JAVMA

AVMA

Velagliflozin, a once-daily, liquid, oral SGLT2 inhibitor, is effective as a stand-alone therapy for feline diabetes mellitus: the SENSATION study

Ellen N. Behrend, VMD, PhD, DACVIM[1*]; Cynthia R. Ward, VMD, PhD, DACVIM[2]; Victor Chukwu, DrPH[3]; Audrey K. Cook, BVM&S, DACVIM, DECVIM, DABVP[4]; Carla Kroh, Dr med vet[5]; Patty Lathan, VMD, MS, DACVIM[6]; Jacky May, DVM[7]; Thomas Schermerhorn, VMD, PhD, DACVIM[8]; J. Catharine Scott-Moncrieff, VetMB, MS, DACVIM, DECVIM[9]; Rebecca Voth, DVM[10]

[1]Veterinary Information Network, Davis, CA
[2]College of Veterinary Medicine, University of Georgia, Athens, GA
[3]Boehringer Ingelheim Animal Health USA Inc, Duluth, GA
[4]Department of Small Animal Clinical Sciences, School of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX
[5]Boehringer Ingelheim Vetmedica GmbH, Ingelheim am Rhein, Germany
[6]Department of Veterinary Clinical Sciences, School of Veterinary Medicine, Louisiana State University, Baton Rouge, LA
[7]Scout Bio, Philadelphia, PA
[8]Department of Clinical Sciences, College of Veterinary Medicine, Kansas State University, Manhattan, KS
[9]Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Purdue University, West Lafayette, IN
[10]Boehringer Ingelheim Animal Health USA Inc, St Joseph, MO

*Corresponding author: Dr. Behrend (behreen@auburn.edu)

OBJECTIVE
To investigate safety and effectiveness of velagliflozin oral solution as sole therapy in naïve and previously insulin-treated diabetic cats.

ANIMALS
252 client-owned cats receiving ≥ 2 doses of velagliflozin; 214 (85%) naïve diabetics and 38 (15%) insulin-treated diabetics.

PROCEDURES
Prospective, baseline-controlled, open-label clinical field trial. Cats received velagliflozin orally, once daily. Physical examinations and blood collections were performed days 0, 3, 7, 30, 60, 120, and 180.

RESULTS
Data are median (range). Screening blood glucose (BG) was 436 mg/dL (272 to 676 mg/dL). On days 30, 60, 120, and 180, single BG after receiving velagliflozin was 153 mg/dL (62 to 480 mg/dL), 134 mg/dL (64 to 414 mg/dL), 128 mg/dL (55 to 461 mg/dL), and 125 mg/dL (77 to 384 mg/dL), respectively. Screening fructosamine was 538 µmol/L (375 to 794 µmol/L). On the same recheck days, fructosamine was 310 µmol/L (204 to 609 µmol/L), 286 µmol/L (175 to 531 µmol/L), 269 µmol/L (189 to 575 µmol/L), and 263 µmol/L (203 to 620 µmol/L). At day 180, 81% of 158 cats remaining had BG and/or fructosamine within reference ranges; 88.6% (124 of 140) and 87.7% (121 of 138) showed improvement in polyuria and polydipsia, respectively. Ketonuria developed in 35 cats (13.9%), including 18 (7.1%) that had ketoacidosis. Ketoacidosis was less common in naïve diabetic cats (11 of 214 [5.1%]) compared to insulin-treated diabetic cats (7 of 38 [18.4%]). At ketoacidosis diagnosis, 14 of 18 cats (77.8%) were euglycemic (ie, BG < 250 mg/dL). Most episodes of ketosis or ketoacidosis (30 of 35 [85.7%]) occurred within the first 14 days of treatment. Insulin-treated diabetic cats were less likely to complete the trial. No clinical hypoglycemia occurred.

CLINICAL RELEVANCE
Velagliflozin improved glycemic parameters and clinical signs in diabetic cats. Velagliflozin provides an alternative to insulin as a stand-alone treatment of diabetic cats.

Keywords: hyperglycemia, cat, diabetes mellitus, oral hypoglycemic agent, SGLT2 inhibitor

Received March 12, 2024
Accepted July 18, 2024
Published online August 14, 2024

doi.org/10.2460/javma.24.03.0174

The prevalence of feline diabetes mellitus (DM) is rising, with a reported range of 0.12% to 0.6%.[1–3] Feline DM is similar to type 2 DM in people, characterized by a combination of peripheral insulin resistance and inadequate insulin secretion.[4,5] With continued hyperglycemia, pancreatic β cells undergo

oxidative stress and apoptosis and cease secreting insulin (glucose toxicity).[6,7]

The mainstay of treatment for feline DM is insulin therapy, often twice daily.[8] Many owners find the injection schedule onerous and are fearful of needles and disruption of the human-animal bond.[9] Additionally, insulin requires exact dosing; miscalculation can be life-threatening. Insulin therapy requires close monitoring to ensure appropriate glycemic control, demanding owner time and financial resources. Unfortunately, owners elect euthanasia in up to 30% of cats at or within the first year after DM diagnosis.[9]

The first sodium-glucose cotransporter 2 inhibitor (SGLT2i) for treatment of type 2 DM in people was approved in 2013.[10] Sodium-glucose cotransporter 2 inhibitors decrease glucose reabsorption in the renal proximal tubules, thereby increasing urinary glucose excretion. In people with DM, SGLT2i administration results in euglycemia and reduced clinical signs. With resolution of hyperglycemia, β cells may regain insulin-secreting ability.[11]

Sodium-glucose cotransporter 2 inhibitors have been assessed in cats. Velagliflozin increased insulin sensitivity in 6 nondiabetic insulin-resistant obese cats[12] and, in diabetic cats, improved clinical signs and hyperglycemia similarly to lente insulin.[13] Bexagliflozin reduced insulin dose and improved glycemic control in combination with insulin in 5 diabetic cats[14] and controlled hyperglycemia and clinical signs as the sole therapy in 84 cats with newly diagnosed DM.[15]

The present report is of the SENSATION (**S**afety and **E**fficacy of **N**ovel **S**GLT2-inhibitor vel**A**gliflozin in ca**T**s with DM, **I**nsulin pretreated **O**r **N**aïve) study, a large field trial of SGLT2i administration in cats with DM. Our goal was to investigate the safety and effectiveness of velagliflozin oral solution as sole therapy in naïve and previously insulin-treated diabetic cats. Our hypothesis was that > 70% of cats would have improvement in at least 1 clinical sign (polyuria, polydipsia, polyphagia, or neuropathy) on day 180 and in at least 1 glycemic parameter as defined by (1) mean blood glucose concentration (BG) < 250 mg/dL over a 9-hour BG curve after velagliflozin administration on day 60, (2) BG within the reference interval (RI [72 to 175 mg/dL]) on day 180, and (3) fructosamine within the RI (191 to 349 µmol/L) on day 180. We further hypothesized that over 180 days, velagliflozin would not cause hypoglycemia as defined by (1) BG < 60 mg/dL, (2) presence of clinical signs of hypoglycemia (eg, seizures, obtundation, lethargy, ataxia, weakness), or (3) fructosamine below RI. Last, we hypothesized that over 180 days, velagliflozin would have a favorable safety profile, defined as < 15% of cats being removed due to ketonuria or ketoacidosis.

Methods

This was a prospective, baseline-controlled, open-label clinical field trial conducted according to Good Clinical Practice guidelines at 1 university teaching hospital and 20 general practice veterinary clinics in the US between September 2018 and February 2021. It was approved by the Boehringer Ingelheim Animal Health IACUC. The final study design, including inclusion and exclusion criteria, data collected, and patient monitoring, was agreed to with the FDA Center for Veterinary Medicine (FDA CVM). Written owner consent was obtained prior to screening of each cat.

