Date of Approval: February 25, 2026

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-596

Numelvi™

(atinvicitinib tablets)

Dogs

Numelvi™ is indicated for the control of pruritus associated with allergic dermatitis in dogs 6 months of age and older.

Sponsored by:

Intervet, Inc.

Executive Summary

Numelvi™ (atinvicitinib tablets) is approved for the control of pruritus associated with allergic dermatitis in dogs 6 months of age and older. The drug is a Janus kinase (JAK) inhibitor that is administered orally, once daily, with food.

Safety and Effectiveness

The sponsor conducted a field study in client-owned dogs to demonstrate that Numelvi™ is effective at controlling pruritus associated with allergic dermatitis for up to 28 days. The study included mixed breed and purebred dogs of both sexes, with a range of ages and weights. To be enrolled in the field study, a dog had to be diagnosed with allergic dermatitis by a veterinarian and have moderate pruritus as assessed by the owner. In a 1:1 ratio, dogs received either Numelvi™ or placebo tablets once daily beginning on Day 0. Treatment was given with food, and the placebo tablets were identical to the Numelvi™ tablets but did not contain the active ingredient, atinvicitinib.

A dog was considered a treatment success if the pruritus was reduced by ≥50% from baseline (Day 0) on at least 5 of the first 7 days of treatment. Compared to the placebo group, a higher proportion of dogs in the Numelvi™ group were treatment successes. Adverse reactions related to treatment with Numelvi™ included gastrointestinal signs (vomiting, upset stomach), and hematology and serum chemistry abnormalities, including leukopenia and increased hepatobiliary values. Current field safety data is limited to 28 days.

The sponsor conducted a laboratory margin of safety study in young, healthy, male and female beagles. The dogs were administered Numelvi™ once daily at 0X, 1X, 3X, or 5X the maximum intended dose of 1.2 mg/kg per day for 183 to 184 consecutive days. Dogs in the 0X group were sham dosed. The tablets were given to dogs in the fed state for maximum drug exposure. Treatment with Numelvi™ was associated with generalized demodicosis with secondary dermal inflammation in the 5X group (1 dog), interdigital furunculosis in the 3X and 5X groups (1 dog in each group), and with lower mean testes weight in all Numelvi™ groups.

The sponsor also conducted a vaccine response study to evaluate how Numelvi™ affects the response to vaccination. Young, healthy, male and female beagles that had never been previously vaccinated were administered Numelvi™ once daily at 0X or 3X the maximum intended dose of 1.2 mg/kg per day for 84 consecutive days. Dogs in the 0X group received a placebo. The tablets were given to dogs in the fed state for maximum drug exposure. A canine multivalent modified live virus (MLV) vaccine was administered on Days 28 and 56. A single dose of a killed rabies virus (RV) vaccine was administered on Day 28. Starting on Day 84, there was an 84-day recovery period in which all dogs did not receive Numelvi™ or placebo. The results of the study demonstrate that Numelvi™ administration at 3X the maximum labeled dose for 84 days did not interfere with the ability to mount adequate immune responses to canine adenovirus type-2 (CAV), canine distemper virus (CDV), canine parvovirus (CPV), and rabies virus vaccinations.

Conclusion
Based on the data submitted by the sponsor for the approval of Numelvi™, the Food and Drug Administration (FDA) determined that the drug is safe and effective when used according to the labeling.

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I. GENERAL INFORMATION

A. File Number

NADA 141-596

B. Sponsor

Intervet, Inc.
126 E Lincoln Ave
Rahway, NJ 07065

Drug Labeler Code: 000061

C. Proprietary Name

Numelvi™

D. Drug Product Established Name

atinvicitinib tablets

E. Pharmacological Category

Immunosuppressant

F. Dosage Form

Tablet

G. Amount of Active Ingredient

4.8, 7.2, 21.6, or 31.6 mg of atinvicitinib per tablet

H. How Supplied

Numelvi™ is available in scored tablets in four strengths: 4.8 mg, 7.2 mg, 21.6 mg, and 31.6 mg per tablet. Each tablet strength is available in 30 and 90 count bottles. Each tablet is marked with an S, M, L, or XL that corresponds to the different tablet strengths.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Numelvi™ should be administered orally, once daily, with food, at a dose of 0.36 to 0.54 mg atinvicitinib/lb (0.8 to 1.2 mg atinvicitinib/kg) body weight.

