STANDARD ARTICLE

Safety and efficacy of orally administered telmisartan for the treatment of systemic hypertension in cats: Results of a double-blind, placebo-controlled, randomized clinical trial

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Background: Information regarding the efficacy of telmisartan for feline systemic arterial hypertension is limited.

Objectives: To evaluate the safety and efficacy of PO administered telmisartan solution in hypertensive cats.

Animals: Client-owned cats with indirect systolic arterial blood pressure (SBP) of 160-200 mm Hg, based on multiple measurements.

Methods: This multicenter trial consisted a 28-day, prospective, randomized, double-blind, placebo-controlled, parallel group, efficacy phase and a 154-day extended-use telmisartan phase. Hypertensive cats were randomly assigned to receive 1.5 mg telmisartan/kg PO q12h for 14 days, followed by 2 mg telmisartan/kg PO q24h, or equivalent volume of placebo. Systolic blood pressure was measured on days 0, 14, and 28. Change in SBP compared to baseline was calculated for days 14 and 28. Telmisartan efficacy was defined as significant decrease in SBP at day 14 compared to placebo and a clinically relevant (>20 mm Hg) decrease in SBP at day 28.

Results: Two-hundred twenty-one cats were included. On day 14, least squares mean (95% confidence interval) SBP decrease was significantly larger in telmisartan-treated (−23.3 mm Hg [−28.2 to −18.3]) versus placebo-treated (−7.5 mm Hg [−13.6 to −1.5]) cats (P = .0005). On day 28, telmisartan treatment resulted in a clinically relevant SBP decrease (−23.9 mm Hg [−27.8 to −20.0]) whereas placebo did not (−11.6 mm Hg [−17.4 to −5.9 mm Hg]). The decrease in SBP persisted over the 6-month trial in telmisartan-treated cats.

Conclusions and Clinical Importance: Telmisartan significantly decreased SBP to a clinically relevant extent and was well tolerated in hypertensive cats.

KEYWORDS
angiotensin receptor blocker, antihypertensive, blood pressure, cardiovascular, cat, RAAS, renin-angiotensin-aldosterone system

1 INTRODUCTION

Systemic arterial hypertension (HT) is an important cause of morbidity in older cats, frequently occurring in cats with chronic kidney disease (CKD) or hyperthyroidism.1–4 However, in approximately 20% of the affected cats, no apparent underlying condition is identified, and HT is considered idiopathic.4 Regardless of etiology, persistent, pathological increases in blood pressure (BP) may lead to ocular, cardiovascular,
and central nervous system injury,5–7 and may accelerate the decline in kidney function and worsen glomerulosclerosis in cats with CKD.5,9 Furthermore, HT is known to exacerbate proteinuria, a negative prognostic indicator in cats with CKD.10

Several factors likely contribute to the pathogenesis of HT in cats. In people, impaired renal sodium handling, excessive activation of the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system hyperactivity, and endothelial dysfunction, among other factors, may contribute to HT of renal origin.11 Results of clinical trials have identified the beneficial renoprotective and cardioprotective effects of RAAS blockade in people, which highlights the importance of the RAAS in HT development.12–14 The role of the circulating RAAS has been investigated in hypertensive cats with naturally occurring15–18 and experimentally-induced19,20 CKD, hyperthyroidism,21 and idiopathic hypertension.22 Hyperactivity of the RAAS has been identified in some, but not all, cases.

Drugs that inhibit the RAAS, including angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs), may be prescribed for their antihypertensive effects. The ARBs selectively antagonize the angiotensin II, subtype-1 (AT₁) receptor, which mediates the pathologic effects of the RAAS’s major effector, angiotensin II. These effects include vasoconstriction, intravascular volume expansion, and sympathetic nervous system activation, as well as induction of pro-inflammatory and profibrotic pathways and oxidative stress, among other factors.22

Telmisartan is a nonpeptide ARB used for the control of HT and cardiovascular protection in human patients. In a preclinical study of healthy cats, telmisartan more effectively attenuated the angiotensin I-induced increase in systolic arterial blood pressure (SBP) than did benazepril, losartan, irbesartan, and placebo, suggesting a potential advantage for the treatment of cardiovascular and renal diseases in this species.23 In a separate study, telmisartan treatment was associated with measurable decreases in indirectly measured SBP in awake, unstimulated cats.24 Most recently, the results of a large, double-blind, randomized clinical trial in Europe showed that, compared to placebo, daily PO administered telmisartan was associated with a significantly greater decrease in SBP (−19 ± 22.0 mm Hg versus −9 ± 17.7 mm Hg, respectively) after 14 days of treatment.25

Our objectives were to evaluate the safety and efficacy of PO administered telmisartan solution for decreasing SBP in cats with spontaneous HT. It was hypothesized that compared to placebo, daily telmisartan treatment would be associated with a significant and clinically relevant decrease in SBP within 28 days, that this effect would persist over a 6-month treatment period, and that drug administration would be safe over the same period.