Inclusion criteria

All cats were client-owned. Diabetes mellitus was diagnosed based on the criteria of having a fasting BG > 270 mg/dL, fructosamine > 400 µmol/L, and glucosuria, along with an owner report of polyuria, polydipsia, or unintentional weight loss despite good appetite.[16] Cats in the naïve diabetic group (NDM) were naïve to treatment or had been treated with insulin for ≤4 days. Insulin-treated cats (ITDM) were receiving insulin, but clinical signs of DM were still present, and the cats met all criteria for study entrance. For ITDM cats, fasting BG was obtained at least 10 hours after insulin administration.

Exclusion criteria

Cats with a recent or chronic history of decreased appetite, vomiting, or diarrhea or that had a suspicion of active pancreatitis (appropriate clinical signs and feline pancreatic lipase > 12 µg/L; RI, 0 to 3.5 ug/L) were excluded. Cats with a suspicion of pancreatitis in the past month based on clinical signs, appropriate ultrasound findings, or elevated feline pancreatic lipase concentration but without current clinical signs could be excluded at the veterinarian's discretion. Cats with a total T4 (TT4) > 4.3 µg/dL (RI, 0.8 to 4.7 ug/dL) or receiving medical or dietary therapy for hyperthyroidism were excluded; cats that completed radioiodine therapy or thyroidectomy and had a TT4 concentration within the RI for ≥ 3 months were eligible. Cats with a positive urine culture were not excluded; antibiotics could be prescribed at the veterinarian's discretion. Serum creatinine > 2.0 mg/dL (RI, 0.9 to 2.5 mg/dL), serum bilirubin > 0.5 mg/dL (RI, 0 to 0.2 mg/dL), history of ketonuria or ketoacidosis, and having ketonuria at the time of screening were exclusion criteria. Cats with an IGF-1 concentration above RI (12 to 92 nmol/L) could be excluded at the clinician's discretion. Cats with known concurrent conditions (eg, neoplasia) that decreased the likelihood of completing the study were excluded. Changes in diet were not allowed within the 2 weeks before screening and until after day 30. Cats treated with glucocorticoids, gestagens, antiemetics, appetite stimulants, or diuretics within the past 30 days were excluded.

Study design

The effectiveness and safety of velagliflozin were evaluated over 30 days with the option for continued use during an extended phase (days 30 to 180). On day −7 to day −2, a history was obtained, physical examination performed, and presence of polyuria, polydipsia, polyphagia, weight loss, or diabetic neuropathy was recorded. Diabetic neuropathy was defined as a bilateral plantigrade and/

or palmigrade stance in the opinion of the attending veterinarian. Blood was collected for CBC, serum chemistry profile, and measurement of single fasted BG, fructosamine, feline pancreatic lipase (Spec fPL; Idexx Laboratories), TT4 (DRI Thyroxine Assay; Microgenics Corp), and IGF-1 (RIA; Mediagnost). Urine was obtained for urinalysis and bacterial culture. Abdominal ultrasound could be performed if pancreatitis was suspected **(Table 1)**.

Treatment with velagliflozin (Senvelgo, Boehringer Ingelheim) started day 0 (1 mg/kg, q 24 h). Dosing was performed in the morning, and owners were instructed to give the dose around the same time each day. The dose was chosen based on pharmacodynamic and pharmacokinetic studies.[17] For ITDM cats, insulin was not administered the previous evening. Administration was given directly into the mouth via supplied syringe or applied to a small amount of canned cat food. A dosing diary was provided to owners to record daily time and dose of medication, adverse events, and health-related abnormal observations **(Supplementary Figure S1)**. Medication could be redosed within 30 minutes if the first attempt was unsuccessful. Dose was adjusted according to body weight at each visit.

Evaluations occurred on days 2 or 3, 7 (± 2), and 30 (± 2) after enrollment (Table 1). Cats were eligible for the extended phase of the study (days 30 to 180) if they had improvement in at least 1 clinical sign that had been present at screening and a fructosamine that was decreased from the baseline and ≤ 550 µmol/L. Rechecks were scheduled on days 60, 90, 120, 150, and 180, all ± 7 days. A 6-hour fast was required only for screening blood work. Unscheduled rechecks could occur any time a cat was ill. Owners could decline further study participation at any time. Velagliflozin administration during the extended phase was as previously described.

Analytical methods

Blood and urine samples were sent to a commercial laboratory (Idexx Preclinical Research Services) and evaluated according to standard laboratory procedures. In-clinic urine testing utilized Keto Diastix (Bayer) according to manufacturer's guidelines. Urine was obtained via cystocentesis, if possible. A validated veterinary portable blood glucose monitor[18] (AlphaTRAK 2; Abbott Animal Health) was used to measure glucose during the 9-hour BG curves performed on days 7, 30, and 60 and spot BG on days 2 or 3, 30, 60, 90, 120, 150 and 180. Detectable limits for BG were 20 and 750 mg/dL. A BG > 750 mg/dL, which registered as "HI" on the machine, was arbitrarily assigned a value of 751 mg/dL for analysis; no values < 20 mg/dL were encountered, and assignment of an arbitrary value was not needed. Fructosamine was measured with a nitroblue tetrazolium dye technique (Fructosamine assay; Catachem).

Assessment of effectiveness and safety

Clinical parameters for treatment effectiveness included owners' subjective assessment of polyuria, polydipsia, and polyphagia and the veterinarian's detection of neuropathy. To qualify for inclusion in the effectiveness analysis with regard to polyuria, polydipsia, polyphagia, or neuropathy, the abnormality had to be present at screening. Blood glucose concentration and fructosamine were the laboratory parameters used to assess effectiveness.

Adverse events were recorded by attending clinicians and defined as any observation or event that was unfavorable and/or unintended, whether or not the event was considered to be product related. Relevant adverse events were judged to be clearly or potentially related to velagliflozin; if any suspicion existed that the observed event was due to velagliflozin, it was included in the analysis. "Diarrhea" included any loosening of the stool, even if mild. Diabetic ketoacidosis (DKA) was defined as the presence of ketonemia and/or ketonuria with metabolic acidosis in a diabetic patient. If blood pH could not be measured, DKA was deemed present on the basis of ketonemia or ketonuria in an ill diabetic cat.[16] Euglycemic DKA (EDKA) was defined as DKA with BG < 250 mg/dL.[19]

Table 1—Interventions completed for each cat at various time points from enrollment throughout the 180-day study period.

Event	Day −7 to −2	Day 2/3	Day 7 (± 2)	Day 30 (± 2)	Day 60 (± 7)	Day 90 (± 7)	Day 120 (± 7)	Day 150 (± 7)	Day 180 (± 7)
Signed owner informed consent	X								
Medical history including signs of diabetes mellitus and medications	X								
Physical examination including weight	X	X	X	X	X	X	X	X	X
Evaluation of owner's diary and perception		X	X	X	X	X	X	X	X
CBC	X		X	X	X		X		X
Chemistry	X			X	X		X		X
fPL, TT4, IGF-1	X								
Complete urinalysis	X			X			X		X
Urine dipstick, USG*	X	X	X		X	X		X	
Urine bacterial culture and sensitivity	X			X					X
9-h blood glucose curve (1, 3, 5, 7, 9 h after dose)**			X	X	X				
Single blood glucose concentration (3–9 h after dose)		X				X	X	X	X
Serum fructosamine concentration	X			X	X		X		X
Abdominal ultrasound***	X								

*Urine specific gravity (USG) performed using in-house laboratory at enrolling site. **Performed using the AlphaTrak 2 glucometer. ***Performed at the discretion of the attending veterinarian.

fPL = Feline pancreatic lipase (performed using the Spec fPL test). TT4 = Total thyroxine.