K. Route of Administration

Oral

L. Species

Dogs

M. Indication(s)

Numelvi™ is indicated for the control of pruritus associated with allergic dermatitis in dogs 6 months of age and older.

II. EFFECTIVENESS

A. Dosage Characterization

1. Pharmacological Properties of Numelvi™

Atinvicitinib is a Janus kinase (JAK) inhibitor. It inhibits the function of a variety of pruritogenic, pro-inflammatory, and allergy related cytokines that are dependent upon JAK enzymes. Atinvicitinib is more selective for JAK1 compared to JAK2, JAK3, and tyrosine kinase 2 (TYK2). Atinvicitinib is not a corticosteroid or an antihistamine.

Following a single oral (1.2 mg/kg) or intravenous (0.3 mg/kg) administration of atinvicitinib in the fed state, the geometric mean oral bioavailability based on area under the curve from the time of dosing to the last quantifiable plasma concentration (AUC_{last}) was 45.5%. The mean systemic clearance following intravenous administration was 1,074 mL/h/kg with a geometric mean terminal half-life of 1.1 hour. The mean volume of distribution was 1,651 mL/kg (n=8).

Following a single oral administration of atinvicitinib at 1.2 mg/kg, the maximum plasma concentration (C_{max}) and AUC_{last} were 280% and 120% higher, respectively, in the fed state as compared to the fasted state (n=16). Atinvicitinib is mainly excreted in the feces while urinary elimination is a minor route of excretion. Atinvicitinib has moderate protein binding with 82.3% bound in fortified canine plasma at concentrations of 1,802 ng/ml (5 µM).

2. Dose Selection

Pharmacokinetic modeling and *in vitro* potency cell-based pathway engagement assays were used to select doses of atinvicitinib that would result in a maximum plasma concentration near the JAK1 half-maximal inhibitory concentration (IC_{50}). Oral doses of 0.5 mg/kg and 1 mg/kg of atinvicitinib were then evaluated *in vivo* using a canine IL-31 challenge model. Both doses were associated with a reduction in pruritus scores.

A masked, randomized, placebo-controlled, multi-site pilot field study was conducted in 61 client-owned dogs (42 atinvicitinib, 19 placebo) diagnosed with atopic dermatitis. Dogs were administered atinvicitinib at 2 dose ranges (0.4 to 0.6 mg/kg orally twice daily for 14 days, followed by the same dose administered once

daily for an additional 14 days, or 0.8 to 1.2 mg/kg orally once daily for 28 days) or placebo for 28 days. Effectiveness was assessed by owner scoring of pruritus utilizing a validated pruritus visual analog scale (PVAS), and investigator scoring for the extent and severity of skin lesions using the Canine Atopic Dermatitis Extent and Severity Index version 4 (CADESI-4). When comparing the 2 dosing regimens, dogs treated with 0.8 to 1.2 mg/kg of atinvicitinib once daily achieved more effective control of pruritus and improvement of skin lesions associated with atopic dermatitis than dogs administered 0.4 to 0.6 mg/kg of atinvicitinib twice daily. Therefore, a dosage of 0.8 to 1.2 mg/kg administered orally once daily was selected for further investigation.

B. Substantial Evidence

1. Field Study for Control of Allergic Dermatitis

Title: Evaluation of Field Safety and Effectiveness of a Novel Oral JAK-1 Inhibitor (AH386526 30 mg/g oral tablets for dogs) Compared to Placebo Control for the Control of Pruritus Associated with Allergic Dermatitis in Dogs. (Study Number S21069-00)

Study Dates: February 28, 2022 to July 8, 2024

Study Locations:

Investigators included board-certified diplomates of the American College of Veterinary Dermatology (DACVD) and general veterinary practitioners.

