Date of Approval: May 1, 2023

FREEDOM OF INFORMATION SUMMARY

APPLICATION FOR CONDITIONAL APPROVAL

Application number 141-571

Varenzin™-CA1

(molidustat oral suspension)

Cats

Varenzin™-CA1 is indicated for the control of nonregenerative anemia associated with chronic kidney disease (CKD) in cats.

Sponsored by:

Elanco US Inc.

Executive Summary

Varenzin™-CA1 (molidustat oral suspension) is conditionally approved for the control of nonregenerative anemia associated with chronic kidney disease (CKD) in cats. The drug is given to cats orally once daily for up to 28 days. Treatment may be repeated after a minimum 7-day pause.

An animal drug that addresses a serious or life-threatening disease, or addresses an unmet animal or human health need, for which demonstrating effectiveness would require a complex or particularly difficult study or studies is eligible for conditional approval. Nonregenerative anemia associated with CKD is a disease or condition associated with mortality and morbidity that has substantial impact on the day-to-day functioning in cats. Therefore, the conditionally approved use addresses a serious or life-threatening disease or condition. The control of nonregenerative anemia associated with CKD in cats is an unmet animal health need because there is no approved animal drug currently marketed in the United States for this use in cats. Finally, because of the long study duration needed to determine effectiveness for this use, demonstrating effectiveness would require a complex or particularly difficult study or studies. Therefore, FDA determined that Varenzin™-CA1 met the eligibility criteria for conditional approval.

Safety and Reasonable Expectation of Effectiveness
The sponsor conducted a two-phase exploratory field study to evaluate the safety and effectiveness of Varenzin™-CA1 in client-owned cats with nonregenerative anemia associated with CKD. Enrolled cats included both sexes, ranged in age from 4 to 17 years, and were a variety of weights and breeds. In the 1st (effectiveness) phase of the study, cats received either molidustat oral suspension (not the final formulation of Varenzin™-CA1) or a vehicle control administered at home by the owner for 28 days. Success was defined on Day 28 as either a relative increase in hematocrit (HCT) of > 25% above baseline or an absolute increase in HCT of ≥ 4% points above baseline. Half of the cats (7/14) in the treatment group were considered successes compared to only 16.7% of control cats (1/6).

After the 28-day effectiveness phase, owners could voluntarily include their cat in the second (continuation) phase of the study for an additional 8 weeks. Eight cats were included in the continuation phase, all of which received molidustat oral suspension once daily for varying lengths of time. Using the same success criteria as that used during the effectiveness phase, most cats in the continuation phase were successes on Day 56 (75%; 6/8) and Day 84 (62.5%; 5/8).

Vomiting was the most frequent adverse reaction seen in cats in the field study. Increases in systolic blood pressure were also observed. The most serious adverse reaction was a cat with a suspected thromboembolism.

The sponsor conducted a laboratory safety study in healthy, adult male cats that were treated with 0X, 0.5X, or 1X the labeled dose of molidustat administered orally in an oily suspension (non-final formulation) once daily for 4 or 8 weeks or until the cat's HCT reached 60%. The observed adverse reactions were considered related to overstimulation of red blood cell production and included abnormal mucous membrane color; prolonged capillary refill time (about 3 seconds); heart pounding; tachycardia; mild increases in serum creatinine and potassium; dose-dependent

numerical decrease in the mean kidney to brain ratio; and congestion, thrombosis, and hemostasis in multiple organs.

The sponsor conducted a pharmacokinetic and pharmacodynamic study to evaluate the effects of daily treatment with molidustat oral suspension administered orally at different dosages and in different non-final formulations (oily and an aqueous suspension) on red blood cell parameters in healthy, adult male and female cats. Cats were administered 0X, 1X, or 2X the labeled dose for 16 or 24 consecutive days. Vomiting was the most frequent adverse reaction. Observed hematology changes were consistent with overstimulation of red blood cell production. Mild treatment-related increases in serum creatinine and phosphorus were seen, but both decreased to baseline after treatment was stopped.

The sponsor also evaluated the interim safety data collected during the second (continuation) phase of a larger, two-phase field effectiveness study conducted in client-owned cats with nonregenerative anemia and CKD. Cats that survived through Phase 1 automatically continued into Phase 2. Cats received Varenzin™-CA1 once daily in 28-day treatment cycles, repeated up to four times, with a minimum 7-day treatment pause between cycles. Potential adverse reactions included an increased risk for vomiting, and one cat with a history of a previous seizure had seizure activity while receiving the drug. The results support the safety of Varenzin™-CA1 when given in repeated 28-day treatment cycles. The results also indicate that most cats should only need to be off Varenzin™-CA1 for at least 7 days before starting a new treatment cycle.

User Safety
People exposed to Varenzin™-CA1 should seek medical advice and may experience the following symptoms: gastrointestinal effects (nausea, vomiting, and diarrhea), blood and clotting effects (increases in reticulocytes, erythropoietin, and hemoglobin), dizziness, fainting, hypertension, changes in cardiac output and cardiac index, and increases in heart rate. Symptoms may not occur immediately; therefore, the exposed person should be monitored. Women who are pregnant or may become pregnant should use caution when administering Varenzin™-CA1 to cats.

