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Efficacy and safety of once daily oral administration of sodium-glucose cotransporter-2 inhibitor velagliflozin compared with twice daily insulin injection in diabetic cats

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Abstract

Background: Options for treatment of diabetes mellitus in cats are limited to insulin injections and monitoring for hypoglycemia.

Hypothesis: Once daily sodium-glucose cotransporter-2 inhibitor velagliflozin PO is noninferior to insulin injections.

Animals: Client-owned diabetic cats (127 safety; 116 efficacy assessment).

Methods: Prospective, randomized (1 mg/kg velagliflozin), positive controlled (titrated Caninsulin), open label, noninferiority field trial, comparing number of cats with treatment success in ≥1 clinical variable and ≥1 glycemic variable (margin Δ: 15%) on Day 45; secondary endpoints included glycemic and clinical assessments during 91 days.

Results: On Day 45, 29/54 (54%) velagliflozin-treated cats and 26/62 (42%) Caninsulin-treated cats showed treatment success, demonstrating noninferiority (difference −11.8%; upper 1-sided 97.5% confidence interval, −∞ to 6.3%). By Day 91, quality of life (QoL), polyuria, and polydipsia had improved in 81%, 54% and 61% (velagliflozin); on blood glucose (BG) curves, mean BG was <252 mg/dL in 42/54 (78%; velagliflozin) and 37/62 (60%; Caninsulin); minimum BG was <162 mg/dL in 41/54 (76%; velagliflozin) and 41/62 (66%; Caninsulin); serum fructosamine was <450 µmol/L in 41/54 (76%; velagliflozin) and 38/62 (61%; Caninsulin). Velagliflozin's most frequent adverse events were loose feces/diarrhea (n = 23/61, 38%), positive urine culture (n = 19/61, 31%), and nonclinical hypoglycemia (BG <63 mg/dL; n = 8/61, 13%); Caninsulin's: clinical and nonclinical hypoglycemia (n = 35/66, 53%), positive urine culture (n = 18/66, 27%), and loose feces/diarrhea (n = 10/66, 15%). Diabetic ketoacidosis occurred in 4/61 (7%; velagliflozin) and 0/66 (Caninsulin).

Abbreviations: AE, adverse health effect; BCS, body condition score; BGC, blood glucose curves; DKA, diabetic ketoacidosis; DM, diabetes mellitus; FAS, full analysis set; MMRM, mixed model repeated measures; QoL, quality of life; SGLT2, sodium-glucose cotransporter-2.

Conclusions and Clinical Importance: Once daily oral administration of velagliflozin was noninferior to insulin injections, showed good QoL and glycemia without clinical hypoglycemia.

KEYWORDS
antidiabetic, beta-cell, compliance, feline diabetes mellitus, glucosuria, glucotoxicity, glycemic control, prospective clinical trial, sodium-glucose cotransporter-2 (SGLT2) inhibitor

1 | INTRODUCTION

Current recommendations for treatment of diabetes mellitus (DM) in cats constitute excluding and treating underlying causes, insulin injections (mostly twice daily), and feeding a low carbohydrate diet, aiming for reduction of clinical signs and providing good quality of life (QoL) while reducing the risk for hypoglycemia and diabetic ketoacidosis (DKA).[1-3] Hypoglycemia is a frequent occurrence, with biochemical hypoglycemia reported in 40% to >90% of cats, depending on intensity of monitoring.[4-7] This imposes a psychosocial burden on pet owners causing stress and ongoing need to monitor glucose concentrations, costing money and time, with adverse effects on social and work life.[8] Estimates indicate 3 in 10 diabetic cats are euthanized during the 1st year after diagnosis.[9] Whether the increasingly widespread use of continuous glucose monitoring systems and improved education will result in different rates remains unknown.

In people, a range of oral antidiabetic treatment options are available. Studies of these medications as a stand-alone treatment in diabetic cats (biguanides, α-glucosidase inhibitors, sulfonylureas) have proven disappointing for most cats.[10-12] A new class of oral drugs, sodium-glucose cotransporter-2 (SGLT2) inhibitors, are beneficial in treating human type 2 DM.[13,14] By reducing renal tubular glucose reabsorption, euglycemia can often be obtained. It is speculated that marked and consistent reduction in hyperglycemia reduces glucotoxicity-induced beta-cell dysfunction because it is associated with partial recovery of beta-cell function in both rodent and cat studies.[15-17] Sodium-glucose cotransporter-2 inhibitors were well tolerated and improved insulin sensitivity in obese nondiabetic cats[18]; in 5 diabetic cats with concurrent insulin injection treatment, insulin treatment could be discontinued in 2,[19] and 84 previously untreated diabetic cats in a noncontrolled field trial were also largely successfully treated.[20]

The aim of the current randomized controlled study was to evaluate whether oral administration once daily of SGLT2 inhibitor velagliflozin provides a noninferior alternative to insulin injection treatment in diabetic cats, both naïve and previously treated with insulin.

2 | MATERIALS AND METHODS

2.1 | Study design

Preliminary studies with velagliflozin in nondiabetic[18] (published) and diabetic cats (unpublished), suggested a positive risk-benefit balance would be achieved in pet cats treated with velagliflozin alone. Therefore, a prospective, randomized, positive controlled, open label, noninferiority clinical field study was designed and conducted according to Good Clinical Practice (VICH GCP GL09, 2000) and with prior ethical approval of the investigator's institutions, as well as the appropriate national authorities of each country (Germany, France, the Netherlands).

Noninferiority was tested during a 45-day efficacy phase (Day −7 to Day 45). Sustained safety and effect of velagliflozin and porcine lente insulin were evaluated during a 46-Day extended use phase (Day 45-Day 91). Candidate client-owned diabetic cats were considered suitable for inclusion in case of signed informed consent and fulfillment of all inclusion and none of the exclusion criteria (Table 1) at time of screening on Day −7 to Day −1 before trial start (Day 0). Screening and test procedures are detailed in Table 2. Included cats were randomized (using permuted-block randomization lists) in a 1 : 1 ratio to oral q24h velagliflozin (velagliflozin group; 1 mg/kg; given with or without feeding at a time convenient to the owner; 24 hours apart) or q12h SC Caninsulin injection (insulin group; given at time of food, 12 hours apart). The dose of velagliflozin was kept unaltered and was informed by pharmacokinetic and pharmacodynamic studies demonstrating the most rapid and consistent effect with a dose of 1 mg/kg q24h. The insulin dose was adjusted by attending clinicians, following manufacturer's instructions, on the basis of clinical signs, the results of 9-hour blood glucose (BG) curves (BGC) and serum fructosamine. Nevertheless, clinicians were allowed to use their clinical judgment to accelerate dose titration. Naïve diabetic cats (defined as cats not having received insulin treatment for >4 days) were started at the discretion of the attending clinician, at a dose of 0.25 to 0.5 units/kg and generally not more than 2 units/cat q12h; a higher dose was allowable, especially in cats with a higher ideal body weight. Only whole or half units were given. In accordance with the manufacturer's instructions, doses were increased with a maximum of 1 unit per change and not more frequently than every 4 days. Insulin-pretreated diabetic cats started on their current dose and had their insulin dose titrated in the same fashion. No dietary change was allowed from 14 days before enrollment and during the study period. At each visit, a complete history and physical examination (including body weight and body condition score [BCS] on a scale of 1 to 9[21]), routine blood (comprehensive metabolic panel, at screening IGF-1 and total T4) and urinalysis (Table 2), owner assessment of the clinical signs (Table 3), as well as quality of life (QoL) assessment (Table 4) were performed.

