in the 1.0 mg/kg group, 8 dogs in the 1.5 mg/kg group, and 3 dogs in the 1.75 mg/kg group. The greatest incidence of low lymphocyte counts occurred on Day 91. The lowest lymphocyte count was in a dog in the 1.5 mg/kg group on study day 91 with a lymphocyte count of 1.22 k/uL.

Beginning on study day 32 throughout the dosing period, there were non-dose-dependent decreases in mean eosinophil counts compared to sham controls in all LAVERDIA™-CA1 groups.

Individually, there were 15 dogs with eosinophil counts < 0.08 k/uL (reference range low 0.08 k/uL for male; 0.06 k/uL for female) at various timepoints throughout the study. Decreased eosinophil counts were observed in 3 dogs in the sham control, 5 dogs in the 1.0 mg/kg group, 4 dogs in the 1.5 mg/kg group, and 3 dogs in the 1.75 mg/kg group. The incidence of low eosinophils was similar at days 32, 60, and 91 (with fewer incidences on Day 4). The lowest eosinophil count was in a dog in the 1.0 mg/kg group on study day 60 with an eosinophil count of 0.02 k/uL.

Mean monocyte counts were lower in a non-dose-dependent manner in all LAVERDIA™-CA1 groups compared to controls overall (i.e. pooled timepoints).

Individually, there were 17 dogs with monocyte counts < 0.27 k/uL (reference range low 0.27 k/uL for male; 0.26 k/uL for female) at various timepoints throughout the study. Decreased monocyte counts were observed in 2 dogs in the sham control, 5 dogs in the 1.0 mg/kg group, 6 dogs in the 1.5 mg/kg group, and 4 dogs in the 1.75 mg/kg group. The incidence of low monocytes was similar at all time points. The lowest monocyte count was in a dog in the 1.75 mg/kg group on study day 60 with a monocyte count of 0.12 k/uL.

Coagulation: Mean fibrinogen concentrations were higher in dogs in the 1.75 mg/kg group compared to sham controls overall (i.e. pooled timepoints).

Individually, there were 14 dogs with fibrinogen > 288 mg/dL (reference range high 343 mg/dL male; 288 mg/dL female) at various timepoints throughout the study. Elevated fibrinogen levels were observed in 1 dog in the sham control, 4 dogs in the 1.0 mg/kg group, 5 dogs in the 1.5 mg/kg group, and 4 dogs in the

1.75 mg/kg group. The highest fibrinogen level was observed in a dog in the 1.75 mg/kg group on study day 91 with a fibrinogen level of 428 mg/dL.

Clinical Chemistry: Beginning on study day 4 and persisting throughout the dosing period, non-dose-dependent mean serum albumin levels were higher than sham controls in all LAVERDIA™-CA1 treatment groups.

Individually, there were 15 dogs with albumin > 3.3 g/dL (reference range high 3.3 g/dL for male; 3.4 g/dL for female) at various timepoints throughout the study. Elevated albumin levels were observed in 0 dogs in the sham control, 5 dogs in the 1.0 mg/kg group, 4 dogs in the 1.5 mg/kg group, and 6 dogs in the 1.75 mg/kg group. The majority of elevated albumin levels were observed on study days 32 and 60. The highest albumin level was observed in a dog in the 1.0 mg/kg group on study day 32 with an albumin level of 3.7 g/dL.

Beginning on study day 32 and generally persisting throughout the dosing period, non-dose-dependent mean serum blood urea nitrogen levels were higher than sham controls in all LAVERDIA™-CA1 treatment groups.

Individually, there were 11 dogs with blood urea nitrogen > 21 mg/dL (reference range high 21 mg/dL for male; 22 mg/dL for female) at various timepoints throughout the study. Elevated blood urea nitrogen levels were observed in 0 dogs in the sham control, 2 dogs in the 1.0 mg/kg group, 4 dogs in the 1.5 mg/kg group, and 5 dogs in the 1.75 mg/kg group. The majority of elevated blood urea nitrogen levels were observed on study days 32 and 60. The highest blood urea nitrogen level was observed in a dog in the 1.0 mg/kg group on study day 60 with a blood urea nitrogen level of 31 mg/dL.