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

Table of Contents

I. GENERAL INFORMATION

A. File Number

Application number 141-571

B. Sponsor

Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140

Drug Labeler Code: 058198

C. Proprietary Name

Varenzin™-CA1

D. Drug Product Established Name

molidustat oral suspension

E. Pharmacological Category

Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor

F. Dosage Form

Suspension

G. Amount of Active Ingredient

25 mg/mL

H. How Supplied

27 mL in a bottle with oral dosing syringe

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

The dosage of Varenzin™-CA1 is 2.3 mg/lb (5 mg/kg) body weight (BW) administered orally once daily for up to 28 consecutive days, rounded up to the nearest 0.1 mL using the dosing syringe provided in the package. Treatment may be repeated after a minimum 7-day pause.

K. Route of Administration

Oral

L. Species

Cats

M. Indication

Varenzin™-CA1 is indicated for the control of nonregenerative anemia associated with chronic kidney disease (CKD) in cats.

II. EFFECTIVENESS

Conditional Dose: The conditional dose for the indication "for the control of nonregenerative anemia associated with chronic kidney disease (CKD) in cats" is 2.3 mg/lb (5 mg/kg) body weight (BW) administered orally once daily for up to 28 consecutive days. Treatment may be repeated after a minimum 7-day pause.

The results from studies in healthy cats and in cats with nonregenerative anemia associated with CKD support dosage characterization and demonstrate reasonable expectation of effectiveness. The safety data and the data to demonstrate reasonable expectation of effectiveness provide support for this conditional dose.

A. Dosage Characterization

The 5 mg molidustat/kg BW dose was selected for further evaluation based on a series of laboratory studies in healthy cats. In these studies, a non-final formulation of molidustat oral suspension was tested at doses including 1, 2.5, 3, 5, 6, and 10 mg/kg BW to fed or fasted cats. Although administration of 3 mg/kg BW to healthy cats briefly increased erythropoietin (EPO) and hematocrit (HCT), doses above 3 mg/kg BW achieved a more sustained EPO response. Additionally, no clinically relevant effects of food were observed at doses above 3 mg/kg BW. Further studies showed the higher dosage of 10 mg/kg BW had no further benefit in healthy cats over the 5 mg/kg BW dose. The data supporting the 28-day dosing cycle are summarized below in the Reasonable Expectation of Effectiveness section. The data supporting subsequent dosing cycles is summarized in the Target Animal Safety section under Field Safety from Interim Safety Analysis of Field Effectiveness Study.

B. Reasonable Expectation of Effectiveness

1. Exploratory Field Effectiveness and Safety Study

Title: Evaluate the Efficacy and Safety of BAH002248 [molidustat] in Cats with Anemia Associated with Chronic Kidney Disease (CKD) (Study No. 203575)

Study Dates: August 12, 2015 to June 20, 2016

Study Locations: Clinics in the United States (US) and European Union (EU) from the following locations enrolled cases in this study:

US Locations	**EU Locations**
Ft. Collins, CO	Elmshorn, Germany
Largo, FL	München, Germany

Tampa, FL
Zachary, LA
Falmouth, ME
Springfield, MO
Quakertown, PA
Virginia Beach, VA
Aveiro, Portugal
Ferreiros Amares, Portugal
Trofa, Portugal
Porto, Portugal

Study Design: The study had two phases. The first (effectiveness) phase was a multi-center, double-masked, randomized, placebo-controlled field effectiveness and safety study. The second (continuation) phase was a multi-center, unmasked, non-randomized, uncontrolled field safety and effectiveness study.

Objective: The study was designed to evaluate the safety and effectiveness of molidustat oral suspension to control anemia associated with CKD at an oral dose of 5 mg/kg BW.

Study Animals: The study enrolled 23 client-owned cats (12 females; 11 males) with nonregenerative anemia associated with CKD. The enrolled cats were 4 to 17 years of age with initial body weights between 2 to 6 kg and were of various breeds or mixed breeds.

Experimental Design: For the effectiveness phase of the study, the cats were randomized at a ratio of 2:1 to receive a non-final formulation of molidustat oral suspension or a vehicle control (16 cats in the molidustat group and 7 cats in the control group). Cats that received vehicle control were allowed to re-enroll in the effectiveness phase of the study provided they met the inclusion criteria. These cats received molidustat during the second enrollment. After the 28-day effectiveness phase the owners could voluntarily include their cat in the continuation phase for up to 8 additional weeks.

Treatment Groups: There were 2 treatment groups in the effectiveness phase of the study.

Table II.1. Treatment Groups During the Effectiveness Phase of the Study

Treatment Group	Dose	Number of Cats Enrolled
1 (molidustat oral suspension)	5 mg molidustat/kg BW (0.2 mL/kg BW) orally for 28 consecutive days	16
2 (vehicle control)	0.2 mL vehicle/kg BW orally for 28 consecutive days	7

There were eight cats included in the continuation phase, all of which received molidustat oral suspension.

Inclusion Criteria: Client-owned cats that had been diagnosed with nonregenerative anemia with packed cell volume (PCV) at 27% or below at

Study Day (SD) -7 and SD 0, and CKD (baseline serum creatinine greater than 1.8 mg/dL) at or before SD -7. Cats were otherwise in good general health or had stable chronic conditions that would not interfere with the study assessments. Cats were also required to have a blood pressure less than 165 mmHg on either SD -7 or SD 0.

Exclusion Criteria: Cats intended for breeding, pregnant or lactating female cats, or cats with conditions that would confound the study assessments or prevent completion of the study were excluded.