Decisions regarding treatment of cats with ketonuria or DKA were made by the attending clinician. For the initial 8 months of the study, cats that were ketonuric during a scheduled recheck examination continued receiving velagliflozin if clinically stable. After 65 cats had been enrolled, a protocol amendment was instituted that required immediate removal of cats with ketonuria, irrespective of clinical status.

Hypoglycemia was defined as a BG < 60 mg/dL.[16] Hypoglycemic cats were assessed for presence of related clinical signs (eg, weakness, seizures).

Data analysis

Mean BG and fructosamine were analyzed via a mixed model with time point as a fixed effect and clinic site as a random effect (SAS, version 9.4; SAS Institute Inc). Least squares means with 95% CI were calculated. Mean BG curve concentrations were analyzed via a mixed model with time point (hour) included as fixed effect and compared to the 1-hour time point. *F* values were calculated by visit day and treatment status. Pairwise comparisons of BG and fructosamine were analyzed via a mixed model with treatment status as fixed effect (comparing treatment status at different visit days). *T* values were calculated by visit day. Pairwise comparisons of BG and fructosamine were also analyzed via a mixed model with visit day as fixed effect (comparing screening day with other visit days by treatment status). *T* values were calculated by treatment status and visit days. Secondary variables of a continuous nature were summarized with mean, median, minimum, maximum, SE and/or SD, and lower and upper confidence intervals. Data were tested for normality with the Shapiro-Wilk test. Medians were compared by means of the Mann-Whitney test.

Variables categorical in nature were summarized with frequency distributions. Relative risk was calculated via the Fischer exact test, and Mann-Whitney tests were used to compare insulin duration and serum triglyceride and fructosamine between cats with DKA/ketosis and those without (GraphPad Prism 9; Dotmatics). Significance was set at the $P < .05$ level. Data are presented as median (range) unless otherwise noted.

Results

Population

For the study, 412 cats were screened. The study population included 252 cats that received ≥ 2 velagliflozin doses; 160 cats were not enrolled due to failure to meet the inclusion criteria. Median age was 11 years (range, 4 to 18 years). The majority (176 of 252 [69.8%]) were castrated males, and 76 (30.2%) were spayed females. Mixed breeds (ie, domestic shorthair, medium hair, or longhair) accounted for 237 cats (94.0%); 15 (6.0%) were purebreds. Body weight at enrollment was 5.3 kg (range, 2.6 to 12.1 kg).

Thirty-eight cats (15.1%) were in the ITDM group; 214 (84.9%) were in the NDM group. Duration of insulin therapy for ITDM cats was 83 days (5 to 2,549 days). Median ages (ITDM, 12 years [range, 6 to 18 years]; NDM, 11 years [range, 4 to 18 years]; $P = .287$) and body weights (ITDM, 6.4 kg [range, 3.2 to 12.1 kg]; NDM, 5.2 kg [range, 2.6 to 9.5 kg]; $P = .224$) were similar between groups.

Overall outcomes

Of 252 cats, 27 (10.7%) were removed for reasons unrelated to velagliflozin **(Figure 1)**. On day 180, 158

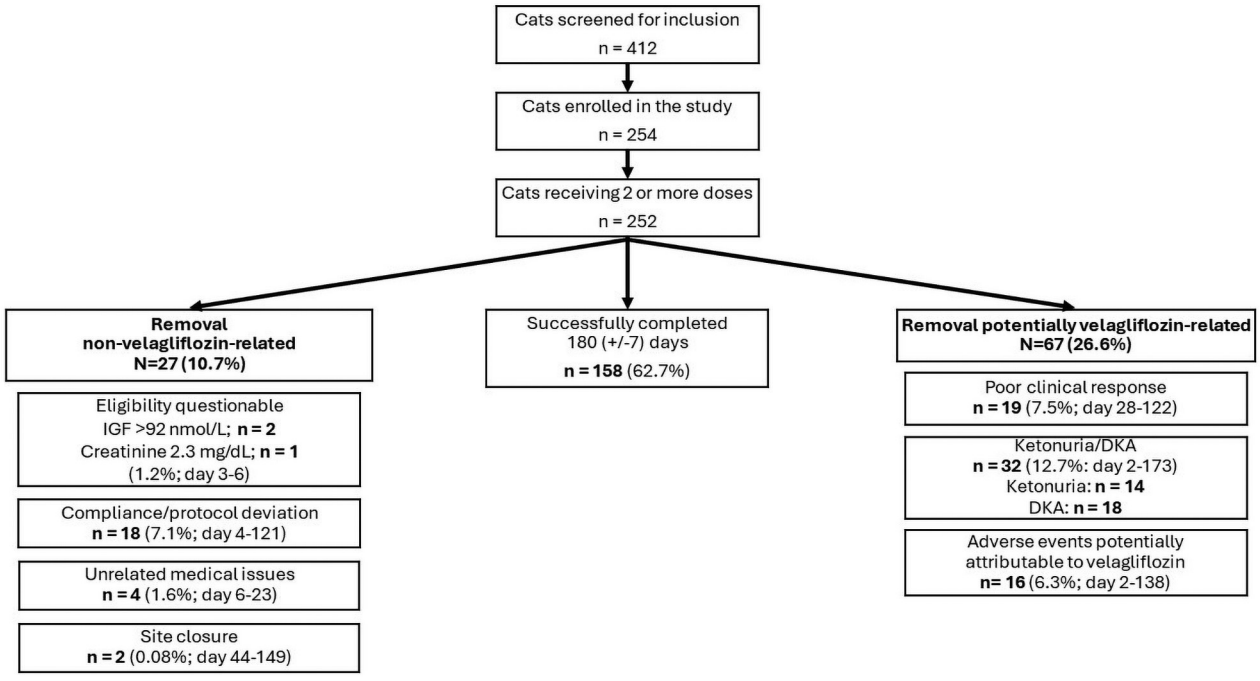

Figure 1—Flowchart showing details of screening and disposition of cats in the study population.

cats (62.7%) remained in the study; 67 cats (26.6%) were removed prior to day 180 for reasons potentially related to velagliflozin. These included ketonuria/DKA (n = 32; days 2 to 173), poor clinical response (19; days 28 to 122), persistent diarrhea (2; days 21 and 57), drooling and hiding (1; day 90), hepatopathy (1; day 97), incontinence (2; days 60 and 68), weight loss/muscle loss (3; days 2, 4 and 28), pancreatitis (2; days 45 and 138), progressive increase in serum creatinine (1; days 90), acute azotemia (2; days 6 and 24), hematuria and inappropriate urination (1; day 59), and aggressive behavior toward the owner (1; day 90).

Cats in the ITDM group were more likely to be removed due to an adverse event or poor response (18 of 33) than NDM cats (49 of 192), with a relative risk of 2.83 (P = .0016; 95% CI, 1.54 to 5.21). Almost three-quarters (74.9%) of NDM cats completed the 180-day study.

Screening IGF-1 concentration above the RI was present in 37 of 245 cats (15.1%; 186 nmol/L [93 to 521]; RI, 12 to 92 nmol/L); for 7 of 252 cats in the study, IGF-1 concentration was unavailable. Of the 37 cats, 24 (64.9%) completed the study and 13 (35.1%) did not; IGF-1 concentrations were similar for the 2 groups (188 nmol/L [range, 93 to 444 nmol/L] and 148 nmol/L [range, 95 to 521 nmol/L], respectively [P = .121]). Two cats were removed by the attending veterinarian because of elevated IGF-1 (IGF-1, 193 and 301 nmol/L) by day 2/3. Seven of 13 cats with elevated IGF-1 that did not complete the study were removed due to an adverse event potentially related to velagliflozin, including ketonuria (n = 1) and DKA (1). Two cats were removed due to noncompliance; 2 did not advance to the extended phase. Twenty-three cats had IGF-1 ≥ 131 nmol/L, a concentration with a 95% positive predictive value for presence of hypersomatotropism[20]; 16 of these (69.6%) completed the study.