Mean serum chloride levels were lower than sham controls on study days 4 and 32 in the 1.5 and 1.75 mg/kg groups, on study day 60 in the 1.75 mg/kg group, and on study day 91 in a non-dose-dependent manner in all LAVERDIA™-CA1 treatment groups.

Individually, there were 7 dogs with chloride < 108 mEq/L (reference range low 108 mEq/L for male and female) at various timepoints throughout the study. Decreased chloride levels were observed in 0 dogs in the sham control and 1.0 mg/kg groups, 4 dogs in the 1.5 mg/kg group, and 3 dogs in the 1.75 mg/kg group. The majority of decreased chloride levels were observed on Days 4 and 32. The lowest chloride level was observed in a dog in the 1.75 mg/kg group on Day 91 with a chloride level of 105 mEq/L.

Urinalysis: There were no LAVERDIA™-CA1 related findings on urinalysis.

Gross Pathology and Histopathological Findings

Macroscopically, body thinness was observed in 1 dog in the sham control group, 2 dogs in the 1.0 mg/kg group, 3 dogs in the 1.5 mg/kg group, and 6 dogs in the 1.75 mg/kg group. Sparse hair was observed in 1 dog in the 1.0 mg/kg group (cranial region), 1 dog in the 1.5 mg/kg group (cranial region), and 2 dogs in the 1.75 mg/kg group (right ear and nose/muzzle).

Compared to sham control dogs, there were lower mean testes weights (absolute and relative to body and brain weights) in males in all LAVERDIA™-CA1 treatment groups, lower mean thymus weights (absolute and relative to body and brain weights) in the 1.5 mg/kg and 1.75 mg/kg groups, and lower thyroid/parathyroid gland weights (absolute and relative to body and brain weights) in all LAVERDIA™-CA1 treatment groups.

Dose-dependent microscopic findings were present in the testes and epididymides (moderate to marked seminiferous tubules degeneration/atrophy, minimal to moderate vacuolation, and minimal Leydig cell hypertrophy in the testes; and severe oligospermia/germ cell debris in the epididymides) in males in all LAVERDIA™-CA1 treatment groups, and in the thymus (minimal to mild cortical lymphoid depletion) in all LAVERDIA™-CA1 treatment groups.

Conclusions: The study demonstrated that LAVERDIA™-CA1 has an adequate margin of safety for the treatment of lymphoma when administered at an initial dose of 1.25 mg/kg administered orally twice per week with at least 72 hours between doses, with an increase to 1.5 mg/kg after two weeks. Clinical observation/examination findings related to the administration of LAVERDIA™-CA1 included vomiting, abnormal feces, inappetence, thin body condition, decreased body weight, excessive shedding, sparse hair, loss of skin elasticity, lacrimation, slight depression, and slight decrease of forelimb strength. Clinical pathology findings related to the administration of LAVERDIA™-CA1 included decreases in lymphocytes, eosinophils, monocytes, and chloride; and increases in fibrinogen, albumin, and blood urea nitrogen. Anatomic pathology findings related to the administration of LAVERDIA™-CA1 included lower testes, thymus, and thyroid/parathyroid gland weights with histologic lesions in the testes, epididymides, and thymus.

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 Application Number.

V. USER SAFETY

User safety data, including published literature (Sadowksi, et al., 2018)[3], indicate that the plasma half-life of verdinexor in dogs is approximately 4 - 6 hours. Within 60 hours, verdinexor is expected to undergo at least 10 half-lives of drug elimination and less than 0.09% of the initial drug dose is present. Therefore, the potential risk of drug exposure to humans from coming into contact with bodily fluids of a treated dog (such as feces, urine, vomit, and saliva) is minimal beyond 3 days (72 hours) following treatment and a 3-day precautionary period following treatment with LAVERDIA™-CA1 is recommended to ensure user safety.

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to LAVERDIA™-CA1:

On the package insert:

USER SAFETY WARNINGS:
NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. CHILDREN SHOULD NOT COME INTO CONTACT WITH LAVERDIA™-CA1. Children should not come in contact with the feces, urine, vomit, or saliva of treated dogs.