Drug Administration: Cats in treatment Group 1 received a non-final formulation of molidustat oral suspension. The differences in composition between the non-final formulation and final formulation are not expected to have significant impact on the bioavailability; therefore, it is reasonable to expect the effectiveness and safety profiles seen with the non-final formulation in this study would also be seen with the final formulation. Cats in Group 2 received the vehicle formulation (no active ingredient). During the effectiveness phase, enrolled cats were orally treated once daily for 28 consecutive days (SD 0 to SD 27) with the vehicle control or molidustat oral suspension. Eight cats from the effectiveness phase enrolled in the continuation phase. Three cats received 5 mg/kg BW daily throughout the continuation phase; three cats were intermittently treated with 2.5 mg/kg BW; one cat received 5 mg/kg BW daily until at least SD 42, then received 2.5 mg/kg BW daily for one week (from SD 70 to 77); and one cat received 5 mg/kg BW daily until SD 49. The starting, stopping, and adjusting of dosages was based on the prior week's PCV result with the goal to maintain the PCV ≥ 29% and ≤ 40%. If the PCV increased above 29%, then treatment was paused until it was ≤ 29%. Once the PCV was < 29%, treatment with molidustat oral suspension was started again. Owners administered the treatments at home.

Measurements and Observations: During the effectiveness phase of the study, baseline physical examination, body weight, hematology, serum chemistry, and urine culture were obtained prior to the initial dose administration. Hematological parameters were assessed on SDs 0, 7, 14, 21, and 28 (± 2 days for all time points except SD 0). Serum chemistry (except creatinine) was also re-evaluated on SD 28 (± 2 days).

During the continuation phase of the study, PCV was evaluated weekly. In addition, hematology (including HCT), serum chemistry (except creatinine), and a physical examination were evaluated on SDs 56 and 84 (± 2 days for all time points). Body weight and blood pressure measurements were recorded on SDs 42, 56, 70, and 84. The results of the continuation phase were evaluated separately from the 28-day effectiveness phase.

Statistical Methods: Descriptive statistics were used to compare the proportions of treatment success in each group. For determining a reasonable expectation of effectiveness, success was defined as a cat with, on SD 28, either a relative increase in HCT of > 25% above baseline or an absolute increase in HCT of ≥ 4% points above baseline. The experimental unit was the individual cat.

The pre- and post-treatment physical examinations, daily general health observations, and clinical pathology variables were evaluated clinically but were not statistically analyzed. Additionally, body weights were only evaluated by descriptive statistics.

Results: One cat in each group was excluded from the effectiveness analysis due to poor owner compliance. A control cat was removed after one week because the owner was unable to administer the drug product. A molidustat-treated cat did not return to the clinic after SD 0; no reason was given for not returning. A second molidustat-treated cat was excluded from the SD 28 effectiveness analysis because the cat was dehydrated, potentially affecting the HCT results. Table II.2 provides the calculated treatment success rate per treatment group.

Table II.2. Percent Success on Study Day 28 (Effectiveness Phase)

Treatment Group	Percent (Ratio) of Cats with Relative Increase in HCT of > 25% or Absolute Increase in HCT of ≥ 4% Points Above Baseline
1 (molidustat oral suspension)	50% (7/14)
2 (vehicle control)	16.7% (1/6)

Eight cats (six of the seven successes and two of the failures from the molidustat oral suspension group) enrolled in the continuation phase. Using the same success criteria during the continuation phase as that used during the effectiveness phase, most of the cats that enrolled in the continuation phase were successes on SD 56 and SD 84. Table II.3 provides the calculated treatment success rate per treatment group during the continuation phase of the study.

Table II.3. Percent Success on Study Days 56 and 84 (Continuation Phase)

Study Day	Percent (Ratio) of Cats with Relative Increase in HCT of > 25% or Absolute Increase in HCT of ≥ 4% Points Above Baseline
56	75% (6/8)
84	62.5% (5/8)

A possible association of hypertension with treatment was found for two cats in this study. One cat, a treatment failure in the molidustat oral suspension group, had systolic blood pressure increases from 160 mmHg before treatment to 207 mmHg (SD 14) and 205 mmHg (SD 28) during treatment. A second cat, also a treatment failure in the molidustat oral suspension group during the effectiveness phase, had a transient episode of hypertension during treatment in the continuation phase of the study. The cat's systolic blood pressure increased from 165 mmHg before treatment to 182 mmHg (SD 42) and 192 mmHg (SD 56) during treatment. The cat's blood pressure decreased to baseline on SD 70 (159 mmHg) and SD 84 (151 mmHg) while still receiving molidustat oral suspension. The cat's HCT was low from SD -7

to SD 28 (the effectiveness phase) but was normal during the continuation phase. A non-treatment related cause for the transient hypertension was not found, and therefore, it was concluded that the hypertension was possibly related to molidustat treatment.

Adverse Reactions: Vomiting was the most frequently reported adverse reaction, occurring in 6 of the 15 (40%) cats in the molidustat oral suspension group and no cats in the vehicle control group. Two cats in the molidustat oral suspension group had decreased appetite, which was associated with the vomiting episode. A 17-year-old cat in the molidustat oral suspension group presented on SD 28 in lateral recumbency with a cold front leg; the veterinarian suspected the cat had a thromboembolism and the cat was euthanized with no necropsy performed.

Conclusion: The study results support a reasonable expectation of effectiveness and an acceptable safety profile for molidustat oral suspension administered orally once daily at 5 mg/kg BW for up to 28 days for the control of nonregenerative anemia associated with chronic kidney disease (CKD) in cats. The most frequent adverse reaction was vomiting. Increases in systolic blood pressure were also observed. The most serious adverse event was a cat with a suspected thromboembolism

III. TARGET ANIMAL SAFETY

The results from two laboratory studies in healthy cats and from two field studies in cats with nonregenerative anemia associated with CKD support the safety of molidustat oral suspension for the control of nonregenerative anemia associated with CKD.