TABLE 1 Inclusion and exclusion criteria.

Inclusion criteria—screening	Exclusion criteria—screening	Exclusion—postinclusion
Signed owner consent in accordance with GCP and local legislation	History of inappetence within 14 days before screening visit	Withdrawal of owner consent
Age ≥1 year	History of chronic or acute vomiting within 14 days before screening visit[a]	Repeated clinical hypoglycemia
Naïve diabetic (defined as not insulin pretreated for more than 4 days) or previously treated with insulin	History of chronic or acute diarrhea within 14 days before screening visit	Occurrence of an adverse event that requires withdrawal (eg, persistent diarrhea)
Glucosuria	Clinical suspicion for acute pancreatitis (eg, lethargy, anorexia, vomiting, abdominal pain, fever,) and ≥1 of the following: ultrasound findings suggestive of pancreatitis (performed at discretion of attending clinician); serum feline spec PLI >12 µg/L	A condition requiring additional medications that might interfere with studied drugs (eg, prednisolone for enteropathy)
Serum fructosamine >400 µmol/L	…	Presence of ketones in urine or blood and clinical signs suggestive of DKA OR documentation of lower blood pH
Fasting blood glucose >250 mg/dL (13.9 mmol/L) (preinsulin and ≥10 hours postinsulin if pretreated)	History of recurrent, symptomatic chronic pancreatitis	A life-threatening disease or severe clinical signs of illness
≥1 clinical sign consistent with DM (i.e., pu, pd, polyphagia as observed by the owner and documented by attending clinician, plantigrade and/ or palmigrade stance related to diabetic polyneuropathy as assessed by the investigator)	Ketonuria at screening visit	If deemed necessary by the Investigator for animal welfare reasons
…	Suspicion or confirmed uncontrolled hyperthyroidism defined as serum TT4 >55 nmol/L (euthyroid cats previously treated with I-131 or thyroidectomy were allowed)	The cat was euthanized or died
…	Cats currently on medication for hyperthyroidism	The owner became noncompliant with the study procedures
…	History of recurrent, symptomatic chronic pancreatitis	The cat became noncompliant with study procedures
…	Ketonuria at screening visit	If treatment became required with drugs that could interfere with study results
…	Other known concomitant disease/condition (excluding urinary tract infection) that might have interfered with the study results (eg, hypersomatotropism [acromegaly], renal failure)	…
…	Creatinine >180 µmol/L on screening	…
…	Bilirubin >7 µmol/L on screening	…
…	Treatment with systemic, topical or inhaled steroids within 30 days before screening	…
…	Treatment with systemic steroids >2 days within 3 months before screening	…
…	Treatment with depot steroids (eg, depo-medrol) or gestagen treatment within 3 months before screening	…
…	Treatment with antiemetics, antacids, appetite stimulants, or other similar medications for treatment of gastrointestinal illness with or without pancreatitis <30 days before screening	…

(Continues)

TABLE 1 (Continued)

Inclusion criteria—screening	Exclusion criteria—screening	Exclusion—postinclusion
...	Treatment with diuretic agents <14 days before screening	...
...	Switch from nondiabetic diet to high protein/low carbohydrate diet within 14 days before screening	...
...	Owners not able to give study medications or cat not amenable to study procedures	...
...	Pregnancy, lactation, or planned breeding during study	...
...	Ongoing participation in another study	...
...	Any condition that might have resulted in premature discontinuation of the study (eg, advanced renal disease)	...

Abbreviations: DKA, diabetic ketoacidosis; DM, diabetes mellitus; GCP, Good Clinical Practice; pd, polydipsia; PLI, pancreatic lipase immunoreactivity; pu, polyuria; TT4, total thyroxin.
[a]Occasional vomiting (eg, vomiting of hairballs, vomiting < once per week, etc.) was not a reason for exclusion.

TABLE 2 Schedule of events.

	Screening visit: Day −7 to −1	Baseline visit: Day 0	Start of treatment: Day 1	Visit 1: Day 3 (+1)	Visit 2: Day 7 (±2)	Visit 3: Day 21 (±2)	Visit 4: Day 45 (±2)	Visit 5: Day 91 (±3)	Unscheduled visit
Owner assessment (clinical signs/QoL)	X	...	...	X	X	X	X	X	(X)[a]
Investigator assessment	X	...	...	X	X	X	X	X	(X)[a]
Physical examination + body weight	X	...	...	X	X	X	X	X	X[a]
Body condition score	X	...	...	...	X	X	X	X	X[a]
CBC	X	...	...	...	...	...	X	X	(X)[a]
Serum clinical chemistry + full urinalysis + urine culture	X	...	...	...	...	X	X	X	(X)[a]
Fasted BG, specific fPL, TT4, IGF-1	X	...	...	...	...	...	...	...	(X)
Urine dipstick	...	...	...	X	X	...	...	...	(X)
9-hour BG curve (1, 3, 5,7, 9 hours after velagliflozin or morning insulin; t = 0 hours at screening only) + fructosamine	X	...	...	...	X	X	X	X	(X)[a]

Note: (X): optional at unscheduled visits.
Abbreviations: BG, blood glucose; CBC, complete blood count; fPLI, feline pancreatic lipase immunoreactivity; IGF-1, insulin-like growth factor 1; QoL, quality of life; TT4, total thyroxine.
[a]Mandatory if the cat was withdrawn from the study at an unscheduled visit before Visit 5 and animal welfare was not compromised; blood for BG curve was preferentially taken from capillaries, though venous puncture was permitted; blood and urine samples were analyzed at IDEXX Laboratories; urine dipstick analyses were performed in-clinic using Keto Diastix according to manufacturer's guidelines; urine for urinalysis and culture were obtained via cystocentesis technique, if possible; or alternatively, via free catch (and result interpretation adjusted according to collection method).

Plantigrade or palmigrade stance, if present, was graded by the attending clinician (absent/mild/moderate/severe) and at every subsequent visit compared with screening (improved/same/worsened/not known).

2.2 | Primary efficacy endpoint

The primary efficacy assessment was to assess for noninferiority of the velagliflozin group compared with the insulin group at the end

TABLE 3 Owner assessment of clinical signs at screening and at visits after inclusion.

Parameter	Question	Answer options
Owner assessment of clinical signs at screening		
Water consumption	The water consumption of my cat is…	…excessive/normal/minimal/not known
Urination	The frequency or volume of urination of my cat is…	…excessive/normal/minimal/not known
Appetite	The appetite of my cat is…	…excessive/normal/poor/not known
Owner assessment of clinical signs at visits after inclusion		
Water consumption	Compared with the very 1st visit before inclusion (screening visit), the water consumption of my cat is…	…increased/same/decreased/not known
Urination	Compared with the very 1st visit before inclusion (screening visit), the frequency or volume of urination of my cat is…	…increased/same/decreased/not known
Appetite	Compared with the very 1st visit before inclusion (screening visit), the appetite of my cat is…	…increased/same/decreased/not known

TABLE 4 Owner assessment of quality of life at screening visit and at visits after inclusion.

Parameter	Question	Answer options
Owner assessment of quality of life at screening visit		
Quality of life	I feel that the quality of my cat's life is…	…excellent/very good/good/fair/poor/not known
Owner assessment of quality of life at visits after inclusion		
Quality of life	Compared with the very 1st visit before inclusion (screening visit), I feel that the quality of my cat's life is…	…improved/same/worsened/not known

TABLE 5 Definition of treatment success on the basis of blood glucose curve measurements and serum fructosamine.