Pregnant women, women who may become pregnant, and nursing women should not handle or administer LAVERDIA™-CA1 or come in contact with the feces, urine, vomit, or saliva from LAVERDIA™-CA1-treated dogs. LAVERDIA™-CA1 may cause birth defects and can affect female fertility based on animal studies.

LAVERDIA™-CA1 can affect male fertility based on animal studies and studies in humans.

Wear protective disposable chemotherapy resistant gloves when handling LAVERDIA™-CA1 to avoid exposure to drug.

Wear protective disposable chemotherapy resistant gloves to prevent direct contact with moistened, broken, or crushed LAVERDIA™-CA1 tablets.

Wear protective disposable chemotherapy resistant gloves to prevent contact with feces, urine, vomit, and saliva during treatment and for **3 days** after the dog has received the last treatment. Place all waste material in a plastic bag and seal before general disposal. Wash hands immediately and thoroughly with soap and water if contact occurs with the feces, urine, vomit, or saliva from LAVERDIA™-CA1 treated dogs.

Any items that come in contact with feces, urine, vomit, or saliva should not be washed with other laundry during treatment and for **3 days** after the last treatment with LAVERDIA™-CA1.

Wear protective disposable chemotherapy resistant gloves when handling the dog's toys, food bowl, and water bowl. Wash food and water bowls separately from other items during treatment and for **3 days** after the dog has received the last treatment.

If LAVERDIA™-CA1 is accidentally ingested, or if there is significant contact with feces, urine, vomit, or saliva of dogs during treatment or within **3 days** after the last treatment without proper precautions, seek medical advice immediately. It is important to show the treating physician a copy of the package insert, label, or client information sheet.

Special instructions for handling and administering the product

- It is recommended that LAVERDIA™-CA1 be administered under the supervision of, or in consultation with, a veterinarian experienced in the use of cancer therapeutic agents.
- Use standard measures for the safe handling of all chemotherapeutic drugs. Refer to Occupational Safety and Health Administration (OSHA) for appropriate guidelines, recommendations, and regulations for handling antineoplastic agents.
- Do not eat, drink or smoke while handling the product.

- Do not store near food in or near a food preparation area, or with medications intended for use in humans.

Skin contact
- In case of contact with the skin, wash the affected area immediately and thoroughly with soap and water.

Accidental eye exposure
- Rinse the eyes with large amounts of tap water (use eyewash station if present) for 10 minutes while holding back the eyelid.
- Remove contact lenses.
- Seek medical advice immediately and show the package insert or label to the physician.

Accidental oral exposure or ingestion
- Seek medical advice immediately and show the package insert or label to the physician.

On the Client Information Sheet:

Handling Instructions:

What do I need to know to handle LAVERDIA™-CA1 (verdinexor tablets) safely?
Because LAVERDIA™-CA1 is an anti-cancer drug, extra care must be taken when handling the tablets, giving the drug to your dog, and cleaning up after your dog.
- LAVERDIA™-CA1 is not for use in humans.
- Do not eat, drink, or smoke while handling the product.
- Keep LAVERDIA™-CA1 in a secure storage area:
  - Out of the reach of children. Children should not come in contact with LAVERDIA™-CA1.
  - Out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.
- Do not store near food or near a food preparation area, or with medications intended for use in humans.
- Pregnant women, women who may become pregnant, and nursing women should not handle or administer LAVERDIA™-CA1 or come in contact with the feces, urine, vomit, or saliva from LAVERDIA™-CA1 treated dogs.
- LAVERDIA™-CA1 may harm an unborn baby. For pregnant and nursing women, accidental ingestion of LAVERDIA™-CA1 may have adverse effects on pregnancy or the nursing baby.
- LAVERDIA™-CA1 may affect female and male fertility.

How to minimize exposure to the active ingredient when handling LAVERDIA™-CA1?