On day 7, median BG 1 hour after receiving oral velagliflozin was 214 mg/dL (range, 73 to 643 mg/dL) in NDM and 202.5 mg/dL (range, 114 to 488 mg/dL) in ITDM cats (RI, 72 to 175 mg/dL). Median BG decreased significantly over the 9-hour BG curve in both groups **(Figure 2; Supplementary Table S1)**. Similar results were observed in both groups for 9-hour BG curves performed on days 30 and 60.

In NDM and ITDM cats, spot BG measured 3 to 9 hours after velagliflozin on days 30, 60, 120, and 180 were significantly lower than at screening **(Figure 3)**. There was no difference in median BG between ITDM and NDM cats except at screening (P = .009). On day 180, 80.3% and 86.7% of NDM and ITDM cats, respectively, had BG within RI **(Table 2)**.

Median fructosamine for all cats at screening was 538 µmol/dL (range, 375 to 794 µmol/dL; RI, 191 to 349 µmol/dL). Fructosamine was significantly lower in both NDM and ITDM cats at days 30, 60, 120, and 180 compared to screening (P < .0001 for all; Figure 3; **Supplementary Table S2**). No significant difference in fructosamine was detected between NDM and ITDM cats at any time (days 0, 30, 60, 120, and 180). The percentage with serum fructosamine concentration within RI increased over time (Table 2); 81.7% and 73.3% of NDM and ITDM cats, respectively, had serum fructosamine within RI day 180.

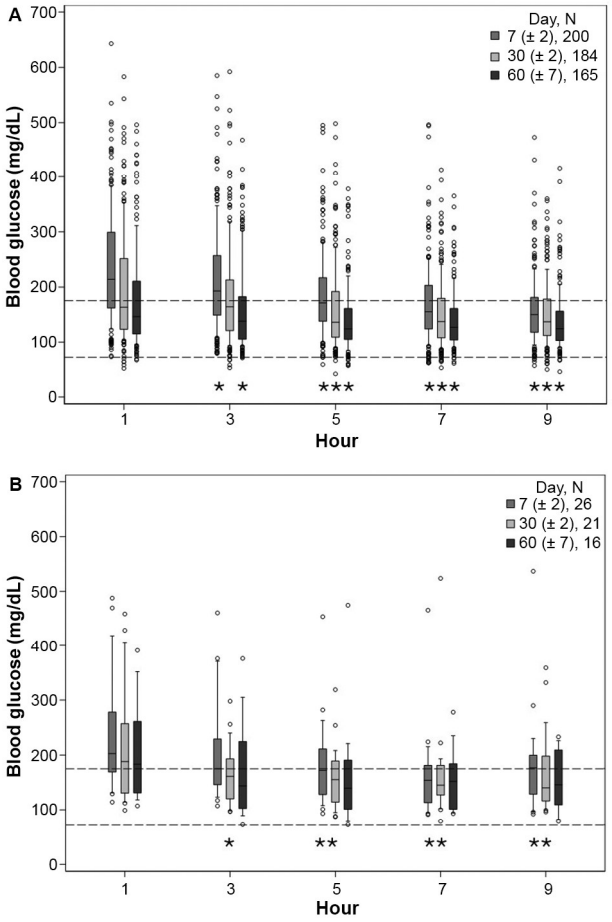

Figure 2—Box-and-whisker plots showing results of 9-hour glucose curves after receiving velagliflozin in naïve (panel A) and previously insulin-treated (panel B) diabetic cats. Dotted horizontal lines define the lower and upper limits of the reference range. For each time period, median values are shown by a horizontal line within a box that encompasses the 25th to 75th percentiles of data. The whiskers define the 10th to 90th percentiles of the data; remaining data are shown as open circles. n = number of cats at each time point. *Significantly different from hour 1 on same day.

The hypotheses related to biochemical parameters were met by 80.9% to 99.2% of cats **(Supplementary Table S3)**.

At screening 230 of 252 (91.3%), 226 of 252 (89.7%), and 103 of 252 cats (40.9%) had owner-reported polyuria, polydipsia, and polyphagia, respectively. Already by day 7, 54.3%, 55.1%, and 31.0% showed improvement in polyuria, polydipsia, and polyphagia, respectively. By day 180, 140 of 230 cats with polyuria at screening and 138 of 226 with polydipsia at screening remained in the study, and improvement in polyuria and polydipsia was reported in 124 (88.6%) and 121 (87.7%), respectively, compared to baseline **(Table 3)**. By day 180, 68 of 103 cats with polyphagia at screening remained in the study, and improvement was reported in 48 (70.6%) compared to baseline.

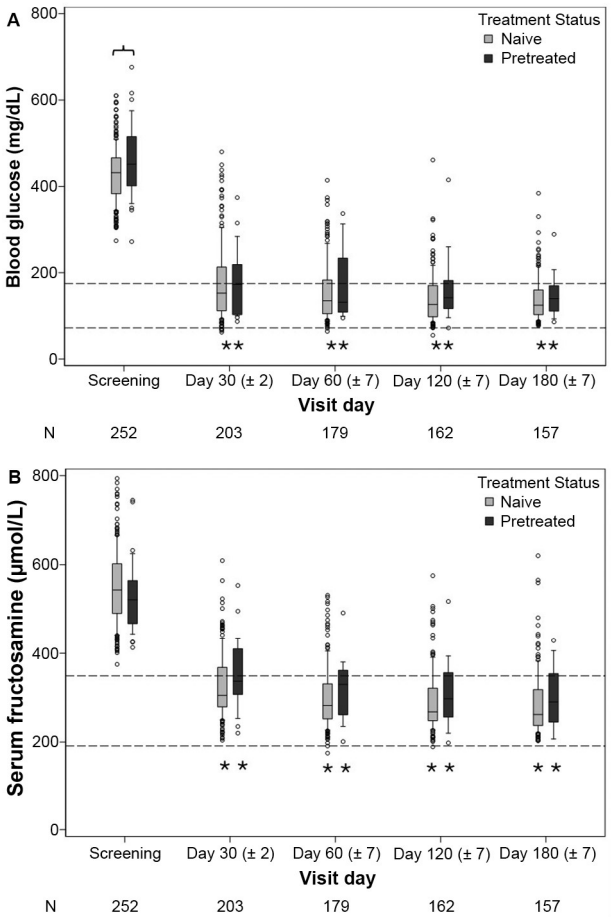

Figure 3—Box-and-whisker plots showing changes over the course of the study in spot check serum glucose in naïve diabetic cats and previously insulin-treated (panel A) cats receiving velagliflozin and in serum fructosamine concentrations in naïve diabetic cats and previously insulin-treated cats (panel B) receiving velagliflozin. Dotted horizontal lines define the lower and upper limits of the reference range. For each time period, median values are shown by a horizontal line within a box that encompasses the 25th to 75th percentiles of data. The whiskers define the 10th to 90th percentiles of the data; remaining data are shown as open circles. *Significantly different from screening within same treatment group. Bars connected by a bracket denote significant differences between treatment groups.

Neuropathy was present in 38 of 252 cats (15.1%) at screening. On day 180, 26 were still in the study, and 20 (76.9%) had resolution of neuropathy. One cat had recurrence of neuropathy at day 90 that resolved by day 150. Two cats developed neuropathy during the study on days 62 and 156.