Blood variable/classification	Success
Mean BG (mg/dL)	≤252.3
Min BG (mg/dL)	≤162.2
Fructosamine (μmol/L)	≤450

Abbreviation: BG, blood glucose.

of the efficacy phase (Day 45). To comply with CONSORT[22] guidelines, a composite measure of overall treatment success was used and a priori defined as number of cats that showed treatment success in at least 1 clinical variable (polyuria, polydipsia, polyphagia, plantigrade/palmigrade stance) and at least 1 glycemic variable (average BG, minimum BG of BGC, serum fructosamine). The definition of treatment success of a clinical sign was improvement if the variable was abnormal at time of screening. The definition of treatment failure of a clinical sign was absence of improvement or worsening of the clinical sign, whether normal or abnormal at time of screening. The definition of treatment success/failure on the basis of glycemic variables are outlined in Table 5; cutoff values were adopted from ISFM Consensus Guidelines.[23]

Efficacy analysis was based on the full analysis set (FAS), which constituted all cats randomized in the study that received at least 1 dose of study medication, satisfied entry criteria, had a baseline value, and at least 1 clinical and blood primary variable value at Day 21 or later (this allowed sufficient time for insulin titration and equilibration). Missing values were imputed on the following visits using the last-observation-carried-forward method if the cat was excluded from the study on Day 21 or later.

2.3 | Secondary efficacy endpoints

The secondary outcomes of interest constituted presence or absence of treatment success (defined in Tables 3–5) according to the individual clinical- and blood-based variables of glycemic control which formed part of the composite success variable mentioned above. Glycemic changes were assessed over time. Owner-assessed QoL and BCS were assessed for improvement from screening. Secondary efficacy outcomes were assessed until Day 91.

2.4 | Safety assessment

The safety assessment group constituted all cats that received at least 1 dose of study medication. All potential adverse health effects (AEs) were recorded by attending clinicians, whether or not considered to be treatment related. Clinical urinary tract infection, DKA, diarrhea, and hypoglycemic events were identified as AEs of special interest. All hypoglycemic events were categorized as nonclinical hypoglycemia (event not accompanied by typical signs consistent with hypoglycemia, eg, lethargy, ataxia, seizure, but BG measurement <63 mg/dL [<3.5 mmol/L]) and clinical hypoglycemia (event accompanied by typical signs of hypoglycemia requiring treatment, eg, IV or forced oral administration of glucose, accompanied by at least 1 BG measurement <63 mg/dL [<3.5 mmol/L]). Diarrhea or loose feces was further characterized by having the owner use the 7-point Nestle Purina Fecal Scoring System[24]; a score of 4 or 5 was considered loose feces/

diarrhea, ≥6 was considered diarrhea; half point scores were permitted. Urine culture was defined as positive with >1000 CFU/mL for cystocentesis samples and >100 000 CFU/mL for free catch samples.[25] In the absence of ability to measure blood pH, diabetic ketoacidosis was defined according to the ALIVE definition of "suspected DKA"[1] on the basis of demonstration of ketones in urine or blood in an acutely unwell diabetic cat (i.e., lethargic, inappetent with or without vomiting).

2.5 | Statistical analysis

For the purpose of primary efficacy endpoint analysis, noninferiority was tested with hypotheses: H0: Overall treatment success rate of insulin group−overall treatment success rate of velagliflozin group ≥15%; H1: Overall treatment success rate of insulin group−overall treatment success rate of velagliflozin group <15%, implying that 15% was the prespecified noninferiority margin. The decision to accept or reject the null hypothesis was made based on the 1-sided 97.5% confidence interval for the difference of the overall treatment success rates. Sample size calculation is detailed in Data S1.

Given the subjective nature of some clinical signs (observed polyuria, polydipsia, polyphagia, quality of life), as well as risk for a type I error caused by a multitude of analyses, statistical comparison of secondary efficacy endpoint variables was limited to changes in serum fructosamine, mean BG of the BGC, and minimum BG of the BGC; a restricted maximum likelihood-based mixed model repeated measures (MMRM) approach was employed with baseline value of the endpoint in question as linear covariate, and treatment, visit, and visit by treatment interaction as fixed effects. Comparison of improvement rates in pu/pd and polyphagia was limited to calculation of 95% confidence intervals for the difference in success rates. Statistical software SAS Version 9.4 (Cary, North Carolina, USA) was used.

3 | RESULTS

3.1 | Recruited study group

Overall, 213 animals were screened; 128 passed the inclusion process; 1 cat did not receive the study medication, resulting in a safety assessment group of 127 cats. Removal process for the FAS are depicted in Figure 1, which led to inclusion of 116 cats in total (91.3% of treated cats), with 54 velagliflozin-treated cats and 62 insulin-treated cats. Table 6 shows demographics and treatment history; Table 7 shows administered daily insulin doses throughout the study.

3.2 | Primary efficacy endpoint analysis

On Day 45, 29/54 (54%) of velagliflozin-treated cats and 26/62 (42%) of Caninsulin-treated cats were classified as treatment success. Difference in success rate was −11.8% (upper 1-sided 97.5% confidence interval −∞ to 6.3%; Table 8). Upper 1-sided 97.5% confidence interval for difference in success rate was below the noninferiority margin of $\Delta = 15\%$, demonstrating noninferiority of velagliflozin to Caninsulin on study Day 45. A minority of cases showed improvement in some observed clinical signs yet worsening in others and vice versa (Table 8).

3.3 | Secondary efficacy endpoint analysis

Improvements were observed in both groups over time (Figure 2). By Day 45, excessive urination frequency/volume had improved in 27/46 (59%) velagliflozin group cats and 32/48 (67%) insulin group cats; excessive water consumption had improved in 31/51 (61%) velagliflozin group cats and 37/54 (69%) insulin group cats; excessive appetite had improved in 4/26 (15%) of the velagliflozin group and 9/23 (39%) of the insulin group cats; and plantigrade/palmigrade stance had improved in 10/15 (67%) velagliflozin group cats and 5/20 (25%) insulin group cats. Mean (±SD) duration of DM before trial enrolment for cats with plantigrade/palmigrade stance was 186 (±383) days for those with improvement versus 90 (±170) days for those without improvement in the Caninsulin group; this was 33 (±104; improvement) versus 14 (±14; no improvement) for the velagliflozin group. Comparison of improvement rates in pu/pd and polyphagia through calculation of 95% confidence intervals did not demonstrate a statistical difference in clinical sign improvement (Data S2).

Average body weight in the velagliflozin group remained similar to the screening value, whereas average body weight in the insulin group showed a constant increase. The proportion of cats with a high BCS (>6/9) decreased from 28% to 19% in the velagliflozin group; it changed from 16% to 14% in the insulin group (Figure 3).

By Day 45, mean BG of the BGC was ≤252 mg/dL (≤14 mmol/L) in 44/54 (82%) of the velagliflozin group, 28/62 (45%) of the insulin group cats; minimum BG of the BGC was ≤162 mg/dL (≤9 mmol/L) in 40/54 (74%) velagliflozin group cats and 32/62 (52%) insulin group cats; serum fructosamine was ≤450 µmol/L in 39/54 (72%) velagliflozin group cats and 27/62 (44%) insulin group cats. The proportion of cats with mean BG, minimal BG and serum fructosamine classified as success in each group and at each time point are detailed in Table 9. Adjusted mean changes in BGC minimum BG and mean BG, as well as serum fructosamine from screening to Day 91 estimated from the MMRM, are shown in Figure 4.