2 | MATERIALS AND METHODS

2.1 | Trial design

This study was a 28-day multicenter, prospective, randomized (2:1), double-blind, placebo-controlled, parallel group trial, followed by a 154-day open-label extended-use telmisartan phase, carried out according to the guidelines of Good Clinical Practice.26

2.2 | Animals

Eligible participants were client-owned cats of either sex, intact, or neutered, and of any breed, for which average, indirect SBP of 160-200 mm Hg, inclusive, was documented on 2 separate clinic visits on different days. Cases were recruited from cats presented to participating veterinarians during routine clinical practice. If cats were affected by CKD, hyperthyroidism, or both, underlying disease had to be considered stable and well controlled, as described below. Informed owner consent was obtained before enrollment in the trial. All study protocols were reviewed by and conformed with the requirements of the US Food and Drug Administration’s Center for Veterinary Medicine before initiation of this study.

Cats were excluded from the trial if ≥1 of the following criteria were met: treatment with BP-modifying drugs (eg, ACEi, ARBs, beta-blockers, and alpha-adrenergic receptor blockers, calcium channel blockers, mineralocorticoid receptor antagonists, and diuretics) in the 7 consecutive days before screening; treatment with >1 dose of a nonsteroidal anti-inflammatory drug in the 14 consecutive days before screening; clinical signs or physical examination findings consistent with severe ocular or neurologic target organ damage (TOD; eg, blindness, retinal detachment, hyphema, moderate, or severe retinal bleeding); azotemia associated or suspected to be associated with prerenal or postrenal causes, acute kidney injury, or pyelonephritis; a diagnosis of CKD with severe renal azotemia as defined by International Renal Interest Society guidelines (ie, serum creatinine concentration >5.0 mg/dL; IRIS CKD stage 4); cats that were pregnant, lactating, or intended for breeding, and documentation of uncontrolled concurrent systemic disease including, but not limited to, uncontrolled hyperthyroidism, diabetes mellitus, or liver disease. Cats with historical or uncontrolled cardiogenic pulmonary edema, benign or malignant neoplasia (with the exception of slowly progressive benign dermal neoplasia), or anemia (HCT < 20%) requiring treatment other than iron supplementation, also were excluded.

Cats were designated according to concurrent disease as belonging to 1 of 4 subpopulations: CKD, hyperthyroidism, CKD and hyperthyroidism, or idiopathic HT. Diagnosis and staging of CKD was based on IRIS recommendations available at the time of data analysis (http://www.iris-kidney.com/guidelines/staging.html; last accessed May 3, 2018). Hyperthyroidism was considered controlled if serum thyroxine concentration was less than or equal to the upper limit of the laboratory reference range with dietary or medical treatment, or after radiotherapy or surgical treatment, for at least 4 weeks before screening. Cats were considered to have idiopathic HT if an underlying cause was not identified on physical examination or by blood and urine testing, which included CBC and serum biochemical analyses, urinalysis, urinary protein-to-creatinine ratio (UPC) and urine culture. Screening abdominal radiographic and ultrasonographic examinations were performed at the discretion of the attending clinician.

2.3 | Trial medications

Telmisartan solution (4 mg/mL) or an equivalent volume of visually identical placebo was administered PO at a dosage of 1.5 mg/kg q12h for 14 days, followed by 2 mg/kg PO q24h. These dosages were based on the results of a previous dose-finding study in normal cats, which identified the most effective decrease in SBP at dosages
Trial medication was administered by the owners, who maintained daily logs that were monitored at re-evaluations. At each visit, trial drug dose was recalculated based on contemporaneous body weight.

### 2.4 | Indirect BP determination

At all applicable visits, indirect SBP was determined by trained trial personnel using Doppler ultrasonography (Model 811-B; Parks Medical Electronics, Aloha, Oregon) in a manner consistent with guidelines set forth by the American College of Veterinary Internal Medicine.27 Efforts were made to maintain consistency by limiting the number of individuals who were responsible for SBP measurement at a given study site and by standardization of procedures. Cats were allowed a minimum of 10 minutes to acclimate in a quiet room before SBP measurement. Measurements were performed before examination or manipulation for any other scheduled procedures. Appropriate BP measurement cuff size was determined during the screening visit and, in addition to cuff location, was kept constant for the remainder of the trial. During each measurement session, 5 consecutive SBP measurements were recorded. The SBP for each session was determined by discarding the highest and lowest SBP results and taking the arithmetic mean of the remaining 3 measurements. Throughout this report, the term SBP refers to this average.

### 2.5 | Schedule of events

This trial consisted of a 28-day, double-blind placebo-controlled phase and a subsequent 154-day open-label extended-use phase, for a total of 182 days (± 1 week) on drug. Only telmisartan-treated cats that completed the efficacy period and for which SBP <180 mm Hg was documented on day 28 ± 2, and for which owner consent was obtained, were eligible for the extended-use phase. Overall trial design is outlined in Figure 1.