A. Laboratory Target Animal Safety Study

Title: Target Animal Safety Study in Male Cats with Once Daily Oral Administration. (Study No. 201184)

Study Dates: January 26, 2015 to May 4, 2016

Study Location: Wuppertal, Germany

Study Design:

Objective: The objective of the study was to investigate the safety of molidustat orally administered as the sodium salt in an oily suspension formulation in cats once daily for a period of 4 and 8 weeks or until a threshold hematocrit of 60% was reached.

Study Animals: A total of 16 male domestic shorthair cats, approximately 10 to 11 months old at start of treatment, and initially weighing between 4.1 to 6.7 kg, were enrolled in the study.

Experimental Design: The study was an unmasked, randomized margin of safety study conducted under Organisation for Economic Co-operation and Development (OECD) Good Laboratory Practices (GLP). Cats were randomly allocated to one of

three treatment groups. Cats were housed in a climate-controlled room, and group housed, with up to six animals per dose group.

Drug Administration: Twelve cats were orally administered a non-final formulation of molidustat oral suspension once every 24 hours as per Table III.1 and four cats were untreated controls. The differences in composition between the non-final formulation and final formulation are not expected to have significant impact on the bioavailability; therefore, it is reasonable to expect the safety profile observed with the non-final formulation in this study would be similar to the final formulation. SD 1 was the first day of drug administration.

Table III.1. Treatment Groups

Treatment Group	Molidustat Oral Suspension Dose and Duration	Number of Animals
1	Untreated (0 mg/kg BW)	4
2	2.5 mg/kg BW orally for 56 consecutive days or until the HCT was ≥ 60%	6
3	5 mg/kg BW orally for 28 consecutive days or until the HCT was ≥ 60%	6

Measurements and Observations: Clinical observations were conducted twice daily from the pre-randomization/pre-dosing period until SD 1. From SD 1, clinical observations were performed at least three times per day: in the morning, about one hour after treatment, and at the end of the working day. Body weights were recorded weekly. Food consumption was measured daily. A physical exam was conducted once before the start of treatment, and on week 2, week 4, and week 8. Hematology parameters were assessed before randomization and SDs 1, 7, 14, 21, 24, 28, 35, 42, 49, 52, and 56. Blood was collected for serum chemistry before randomization and SDs 23, 24, and 52. Blood was collected for coagulation assessments before randomization and SDs 1, 24, and 52. Urine was collected for urinalysis at necropsy. Blood was collected for erythropoietin analysis on SD 1 before administration at 0 hour (hr) and at 2 hr, 6 hr, and 24 hr after administration. Blood was collected for toxicokinetics on SDs 7, 28, and 56 at 2 hr, 6 hr, and 24 hr after administration (except for two cats dosed at 2.5 mg/kg BW and one cat dosed at 5 mg/kg BW that had their last blood samples taken on SD 23 and were then prematurely euthanized on SD 23 because of their HCT level). Gross pathology and histopathology were evaluated.

Statistical Methods: Descriptive statistics summaries of clinical pathology endpoints by treatment group and by time point were evaluated. Descriptive statistics summaries of organ weights by treatment group, time point, and scheduled euthanasia were also evaluated.

Food consumption of each group was recorded by weighing the daily ration before and after feeding and reported by treatment group.

Descriptive statistics were provided per dose group and time point for all parameters that were recorded with a specified unit. This included measures of general tendency (mean and median) and general variability (standard deviation, minimum and maximum) as appropriate.

Results: Due to hematocrit values over the threshold of 60%, two Group 2 cats and one Group 3 cat were prematurely euthanized on SD 23, and another Group 3 cat prematurely euthanized on SD 25.

Vomiting was observed in one Group 2 and one Group 3 cat on the first day of treatment (SD 1). No further vomiting was noted during the study.

Clinically relevant observations noted on physical exam included abnormal mucous membrane color, prolongation of capillary refill time (about 3 seconds), heart pounding, and tachycardia. These observations were noted in conjunction with polycythemia (all cats had HCTs greater than 50%). Because polycythemia can cause these effects, they were considered most likely secondary effects from polycythemia rather than direct effects from the drug product.

There were no clinically relevant changes noted in body weight or food consumption.

Clinical Pathology and Post-Mortem Observations: Hematology changes were consistent with overstimulation of red blood cell production, with total RBCs, HCT, and hemoglobin increasing in all cats in Groups 2 and 3. For example, mean HCT on SD 21 was 38.1% in Group 1, 55.2% in Group 2, and 56.7% in Group 3.

Group 3 cats had mild increased values of serum potassium (about 15% higher than pre-treatment values), but no cats became hyperkalemic during the study.

The cats in Group 1 had increases in serum creatinine by an average of less than 2% on SDs 23 and 52 compared to baseline. The cats in Group 2 had increases in creatinine by an average of 8.4% on SD 23 and 5.2% on SD 52, and the cats in Group 3 had increases by an average of 14% on Day 23. The increase in Group 2 was driven by 4 of the 6 cats having increases ranging from 6.9% to 21.6%. Although this level of increase is generally within the limits of biological variability, the numerically greater mean increase in creatinine compared to baseline and the greater incidence of increase in creatinine compared to baseline suggest a possible drug effect. However, because polycythemia can cause these effects, it was not possible to determine whether the increases in creatinine were a direct effect from the drug product or a secondary effect from polycythemia, although the latter was considered more likely.