The decrease in serum fructosamine proved significantly more pronounced for velagliflozin cats than insulin cats at all assessed time points, as was the case for minimum BG and mean BG of the BGC for time points Day 7, Day 21, and Day 45 (Table 10). Proportion of cats with reduction of maximum BG <270 mg/dL (15 mmol/L) increased from 57% at study Day 7 to 76% at study Day 91.

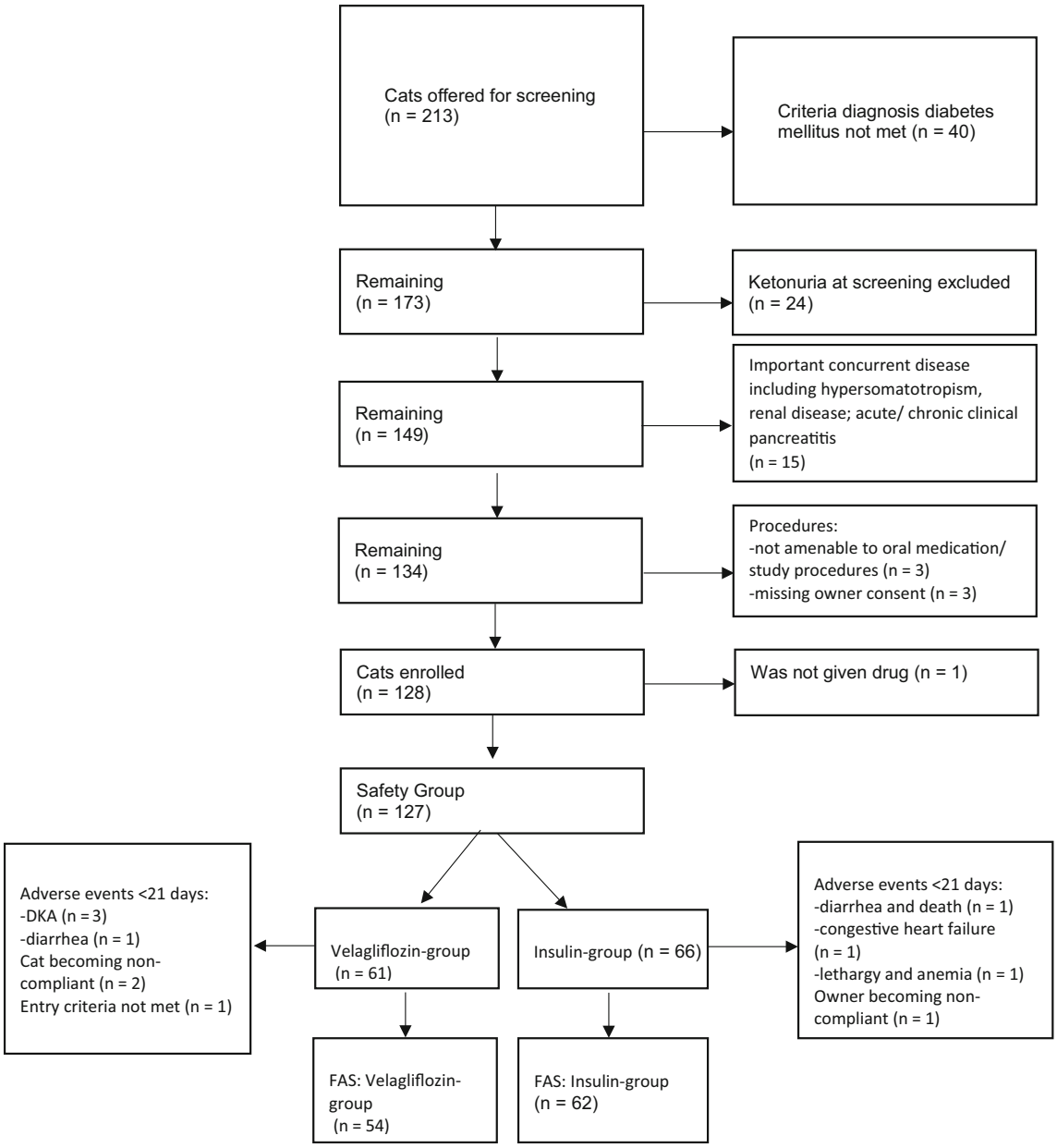

FIGURE 1 Results of the inclusion/exclusion process of the study. DKA, diabetic ketoacidosis; FAS, full analysis set.

Mean BG values of individual BGC time points are depicted in Figure 5.

3.4 | Owner-assessed QoL

Forty-eight percent of velagliflozin group owners and 50% of insulin group owners reported poor or fair QoL at screening (Table 11). Improvements in QoL (Day 91: 81% in the velagliflozin group, 74% in insulin group) were detected over time in both treatment groups in most cats (Figure 6), with worsened QoL reported for 1 velagliflozin cat on Day 21 and for 2 velagliflozin cats on Day 45. For insulin cats, worsened QoL was reported for 2 or 3 individual cats at every revisit.

3.5 | Safety assessment

In velagliflozin cats 84% and in insulin cats 89% of the safety assessment group experienced an AE of some kind over the 91-day period. Overall, 9 of 127 cats (7.1%) died or were euthanized during the course of the study (4 of 61 velagliflozin cats [7%]; 5 of 66 insulin cats [8%]). Circumstances are detailed in Data S3. The 3 most frequent adverse events reported by attending clinicians in velagliflozin cats were loose feces/diarrhea (n = 23, 38%), clinician-reported clinical cystitis/urinary tract infection (n = 13, 21%), and nonclinical hypoglycemia (n = 8, 13%). For insulin cats, the top 3 were hypoglycemia (n = 35, 53%), clinical (n = 5, 8%) and nonclinical (n = 34, 52%), 4 cats experiencing both, clinician-reported clinical cystitis/urinary tract infection (n = 10, 15%), and loose feces/diarrhea (n = 10, 15%).

TABLE 6 Demographics and diabetic history of included cats.