At the time of enrollment (day 0), physical examination data and SBP were obtained in all cats. Baseline fasted blood samples for CBC and serum biochemical analyses, and urine for urinalysis, UPC, and urine culture were collected at this visit if these data were not obtained at the time of screening or if screening did not occur within the 14 days preceding enrollment. For all visits, blood and urine samples were shipped by overnight courier to, and analyzed by, a single laboratory (IDEXX Laboratories, Inc, North Grafton, Massachusetts).

Scheduled re-evaluations were performed on days 14 ± 2, 28 ± 2, 56 ± 7, 98 ± 7, 140 ± 7, and 182 ± 7. During each visit, physical examination and SBP measurement were performed in all cats. In addition, CBC, serum biochemical analyses, urinalysis, UPC, and urine culture were repeated on days 28 ± 2, 98 ± 7, and 182 ± 7 in all cats, if deemed medically necessary by the attending veterinarian at other scheduled or unscheduled visits and at the time of removal from the trial.

Cats for which SBP of 120-180 mm Hg was documented at reevaluation were maintained on 2 mg/kg telmisartan q24h or an equivalent volume of placebo until removal from the trial. Trial drug dosage decreases were allowed in cats for which SBP <120 mm Hg was documented at any visit on or after day 14, scheduled or unscheduled. Dosage decreases were to 1 mg/kg q24h for cats receiving 1.5 mg/kg q12h or 2 mg/kg q24h, and to 0.5 mg/kg q24h for cats receiving 1 mg/kg q24h. During the extended-use phase of the study, dose escalation of telmisartan was allowed in those cats having undergone dosage reduction. If at any recheck, the cat's SBP was 160-180 mm Hg, and the previously prescribed dose was known to be too high, the investigator was allowed to choose an intermediate dosage (within the allowed range of 0.5-2.0 mg/kg q24h) to maintain SBP in the target range (120-160 mm Hg). Dosage escalation beyond 2 mg/kg PO q24h was not allowed.

Cats were removed from the trial (ie, “rescued”) and provided standard-of-care treatment for HT if SBP >180 mm Hg was measured on or after day 14. In addition, cats were removed from the trial if hypotension was documented at any visit, scheduled or unscheduled, and after dosage decrease to 0.5 mg/kg of telmisartan q24h (or equivalent volume of placebo) as described above. For the purposes of this trial, hypotension was defined as SBP <120 mm Hg in a cat with clinical signs of hypotension, or SBP <80 mm Hg with or without concurrent clinical signs of hypotension.

### 2.6 | Randomization and allocation

For each trial site, cats were block randomized to treatment group based on order of enrollment, using blocks of 3 with a ratio of 2:1 (telmisartan: placebo). Randomization tables were generated by the trial sponsor using a computer software program (SAS version 9.2; SAS

![Figure 1](image-url)  
**FIGURE 1** Overview of trial design. Bloodwork, complete blood count, and serum biochemical analyses; SBP, systolic arterial blood pressure measurement; UA, urinalysis; UC, urine culture; UPC, urinary protein-to-creatinine ratio.
Institute Inc., Cary, North Carolina). Treatment assignment was performed using a web-based, secure, electronic data capture system (VISION; Prelude Dynamics, LLC, Austin, Texas). For cases from a given trial site to be considered in the final analysis, the site must have ≥2 evaluable cats per treatment group. No more than 40% of the total number of enrolled cases could be contributed by a single study site.

2.7 | Blinding

Cat owners, trial monitors, participating veterinarians, and personnel participating in the clinical management of cases and samples were blinded to treatment assignment. Study drugs were prepared by the sponsor and provided directly to each study site with no further product preparation required. During the 28-day efficacy period, treatment assignment was disclosed only if necessary for the evaluation, treatment, or both of an adverse event; if such an event occurred before day 28 ± 2, the animal was removed from the trial. To determine the cat's eligibility for the extended-use phase of the trial, unblinding also occurred after a cat completed the entire 28-day efficacy period and the owner approved participation.

2.8 | Populations considered

Cats that were randomized and received at least 1 dose of trial medication comprised the intention-to-treat population. Cats that successfully fulfilled all trial eligibility criteria, had analyzable data available from at least the first scheduled visit (day 14 ± 2) and that adhered to the trial protocol with no major deviations, comprised the per-protocol population. Cats were designated according to concurrent disease as belonging to 1 of 4 subpopulations: CKD, hyperthyroidism, CKD and hyperthyroidism, or idiopathic HT; these designations were used for descriptive purposes only.