Arlington, MA	Leawood, KS
Bartlesville, LA	Maple Grove, MN
Baton Rouge, LA	Muncy, PA
Battle Creek, MI	Navarre, FL
Bethlehem, PA	Overland Park, KS
Brandon, MS	Pittsburgh, PA
Columbia, SC	Quakertown, PA
Crescent Springs, KY	Raleigh, NC
Dallas, TX	Salt Lake City, UT
Decatur, IL	Spring Hill, TN
Fort Collins, CO	Wendell, NC
Gainesville, FL	West Palm Beach, FL
Harrisburg, PA	Zachary, LA

Study Design:

Objective: To evaluate the effectiveness and safety of once daily oral administration of Numelvi™ for the control of pruritus associated with allergic dermatitis.

Study Animals: The study enrolled 289 client-owned dogs, 152 males and 137 female dogs, diagnosed with allergic dermatitis. Of the enrolled dogs, 144 were mixed-breed and 145 were pure-bred dogs, ranging in age from 7.9 months to 15

years old and weighed between 2.5 kg to 58.2 kg. Commonly represented breeds enrolled were the American Pit Bull Terrier (4.5%), Golden Retriever (4.2%), and Labrador Retriever (3.8%). Enrolled dogs were diagnosed with at least one of the following presumptive diagnoses for allergic dermatitis: atopic dermatitis, contact dermatitis, flea allergy dermatitis, food hypersensitivity, or unspecified allergic dermatitis. See Table II.1 below for the presumptive diagnoses at enrollment for each treatment group. Enrollment required a PVAS score of 6 (corresponding to moderate itching) as assessed by the owner. Dogs could be enrolled with concurrent health conditions if they were stable with their current treatment regimen and healthy enough to participate, as evaluated by the Investigator. Dogs were required to be on a flea treatment or preventative throughout the study. Concomitant use of therapies which may interfere with the evaluation of effectiveness (glucocorticoids, cyclosporine, topical anesthetics, or other JAK inhibitors) were not allowed on study and required a wash-out period prior to enrollment.

Table II.1. Presumptive Diagnoses at Enrollment

Presumptive Diagnoses for Allergic Dermatitis*	**Numelvi™ Percentage (%) of Dogs N=145†**	**Placebo Percentage (%) of Dogs N=144**
Atopic Dermatitis‡	84.1	84
Contact Dermatitis	9.7	14.6
Flea Allergy Dermatitis	10.3	11.1
Food Hypersensitivity	29.7	34
Unspecified	24.8	28.5

* Dogs may have more than one diagnosis at enrollment.
† One dog was enrolled but did not receive any treatment.
‡ 40.7% of Numelvi™-treated dogs and 36.1% placebo dogs had atopic dermatitis as the sole presumptive diagnosis.
N=Number of dogs

Experimental Design: This study was a masked, randomized, placebo-controlled, multi-site field study to assess the effectiveness and safety of Numelvi™ for the control of pruritus in dogs diagnosed with allergic dermatitis. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Effectiveness was determined on Day 7 by the reduction from baseline of pruritus as assessed by the owner on the PVAS. Dogs enrolled in the study were randomized to receive once daily Numelvi™, at 0.8 to 1.2 mg/kg, or placebo for 7 days. An optional continuation phase was offered from Days 8 to 28, in which a dog could continue their assigned treatment.

Dogs were randomly assigned within each site, in a 1:1 ratio of Numelvi™ to placebo, in order of enrollment. The treatment dispenser was the only unmasked study participant at each study site. The investigator, owner(s), and all other site personnel were masked to treatment assignments.

Table II.2. Treatment Groups

Treatment Group	Daily Dose Administered	Number of Dogs
Numelvi™	0.8 – 1.2 mg/kg	144
Placebo*	0.0 mg/kg	144

*Placebo was the formulated tablet without the active ingredient, atinvicitinib.