				Velagliflozin group (n = 54)	Insulin group (n = 62)	Total (n = 116)
Demographics	Age [years]	...	N (%)	54 (100.0)	62 (100.0)	116 (100.0)
			Mean	11.4	10.7	11.0
			SD	2.9	3.0	2.9
			Min	6	5	5
			Median	11.5	10.0	11.0
			Max	18	18	18
	Sex	Female	N (%)	14 (25.9)	27 (43.5)	41 (35.3)
		Male	N (%)	40 (74.1)	35 (56.5)	75 (64.7)
	Breed	Abyssinian	N (%)	...	1 (1.6)	1 (0.9)
		British (BSH, BLH)	N (%)	...	1 (1.6)	1 (0.9)
		Crossbred	N (%)	1 (1.9)	5 (8.1)	6 (5.2)
		European (ESH, ELH, DSH, DLH)	N (%)	47 (87.0)	52 (83.9)	99 (85.3)
		Maine Coon	N (%)	2 (3.7)	1 (1.6)	3 (2.6)
		Norwegian Forest	N (%)	...	1 (1.6)	1 (0.9)
		Oriental	N (%)	1 (1.9)	...	1 (0.9)
		Other felid/cat	N (%)	1 (1.9)	...	1 (0.9)
		Persian	N (%)	1 (1.9)	1 (1.6)	2 (1.7)
		Scottish Fold Shorthair	N (%)	1 (1.9)	...	1 (0.9)
	Reproductive status	Intact	N (%)	1 (1.9)	2 (3.2)	3 (2.6)
		Spayed/castrated	N (%)	53 (98.1)	60 (96.8)	113 (97.4)
	Housing	Indoor	N (%)	25 (46.3)	35 (56.5)	60 (51.7)
		Outdoor	N (%)	3 (5.6)	2 (3.2)	5 (4.3)
		Both	N (%)	26 (48.1)	25 (40.3)	51 (44.0)
	Diet information	Standard	N (%)	42 (77.8)	45 (72.6)	87 (75.0)
		High protein/ low carbohydrate	N (%)	11 (20.4)	16 (25.8)	27 (23.3)
		Unknown	N (%)	1 (1.9)	1 (1.6)	2 (1.7)
	Feeding frequency	Once daily	N (%)	...	1 (1.6)	1 (0.9)
		Twice daily	N (%)	14 (25.9)	15 (24.2)	29 (25.0)
		More than 2 times/ day	N (%)	15 (27.8)	16 (25.8)	31 (26.7)
		Ad libitum	N (%)	25 (46.3)	30 (48.4)	55 (47.4)
	Treatment history	Naïve	N (%)	41[a] (75.9)	39[a] (62.9)	80 (69.0)
		Pretreated	N (%)	13 (24.1)	23 (37.1)	36 (31.0)
	Previous diabetes treatment	CANINSULIN	N (%)	6 (11.1)	15 (24.2)	21 (18.1)
		INSUMAN'BASAL[b]	N (%)	...	1 (1.6)	1 (0.9)
		LANTUS	N (%)	1 (1.9)	...	1 (0.9)
		PROZINC	N (%)	7 (13.0)	8 (12.9)	15 (12.9)
		No pretreatment	N (%)	40[a] (74.1)	38[a] (61.3)	78 (67.2)
Investigator assessment	Plantigrade or palmigrade stance related to diabetic polyneuropathy	Absent	N (%)	39 (72.2)	42 (67.7)	81 (69.8)
		Mild	N (%)	10 (18.5)	10 (16.1)	20 (17.2)
		Moderate	N (%)	2 (3.7)	7 (11.3)	9 (7.8)
		Severe	N (%)	3 (5.6)	3 (4.8)	6 (5.2)

TABLE 6 (Continued)

				Velagliflozin group (n = 54)	Insulin group (n = 62)	Total (n = 116)
Owner assessment	Appetite	Poor	N (%)	7 (13.0)	6 (9.7)	13 (11.2)
		Normal	N (%)	21 (38.9)	32 (51.6)	53 (45.7)
		Excessive	N (%)	26 (48.1)	23 (37.1)	49 (42.2)
		Not known	N (%)	…	1 (1.6)	1 (0.9)
Owner assessment	Urination frequency/ volume	Normal	N (%)	3 (5.6)	9 (14.5)	12 (10.3)
		Excessive	N (%)	46 (85.2)	48 (77.4)	94 (81.0)
		Not known	N (%)	5 (9.3)	5 (8.1)	10 (8.6)
Owner assessment	Water consumption	Normal	N (%)	3 (5.6)	8 (12.9)	11 (9.5)
		Excessive	N (%)	51 (94.4)	54 (87.1)	105 (90.5)
Blood glucose curve measurements	Minimum blood glucose [mg/dL]	…	N (%)	53 (98.1)	60 (96.8)	113 (97.4)
			Mean	345.1	326.8	335.4
			SD	98.5	114.3	107.1
			Min	70.3	59.5	59.5
			Median	355.0	336.0	345.9
			Max	598.2	538.7	598.2
	Mean blood glucose [mg/dL]	…	N (%)	53 (98.1)	60 (96.8)	113 (97.4)
			Mean	432.4	416.4	423.9
			SD	83.1	102.5	93.8
			Min	206.1	166.5	166.5
			Median	429.2	415.1	426.7
			Max	667.0	628.8	667.0
	Serum fructosamine [µmol/L]	…	N (%)	54 (100.0)	61 (98.4)	115 (99.1)
			Mean	599.7	600.2	600.0
			SD	106.1	102.1	103.5
			Min	405	403	403
			Median	606.5	591.0	596.0
			Max	859	911	911

Abbreviations: BLH: British Long Hair; BSH, Bitish Short Hair; DLH, Domestic Long Hair; DSH, Domestic Short Hair; ESH, European Short Hair; SD, standard deviation.

[a]The discrepancy for number of cats with treatment history "Naïve" and previous diabetes treatment "no pretreatment" are explained by the definition of naïve being cats that have not been pretreated with insulin for more than 4 days.

[b]Intermediate-acting insulin suspension containing isophane insulin.

3.6 | Hypoglycemia

Hypoglycemia (clinical and nonclinical) event rate was 1.17 per 91 days in insulin cats and 0.21 per 91 days in velagliflozin cats. Most hypoglycemic events and all clinical hypoglycemic events were observed in insulin cats (Table 12). In velagliflozin cats, hypoglycemia was never clinical. All clinical hypoglycemic episodes were attended to successfully without lasting adverse health effects.

3.7 | Ketonuria and suspected DKA

Per study's exclusion criteria, no included cats had ketone bodies at screening in any of the collected urine samples. During planned reexamination, 1 velagliflozin cat (1/61 [2%]) had ketone bodies detected on study Day 91 compared with 4 insulin cats (4/66 [6%]) on different study days. In 4/61 (7%) velagliflozin cases, suspected DKA was diagnosed by attending clinicians during additional, unscheduled, veterinary visits arranged because the cat was not doing well (3 naive; 1 pretreated); all presented with euglycemia. DKA event rate for velagliflozin was 0.076 per 91 days. Time to 1st DKA event ranged from 3 to 80 days (median: 5), with 3 of the 4 events occurring within the 1st week after treatment start (1 DKA cat being inappropriately included in the study despite suspected CKD and pretreatment with IV fluid treatment). In all cases, velagliflozin was stopped according to study protocol; 3 were treated successfully with insulin and supportive care. A 4th case was not started on DKA treatment; instead, euthanasia was elected by the owner. Suspected DKA was not encountered in the insulin group.

TABLE 7 Insulin dose changes of pretreated (n = 23) and naïve (n = 39) diabetic cats in control group.