Plasma erythropoietin levels increased 6 hours after administration of either dose of molidustat oral suspension, with higher levels seen in Group 3 cats.

Gross evaluation at necropsy did not reveal any drug-related findings.

There was an apparent dose-dependent numerical decrease in the mean kidney to brain ratio (Group 1: 45.5; Group 2: 39.3; Group 3: 36.5); however, the clinical relevance of this finding, including its relationship to the creatinine results, was not able to be determined.

Lower mean thymus weight (57.17% of control group mean) was recorded in Group 3 cats; these cats also had lower mean relative thymus weights. Lower thymus weights were also noted in Group 2 cats, however, to a lesser degree. Increased thymus atrophy and involution were found on histopathologic examination in Groups 2 and 3. It was not possible to determine if this was a direct effect or a secondary effect from polycythemia or another mechanism.

The administration of molidustat oral suspension was associated with histopathological findings related to the pharmacologic mode of action (erythropoiesis via HIF-PH inhibition) in the brain, heart, lung, spleen, and bone marrow. Findings consisted of congestion of the vasculature in the brain, thrombosis and hemostasis in the heart, prominent myocardial vessels, minimal edematous change of valves in the heart, and acute thrombosis of large pulmonary arteries in the lung.

An increased cellular density of the bone marrow, mainly due to increased erythropoietic activity, was observed in all cats administered molidustat. Extra medullary hematopoiesis was increased in several Group 3 cats.

Conclusion: The study results support the safety of molidustat oral suspension administered at the conditional oral daily dose of 5 mg/kg BW for the control of nonregenerative anemia associated with chronic kidney disease (CKD) in cats. The observed adverse findings were considered related to polycythemia secondary to HIF-PH inhibition. Such findings included abnormal mucous membrane color; prolongation of capillary refill time (about 3 seconds); heart pounding; tachycardia; mild increases in serum creatinine and potassium; dose-dependent numerical decrease in the mean kidney to brain ratio; and congestion, thrombosis, and hemostasis in multiple organs. The mechanism of dose-dependent decrease in thymus weight and increased thymus atrophy and involution was not determined

B. Pharmacokinetic and Pharmacodynamic Study

Title: Molidustat: Pharmacodynamic Effects on Hematologic Parameters of Three Different Dosages After Multiple Oral Administrations in Healthy Cats. (Study No. 202521)

Study Dates: August 13, 2014 to December 9, 2014

Study Location: Monheim, Germany

Study Design:

Objective: The objective of this study was to evaluate the effects of daily treatment with molidustat oral suspension administered orally at different dosages and in different non-final formulations (oily and an aqueous suspension) on red blood cell parameters in healthy adult cats for up to 57 days.

Study Animals: Ten male and twelve female domestic shorthair cats, approximately 22 to 24 months old at the start of treatment, and initially weighing between 3 to 5.5 kg, were enrolled in the study.

Experimental Design: The study was a prospective, randomized, controlled, and unmasked exploratory study. Cats were randomly allocated to one of four treatment groups, pair housed until SD 35, and group housed from SD 36 onward. The cats were in the study for a total of 118 days, including a 14-day acclimation period.

Drug Administration: Cats were administered one of three molidustat oral suspension formulations or vehicle control, orally as described in Table III.2. The differences in composition between the non-final formulations and final formulation are not expected to have significant impact on the bioavailability; therefore, it is reasonable to expect that the safety profile observed with the non-final formulations would be similar to the final formulation. SD 0 was the first day of drug administration. The cats were to receive molidustat oral suspension for up to 57 days; however, molidustat oral suspension administration ended early because the mean group HCT levels exceeded the HCT threshold on SD 14 in Groups 3 and 4 and on SD 21 in Group 2. The last day of treatment administration was SD 15 for Groups 3 and 4 and SD 23 for Groups 1 and 2. All cats remained in the study for continued evaluation until SD 104.

Table III.2. Treatment Groups

Treatment Group	Molidustat Oral Suspension or Vehicle Control Dose and Duration	Number of Animals
1	Vehicle (0 mg/kg BW; 0X) orally for 24 consecutive days (0% oily suspension)	6
2	5 mg/kg BW (1X) orally for 24 consecutive days (5% oily suspension)	6
3	10 mg/kg BW (2X) orally for 16 consecutive days (10% oily suspension)	5
4	10 mg/kg BW (2X) orally for 16 consecutive days (10% aqueous suspension)	5

Measurements and Observations: Clinical observations, which included general health observation, feed consumption, and fecal consistency, were conducted once daily from SD -14 to SD 104. Body weights were recorded weekly from SD -14 to SD 97. A physical examination was conducted approximately every two weeks from SD -14 to SD 97. Hematology parameters were assessed before randomization and SDs -14, -7, 0, 7, 14, 21, 28, 35, 42, 49, 56, 70, 84, and 98. Blood samples were collected as fasted samples for clinical chemistry analysis from all cats on SDs -14 and 97. Blood samples were also collected on SD 12 in Group 3 and 4 cats and on SD 23 in Group 1 and 2 cats. These dates loosely coincided with the last day of treatment administration. Plasma samples were

collected on SDs 0, 7, and 23, before and after treatment administration, to analyze the concentration of erythropoietin and molidustat.

Statistical Methods: Descriptive statistics (mean and standard deviation) were used for the analysis of molidustat concentrations and EPO.