Drug Administration: Dogs were administered Numelvi™ or placebo tablets once daily, at approximately the same time each day, beginning on Day 0. The appropriate combination of tablet strengths (including half tablets) or the equivalent number of placebo tablets was administered to each dog based on their body weight. Placebo tablets were identical in appearance to the Numelvi™ tablets, containing all the same ingredients except for atinvicitinib. The assigned treatment was to be given with food.

Measurements and Observations: Physical examinations, hematology, serum chemistry, urinalysis, baseline assessments of pruritus on PVAS (by owner), and baseline assessment of dermatitis by the veterinarian using a dermatitis visual analog scale (DVAS) were recorded at enrollment on Day 0.

Owner assessments of pruritus on the PVAS were recorded daily at home on Days 1 to 7. The PVAS is a 10 cm vertical line with text descriptors of severity and behavior corresponding to degrees of itchiness, with 0 being a normal dog and 10 indicating extremely severe itching. Investigator assessments of dermatitis on the DVAS were recorded at clinic visits on Day 7. The DVAS is a scale from 0 to 10, with 0 being no dermatitis present, and 10 being extremely severe dermatitis. Owner diaries recording treatment administration and owner observations were completed daily while the dog was in the study. Physical examinations, hematology, serum chemistry, and urinalysis were conducted at Day 7.

For dogs enrolling in the optional continuation phase, physical examinations, hematology, serum chemistry, urinalysis, and investigator assessment of dermatitis (using the DVAS) were conducted on Day 28.

Treatment success for each dog was defined as at least a 50% reduction from baseline (Day 0) in owner assessed PVAS score for pruritus on at least 5 out of the first 7 days of treatment. Dogs that did not achieve at least 50% reduction in pruritus on 5 out of the first 7 days were considered treatment failures. Dogs that were electively withdrawn from the study due to perceived lack of effectiveness, or due to an adverse event on or before Day 7, were considered treatment failures.

Statistical Methods: Treatment success on Day 7 was assessed as a comparison of treatment success in each group, using a generalized linear mixed model (GLMM) for binomials with a logit link. The statistical model included treatment as a fixed effect, and site and the site-by-treatment interaction as random effects. Estimated success proportions, their standard

errors and corresponding 95% confidence intervals (CI) were obtained by back transformations (ILINK) from the GLMM least squares (LS) estimates.

Effectiveness was established if the proportion of dogs achieving treatment success in the Numelvi™ group was statistically significantly different from ($p \leq 0.05$) and numerically greater than that in the placebo group.

Results:

Two hundred fifty dogs (125 Numelvi™, 125 placebo) were included in the effectiveness analysis.

Primary Effectiveness at Day 7:
The proportion of dogs that were treatment successes in the Numelvi™ group was significantly different from (p=0.0128) and greater than the placebo group. See Table II.3 below.

Table II.3. Estimated Proportion of Dogs Achieving Treatment Success on Day 7

Treatment Group	Number of Dogs with Treatment Success	Estimated Proportion of Success*	95% Confidence Interval
Numelvi™ (N=125)	31	0.23	(0.14, 0.36)
Placebo (N=125)	10	0.07†	(0.03, 0.15)

* Based on back-transformed least squares means
† Placebo vs Numelvi™ p=0.0128
N=Number of dogs

Secondary Effectiveness Variables Assessed for PVAS Scores:
The estimated mean PVAS scores for the Numelvi™ group were lower than the placebo group at all time points after Day 0.

Table II.4. Mean Owner-Assessed PVAS Scores (in cm) by Day

Day	Numelvi™ Group Mean* (N)	Placebo Group Mean* (N)
0	7.4 (125)	7.6 (125)
1	5.9 (113)	6.7 (114)
2	5.2 (123)	6.3 (124)
3	4.7 (123)	6.1 (122)
4	4.1 (123)	5.8 (122)
5	3.7 (120)	5.6 (122)
6	3.4 (123)	5.4 (120)
7	3.3 (113)	5.4 (106)

* The arithmetic mean of owner-assessed PVAS scores.
N=Number of dogs with data for that time point

Secondary Effectiveness Variables Assessed for Investigator DVAS Scores:
The mean DVAS scores for the Numelvi™ group were lower than the placebo group at all time points.