2.9 | Primary outcome variables

The primary outcome variables with respect to efficacy were change in SBP from baseline to day 14 ± 2 and from baseline to day 28 ± 2, calculated by subtracting baseline SBP from SBP at the time point of interest. A composite primary efficacy end point, defined a priori, was evaluated in the per-protocol population. First, to be considered effective, the magnitude of SBP decrease from baseline to day 14 ± 2 had to be significantly larger in the telmisartan as compared to placebo-treated group. Second, to establish clinical relevance, the magnitude of decrease in SBP from baseline to day 28 ± 2 must have been >20 mm Hg in the telmisartan-treated group. This threshold for clinical relevance was chosen to ensure a decrease in category of risk for future TOD regardless of baseline SBP, as advocated by the American College of Veterinary Internal Medicine consensus statement.27 The composite primary efficacy end point also was evaluated in the intention-to-treat population.

2.10 | Secondary outcome variables

Additional efficacy and safety outcomes of interest included percentage of cats requiring rescue, laboratory test findings, and adverse events. To facilitate comparison with the results of a previous study,28 the percentage of cats classified as “responders” also was calculated for each scheduled visit. Responders were defined as those for which SBP decrease to <150 mm Hg, or by at least 15% of baseline, was documented at the time point of interest. Percentage of cats classified as responders was calculated as (number of responders at the visit of interest/number of cats with SBP data available at the visit of interest) × 100%.

Adverse events were defined as any unfavorable or unintended observation that occurred after the use of trial medication, regardless of whether it was considered product-related. Adverse events were recorded and classified according to accepted guidelines.29 In addition to conventional serious adverse events (eg, death, severe injury), hypotension associated with clinical signs or requiring removal from the trial, and development or worsening of renal, cardiac, ocular, or central nervous system TOD, were considered serious adverse events for the purposes of this trial.

2.11 | Statistical methods

Commercial software was used for all statistical analyses (SAS version 9.2; SAS Institute Inc). Sample size was calculated by simulations that used estimates of SBP decrease variability and assumed that placebo- and telmisartan-treated cats would experience SBP decreases of 0 and 18 mm Hg, respectively. These estimates were based on data generated in a study of normal cats.24 Simulations conducted at 30 trial sites, each with 4 telmisartan- and 2 placebo-treated cats, indicated a power of at least 80% to detect a significant difference in SBP decrease between treatment groups, with an alpha level of 5%.

Analyses with respect to the composite primary efficacy end point and for the secondary outcomes of changes in laboratory variables were carried out by comparing treatment groups in the per-protocol population. The primary efficacy end point also was evaluated in the intention-to-treat population.

Change in SBP from baseline to day 14 was performed using a mixed linear model, which included a fixed effect of treatment group and the random effects of site and site-by-treatment group interaction and included the covariate baseline SBP and its interaction with treatment group. The interaction of baseline SBP with treatment group was not significant (P = .37); therefore, the final model did not include this interaction. Treatment group least squares means (LSM; 95% confidence interval [CI]) are reported. Evaluation of cats classified as responders at day 14 was performed using a generalized linear mixed model. The model included the fixed effect of treatment group and the random effects of site and site-by-treatment group interaction. The model utilized a binomial distribution and logit link. Treatment group LSM (95% CI) are reported. For day 28, frequency of responders for each treatment group is reported.

A nonparametric approach was utilized for the analyses of changes in laboratory variables from baseline to day 28 ± 2. The FREQ procedure of SAS with scores = rank was utilized for analysis, and the Cochran-Mantel-Haenszel statistic (generalization of Friedman’s test) controlling for site was used to determine if there was a significant treatment effect.
3 | RESULTS

Case recruitment, enrollment, and follow-up were conducted from August 2012 to October 2016 at 33 primary care veterinary clinics in the United States and Canada. A total of 7605 cats were screened; of these, 290 met the criteria for enrollment (Figure 2). Data from 2 cats that were enrolled initially were excluded, because these cats were removed from the trial before receiving trial medication. The remaining 288 cats comprised the intention-to-treat population, representing 33 trial sites. A total of 67 cats were excluded from the intention-to-treat population for various reasons, leaving 221 cats in the per-protocol population that represented 20 trial sites. Of the 121 telmisartan-treated cats successfully completing the 28-day efficacy period, 107 entered the subsequent extended-use phase.

Baseline demographic and clinical characteristics, including SBP, were similar between treatment groups in both the intention-to-treat and per-protocol populations. Any observed differences were small and considered clinically irrelevant (Table 1).

Of the per-protocol population, 173 of 221 (78.3%) cats completed the 28-day efficacy period. A total of 62 of 221 (28.1%) cats required rescue for SBP >180 mm Hg on or after the day 14 ± 2 visit, representing 30 of 142 (21.1%) telmisartan- and 32 of 79 (40.5%) placebo-treated cats. The majority of the 62 cats requiring rescue (25 placebo- and 16 telmisartan-treated) were rescued before the day 28 ± 2 visit, with the remaining cats (7 placebo- and 14 telmisartan-treated) rescued at the day 28 ± 2 visit. The SBP data for the 16 (11.2%) telmisartan-treated cats rescued before the day 28 ± 2 visit therefore were not available for analysis of the coprimary efficacy end point of clinical relevance. Five additional telmisartan-treated cats did not have analyzable SBP data for the day 28 ± 2 visit; 3 were removed from the trial because of development of new or worsening TOD, and data from the remaining 2 were not included because, in both instances, the cat was known to have missed >3 doses of trial medication before that visit.