The hypotheses related to clinical parameters were met by 76.9% to 89.9% of cats (Supplementary Table S3).

At day 180, change in body weight was 5.6% (−33.5% to +45.2%). In the 158 cats, weight was lost by 43 (27.2%), did not change in 1 (0.1%), and was gained by 114 (72.2%).

Ketonuria and DKA

Of 252 cats, 35 (13.9%) had ketonuria or DKA during the 180-day study period, meeting our hypothesis that ketonuria or DKA would occur in < 15% of cats. Seventeen (6.7%) were ketonuric without DKA, and 18 (7.1%) had DKA. Two cats with DKA (onset, days 2 and 8) had a history of DKA and should not have been enrolled.

Median BG at diagnosis of ketonuria and DKA were 171 and 129 mg/dL, respectively. Of 18 cats with DKA, 14 (77.8%) had EDKA. At DKA diagnosis, BGs in cats that were not euglycemic were 290, 295, 408, and 419 mg/dL.

Most episodes of ketonuria and DKA (30 of 35 [85.7%]) occurred within the first 14 study days (3 [1 to 9] days). Sixteen were ketonuric but clinically well; 14 had DKA. Before the protocol change regarding ketonuria, 3 cats that developed ketonuria initially remained in the study; 2 were later removed for noncompliance, and 1 completed the study. The ketonuria resolved after 2 days in 2 cats and after 4 days (day of first recheck) in the third. Thirteen ketonuric cats were removed; 12 were started on insulin, and postremoval treatment was not reported for 1 cat. Ten early DKA cats were successfully treated with insulin, while 4 were euthanized. Three were treated with an insulin continuous-rate infusion; the others were placed on maintenance insulin. Two were not hospitalized. Length of hospital stay for the 8 hospitalized cats was 6 days (2 to 11 days). Review of available medical records for the 14 early DKA cats indicates that anorexia and vomiting often preceded ketonuria.

Table 2—Number and percentage of cats with serum glucose concentration and serum fructosamine concentration within reference range.

		Cats with blood glucose concentration in the reference range	Cats with serum fructosamine concentration in reference range
Visit day	**Treatment status**	**N (%)**	**N (%)**
Day 30 (± 2)	Insulin-treated (N = 21)	11 (52.4%)	11 (52.4%)
	Naïve diabetic (N = 181)	102 (56.0%)	126 (69.2%)
Day 60 (± 7)	Insulin-treated (N = 16)	9 (56.3%)	10 (62.5%)
	Naïve diabetic (N = 164)	115 (70.1%)	127 (77.4%)
Day 120 (± 7)	Insulin-treated (N = 14)	10 (71.4%)	10 (71.4%)
	Naïve diabetic (N = 148)	114 (77.0%)	121 (81.8%)
Day 180 (± 7)	Insulin-treated (N = 15)	13 (86.7%)	11 (73.3%)
	Naïve diabetic (N = 142)	114 (80.3%)	116 (81.7%)

Reference ranges for glucose and fructosamine were 72 to 175 mg/dL and 191 to 349 µmol/dL, respectively.

Table 3—Changes in owner-reported clinical signs in cats receiving velagliflozin over the 180-day study period for polyuria, polydipsia, and polyphagia. Resolution of neuropathy was judged by the attending veterinarian.

	Polyuria		Polydipsia		Polyphagia		
Visit day	Improved	Worsened	Improved	Worsened	Improved	Worsened	Neuropathy resolution
Day 2/3	69/227 (30.4%)	5/227 (2.2%)	84/222 (37.8%)	4/222 (1.8%)	26/103 (25.2%)	3/103 (2.9%)	0/26 (0.0%)
Day 7 (± 2)	108/199 (54.3%)	6/199 (3.0%)	108/196 (55.1%)	5/196 (2.6%)	27/87 (31.0%)	0/160 (0.0%)	3/26 (11.5%)
Day 30 (± 2)	132/183 (72.1%)	5/183 (2.7%)	137/182 (75.3%)	6/182 (3.3%)	37/83 (44.6%)	2/83 (2.4%)	6/26 (23.1%)
Day 60 (± 7)	127/160 (79.4%)	5/160 (3.1%)	129/158 (81.6%),	5/158 (3.2%)	46/76 (60.5%)	4/76 (5.3%)	8/26 (30.8%)
Day 90 (± 7)	124/154 (80.5%)	4/154 (2.6%)	126/153 (82.4%)	5/153 (3.3%)	47/75 (62.7%)	4/75 (5.3%)	11/26 (42.3%)
Day 120 (± 7)	123/144 (85.4%)	1/144 (0.7%)	123/144 (85.4%)	3/144 (2.1%)	45/72 (62.5%)	6/72 (8.3%)	12/26 (46.2%)
Day 150 (± 7)	123/143 (86%)	1/143 (0.7%)	127/142 (89.4%)	0/142 (0.0%)	48/71 (67.6%)	9/71 (12.7%)	18/26 (69.2%)
Day 180 (± 7)	124/140 (88.6%)	2/140 (1.4%)	121/138 (87.7%)	1/138 (0.0%)	48/68 (70.6%)	4/68 (5.9%)	21/26 (76.9%)

Data provided as n/population (%).

Five cats developed ketonuria (n = 1) or DKA (4) more than 14 days after starting velagliflozin; median time to onset was 119 days (range, 30 to 173 days). The cat with ketonuria was removed and started on insulin. Two cats with DKA were euthanized, and 2 were treated with insulin. Comorbidities in these 5 cats included pancreatitis (n = 2), severe hypertriglyceridemia (2; serum triglycerides, 3,432 and 5,816 mg/dL), hepatopathy (1) and cardiomyopathy (1).

Almost one-third of ITDM cats (12 of 38 [31.6%]) developed ketonuria or DKA, compared to only 10.7% of ND cats (23 of 214). Previous insulin therapy significantly increased the likelihood (relative risk, 2.94; 95% CI, 1.58 to 5.23; *P* = .0017). Insulin duration prior to study enrollment for ITDM cats experiencing ketonuria or DKA was 83 days (range, 19 to 2,549 days) and not significantly different from duration of insulin therapy for the ITDM cats that did not develop ketonuria or DKA (153 days [range, 5 to 2,079 days]; *P* = .54).

For the 14 cats that developed DKA by day 14, weight change on day 2/3 was –4.7% (–15.4% to +1.9%). For 235 cats that did not develop DKA by day 14, weight change on day 2/3 was –0.7% (–9.3% to +11.1%). Weight was not recorded for 3 cats on day 2/3. For cats with 5% or more weight loss at the day 2/3 recheck, the relative risk of developing DKA within 2 weeks of starting velagliflozin was 12.63 (95% CI, 4.924 to 30.59; *P* < .0001).

Triglyceride and fructosamine concentrations for the 30 cats diagnosed with ketonuria or DKA within the first 14 days were 100 mg/dL (range, 40 to 4,440 mg/dL) and 528 µmol/L (range, 417 to 741 µmol/L), respectively; these concentrations were not significantly different from those of the 217 cats that did not develop ketonuria/DKA (triglycerides, 93 mg/dL [range, 27 to 5,369 mg/dL; *P* = .689]; fructosamine, 543 µmol/L [range, 375 to 794 µmol/L; *P* = .206]). Substantial hypertriglyceridemia (ie, triglycerides > 500 mg/dL; RI, 20 to 90 mg/dL) at any time point (days 30, 60, 120, and 180) was modestly associated with increased risk of ketonuria or DKA (relative risk, 2.07; CI, 1.13 to 3.55; *P* = .029). Additionally, triglyceride concentrations were more than 10-fold higher than at enrollment in 7 of 35 cats prior to the onset of ketonuria/DKA. Only 3 of 157 cats that completed the study without developing ketonuria or DKA experienced a similar increase in triglycerides at any point in the 180-day period; those that had a 10-fold increase in triglycerides had a relative risk for developing DKA of 10.98 (CI, 3.21 to 37.21; *P* = .0002).