Treatment History	Variable	Visit	N (%)	Mean	SD	Min	Median	Max
Pretreated	Dose per injection per cat [IU] (administered q12h)	Day 0	23 (100.0)	2.35	1.11	0.5	2.50	4.5
		Day 3	23 (100.0)	2.57	0.97	1.0	2.50	4.5
		Day 7	23 (100.0)	2.91	1.08	1.5	3.00	5.0
		Day 21	23 (100.0)	3.54	1.18	1.0	3.50	5.5
		Day 45	22 (95.7)	3.68	1.49	1.0	3.75	6.0
		Day 91	17 (73.9)	3.88	2.48	0.5	3.50	9.5
Pretreated	Change from baseline dose per injection per cat [IU] (administered q12h)	Day 3	23 (100.0)	0.22	0.39	0.0	0.00	1.0
		Day 7	23 (100.0)	0.57	0.64	−0.5	0.50	2.0
		Day 21	23 (100.0)	1.20	1.06	0.0	1.50	3.5
		Day 45	22 (95.7)	1.32	1.38	−1.0	1.25	4.0
		Day 91	17 (73.9)	1.56	2.44	−3.0	1.00	6.5
Pretreated	Dose per injection [IU/kg] (administered q12h)	Day 0	23 (100.0)	0.55	0.27	0.1	0.56	1.1
		Day 3	23 (100.0)	0.59	0.24	0.2	0.51	1.1
		Day 7	23 (100.0)	0.66	0.26	0.3	0.68	1.3
		Day 21	23 (100.0)	0.81	0.30	0.2	0.78	1.5
		Day 45	22 (95.7)	0.80	0.33	0.2	0.77	1.4
		Day 91	17 (73.9)	0.75	0.50	0.1	0.65	2.2
Pretreated	Change from baseline dose per injection [IU/kg] (administered q12h)	Day 3	23 (100.0)	0.04	0.11	−0.2	0.00	0.3
		Day 7	23 (100.0)	0.11	0.17	−0.1	0.09	0.5
		Day 21	23 (100.0)	0.25	0.26	−0.1	0.23	0.7
		Day 45	22 (95.7)	0.24	0.31	−0.2	0.24	0.9
		Day 91	17 (73.9)	0.23	0.53	−0.8	0.21	1.4
Naïve	Dose per injection per cat [IU] (administered q12h)	Day 0	39 (100.0)	1.90	0.72	1.0	2.00	4.0
		Day 3	39 (100.0)	1.95	0.73	1.0	2.00	4.0
		Day 7	39 (100.0)	2.28	0.95	1.0	2.00	6.0
		Day 21	39 (100.0)	2.49	1.20	0.5	2.00	6.0
		Day 45	37 (94.9)	2.75	1.34	0.5	3.00	6.0
		Day 91	33 (84.6)	2.88	1.51	0.5	3.00	6.0
Naïve	Change from baseline dose per injection per cat [IU] (administered q12h)	Day 3	39 (100.0)	0.05	0.27	−0.5	0.00	1.0
		Day 7	39 (100.0)	0.38	0.58	−0.5	0.00	2.0
		Day 21	39 (100.0)	0.59	0.95	−1.5	0.80	3.0
		Day 45	37 (94.9)	0.82	1.26	−1.5	1.00	4.0
		Day 91	33 (84.6)	0.95	1.41	−1.5	1.00	4.0
Naïve	Dose per injection [IU/kg] (administered q12h)	Day 0	39 (100.0)	0.40	0.13	0.2	0.39	0.8
		Day 3	39 (100.0)	0.42	0.15	0.2	0.38	0.9
		Day 7	39 (100.0)	0.49	0.20	0.2	0.43	1.2
		Day 21	39 (100.0)	0.52	0.23	0.1	0.44	1.1
		Day 45	37 (94.9)	0.56	0.27	0.1	0.54	1.2
		Day 91	33 (84.6)	0.55	0.26	0.1	0.54	1.1
Naïve	Change from baseline dose per injection [IU/kg] (administered q12h)	Day 3	39 (100.0)	0.01	0.07	−0.2	0.00	0.3
		Day 7	39 (100.0)	0.09	0.14	−0.1	0.01	0.5
		Day 21	39 (100.0)	0.12	0.20	−0.3	0.12	0.6
		Day 45	37 (94.9)	0.15	0.28	−0.3	0.17	0.8
		Day 91	33 (84.6)	0.14	0.28	−0.3	0.15	0.7

Abbreviations: IU, international unit; Max, maximal value; Min, minimal value; SD, standard deviation.

TABLE 8 Primary endpoint analysis on Day 45.

	Velagliflozin group	Insulin group
Number of animals (N)	54	62
Treatment success (N) (% analyzed)	29 (54%)	26 (42%)
Treatment success with worsening of other clinical parameter(s) (N) (% analyzed)	8 (15%) Worsened clinical sign: increase in appetite (n = 8, 100%)	1 (2%) Worsened clinical sign: increase in appetite (n = 1, 100%)
Treatment failure with improvement of other clinical parameter(s) (N) (% analyzed)	5 (9%) Improved clinical sign: decrease appetite (n = 1), decrease urination and drinking (n = 2), decreased drinking (n = 1)	14 (23%) Improved clinical sign: decrease appetite, urination & drinking (n = 3), decrease urination and drinking (n = 8), decreased drinking (n = 2), decreased appetite & drinking (n = 1)
Difference (insulin-velagliflozin group) (%)	−11.8	
Upper 1-sided 97.5% CI for difference (%)	(−∞ to 6.3)	
Noninferiority margin (%)	15	

Abbreviation: CI, confidence interval.

3.8 | Loose feces and diarrhea

Within the velagliflozin group, diarrhea was reported 15 times and in 13 of 61 cats (21%), whereas 6 diarrhea events were reported in 5 of 66 cats (8%) within the insulin group. Loose feces was reported 17 times in 15 of 61 cats (25%) in the velagliflozin group and 5 times in 5 of 66 insulin cats (8%). The majority of events were transient and resolved without treatment within 7 days in both groups (velagliflozin: 17/32 events [53%]; insulin: 7/11 events [64%]). In the velagliflozin group, 11 of 61 cats (18%) had abnormal feces for longer than 8 days (n = 4 diarrhea; n = 6 loose feces; n = 1 displayed both, diarrhea and loose feces), and in the insulin group, 4 of 66 cats (6%) were reported with feces changes (n = 1 diarrhea; n = 3 loose feces) for longer than 8 days.

The event rate per 91 days of chronic loose feces was therefore 0.323 for velagliflozin and 0.087 for insulin; for diarrhea this was 0.285 for velagliflozin and 0.105 for insulin.

3.9 | Hematology, biochemistry, urine

Hematological and biochemistry profile analysis did not reveal changes of concern in terms of effect on bone marrow, renal, or hepatic health or function during the 91-day study in either group. Urine culture findings are shown in Table 13. The event rate for "positive urine culture" was 0.55 per 91 days in the velagliflozin group and 0.49 in the insulin group. Identified infectious agents (postscreening) are shown in Data S4.

4 | DISCUSSION

Oral administration once daily of SGLT2 inhibitor velagliflozin treated naïve and pretreated cats with DM successfully without the need for insulin injection treatment, resulting in improvement of many clinical signs, owner-reported QoL, and all documented glycemic variables in most cats. Treatment success, as defined in our study, with oral once daily solution proved noninferior to twice daily Caninsulin injection treatment. The 15% noninferiority delta was chosen in line with FDA guidelines (https://www.fda.gov/media/78504/download), also considering the day-to-day variability in glycemic laboratory variables in treated diabetic cats,[26] as well as a clinically identifiable and relevant difference from the reported success rate of the comparator veterinary licensed insulin option.[4] Robust glucose lowering effects, more rapidly than with insulin (Table 10) and, like with insulin, improvement of several clinical signs occurred already within 1 week. Sample size calculation was not performed for the comparison of clinical signs alone (instead for the composite variable of improvement in 1 clinical signs and simultaneous improvement in 1 glycemic variable), which means a type II statistical error cannot be excluded. With clinical hypoglycemia not occurring at all and nonclinical hypoglycemia occurring uncommonly, intense ongoing monitoring of glucose, as with insulin treatment, seems not necessary. Hypoglycemia (including nonclinical episodes) occurred nearly 6-fold less frequently than in cats treated with insulin.

The FAS has a number of underlying conditions (eg, hypersomatotropism) or comorbidities (eg, active pancreatitis) excluded, and a minority of cats (<25%) were receiving low carbohydrate diets. In addition, a mix of naïve and insulin-pretreated cats were assessed with a predominance of naïve cats. Naïve cats are cats with a shorter duration of DM and could therefore have superior beta-cell function/endogenous insulin production. Nevertheless, several pretreated cats were successfully treated in our study, and success rates appeared similar; this suggests that longer standing DM does not have to be an exclusion criterion for use. Given the often-frustrating nature of insulin treatment of diabetic cats with underlying hypersomatotropism, it will be both interesting and anticipated that SGLT2 inhibition could play a positive role in its management.