Table II.5. Mean Investigator-Assessed DVAS Scores by Day

Day	Numelvi™ Group Mean* (N)	Placebo Group Mean* (N)
0	4.9 (125)	5.2 (125)
7	2.4 (122)	3.9 (119)
28	1.5 (75)	2.7 (41)

* Arithmetic means
N=Number of dogs with data for that time point

Adverse Reactions: Two hundred eighty-eight (144 Numelvi™, 144 placebo) enrolled dogs received at least one dose of their assigned treatment and were evaluated for safety.

Adverse reactions seen during the field study are summarized in Table II.6 below.

Table II.6. Adverse Reactions through Day 28

Adverse Reaction	Numelvi™ (N=144) Number of dogs (%)	Placebo (N=144) Number of dogs (%)
Vomiting or nausea	10 (6.9%)	6 (4.2%)
Otitis externa	9 (6.3%)	8 (5.6%)
Hematuria (without urinary tract infection)	7 (4.9%)	6 (4.2%)
Anorexia	6 (4.2%)	5 (3.5%)
Bacterial skin infection	6 (4.2%)	10 (6.9%)
Diarrhea	6 (4.2%)	15 (10.4%)
Crystalluria	5 (3.5%)	2 (1.4%)
Lethargy	5 (3.5%)	5 (3.5%)
Urinary tract infection	5 (3.5%)	5 (3.5%)
Upset stomach, including flatulence, retching, and bloating	3 (2.1%)	0 (0%)
Neurological disorder (e.g., tremors, ataxia)	2 (1.4%)	1 (0.7%)
Ocular discharge	2 (1.4%)	1 (0.7%)
Coughing	1 (0.7%)	0 (0%)
Granuloma	1 (0.7%)	0 (0%)
Increased urination	1 (0.7%)	0 (0%)

Abnormal hematology results likely related to Numelvi™ administration included leukopenia, neutropenia, eosinopenia, monocytopenia, and lymphocytosis.

Abnormal serum chemistry results likely related to Numelvi™ administration included increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), symmetric dimethylarginine (SDMA), and hypercholesterolemia.

Three Numelvi™ treated dogs withdrew from the study early due to an adverse reaction, two of which were considered likely related to Numelvi™ treatment (i.e., diarrhea). Two placebo treated dogs also withdrew from the study early due to an adverse reaction (i.e., diarrhea).

Conclusions: Once daily treatment with Numelvi™ at the dose of 0.8 to 1.2 mg/kg was effective for the control of pruritus associated with allergic dermatitis in client-owned dogs. Gastrointestinal (e.g., vomiting, upset stomach) signs, and leukogram and serum chemistry abnormalities, including increased hepatobiliary parameters, are considered related to Numelvi™ administration.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study

Title: A 6-Month (183/184-Day) Pivotal Target Animal Safety (TAS) Study of AH386526 30 mg/g Oral Tablets in Beagle Dogs (Study Number S21024-00-JKD-TAS-CN)

Study Dates: June 30, 2021 to May 16, 2023

Study Location: Tranent, East Lothian, United Kingdom

Study Design:

Objective: To evaluate the safety of Numelvi™ when orally administered once daily at 1, 3, and 5X the maximum labeled dose (1.2 mg/kg/day), in the fed state, to 6-month-old Beagle dogs for 183 to 184 consecutive days.

Study Animals: The study included 32 6-month-old beagle dogs (16 male and 16 female) weighing between 4.3 and 9.0 kg and determined to be healthy based on physical examination, food consumption data, clinical pathology findings, and results from fecal analyses for parasitic ova during acclimation.

Experimental Design: Within each sex, a complete randomization of dogs to dose group was performed. Within each sex and dose group, dogs were then randomly assigned to pairs, and the pairs were randomized to cage location. For pair-housing, a divider between two cages was open to permit co-mingling of the dog pair. Dogs were separated for dosing, post-dose observations, feeding, monitoring, and/or health purposes. All study personnel conducting clinical observations were masked to treatment assignment. The study was conducted in accordance with Good Laboratory Practice (GLP) regulations.