During the 28-day efficacy period, no cat required removal from the trial because of hypotension. Dosage decreases were required in 19 of 142 (13.4%) telmisartan- and 4/79 (5.1%) placebo-treated cats.

On days 14 ± 2 and 28 ± 2, both telmisartan- and placebo-treated cats experienced a decrease in SBP (Figure 3A). Least squares mean (95% CI) change in SBP (mm Hg) from baseline to day 14 ± 2 was −23.3 (−28.2 to −18.3) and −7.5 (−13.6 to −1.5) for the telmisartan- and placebo- treated groups, respectively (P = .005). Furthermore, mean (95% CI) change in SBP (mm Hg) from baseline to day 28 ± 2 was −23.9 (−27.8 to −20.0) for telmisartan-treated cats, successfully achieving the criterion for clinical relevance (Figure 3B). Thus, the composite primary efficacy end point was satisfied. Similar evaluation of the intention-to-treat population supported this finding; LSM (95% CI) change in SBP from baseline to day 14 ± 2 was −22.1 (−26.4 to −17.7) and −7.5 (−13.2 to −1.9) for the telmisartan- and placebo- treated groups, respectively (P = .003). Additionally, mean (95% CI) change in SBP from baseline to day 28 ± 2 was −21.7 (−25.7 to −17.8) for the telmisartan-treated cats in this population. The percentage of cats in the per-protocol population classified as “responder” at the day 14 ± 2 visit was 52.1% in the telmisartan-treated group and 19.0% in the placebo-treated group (Table 2).
TABLE 1  Baseline demographic and clinical characteristics of spontaneously hypertensive cats enrolled in the 28-day efficacy period that received at least 1 dose of study medication (intention-to-treat population) and whose data were used for analysis of drug efficacy (per-protocol population)

| Variable                      | Intention-to-treat population | Per-protocol population | Extended-use population |
|-------------------------------|------------------------------|-------------------------|-------------------------|
|                               | Placebo | Telmisartan | Placebo | Telmisartan | Placebo | Telmisartan |
| Number of cats                | 96      | 192         | 79      | 142         | 107     |             |
| Age (years)                   | 14.5 (7-20) | 15.0 (5-24) | 14.0 (18-20) | 15.0 (7.0-20) | 14.1 (7-20) |
| Sex, n (%)                    |         |             |         |             |         |             |
| Female                        | 52 (54.2) | 92 (47.9)   | 45 (57.0) | 67 (47.2)   | 51 (47.7) |
| Male                          | 44 (45.8) | 100 (51.0)  | 34 (43.0) | 75 (52.8)   | 56 (52.3) |
| Reproductive status           |         |             |         |             |         |             |
| Neutered                      | 96 (100) | 190 (99.0)  | 79 (100) | 140 (98.6)  | 106 (99.1) |
| Intact                        | 0       | 2 (1.0)     | 0       | 2 (1.4)     | 1 (0.9)  |
| Breed                         |         |             |         |             |         |             |
| Mixed breed                   | 80 (83.3) | 154 (80.2)  | 67 (84.8) | 114 (80.3)  | 87 (81.3) |
| Siamese                       | 4 (4.2)  | 10 (5.2)    | 3 (3.8)  | 9 (6.3)     | 4 (3.7)  |
| Persian                       | 4 (4.2)  | 7 (3.6)     | 2 (2.5)  | 6 (4.2)     | 4 (3.7)  |
| Himalayan                     | 2 (2.1)  | 7 (3.6)     | 2 (2.5)  | 5 (3.5)     | 4 (3.7)  |
| Other pure breed              | 6 (6.3)  | 14 (7.3)    | 5 (6.3)  | 8 (5.6)     | 8 (7.5)  |
| Body weight (kg)              | 4.23 (2.50-10.9) | 4.47 (1.93-11.4) | 4.16 (2.64-10.90) | 4.38 (1.93-11.40) | 4.8 (1.93-11.4) |
| SBP (mm Hg)                   | 176 ± 11 | 177 ± 11    | 175 ± 11 | 177 ± 11    | 176 ± 11 |
| Concurrent disease, n (%)     |         |             |         |             |         |             |
| CKD                           | 53 (55.2) | 111 (57.8) | 42 (53.2) | 82 (57.7)   | 63 (58.9) |
| Idiopathic                    | 33 (34.3) | 51 (26.6)   | 27 (34.2) | 39 (27.5)   | 31 (29.0) |
| CKD and hyperthyroidism       | 9 (9.4)  | 24 (12.2)   | 9 (11.4) | 16 (11.3)   | 10 (9.3)  |
| Hyperthyroidism               | 1 (1.0)  | 6 (3.1)     | 1 (1.3)  | 5 (3.5)     | 3 (2.8)   |
| IRIS stage (CKD cats), n (%)  |         |             |         |             |         |             |
| 1                             | 7 (11)  | 12 (9)      | 5 (10)   | 8 (8)       | 6 (8)     |
| 2                             | 39 (63) | 97 (72)     | 33 (65)  | 72 (73)     | 52 (71)   |
| 3                             | 16 (26) | 25 (19)     | 13 (25)  | 18 (18)     | 15 (21)   |
| Total                         | 62 (100) | 134 (100)   | 51 (100) | 98 (100)    | 73 (100)  |