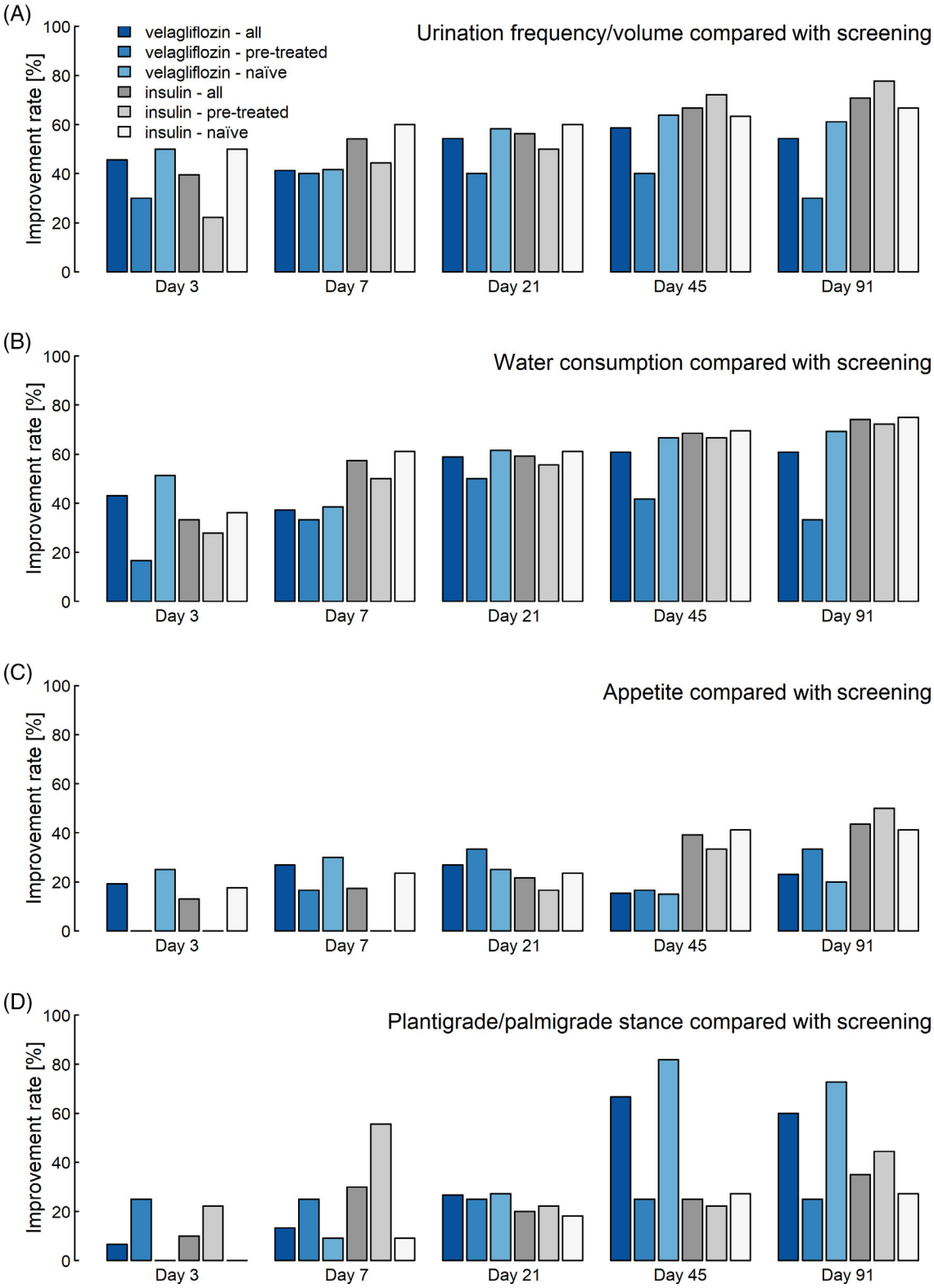

FIGURE 2 Improvement rates compared with screen (%) inrurine frequency/volume (A), water consumption (B), appetite (C) and palmigrade/plantigrade stance (D).

The insulin treatment showed considerable variation in glycemic variables and might have been better optimized. First, by considering the use of different insulin types like Protamine Zinc (PZI) or glargine.[5-7,27-29] Second, only 26% of the insulin group cats were fed a high protein/low carbohydrate diet during the study period. Changing to a high protein/low carbohydrate diet is recommended in

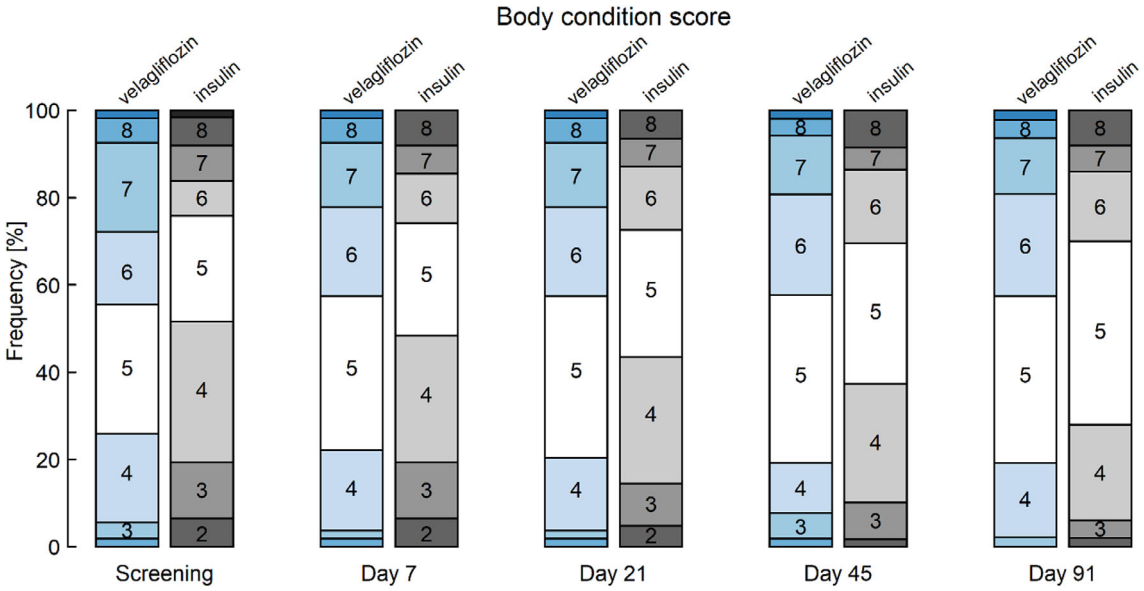

FIGURE 3 Change in body conditions score (BCS; 1-9) over time in velagliflozin- and insulin-treated diabetic cats over time.

TABLE 9 Glycemic data in velagliflozin- and insulin-treated cats.