Table III.1. Treatment Groups

Group	Dose (mg/kg)	Number and Sex of Dogs
Control*	0	4 males, 4 females
1X	1.2	4 males, 4 females
3X	3.6	4 males, 4 females
5X	6.0	4 males, 4 females

*Control group was sham dosed

Drug Administration: Dogs in the Numelvi™ treatment groups were administered the commercial formulation of Numelvi™ once daily at 1, 3, or 5X the maximum labeled dose of 1.2 mg/kg/day for 183 to 184 consecutive days. Dogs in the control group were sham dosed. Dogs were dosed in the fed state, the prandial state of maximum exposure. Treatments started on Day 1.

Measurements and Observations: General health observations were conducted twice daily and detailed clinical observations were conducted once weekly throughout the study. Cage-side observations (once daily during the acclimation period), pre-dose observations (0 to 1 hours before each dose), post-dose observations (0 to 2 hours and 5 to 6 hours after each dose), veterinary physical examinations (Days -30/-28, -1, 2, 8, 15, then every 14 to 5 days, and 1 day prior to euthanasia), ophthalmic examinations (Days -9, -2, 2, 100, and 1 day prior to euthanasia), and fecal screening for endoparasites (during the acclimation period, and Days 5 and 183) were conducted. Body weight (weekly from the day of arrival and on the day of scheduled necropsy) and food consumption (daily) were recorded. Blood and urine samples were collected for clinical pathology evaluation (hematology, coagulation, serum chemistry, C-reactive protein, urinalysis) and feces were evaluated for the presence of abnormalities (e.g., change in consistency, color, presence of blood or mucous) on Days -13, -6, 2, 3, 20, 48, 76, 104, 128, 160, and 183. Blood samples for pharmacokinetic analysis were collected pre-dose and at 1, 2, 4, 6, 8, 10, 12, and 24 hours post-dose on Days 1, 43, 85, 147, and 182. A complete necropsy with organ weights, bone marrow evaluation, and microscopic examination was completed at the end of the study (Day 183 or 184).

Statistical Methods: The dog pair (i.e., cage) was used as the experimental unit for statistical analysis. Descriptive statistics were presented for the following numeric parameters: vital signs (heart rate, respiration rate, body temperature), body weight, weekly food consumption, hematology, serum chemistry, coagulation, C-Reactive protein, urinalysis, and organ weights (absolute, relative to terminal body weight and relative to brain weight). For binary/categorical data, an event that occurred in one or both dogs in a cage was counted as one event for the experimental unit. If both dogs in a cage had events, the worst categorical level of the two dogs was reported for the cage.

Results: One serious adverse reaction occurred in one 5X group dog who developed generalized demodicosis resulting in euthanasia on Day 175.

Clinical Observations and Physical Examinations: Numelvi™-related clinical observations included one dog in the 5X group that developed progressive alopecia, fever, lethargy, generalized lymphadenitis, interdigital furunculosis (cysts), interdigital swelling, and pustules on the border of the oral cavity. The dog had a declining clinical condition under continued treatment with Numelvi™ and was euthanized on Day 175. The dog had greater systemic exposure to Numelvi™ (higher C_{max} and AUC_{last} values) compared to other dogs in the 5X group. One dog in the 3X group developed a single interdigital cyst.

Clinical Pathology: There were no Numelvi™ related effects on clinical pathology.

Pathology: The clinical observations observed in the 5X group dog euthanized on Day 175 correlated histologically with the presence of mild to moderate *Demodex canis* mites in the hair follicles; marked, chronic, active, focal dermal inflammation in the forelimbs; and minimal multifocal neutrophilic infiltration in the mandibular lymph node. The generalized demodicosis in combination with overt clinical disease observed in the 5X group dog was considered due to Numelvi™-induced immunosuppression. *Demodex canis* was not identified in the hair follicles of the 3X group dog with the interdigital cyst.