Data from telmisartan-treated cats included in the 6-month extended-use period are also shown. Data are presented as mean ± SD, median (range), or number (%).

Abbreviations: CKD, chronic kidney disease; IRIS, International Renal Interest Society; SBP, systolic arterial blood pressure.

FIGURE 3  Mean (95% confidence interval) systolic arterial blood pressure (A) and change in systolic arterial blood pressure compared to baseline (B) in cats treated with telmisartan or placebo (per-protocol population) during the blinded efficacy period.
Mean change in SBP from baseline to day 14 ± 2 is presented for the 4 clinical subpopulations in Table 3 and for cats stratified according to baseline SBP in Table 4. More cats belonging to the hyperthyroidism subpopulation were allocated to receive telmisartan than predicted by the 2:1 telmisartan:placebo randomization ratio. Because this trial was not adequately powered to detect differences in BP responses among subpopulations, these data are presented for descriptive purposes only.

The decrease in SBP persisted for the duration of the extended-use phase (Figure 4). At the time of enrollment in the extended-use phase, telmisartan dosages were 2 mg/kg q24h in 97 cats, 1 mg/kg q24h in 8 cats and 0.5 mg/kg q24h in the remaining 2 cats. Of the 107 cats included, 73 (68.2%) completed this phase of the trial. Reasons for removal from the extended-use period included withdrawal (n = 9); rescue because of SBP >180 mm Hg (n = 8); of these, 2 had not received oral telmisartan for >7 days immediately before the rescue visit; adverse events related (n = 8) or unrelated (n = 6) to worsening or new TOD; and owner noncompliance (n = 1). In addition, 2 cats were removed from the trial in error for SBP 80-120 mm Hg, as neither cat had associated clinical signs. For 26 of 107 (24%) cats, telmisartan dosage was decreased during the 156-day extended-use period. The percentage of cats classified as responders at each trial visit in the extended-use phase is presented in Table 2.

Mean values for laboratory variables measured at baseline and on day 28 ± 2 were similar between treatment groups. Any observed differences were small and remained within laboratory reference ranges (Table 5). No clinically relevant differences in change of any laboratory variable between baseline and day 28 ± 2 were noted between treatment groups. Mean values for laboratory variables at trial end (day 182 ± 2) in the telmisartan-treated group also were similar to those noted at baseline and day 28 ± 2 and remained within laboratory reference ranges.

**Table 3** Mean ± SD change in SBP from baseline to day 14 ± 2 for spontaneously hypertensive cats enrolled in the present study (per-protocol population), classified according to concurrent disease

| Subpopulation                      | Placebo | Telmisartan |
|------------------------------------|---------|-------------|
|                                    | n       | Change in SBP (mm Hg) | n       | Change in SBP (mm Hg) |
| CKD                                | 42      | −3.2 ± 19.5  | 82      | −23.8 ± 23.1          |
| CKD and hyperthyroidism            | 9       | −3.1 ± 32.5  | 16      | −9.7 ± 21.4           |
| Hyperthyroidism                    | 1       | −29.7 ± 0    | 5       | −26.0 ± 25.0          |
| Idiopathic hypertension            | 27      | −13.2 ± 26.0 | 39      | −24.6 ± 20.3          |
| Total population                   | 79      | −6.9 ± 23.7  | 142     | −22.5 ± 22.5          |

Abbreviations: CKD, chronic kidney disease; SBP, systolic arterial blood pressure.

The incidence of serious adverse events was similar between treatment groups during the blinded efficacy phase, with 12.0% of telmisartan- and 10.4% of placebo-treated cats experiencing such an event. The majority were considered to reflect the geriatric age and high prevalence of concurrent disease in the trial population. In the same period, at least 1 nonserious adverse event was recorded for 40.6% of placebo-treated and 51.0% of telmisartan-treated cats. The most common nonserious adverse event in both treatment groups was vomiting, with the majority of cases in both groups characterized by single, transient episodes that resolved without intervention. Cats treated with telmisartan experienced multiple-day vomiting more frequently than did placebo-treated cats (noted in 7.3% and 3.1%, respectively). During the extended-use phase, the majority of adverse events reported were considered as expected when the geriatric age and concurrent diseases of the included population were considered (Table 6).