The pre- and post-treatment physical examinations, daily general health observations, and clinical pathology variables were evaluated clinically but were not statistically analyzed. Additionally, body weights were evaluated with descriptive statistical evaluation only.

Results: Vomiting was the most common clinical observation reported through SD 35. Vomiting was reported after initiation of dosing in all treatment groups during the study. Because cats were pair housed during this time, it was not always possible to determine if just one cat or both cats in the cage vomited. However, vomiting occurred more frequently in cats administered molidustat (23 events recorded through SD 35) versus control cats (7 events recorded through SD 35) over the course of the study. The vomiting appeared to increase in a dose-dependent fashion, and cats in Groups 3 and 4, administered 10 mg/kg BW, had more episodes of repeated vomiting compared to cats in the other treatment groups. Defensive behaviors following dosing (e.g., lip smacking, shaking, or choking) were reported in Groups 3 and 4 and the control cats, but the defensive behaviors appeared to be more frequently reported in cats administered molidustat at 10 mg/kg BW (Groups 3 and 4).

Two pair-housed cats (one in Group 3 and one in Group 4) were observed to have repeated bouts of soft feces from SDs 9 to 11. Because the cats were pair-housed, it was not possible to determine if one or both cats in the cage produced the soft feces. Analysis of pooled fecal samples from all study cats showed that the study cats had evidence of feline coronavirus infection and suspected fecal dysbiosis during this time. Feline coronavirus or fecal dysbiosis may have contributed to the observed clinical signs in these two cats, but a specific cause for the soft feces was not determined. Changes in fecal consistency resolved by SD 30 without specific medical treatment. A single episode of dark orange urine was observed at SD 13 in the cage of these same pair-housed Group 3 and Group 4 cats. Results of urinalysis conducted at SD 13 were inconclusive; however, the Group 3 cat had concurrent increases (compared to baseline) in serum creatinine and blood urea nitrogen (BUN) assessed at SD 12. Only the elevation in creatinine was outside of the reported reference ranges for the study. The elevation in creatinine in the cat in Group 3 returned to levels consistent with pre-treatment values by SD 97 without specific medical therapy.

There were no clinically relevant changes noted in body weight, food consumption, or physical examination.

Clinical Pathology: A dose-dependent increase in erythropoietin was observed in the groups administered molidustat oral suspension, which returned to baseline or near baseline 24 hours after dosing. Hematology changes were consistent with overstimulation of red blood cell production, with total RBCs, HCT, and hemoglobin increasing in all cats in Groups 2, 3, and 4. For example, mean HCT

on SD 14 was 40.2% in Group 1, 54.6% in Group 2, 60.6% in Group 3, and 61.8% in Group 4.

All cats in Groups 3 and 4 showed a clinically relevant increase in serum creatinine on SD 12. One Group 3 cat had an increase in creatinine of 86% from baseline to just above the reference range and an increase in BUN of 66% to just below the reference range. Similar increases in BUN were not reported in any of the other cats. All creatinine values returned to baseline by SD 97.

A transient, mild increase in phosphorus was noted in Groups 3 and 4 on SD 12 and in Group 2 cats on SD 23. In Group 3, the serum phosphorus increased in all 5 of the cats. In Group 4, the serum phosphorus increased in 4 of the 5 cats and decreased slightly in 1. In Group 2, the serum phosphorus increased in 5 of the 6 cats and remained unchanged in 1 cat. In comparison, the serum phosphorus in the control group increased slightly in 3 cats and decreased slightly in 3 cats. The increased values did not exceed the reference range for any cat and generally returned to baseline by SD 97.

Another cat in Group 3 showed mild but clinically relevant increases in serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels post-dosing on SD 12. There was no clinically relevant change in other liver enzymes or total bilirubin. This cat also had a concurrent 50% increase in serum creatinine post-dosing on SD 12 that was near the upper end of the reported reference range. The increases in ALT, ALP, and creatinine on SD 12 decreased by SD 97. None of the reported values were outside reported reference ranges for this study and there did not appear to be other clinical signs related to hepatic or renal disease in this cat. The cause for the changes were not identified, but a direct drug effect or an indirect effect from reduced perfusion caused by increased blood viscosity secondary to polycythemia could not be ruled out in this cat.

Conclusion: The study results support the safety of molidustat oral suspension administered at the conditional oral daily dose of 5 mg/kg BW for the control of nonregenerative anemia associated with chronic kidney disease (CKD) in cats. The most frequent adverse reaction was vomiting. A mild treatment-associated increase in serum creatinine and phosphorus was noted, which returned to baseline after cessation of molidustat administration

C. Field Safety from Interim Safety Analysis of Field Effectiveness Study

Title: Interim Safety Data Evaluation of Cats with Anemia Associated with Chronic Kidney Disease (CKD) in Phase II that Received Molidustat Sodium (BAY85-3934 Sodium). (Study No. 204080-1)

Study Dates: December 1, 2020 to June 18, 2021

Study Locations: Clinics in the United States (US) and European Union (EU) from the following locations enrolled cases in this study:

US Locations	EU Locations
Fort Collins, CO	Argenteuil, France
Manchester, CT	Bayonne, France

Putnam, CT
Stamford, CT
Lawrenceville, GA
Savannah, GA
Decatur, IL
Zachary, LA
Battle Creek, MI
Greensboro, NC
Mantua, NJ
Bartlesville, OK
Bryn Mawr, PA
Fort Washington, PA
Harleysville, PA
Quakertown, PA
Antioch, TN
Lumberton, TX

Boos, France
Gaillac, France
Pornic, France
Elmshorn, Germany
Munich, Germany
Pfaffenhofen, Germany
Paks, Hungary
Ermelo, Netherlands
Goutum, Netherlands
Ridderkerk, Netherlands
Braga, Portugal
Ferreiros Amares, Portugal
Padilhó, Portugal
Porto, Portugal

Study Design: The interim analysis of the study included only the second phase of a larger two-phase study. The first (effectiveness) phase (Phase 1) of the study was a multi-center, double-masked, randomized, placebo-controlled field effectiveness and safety study. The second (continuation) phase, which constitutes this interim analysis, was a multi-center, unmasked, non-randomized, uncontrolled field safety and effectiveness study.