Male dogs in the Numelvi™ treatment groups had decreased mean testes weight compared to the control dogs. Microscopic pathology findings in one 1X dog with pre-existing unilateral cryptorchidism and one 3X dog included unilateral, focal, minimal testicular tubular hypoplasia.

Pharmacokinetics: Following oral administration of Numelvi™ to adult beagle dogs, Numelvi™ was rapidly absorbed. Pharmacokinetics were similar between males and females. Minimal accumulation was observed between Days 1 and 182 with geometric mean accumulation ratios for maximum concentration (C_{max}) and area under the curve from the time of dosing to the last quantifiable plasma concentration (AUC_{last}) of 1.0 and 1.2. AUC_{last} and C_{max} increased in a linear but less than proportional manner where a 5-fold increase in dose resulted in a 4.5-fold (95% confidence interval (CI): 3.6 to -5.3) and 3.7-fold (95% CI: 3.1-4.2) increase in AUC_{last} and C_{max}, respectively.

Table III.2. Mean of Atinvicitinib Plasma Pharmacokinetic Parameters (1.2 mg/kg, Day 182)

Parameter	Geometric Mean (Coefficient of Variation %)
C_{max} (ng/mL)	196 (49%)
T_{max} *(h)	2 (range: 1-6)
AUC_{last} (h*ng/mL)	861 (27%)
AUC_{inf} (h*ng/mL)	909 (24%)
$t_{1/2}$ (h)	2.2 (25%)

*Median and range
h=hour
C_{max}=maximum plasma concentration
T_{max}=time to maximum plasma concentration
AUC_{last}=area under the curve from the time of dosing to the last quantifiable plasma concentration
AUC_{inf}=area under the curve from the time of dosing extrapolated to infinity
$t_{½}$=half-life

Conclusion: The study supports the safe use of Numelvi™ when used according to the label directions. Numelvi™ was associated with generalized demodicosis with secondary dermal inflammation, interdigital furunculosis, and lower mean testes weight.

B. Vaccine Response Study

Title: Pivotal Multi-Site Vaccine Response Study in Dogs following Daily Oral Administration of AH386526 30 mg/g Oral Tablets for Dogs at 3 times the Maximum Clinical Dose over 84 Days (Study Number: S21041-00)

Study Dates: October 29, 2021 to October 23, 2023

Study Location: Boxmeer, The Netherlands

Study Design:

Objective: The primary objective of this study was to assess the effect of Numelvi™ administration on the immune response to vaccination in dogs. The secondary objective was to monitor the general health of the dogs following Numelvi™ administration and vaccination.

Study Animals: Twenty, 6-month-old, vaccine-naïve beagle dogs (12 female, 8 male), weighing between 6.9 to 12.3 kg at the initiation of dosing, were included in the study. Dogs were determined to be clinically healthy and confirmed naïve (negative serum titer levels for all viruses tested) during the pre-treatment phase.

Experimental Design: Within each sex, the dogs were randomly assigned to two treatment groups in blocks of two. After randomization, housing groups were manually assigned, and each treatment group was housed in separate bio-contained rooms. The dogs in each treatment group were pair housed and remained with the pre-specified

pairs within a pen. Dogs were separated for dosing for 1 to 2 hours to allow for individual monitoring. Dogs were taken out of the pen and individually assessed during clinical monitoring, veterinary examinations, blood sampling, and vaccination procedures. All study personnel conducting clinical observations were masked to treatment assignment. The study was conducted in accordance with GLP regulations.

Table III.3. Treatment Groups

Group	Dose (mg/kg)*	Number and Sex of Dogs
Numelvi™	3.6	4 males, 6 females
Control (placebo)	0	4 males, 6 females

*Administered once daily for 84 days

Drug Administration: Dogs in the Numelvi™ treatment group and control group were administered the commercial formulation of Numelvi™ once daily at 3X the maximum labeled dose of 1.2 mg/kg/day or placebo tablets, respectively, once daily for 84 consecutive days. Dogs were dosed in the fed state, the prandial state of maximum exposure. After the last dose on Day 84, all dogs were observed for an additional 84 days, for a total study duration of 168 days.