Other adverse events

Changes in stool consistency were reported in 126 of 252 cats (50.0%), most often by day 7 (73 of 126 cats [57.9%]). Stool consistency normalized in 100 of 126 cats (79.3%). For some cats, diarrhea resolved without intervention. Symptomatic treatment such as diet change or antibiotic administration could have been prescribed at the discretion of the veterinarian. Only 2 cats were removed for persistent diarrhea.

Vomiting occurred shortly after velagliflozin administration in 85 of 252 cats (33.7%). Two or more episodes occurred in 51 of the 85 cats (60.0%) between days 2 and 146 (median, day 55).

Eight cats were presumptively diagnosed with clinical pancreatitis at a median of day 55 (range, days 2 to 146). Five of 8 were removed, 3 of which had concurrent DKA. Three cats received supportive therapy and remained in the study.

Five cats had elevated serum total calcium concentration at screening (RI, 8.6 to 10.6 mg/dL); total calcium was elevated in 42 cats of 247 (16.7%) at least once after screening (11.2 mg/dL [range, 10.7 to 14.2 mg/dL]). In most of these cats, hypercalcemia was documented once. However, hypercalcemia was identified on 2, 3, and 4 visits in 3, 7, and 2 cats, respectively. Five cats had elevated phosphorus concentration at screening (RI, 2.9 to 6.3). Phosphorus was increased in 30 of 247 cats (11.9%) at least once after screening (6.7 mg/dL [range, 6.4 to 8.3 mg/dL]).

At screening, 137 cats had a fasting serum triglyceride concentration above RI (20 to 90 mg/dL), with a median of 163 mg/dL (range, 91 to 5,396 mg/dL). Of 115 cats with triglycerides within RI at screening, 70 (60.9%) had elevated triglycerides at least once during the study, with a maximal concentration of 148 mg/dL (range, 92 to 5,102 mg/dL). For 30 cats with elevated triglycerides at screening, triglyceride concentrations while receiving velagliflozin were within the RI.

Serum creatinine increased to > 2.0 mg/dL in 27 cats (RI, 0.9 to 2.5 mg/dL). Two cats developed substantial azotemia, with serum creatinine of 4.3 and 6.3 mg/dL and signs of systemic illness. One of these cats was euthanized due to acute kidney injury; the other was removed due to pneumonia and an

abdominal mass. One cat was removed due to progressive elevation in creatinine; maximum creatinine was 2.9 mg/dL. One month following removal from the study, the creatinine was 2.5 mg/dL, and the cat was doing well. Creatinine in 6 of 27 cats normalized during the study. Ten cats completed the study despite creatinine > 2.0 mg/dL; only 3 cats had a creatinine above RI (2.6, 2.7, and 2.8 mg/dL). Three cats had creatinine > 2.0 but within the RI only on day 180. Eight of these 27 cats were removed from the study for other reasons.

Two cats developed hepatopathy. One had serum ALT of 285 U/L (RI, 27 to 158 U/L) at day 30 that returned to RI at day 180. For the second cat, ALT was 586 and 1,131 U/L at days 30 and 90, respectively, and serum total bilirubin was elevated (0.9 g/dL [RI, 0 to 0.3 g/dL]) at day 90. The cat was removed from the study on day 90 due to the hepatopathy. Ten days after removal, ALT and bilirubin were within the RI.

Thirty-nine cats had 53 positive urine bacterial cultures; 19 were at screening. Of 19 cats with positive culture at screening, 11 never had a positive culture while on velagliflozin. Eight were likely contaminants due to the species involved (*Pantoea* spp, *Stenotrophomonas maltophilia*, *Lactobacillus*, nonhemolytic *Streptococcus*, *Staphylococcus warneri*, and a mixed infection with > 3 species). Thus, once velagliflozin administration began, 25 cats (9.9%) had 34 positive bacterial cultures that potentially indicated a clinically significant urinary tract infection. Information on presence or absence of clinical signs of cystitis was lacking.

In all, 18 cats were euthanized or died during the study. Three deaths were not related to velagliflozin **(Supplementary Table S4)**.

Medication acceptance

The medication was well accepted. Of 30,605 velagliflozin doses, 30,097 doses (98.2%) were administered successfully. Another 406 doses (1.3%) were missed, and 162 (0.5%) had to be readministered.

Discussion

Velagliflozin oral solution given once daily at a dose of 1 mg/kg was successful in controlling glycemic parameters and clinical signs in the majority of NDM and ITDM cats that completed the 180-day study. Approximately 25% of cats were removed from the study for treatment failures or adverse effects that may have been related to velagliflozin. For cats in the study on day 180, spot BG and fructosamine were both within RI in 80.9% and polyuria and polydipsia had improved in 88.6% and 87.7%, respectively. Although differences in study designs do not allow for direct comparisons, the overall success for achieving glycemic control and improvement in clinical signs observed in our study using velagliflozin as a sole DM treatment appears similar to studies using bexagliflozin,[15] Lente insulin,[21] recombinant protamine zinc insulin,[22] insulin detemir,[23] and insulin glargine.[24] In a prospective, randomized trial[25] comparing velagliflozin to porcine lente insulin (Caninsulin; Merck Animal Health) in ITDM and NDM cats, velagliflozin was determined to be noninferior. At the completion of the study's efficacy phase (day 45), 29 of 54 velagliflozin-treated cats (54%) and 26 of 62 Caninsulin-treated cats (42%) showed treatment success in at least 1 each of glycemic and clinical variables. On day 91 at the end of the sustained phase, 42 of 54 velagliflozin-treated cats (78%) had a mean BG < 252 mg/dL compared to 60% of Caninsulin-treated cats (37 of 62 cats). In addition, fructosamine concentration was < 450 µmol/L in 76% of velagliflozin-treated cats (41 of 54 cats) and 61% of Caninsulin-treated cats (38 of 62 cats).

Efficacy of velagliflozin was lower in ITDM cats than NDM cats. The drug class of SGLT2i does not perform as well in previously treated diabetic cats.[26] However, almost half (ie, 45.5%) of ITDM cats completed the study. Almost one-third of ITDM cats (12 of 38 [31.6%]) developed ketonuria or DKA, compared to only 10.7% of ND cats (23 of 214). No relationship was found between insulin treatment duration and DKA development; however, the small number of ITDM cats that developed DKA may have made this difficult to detect. Inability to produce sufficient endogenous insulin to prevent ketosis is 1 explanation for the higher proportion of DKA in the ITDM group. In other studies,[24,27] cats treated with insulin for more than 6 months had a lower chance of obtaining diabetic remission in part because the ability to recover endogenous insulin secretion decreases with time.

Assessing velagliflozin effectiveness in cats with hypersomatotropism was not a study aim. However, almost 70% of cats with an IGF-1 concentration that has a 95% positive predictive value for hypersomatotropism[20] completed the study. Thus, velagliflozin may have a role in controlling hypersomatotropism-related DM; further studies are warranted.