Hypotension associated with clinical signs (n = 2) or requiring removal from the trial according to trial protocol (n = 2) was reported in 4 telmisartan-treated cats in the 28-day efficacy phase and in 3 telmisartan-treated cats in the extended-use phase.

**Table 4** Mean ± SD change in SBP from baseline to day 14 ± 2 for spontaneously hypertensive cats enrolled in the present study (per-protocol population), classified according to baseline SBP

| Baseline SBP (mm Hg) | Placebo | Telmisartan |
|----------------------|---------|-------------|
|                      | n       | Change in SBP (mm Hg) | n       | Change in SBP (mm Hg) |
| 160–179              | 46      | −5.8 ± 23.5  | 88      | −17.7 ± 21.0          |
| 180–200              | 33      | −8.5 ± 24.2  | 54      | −30.4 ± 22.7          |

Abbreviation: SBP, systolic arterial blood pressure.
cats, a similar BP decrease also was seen after 14 days of amlodipine treatment at a dosage of 0.125 mg/kg q24h.28

Studies of hypertensive cats with naturally occurring15–18 and experimentally induced19,20 CKD, hyperthyroidism,21 and idiopathic HT18 suggest that excessive or inappropriate RAAS activation (as assessed by measurement of circulating components of this system) may contribute to the development of HT. Our results are consistent with these findings, because on average, blockade of the AT1 receptor by telmisartan was associated with a clinically relevant, measurable decrease in SBP, with some patients experiencing marked SBP decrease after 14 days of treatment.

The central role of RAAS blockade in the treatment of hypertensive people is well acknowledged, particularly in those with concurrent CKD. In addition to their antihypertensive effects, RAAS-modifying agents have renoprotective properties, largely attributed to their ability to decrease proteinuria and glomerular hypertension,30 effects that also have been documented in cats with CKD.20,31–33 Blockers of this system (specifically, ACEi and ARBs) are recommended along with thiazide diuretics and calcium channel blockers as appropriate first-line antihypertensive drug choices in the general, adult, non-black, human population.34 Furthermore, in those hypertensive patients with CKD, antihypertensive treatment almost always includes an ACEi or ARB to improve renal outcomes, regardless of patient age, race, diabetic status, or presence of proteinuria.34

Of the RAAS-modifying drugs available, ACEi have been the most extensively studied in cats.20,31,35,36 However, reports involving clinically hypertensive cats describe generally inadequate antihypertensive efficacy of ACEi.3,15,17 Possible explanations for this failure may include administration of inappropriately low dosages or failure of these drugs to completely antagonize angiotensin II.22 Because of their specificity for the AT1 receptor, ARBs have a mechanistic advantage over ACEi, because the former preserve the beneficial counter-effects associated with stimulation of angiotensin II subtype-2 receptors. This specificity also allows ARBs to antagonize the detrimental effects of angiotensin II independent of its source, circumventing ACE-independent proteolytic pathways that may contribute to persistent angiotensin II production during treatment with ACEi (ie, “angiotensin breakthrough”).22 In a recent prospective

![FIGURE 4](image.jpg)  Systolic arterial blood pressure (A) and change in systolic arterial blood pressure compared to baseline (B) in 107 cats treated with telmisartan during the open label, extended-use period; only cats eventually enrolled in this period are included. Boxes, median, and IQR; whiskers, ± 1.5 (IQR); +, mean

| Variable | Baseline (day 0)* | Day 28 ± 2* | Day 182 ± 7 |
|----------|------------------|-------------|-------------|
| Number of cats | Placebo 79 | Telmisartan 142 | Placebo 50 | Telmisartan 121 | Placebo 73 |
| Serum creatinine (mg/dL) | 2.0 ± 0.8 | 2.0 ± 0.7 | 2.1 ± 1.3 | 2.0 ± 0.7 | 2.0 ± 0.7 |
| Blood urea nitrogen (mg/dL) | 39 ± 17 | 37 ± 14 | 37 ± 22 | 37 ± 14 | 36 ± 12 |
| Serum potassium (mmol/L) | 4.4 ± 0.5 | 4.4 ± 0.4 | 4.5 ± 0.5 | 4.4 ± 0.5 | 4.5 ± 0.5 |
| Hematocrit (%) | 34.8 ± 5.8 | 35.2 ± 5.8 | 33.9 ± 6.2 | 33.1 ± 5.7 | 31.8 ± 4.6 |
| RBC (M/μL) | 7.9 ± 1.8 | 8.0 ± 1.4 | 7.7 ± 1.5 | 7.5 ± 1.3 | 7.61 ± 1.16 |
| Urinary protein-to-creatinine ratio | 0.3 ± 0.5 (n = 71) | 0.3 ± 0.3 (n = 107) | 0.3 ± 0.4 (n = 37) | 0.2 ± 0.2 (n = 88) | 0.2 ± 0.3 (n = 66) |

Data are presented as mean ± SD. Urinary protein-to-creatinine ratio data obtained from cats with active urinary tract infection at the time of sample collection are not included. Abbreviation: RBC, red blood cell concentration.