A multivalent modified live vaccine containing CAV, CDV, and CPV was administered on Days 28 and 56. A single dose of killed RV vaccine was administered on Day 28.

Measurements and Observations: General health observations and detailed clinical observations were conducted at least once daily throughout the study. During the treatment phase (Days 0 to 84), the clinical observations took place one hour after dosing. Veterinary physical examinations were conducted on Days -14, -1, 28, 56, 84, 112, 140, and 168; and unscheduled veterinary examinations were conducted when abnormal findings were noted during clinical observations. Body weights were recorded weekly during the pre-treatment and treatment phases, and monthly during the post-treatment phase (Days 85 to 168). Fecal screening for endoparasites was conducted prior to the first treatment. *Cryptosporidium* was identified in the feces of dogs of both groups on the fecal screening for endoparasites, therefore the dogs were screened weekly for *Cryptosporidium* until the infection resolved. Blood and urine samples were collected for serology (serum antibody titers) and clinical pathology evaluation (hematology, serum chemistry, urinalysis) on Days -14, -1, 28, 56, 84, and 168. Blood samples for bioanalysis were collected on Days -1, 28, 56, 77/78, and 84.

Statistical methods: The primary variable for immune response was the serum antibody titer levels on Day 84. All dogs were classified as having an adequate immune response if they were at or above the specified adequate titer (CAV≥16, CDV≥32, CPV≥80, and RV>0.5 IU/mL) for each antigen on Day 84. Using the individual animal data and pen data separately, descriptive statistics were performed on clinical pathology, body weights, clinical observations, and serology.

Results: On Day 84, all dogs in the Numelvi™ treatment group achieved adequate serum titer levels. There were no Numelvi™ related adverse clinical effects.

Conclusion: Numelvi™ administered at 3X (3.6 mg/kg) the intended maximum labeled dose of 1.2 mg/kg/day for 84 days does not interfere with the ability of vaccine naïve dogs to mount an immune response to CAV, CDV, CPV, and RV vaccinations. No treatment related adverse clinical effects were observed.

C. Pilot Target Animal Safety Study

In a pilot study (Study No. S16215-00), the safety of atinvicitinib was evaluated in 40 (20 male, 20 female) adult beagle dogs (8 dogs per group). Dogs in the treated groups were administered a non-final formulation of atinvicitinib at 0.83, 2.5, or 4.2X the daily maximum labeled dose of 1.2 mg/kg/day for 42 days. Control dogs received placebo tablets.

Table III.4. Treatment Groups

Group	Dose (mg/kg/dose)	Total Daily Dose (mg/kg/day)	Number and Sex of Dogs
Control*	0	0	4 males, 4 females
0.83X*	0.5	1.0	4 males, 4 females
2.5X*	1.5	3.0	4 males, 4 females
4.2X*	2.5	5.0	4 males, 4 females
4.2X†	5.0	5.0	4 males, 4 females

* Dogs were dosed twice daily
† Dogs were dosed once daily

Atinvicitinib-related clinical pathology findings included a minimal to mild reduction in mean red blood cell mass (red blood cell count (RBC), hemoglobin (HGB), and hematocrit (HCT)). Mean RBC, HGB, and HCT remained within the reference range. A mild to moderate reduction in mean eosinophil counts was observed in the dogs administered atinvicitinib and a mild reduction was observed in the control dogs. Mean eosinophil counts remained within the reference range for all groups.

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, FDA 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 Numelvi™:

This product is not for human use. Keep this and all drugs out of reach of children. Wash hands thoroughly with soap and water immediately after handling tablets. In case of accidental ingestion, seek medical attention immediately.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that Numelvi™, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.

A. Marketing Status

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 rule out other diseases in the diagnosis of allergic dermatitis, and to monitor and ensure the safe use of the product, including treatment of any adverse reactions.

B. Exclusivity

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

C. Patent Information

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