The following handling procedures will help to minimize exposure to the active ingredient in LAVERDIA™-CA1 for you and other members of your household:

- Anyone who administers LAVERDIA™-CA1 to your dog should wear protective disposable chemotherapy resistant gloves (e.g. nitrile or latex gloves tested for use with chemotherapy drugs) when handling LAVERDIA™-CA1. Check with your veterinarian to ensure you have the appropriate gloves.
- Minimize the number of people handling LAVERDIA™-CA1.
- When you or others are handling the tablets:
  - Do not split or crush the tablets to avoid disrupting the protective film coating.
  - LAVERDIA™-CA1 tablets should be administered to your dog immediately after they are removed from the bottle.
  - Protective disposable chemotherapy resistant gloves should be worn if handling broken or moistened tablets. If your dog spits out the LAVERDIA™-CA1 tablet, the tablet will be moistened and should be handled with protective disposable chemotherapy resistant gloves.
  - If the LAVERDIA™-CA1 tablet is "hidden" in a treat, make sure that your dog has eaten the entire dose. This will minimize the potential for exposure to children or other household members to LAVERDIA™-CA1.
- Return any unused LAVERDIA™-CA1 to your veterinarian.

What should I do in case of accidental contact when handling LAVERDIA™-CA1?

- In case of contact with the skin, wash the affected area immediately and thoroughly with soap and water.
- In the case of accidental eye exposure:
  - Rinse the eyes with large amounts of tap water (use eyewash station if present) for 10 minutes while holding back the eyelid.
  - Remove contact lenses.
  - Seek medical advice immediately and show the package insert, label, or client information sheet to the physician.
- If LAVERDIA™-CA1 is accidentally ingested, or if there is significant contact with feces, urine, vomit, or saliva of dogs during treatment or within 3 days after the last treatment without proper precautions, seek medical advice immediately. It is important to show the treating physician a copy of the package insert, label, or client information sheet.

How do I safely clean up after my dog during treatment with LAVERDIA™-CA1?

Because LAVERDIA™-CA1 is a cancer treatment drug, extra care must be taken when cleaning up after your dog for **3 days** after the last treatment with LAVERDIA™-CA1.

- Avoid direct contact with feces, urine, vomit, or saliva during treatment and for **3 days** after the dog has completed treatment with LAVERDIA™-CA1.
- Any skin that comes in contact with feces, urine, vomit, or saliva should be washed immediately with soap and water.
- When cleaning up feces, urine, vomit, or saliva you should wear protective disposable chemotherapy resistant gloves and collect the contaminated

material with disposable absorptive material (such as paper towels) and place them into a plastic bag. Carefully remove the gloves and place them in the bag and tie or fasten it securely. Wash your hands thoroughly afterwards.
- You should not wash any items soiled with feces, urine, vomit, or saliva from your dog with other laundry during treatment and for **3 days** after the dog has completed treatment.
- Do not let your dog urinate or defecate in areas where people may come in direct contact with the urine or feces.
- Children should not come in contact with the feces, urine, vomit, or saliva of treated dogs.

Because LAVERDIA™-CA1 may be present in your dog's saliva during treatment and for **3 days** after the last treatment, wear protective disposable chemotherapy resistant gloves when handling the dog's toys, food bowl, and water bowl. Wash food and water bowls separately from other items.

VI. AGENCY CONCLUSIONS

The data submitted in support of this application satisfy the requirements of section 571(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The data demonstrate that LAVERDIA™-CA1, when used according to the label, is safe and has a reasonable expectation of effectiveness for the treatment of lymphoma in dogs.

A. Conditional Approval Eligibility

Conditional approval is an option for animal drugs intended for use in minor species (all animals other than major species, which are horses, cattle, pigs, chickens, turkeys, dogs, and cats) or for minor uses (diseases or conditions in major species that occur infrequently or in limited geographical areas). A product's eligibility for conditional approval under minor use status requires a sponsor to justify that the disease or condition for which the proposed product is intended afflicts a "small number of animals" of that species in the U.S. annually. The "small number" for each major species is established by regulation (21 CFR § 516.3). At the time of this approval, FDA's "small number of animals" threshold for dogs was 70,000.