Objective: This was an interim safety analysis of the ongoing Study 204080, which is evaluating the effectiveness and safety of Varenzin™-CA1 (molidustat oral suspension) to control anemia associated with CKD in cats. The objective of this interim safety data evaluation was to assess the safety data collected during the second phase (Phase 2) of the ongoing study.

Study Animals: The interim analysis included 55 cats (27 cases from 18 US sites and 28 cases from 17 EU sites [in 16 locations]), consisting of 30 males and 25 females, of various breeds, ranging in age from 5.2 to 23.4 years, and having initial body weights between 2.3 to 5.9 kilograms.

Experimental Design: For Phase 2, cats received 5 mg molidustat/kg BW orally for one to four treatment cycles. Each treatment cycle lasted approximately 28 consecutive days unless a PCV of 45% or greater was recorded. Treatment cycles were separated by a treatment pause of a minimum of 7 days. Treatment cycle length and the inter-treatment period length were at the discretion of the investigator. There was no control group during Phase 2 of the study. The study was conducted in accordance with Good Clinical Practice.

Inclusion Criteria: For Phase 1, the study included client-owned cats that had been diagnosed with nonregenerative anemia with a PCV below 28% at SD -7 (± 2) and SD 0, and chronic kidney disease (baseline serum creatinine greater than 1.8 mg/dL) on SD -7 or 0. Cats were otherwise in good general health or had stable chronic conditions that would not interfere with the study assessments. Cats were also required to have a systolic blood pressure less than 165 mmHg on either SD -7 or SD 0. Cats that survived through Phase 1 were automatically continued into Phase 2. Cats that were administered at least one

dose of Varenzin™-CA1 in Phase 2, and either completed the Phase 2 of the study or were removed from Phase 2 of the study prematurely by November 23, 2020, were included in the interim safety analysis.

Exclusion Criteria: Cats intended for breeding, pregnant or lactating female cats, cats with conditions that would confound the study assessments or prevent completion of the study, or cats with PCV > 28% were excluded from Phase 1 and, thus, from Phase 2 of the study.

Drug Administration: Cats received Varenzin™-CA1 (molidustat oral suspension) once daily in 28-day cycles. Treatment cycles were separated by a minimum treatment pause of 7 days; resuming treatment was at the discretion of the Investigator per in-clinic PCV results evaluated once every 7 to 14 days. The PCV had to be less than 28% to initiate the new treatment cycle. Phase 2 continued through 20 weeks of potential treatment (as appropriate per PCV results) and observation, providing up to four possible 28-day treatment cycles. If, at the end of the 20-week period, the cat was still in an active 28-day treatment cycle, treatment was continued until the cycle was complete and the cat was released from the study after the final office visit and evaluation.

Measurements and Observations: During the Phase 1 of the study, baseline physical examination, blood pressure, body weight, hematology, and serum chemistry were obtained prior to enrollment on SD-7. During Phase 2, physical examination, body weight, hematology, and serum chemistry were obtained on SDs 56, 84, 112, 140, and 168 (± 4 days for all time points) and at the time of any unscheduled visit(s); and if applicable, at the time of early removal from study. Blood pressure was measured prior to blood sampling and recorded on SD 35, 42, 56, 70, 84, 98, 112, 126, 140, 154, and 168 (± 4 days for all time points) and at the time of any unscheduled visit(s). PCV was evaluated at the study site on SDs 35, 42, 56, 70, 84, 98, 112, 126, 140, 154, 168 (± 4 days for all time points), at the time of any unscheduled visit(s), and, where necessary and if possible, at the time of early removal. Urinalysis with sediment examination and specific gravity measured via a refractometer was performed for cases completed at the end of SD 168 ± 4 days.

Statistical Methods: Descriptive summary statistics were provided for adverse events, physical examination data, and laboratory data collected at baseline (before Phase 1) and during Phase 2. The analysis was performed by an independent statistician to protect the masking of the ongoing Phase 1 study.

Results: Most cats responded with a typical pattern of increasing PCV while on treatment and a decrease of PCV when off treatment. The median duration of all treatment cycles was 28 days (range, 4 - 75 days). One cat's PCV rose above 45% by SD 23, causing the treatment cycle to be less than 28 days for this cat. The median treatment pause (time between treatment cycles) was 14 days (range 2 - 84 days). The average absolute change in PCV between treatment cycles was a decrease of 1.5% per week. Based on this interim analysis, it was determined that most cats only need a treatment pause of at least 7 days before a new treatment cycle is initiated to maintain their PCV above 28.

Adverse Reactions: Typical for cats with CKD, hypertension (systolic blood pressure > 160 mmHg) was common in these cats (36 of 55). There was no obvious pattern related to treatment periods or treatment pauses.