*Per-protocol population.
During the 28-day efficacy period of the present trial, persistence of a mean decrease in SBP was documented not only for telmisartan-treated cats but also, to a significantly lesser extent, for placebo-treated cats, emphasizing the importance of including such a control group in clinical trials evaluating BP-modifying treatments. The magnitude of this decrease in SBP in placebo cats, approximately 7 mm Hg at day 14 ± 2, is similar to decreases (ie, 9-10 mm Hg) noted after 14 days of treatment with placebo in 2 previous randomized clinical trials of cats with naturally occurring HT.25,28 This apparent placebo effect may be due to acclimation of the cat to the BP measurement process or to daily handling, thereby lessening the effects of situational BP increases over time (ie, "white-coat" effect27), or could suggest that staff responsible for BP measurement may have unconsciously approached the measurement process differently before, as compared to after, a cat’s enrollment in the trial.

In addition to the a priori composite primary efficacy end point, secondary outcomes of interest included the percentage of cats requiring rescue for SBP >180 mm Hg and percentage of cats classified as “responders” in each treatment group. Almost 41% of placebo-treated cats in a previous randomized, double-blinded, placebo-controlled study were not considered as responders at subsequent time points.

Our results support the safety of telmisartan when administered to cats with CKD of IRIS stages 1-3. No significant difference in change in serum creatinine concentration over the 28-day efficacy period was observed between treatment groups, and a low rate of acute exacerbation of renal azotemia as an adverse event in telmisartan-treated cats was noted. Two telmisartan-treated cats experienced acute kidney injury during the 28-day efficacy period, and 3 of 107 experienced progression of CKD to IRIS stage 4 or renal death or euthanasia during the 6-month extended-use phase. Although outcomes from a similar placebo-treated group are not available for comparison, this rate is considered very low, given the geriatric age and high prevalence of concurrent disease in the trial population, and the progressive nature of CKD in cats.

Our study had some limitations. Because it was considered unethical to withhold antihypertensive treatment in these patients, cats with SBP >200 mm Hg or with evidence of severe TOD were excluded. Therefore, the efficacy of telmisartan in this subset of patients remains to be further investigated. However, when stratified according to baseline SBP, the mean magnitude of SBP decrease at the day 14 ± 2 visit was numerically higher in more severely hypertensive cats (ie, those with SBP of 180-200 mm Hg) compared to those with less severe hypertension (ie, those with SBP of 160-179.9 mm Hg), suggesting that telmisartan treatment would be expected to produce equal, if not larger, decreases in SBP in cats with SBP >200 mm Hg (Table 4). In a recent case report, after amlo- dipine had to be withdrawn because of development of gingival hyperplasia, telmisartan as monotherapy effectively controlled severe hypertension in a cat, whereas benazepril alone was unsuccessful.28 Finally, because cats with severe renal azotemia were excluded from the present trial, the efficacy and safety of telmisartan treatment in these cats also was not evaluated. As discussed above, telmisartan dosage rates exceeding 2 mg/kg/day in the maintenance phase were not studied.

**TABLE 6** Frequency of adverse events (number and % of cats affected in each group) during the 28-day efficacy phase of the present study (intention-to-treat population)

| Condition                  | Telmisartan  | Placebo   |
|----------------------------|--------------|-----------|
|                            | (n = 192) (%)| (n = 96) (%)|
| Vomiting                   | 46 (24.0)    | 14 (14.6) |
| Diarrhea                   | 18 (9.4)     | 4 (4.2)   |
| Lethargy                   | 13 (6.8)     | 3 (3.1)   |
| Weight loss                | 13 (6.8)     | 5 (5.2)   |
| Decreased appetite/ina-petence | 13 (6.8)     | 7 (7.3)   |
| Nonregenerative anemia     | 11 (5.7)     | 2 (2.1)   |
| Dehydration                | 10 (5.2)     | 4 (4.2)   |
| Retinal lesions            | 4 (2.1)      | 6 (6.25)  |
In conclusion, telmisartan oral solution, administered at the dosage studied here, safely and effectively decreased SBP in hypertensive cats. The clinically relevant magnitude and duration of decreased SBP, combined with previously documented beneficial effects on the RAAS system in cats with CKD, make this drug a potentially valuable treatment for cats with systemic HT.

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CONFLICT OF INTEREST DECLARATION

Alicia Zimmerman, Lawrence Bryson, Tanja Zimmering, and Anne Traas are employees of Boehringer Ingelheim Vetmedica GmbH. Amanda Coleman and Scott Brown have served as paid consultants for Boehringer Ingelheim Vetmedica GmbH. A company representative of Boehringer Ingelheim read and approved the final manuscript draft.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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