To justify that the treatment of lymphoma in dogs constitutes a minor use, the sponsor referred to a product for the same intended use that already had minor use status on the published Designations List on the FDA website.[4] A sponsor can refer to an existing designation for any product on the list with the same intended use instead of having to provide a written justification for minor use status.

FDA conducted a minor use assessment in 2012 for the sponsor of a drug product proposed for the same intended use as LAVERDIA™-CA1, and determined that the occurrence of lymphoma in dogs in the U.S. annually is below the published "small number" of 70,000 dogs.

As part of this assessment, FDA reviewed multiple sources of data that were publicly available, as well as additional information that FDA had previously evaluated. Sources included the scientific literature and Brakke Consulting Inc.'s 2009 Report on Cancer in Dogs and Cats,[5] which included data from Brakke's 2009 survey, the Veterinary Cancer Registry, and Banfield Pet Hospital's (Banfield) medical records. The incidence rate of lymphoma in the nearly 6 million dogs in the Banfield medical records database, with an age adjustment factor applied, resulted in an estimate of 55 affected dogs/100,000 dogs, which falls into the range of estimates in other published sources regarding the annual rate of occurrence of lymphoma in dogs. In addition to the Banfield estimate, FDA used three other direct estimates of the annual rate of occurrence of lymphoma in dogs: 30/100,000 dogs,[6] 107/100,000 dogs,[7] and an estimate from a proprietary survey. A weighted mean of these direct estimates is approximately 72/100,000 dogs (.072%). This amounts to 51,900 dogs or, while accounting for uncertainties from this assessment, up to 58,600 dogs with lymphoma in the U.S. annually (utilizing a U.S. canine population of 72,100,000).[8]

In addition, FDA indirectly estimated the number of lymphoma cases in the U.S. based on a ratio between known relative rates of the incidence of canine lymphoma and another canine cancer, mast cell tumor (MCT). FDA had previously established a well-documented estimate of the annual rate of occurrence of MCT in the U.S. canine population of 0.11% +/- 0.01%.

Using eight sources that provided relative rates of occurrence for both canine lymphoma and MCT, [6, 7, 9, 10, 11, 12, 13, 14] FDA determined that the ratio of lymphoma to MCT in dogs is approximately 0.70. Therefore, the estimated annual rate of occurrence of lymphoma (L) is 70% (arithmetic mean of eight L/MCT ratios x 100) of 0.11% (annual rate of occurrence of MCT in the U.S. canine population), which is 0.077%. This amounts to 55,517 dogs, or while accounting for uncertainties from this assessment, up to 62,600 dogs with lymphoma in the U.S. annually (utilizing a U.S. canine population of 72,100,000).

Using the above estimates, FDA determined that the number of dogs with lymphoma in the U.S. on an annual basis is lower than 70,000 dogs. Therefore, the Agency concluded that the use of LAVERDIA™-CA1 (verdinexor tablets) for the treatment of lymphoma in dogs in the U.S. constitutes a minor use, and the product is eligible for conditional approval.

B. Marketing Status

LAVERDIA™-CA1 is conditionally approved for one year from the date of approval and is annually renewable for up to four additional one-year terms.

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose lymphoma, and to monitor safe use of the product, including treatment of any adverse reactions.

C. Exclusivity

LAVERDIA™-CA1, as approved in our approval letter, qualifies for SEVEN years exclusive marketing rights beginning as of the date of our approval letter. This drug qualifies for exclusive marketing rights under section 573(c) of the FD&C Act because it is a designated new animal drug under section 573(a) of the FD&C Act. Except as provided in section 573(c)(2) of the FD&C Act, we may not approve or conditionally approve another application submitted for such new animal drug with the same intended use as LAVERDIA™-CA1. Exclusive marketing rights begin as of the date of our approval letter.

D. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.

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VII. APPENDIX

May 14, 2021 – Updated the FOI Summary to add a Conditional Approval Eligibility section under Agency Conclusion that provides information about how minor use in a major species was determined. Small formatting changes were made to the FOI Summary to improve the consistency throughout the document and to improve the flow of the document.