Clinical parameters improved quickly after velagliflozin initiation, with > 50% of cats showing improvement in polyuria and polydipsia by day 7. After 180 days, > 88% had improved polyuria and polydipsia, and 75% had improved polyphagia. Despite potential concerns with at-home reporting such as placebo effect, owners' perceptions of treatment success are useful data employed as a gold standard to assess glycemic control in veterinary studies.[9,28] As velagliflozin causes glucose to be excreted in the urine, a common question is how polyuria and polydipsia can improve. The main reason is that the great reduction in blood glucose achieved with velagliflozin results in less glucose being presented to the kidneys; with less glucose being filtered into the tubules, less osmotic force exists to keep water in the tubules, and urine volume decreases. Other reasons may also exist. Resolution of neuropathy, which was judged by veterinarians and is a more objective determination of clinical success, occurred in > 75% of the 26 affected cats that completed the study.

Weight gain was more common than weight loss, as occurred in the study by Hadd et al.[15] Interestingly, a perceived benefit of SGLT2i use in diabetic people is weight loss.[10] One limitation to our study was lack of data on body condition score, so whether

weight loss or gain would have been preferred for a cat cannot be determined. Similarly, data on diet type and amount are lacking to be able to assess the role of feeding in weight changes. More research is needed to address these questions.

The incidence of DKA was 7.1%. The DKA was more commonly EDKA (14 of 18 cats with DKA), as is typical during SGLT2i use.[29] Similarly, 6.7% developed ketonuria and were removed from the study. Measurement of plasma or blood β-hydroxybutyrate is more sensitive for detecting ketosis than urine detection of acetoacetate, which was used in the current study.[30] In 2017, when the SENSATION study was designed, ketone meters were not routinely used in veterinary practice. In addition, serum ketone measurements have not historically been reported in studies evaluating insulin and other therapies in diabetic cats. Thus, they were not incorporated into the SENSATION study. It is possible that blood ketone monitoring would have identified more cats with ketosis before DKA onset. Most cats that experienced ketosis and DKA did so in the first 2 weeks of treatment. Risk factors for DKA were previous treatment with insulin, a triglyceride concentration > 500 mg/dL, a ten-fold increase in serum triglyceride concentration, and > 8% loss in body weight in the first 2 weeks.

It is difficult to make reliable conclusions regarding the likelihood of ketosis or DKA in cats receiving SGLT2i versus insulin. First, previous studies regarding insulin had less stringent monitoring protocols, and transient ketonuria or ketosis could have been missed. Second, and more importantly, complete data were not presented.[21–24,31] In comparison, in a study[15] using bexagliflozin in NDM cats, 4 of 84 (4.7%) of cats had DKA. The rate of ketosis without DKA was not stated. In a study[25] comparing porcine Lente insulin and velagliflozin in NDM and ITDM cats, DKA occurred in 4 of 61 (7%; velagliflozin) and 0 of 66 (Caninsulin). Conversely, ketonuria was detected in 1 cat (1 of 61 [2%]) receiving velagliflozin and 4 of 66 cats (6%) receiving insulin. Unfortunately, the numbers are too low to make a meaningful comparison.

Nonetheless, given the mechanism of action of SGLT2i, cats with an inability to secrete insulin that receive treatment with an SGLT2i may be expected to have a higher rate of DKA compared to those receiving insulin. Also, cats with type 1 DM (ie, having a complete insulin deficiency) are more likely to develop DKA when receiving an SGLT2i than cats with type 2 DM, which is the main type of feline DM.[5] Although type 2 diabetics have a minimal ability to secrete insulin at diagnosis, they may regain the ability to secrete more insulin due to reversal of glucose toxicity. The presence of endogenous insulin will minimize DKA. However, as it is impractical to determine whether a diabetic cat has the capacity for insulin secretion and given the rates of ketosis and DKA noted in the studies of diabetic cats treated with an SGLT2i, close monitoring during the first 14 days when DKA is most likely to occur is prudent.

For any adverse event, if the potential existed that velagliflozin was the cause, the data were included in the analysis. Thus, rates of clinically relevant adverse events caused by velagliflozin are likely lower than reported here. Change in fecal consistency was the most common adverse event, ranging from slight softening to watery feces. This finding was typically reported in the first week and was mild and self-limiting. Only 2 owners removed cats due to a stool change. Vomiting shortly after medication administration was noted in approximately 1 of 3 of cats; 40% of cats had only 1 vomiting episode.

The relationship between SGLT2i use and bacterial urinary cystitis in people is controversial.[10,32] In our study, 25 cats with a negative culture at screening had a positive culture during the study. This incidence was similar to the number of cats with a positive culture at initial screening and in cats on insulin,[33,34] suggesting that SGLT2i use did not increase the likelihood for a positive culture. Further study is needed, however, as the study was not designed to investigate the relationship between velagliflozin use and urinary tract infection, and we did not collect data to distinguish subclinical bacteriuria from clinically impactful infection.

The study was not designed to evaluate diabetic remission. However, as velagliflozin produced rapid euglycemia that was sustained over the 180-day treatment period, it is possible that some cats achieved remission and would have remained euglycemic had the drug been discontinued. Further study is needed to develop strategies for assessing occurrence of remission in cats receiving an SGLT2i.

Likewise, the effect of diet, if any, was not assessed by this study. There were no stipulated requirements for diet composition fed during the study. The overall consistent improvements in clinical and glycemic outcomes in velagliflozin-treated cats consuming a variety of diets suggest a minimal role for diet in the response to SGLT2i treatment. Further study is required.

Thus, velagliflozin is a promising new therapy for feline DM with minimal risk of clinical hypoglycemia. Already by day 7, blood glucose concentrations were significantly decreased, and polyuria and polydipsia had improved in > 50% of cats. Acceptance of the medication by cats and owners was excellent. The approximate 14% rate of ketonuria warrants close monitoring in the first 14 days of therapy, when DKA is most likely to occur. Other adverse effects were typically mild and self-limiting.

Acknowledgments

None reported.

Disclosures

Ellen N. Behrend, Audrey K. Cook, Patty Lathan, Thomas Schermerhorn, J. Catharine Scott-Moncrieff, and Cynthia R. Ward are paid consultants of Boehringer Ingelheim. Victor Chukwu, Carla Kroh, and Rebecca Voth are employees of Boehringer Ingelheim. Audrey K. Cook, J. Catharine Scott-Moncrieff, Thomas Schermerhorn, and Cynthia R. Ward are paid consultants of Elanco.

No AI-assisted technologies were used in the generation of this manuscript.

Funding

Funding for the study was provided by Boehringer Ingelheim Animal Health USA Inc.