At enrollment into Phase 1, 31%, 47% and 22% of cats were in International Renal Interest Society (IRIS) Stage 2, 3, and 4 CKD, respectively. Weight loss (29 of 55 cats) and progression of kidney disease (22 of 50 cats) was common during the study. These results are typical for this population of cats; therefore, these results were not considered to be associated with administration of molidustat oral suspension.

Information in humans suggests that phosphate binders may decrease the absorption of HIF-PH inhibitors, which may reduce their effectiveness. Data from a limited number of cats in this analysis (7 cats) suggest that there is no discernable effect of concurrent use of aluminum hydroxide on the effectiveness of molidustat oral suspension as administered in this study.

Vomiting was the most frequently reported adverse reaction, either alone or with other events, reported in 19/55 (34.5%) cats in the analysis. Ten other cats vomited but were not recorded as adverse reactions because the investigator associated the vomiting with CKD. Therefore, in total, 29/55 (52.7%) of the cats in the interim analysis were reported as vomiting at some point in the study. Vomiting was more frequent on treatment days than during treatment pause.

Diarrhea accounted for eight adverse events in seven cats. Four cats had diarrhea observed during treatment pause, and three cats had a single episode of diarrhea on a treatment day.

Two cats had seizures during the study period of the interim analysis. One occurred in a cat with terminal uremia with severe anemia and dehydration, and one occurred in a cat that had severe hypertension and a history of a previous seizure a year or more before the within-study seizure. HIF-PH inhibitors and erythropoiesis-stimulating agents (ESAs) have been associated with seizure activity in humans; therefore, an effect on seizure activity by Varenzin™-CA1 in the second cat could not be excluded.

Conclusion: The interim study analysis results support the safety of repeat 28-day treatment cycles of Varenzin™-CA1 administered at the conditional oral daily dose of 5 mg/kg BW for the control of nonregenerative anemia associated with chronic kidney disease (CKD) in cats. Potential adverse effects observed included an increased risk for vomiting, and one cat with a history of a previous seizure had seizure activity while receiving the drug. Most cats should only need Varenzin™-CA1 treatment to be paused for at least 7 days before starting a new treatment cycle.

D. Exploratory Field Effectiveness Study

The study entitled "Evaluate the Efficacy and Safety of BAH002248 [molidustat] in Cats with Anemia Associated with Chronic Kidney Disease (CKD)" (Study No. 203575), which was summarized above under Reasonable Expectation of

Effectiveness, provided additional data to support the safety of molidustat oral suspension.

IV. HUMAN FOOD SAFETY

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

V. USER SAFETY

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

User Safety Warnings

Not for human use.

Keep this drug, including used syringes, out of reach of children.

Wash hands immediately after use and/or spillage.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician. Symptoms of exposure to molidustat may include the following: gastrointestinal effects (nausea, vomiting, diarrhea), blood and clotting effects (increases in reticulocytes, erythropoietin, and hemoglobin), dizziness, fainting, hypertension, changes in cardiac output and cardiac index, and increases in heart rate.

Symptoms may not occur immediately; therefore, the exposed individual should be monitored.

People with known hypersensitivity to molidustat sodium should avoid direct contact with this product and should administer the product with caution.

Women who are pregnant or may become pregnant should administer the product with caution. Molidustat administered orally to pregnant rats during the period of organogenesis was associated with adverse fetal outcomes.

Do not eat, drink, or smoke while handling this product.

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 Varenzin™-CA1, when used according to the label, is safe and has a reasonable expectation of effectiveness for the control of nonregenerative anemia associated with chronic kidney disease (CKD) in cats.

A. Conditional Approval Eligibility

In 2018, the legislation reauthorizing FDA's animal drug user fee program (Animal Drug User Fee Program, or ADUFA, IV) expanded the conditional approval pathway to allow certain additional new animal drugs that are not Minor

Use/Minor Species (MUMS) drugs to be eligible for conditional approval. As provided in section 571(a)(1)(A)(ii) of the FD&C Act, as amended by ADUFA IV, to qualify for conditional approval, the non-MUMS new animal drug must meet the following two criteria:

1. The new animal drug is intended to treat a serious or life-threatening disease or condition OR addresses an unmet animal or human health need; AND

2. A demonstration of effectiveness would require a complex or particularly difficult study or studies.

Varenzin™-CA1 was determined to be eligible for conditional approval under these provisions because it controls a serious or life-threatening disease or condition, addresses an unmet animal health need, and the demonstration of effectiveness requires a complex or particularly difficult study or studies. The condition, nonregenerative anemia associated with CKD in cats, is a disease or condition associated with mortality and morbidity that has substantial impact on day-to-day functioning in the target animal. Therefore, the conditionally approved use addresses a serious or life-threatening disease or condition. The control of nonregenerative anemia associated with CKD in cats was also determined to be an unmet animal health need because there is no approved animal drug currently being marketed in the United States for this use in cats. Finally, based on the need for a long study duration to establish effectiveness, it was determined that the demonstration of effectiveness requires a complex or particularly difficult study or studies.

B. Marketing Status

Varenzin™-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 nonregenerative anemia associated with CKD in cats and monitor the safe use of the product, including treatment of any adverse reactions.

C. Exclusive Marketing Rights

Varenzin™-CA1, as approved in our approval letter, does not qualify for exclusive marketing rights under section 573(c) of the FD&C Act because it is not a designated new animal drug under section 573(a) of the FD&C Act.

D. Patent Information

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