ORCID

E. N. Behrend https://orcid.org/0000-0002-5010-2983

T. Schermerhorn https://orcid.org/0000-0002-6800-0969

References

1. Prahl A, Guptill L, Glickman NW, Tetrick M, Glickman LT. Time trends and risk factors for diabetes mellitus in cats presented to veterinary teaching hospitals. *J Feline Med Surg*. 2007;9(5):351–358. doi:10.1016/j.jfms.2007.02.004
2. O'Neill DG, Gostelow R, Orme C, et al. Epidemiology of diabetes mellitus among 193,435 cats attending primary-care veterinary practices in England. *J Vet Intern Med*. 2016;30(4):964–972. doi:10.1111/jvim.14365
3. McCann TM, Simpson KE, Shaw DJ, Butt JA, Gunn-Moore DA. Feline diabetes mellitus in the UK: the prevalence within an insured cat population and a questionnaire-based putative risk factor analysis. *J Feline Med Surg*. 2007;9(4):289–299. doi:10.1016/j.jfms.2007.02.001
4. Gostelow R, Hazuchova K. Pathophysiology of pre-diabetes, diabetes, and diabetic remission in cats. *Vet Clin North Am Small Anim Pract*. 2023;53(3):511–529. doi:10.1016/j.cvsm.2023.02.001
5. Osto M, Zini E, Reusch CE, Lutz TA. Diabetes from humans to cats. *Gen Comp Endocrinol*. 2013;182:48–53. doi:10.1016/j.ygcen.2012.11.019
6. Robertson RP, Harmon J, Tran POT, Poitout V. β-Cell glucose toxicity, lipotoxicity, and chronic oxidative stress in type 2 diabetes. *Diabetes*. 2004;53(suppl 1):S119–S124. doi:10.2337/diabetes.53.2007.S119
7. Zini E, Osto M, Franchini M, et al. Hyperglycaemia but not hyperlipidaemia causes beta cell dysfunction and beta cell loss in the domestic cat. *Diabetologia*. 2009;52(2):336–346. doi:10.1007/s00125-008-1201-y
8. Behrend E, Holford A, Lathan P, Rucinsky R, Schulman R. 2018 AAHA diabetes management guidelines for dogs and cats. *J Am Anim Hosp Assoc*. 2018;54(1):1–21. doi:10.5326/JAAHA-MS-6822
9. Niessen SJM, Hazuchova K, Powney SL, et al. The big pet diabetes survey: perceived frequency and triggers for euthanasia. *Vet Sci*. 2017;4(2):4. doi:10.3390/vetsci4020027
10. Dardi I, Kouvatsos T, Jabbour SA. SGLT2 inhibitors. *Biochem Pharmacol*. 2016;101:27–39. doi:10.1016/j.bcp.2015.09.005
11. Wajchenberg BL. β-Cell failure in diabetes and preservation by clinical treatment. *Endocr Rev*. 2007;28(2):187–218. doi:10.1210/10.1210/er.2006-0038
12. Hoenig M, Clark M, Schaeffer DJ, Reiche D. Effects of the sodium-glucose cotransporter 2 (SGLT2) inhibitor velagliflozin, a new drug with therapeutic potential to treat diabetes in cats. *J Vet Pharmacol Ther*. 2018;41(2):266–273. doi:10.1111/jvp.12467
13. Niessen SJM, Voth R, Kroh C, Hennings L. Once daily oral therapy for feline diabetes mellitus: SGLT-2-inhibitor velagliflozin as stand-alone therapy compared to insulin injection therapy in diabetic cats. *J Vet Intern Med*. 2022;36:2455–2551. 32nd ECVIM-CA Congress abstract 101 ESVE-O-11.
14. Benedict SL, Mahony OM, McKee TS, Bergman PJ. Evaluation of bexagliflozin in cats with poorly regulated diabetes mellitus. *Can J Vet Res*. 2022;86(1):52–58.
15. Hadd MJ, Bienhoff SE, Little SE, et al. Safety and effectiveness of the sodium-glucose cotransporter inhibitor bexagliflozin in cats newly diagnosed with diabetes mellitus. *J Vet Intern Med*. 2023;37(3):915–924. doi:10.1111/jvim.16730
16. Niessen SJM, Bjornvad C, Church DB, et al; ESVE/SCE membership. Agreeing Language in Veterinary Endocrinology (ALIVE): diabetes mellitus—a modified Delphi-method-based system to create consensus disease definitions. *Vet J*. 2022;289:105910. doi:10.1016/j.tvjl.2022.105910
17. FDA. Freedom of Information summary, original new animal drug application: NADA 141-568 Senvelgo (velagliflozin oral solution). August 10, 2023. Accessed February 7, 2024. https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/14320
18. Peña LW, Flatland B, Behrend EN, Arzón-Pereira A, Cole JE, Raz ML. Impact on result interpretation of correct and incorrect selection of veterinary glucometer canine and feline settings. *J Vet Diagn Invest*. 2023;35(6):710–720. doi:10.1177/10406387231195386
19. Long B, Lentz S, Koyfman A, Gottlieb M. Euglycemic diabetic ketoacidosis: etiologies, evaluation, and management. *Am J Emerg Med*. 2021;44:157–160. doi:10.1016/j.ajem.2021.02.015
20. Niessen SJ, Forcada Y, Mantis P, et al. Studying cat (*Felis catus*) diabetes: beware of the acromegalic imposter. *PLoS One*. 2015;10(5):e0127794. doi:10.1371/journal.pone.0127794
21. Michiels L, Reusch CE, Boari A, et al. Treatment of 46 cats with porcine lente insulin—a prospective, multicentre study. *J Feline Med Surg*. 2008;10(5):439–451. doi:10.1016/j.jfms.2007.10.013
22. Nelson RW, Henley K, Cole C; PZIR Clinical Study Group. Field safety and efficacy of protamine zinc recombinant human insulin for treatment of diabetes mellitus in cats. *J Vet Intern Med*. 2009;23(4):787–793. doi:10.1111/j.1939-1676.2009.0342.x
23. Roomp K, Rand J. Evaluation of detemir in diabetic cats managed with a protocol for intensive blood glucose control. *J Feline Med Surg*. 2012;14(8):566–572. doi:10.1177/1098612X12446211
24. Roomp K, Rand J. Intensive blood glucose control is safe and effective in diabetic cats using home monitoring and treatment with glargine. *J Feline Med Surg*. 2009;11(8):668–682. doi:10.1016/j.jfms.2009.04.010
25. Niessen SJM, Kooistra HS, Forcada Y, et al. Efficacy and safety of once daily oral administration of sodium-glucose cotransporter-2 inhibitor velagliflozin compared with twice daily insulin injection in diabetic cats. *J Vet Intern Med*. 2024;38(4):2099–2119. doi:10.1111/jvim.17124
26. FDA. Freedom of Information summary, original new animal drug application: NADA 141-566 Bexacat (bexagliflozin tablets). December 8, 2022. Accessed December 9, 2022. https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/13222
27. Zini E, Hafner M, Osto M, et al. Predictors of clinical remission in cats with diabetes mellitus. *J Vet Intern Med*. 2010;24(6):1314–1321. doi:10.1111/j.1939-1676.2010.0598.x
28. Albuquerque CS, Bauman BL, Rzeznitzeck J, Caney SM, Gunn-Moore DA. Priorities on treatment and monitoring of diabetic cats from the owners' points of view. *J Feline Med Surg*. 2020;22(6):506–513. doi:10.1177/1098612X19858154
29. Chow E, Clement S, Garg R. Euglycemic diabetic ketoacidosis in the era of SGLT-2 inhibitors. *BMJ Open Diabetes Res Care*. 2023;11(5):11. doi:10.1136/bmjdrc-2023-003666
30. Zeugswetter F, Pagitz M. Ketone measurements using dipstick methodology in cats with diabetes mellitus. *J Small Anim Pract*. 2009;50(1):4–8. doi:10.1111/j.1748-5827.2008.00657.x
31. Restine LM, Norsworthy GD, Kass PH. Loose-control of diabetes mellitus with protamine zinc insulin in cats: 185 cases (2005–2015). *Can Vet J*. 2019;60(4):399–404.
32. Devi R, Mali G, Chakraborty I, Unnikrishnan MK, Abdulsalim

S. Efficacy and safety of empagliflozin in type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Postgrad Med*. 2017;129(3):382–392. doi:10.1080/00325481.2017.1259544
33. Bailiff NL, Nelson RW, Feldman EC, et al. Frequency and risk factors for urinary tract infection in cats with diabetes mellitus. *J Vet Intern Med*. 2006;20(4):850–855. doi:10.1111/j.1939-1676.2006.tb01797.x
34. Mayer-Roenne B, Goldstein RE, Erb HN. Urinary tract infections in cats with hyperthyroidism, diabetes mellitus and chronic kidney disease. *J Feline Med Surg*. 2007;9(2):124–132. doi:10.1016/j.jfms.2006.09.004

Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org.