Treatment	Variable	Treatment history	Total analyzed N (%)	Success at screening N (%)	Success at Day 7 N (%)	Success at Day 21 N (%)	Success at Day 45 N (%)	Success at Day 91 N (%)
Velagliflozin group	Mean BG ≤252.2 mg/dL	All	54 (100.0)	1 (1.9)	41 (75.9)	42 (77.8)	44 (81.5)	42 (77.8)
		Pretreated	13 (100.0)	0 (0.0)	10 (76.9)	9 (69.2)	11 (84.6)	9 (69.2)
		Naive	41 (100.0)	1 (2.4)	31 (75.6)	33 (80.5)	33 (80.5)	33 (80.5)
Insulin group	Mean BG ≤252.2 mg/dL	All	62 (100.0)	4 (6.5)	16 (25.8)	19 (30.6)	28 (45.2)	37 (59.7)
		Pretreated	23 (100.0)	3 (13.0)	5 (21.7)	3 (13.0)	7 (30.4)	11 (47.8)
		Naive	39 (100.0)	1 (2.6)	11 (28.2)	16 (41.0)	21 (53.8)	26 (66.7)
Velagliflozin group	Min BG ≤162.2 mg/dL	All	54 (100.0)	4 (7.4)	34 (63.0)	36 (66.7)	40 (74.1)	41 (75.9)
		Pretreated	13 (100.0)	3 (23.1)	6 (46.2)	8 (61.5)	10 (76.9)	9 (69.2)
		Naive	41 (100.0)	1 (2.4)	28 (68.3)	28 (68.3)	30 (73.2)	32 (78.0)
Insulin group	Min BG ≤162.2 mg/dL	All	62 (100.0)	8 (12.9)	22 (35.5)	24 (38.7)	32 (51.6)	41 (66.1)
		Pretreated	23 (100.0)	7 (30.4)	8 (34.8)	6 (26.1)	8 (34.8)	13 (56.5)
		Naive	39 (100.0)	1 (2.6)	14 (35.9)	18 (46.2)	24 (61.5)	28 (71.8)
Velagliflozin group	Fructosamine ≤450 µmol/L	All	54 (100.0)	3 (5.6)	19 (35.2)	34 (63.0)	39 (72.2)	41 (75.9)
		Pretreated	13 (100.0)	3 (23.1)	4 (30.8)	7 (53.8)	8 (61.5)	8 (61.5)
		Naive	41 (100.0)	0 (0.0)	15 (36.6)	27 (65.9)	31 (75.6)	33 (80.5)
Insulin group	Fructosamine ≤450 µmol/L	All	62 (100.0)	3 (4.8)	9 (14.5)	26 (41.9)	27 (43.5)	38 (61.3)
		Pretreated	23 (100.0)	2 (8.7)	4 (17.4)	8 (34.8)	8 (34.8)	14 (60.9)
		Naive	39 (100.0)	1 (2.6)	5 (12.8)	18 (46.2)	19 (48.7)	24 (61.5)

Abbreviation: BG, blood glucose.

connection with insulin treatment of diabetic cats, and this could have improved the glycemic control in this group.[29] Third, despite insulin dosages used being comparable to what historically has been reported to be effective[4] (Table 7), and despite conflicting evidence regarding the effectiveness of more aggressive and tighter glycemic control methodology,[6,29,30] insulin dose fine-tuning might have been optimized better (eg, use of continuous glucose monitoring systems, stricter glucose targets). Tighter glycemic control would, however, also have led to a higher event rate for hypoglycemia in the insulin group.[4] Hypoglycemia-incidence in the insulin-treated group (53%) was comparable to the incidence in previous studies with Caninsulin (41%[4]) and PZI (44%[5]; 64%[7]), although lower than in a tight control glargine

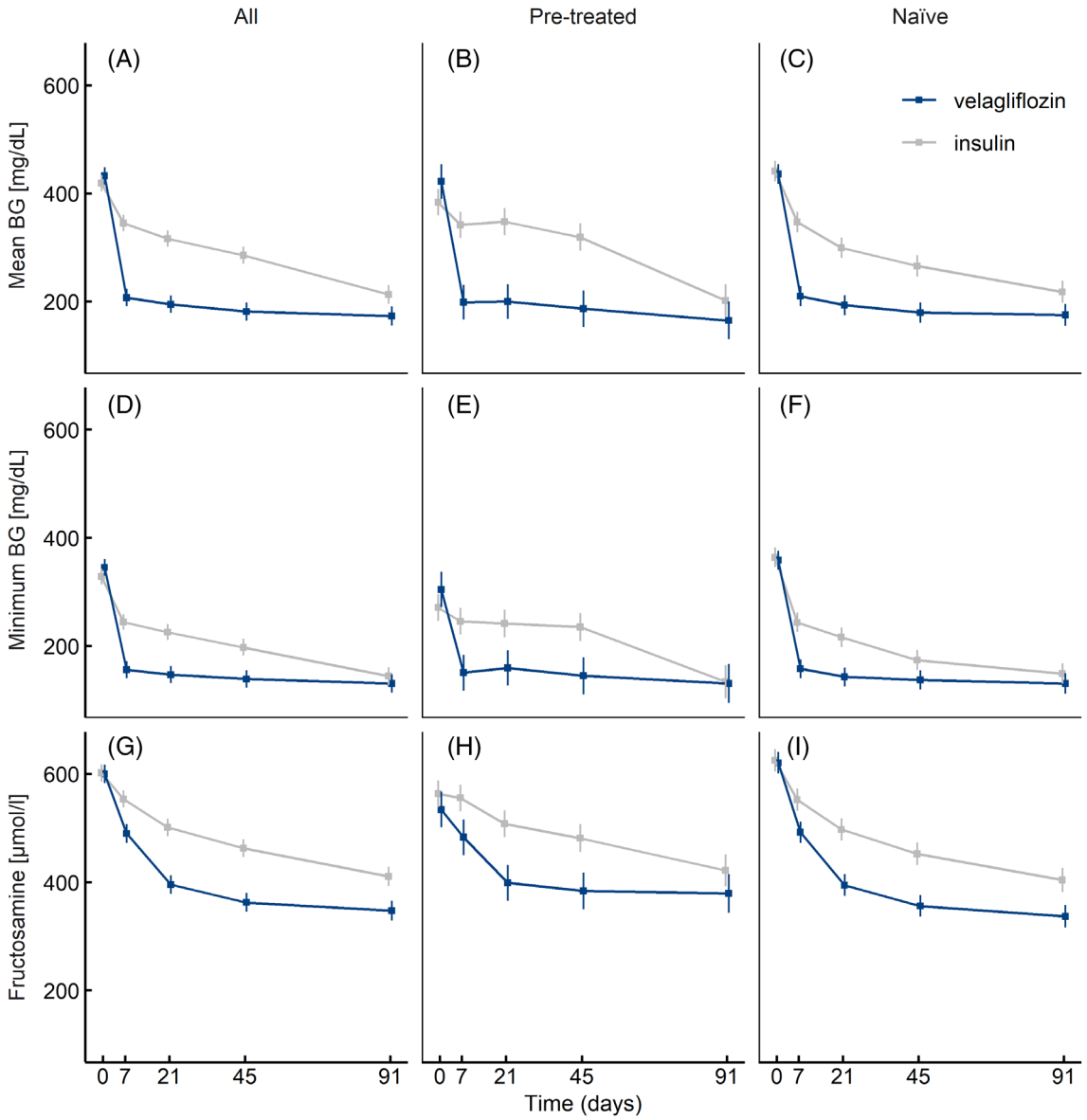

FIGURE 4 Fructosamine, mean blood glucose, and minimum blood glucose (BG) over time in the full analysis set, and in the subgroups of naïve and insulin-pretreated cats in the velagliflozin and insulin groups. Error bars represent adjusted mean ± standard error (SE) from mixed model repeated measures (MMRM) analysis.

study (93%[6]; the latter study included a higher intensity of glucose monitoring). In addition, the variation in glycemic variables is in line with their documented day-to-day variation in insulin-treated cats.[5,26] Most importantly, the purpose of the study was to test the feasibility of this alternative to insulin, with different features (eg, oral once daily solution, lack of clinical hypoglycemia, being able to give the medication with or without food in cats being fed ad libitum or q12h), using a group of insulin-treated diabetic cats managed in real-life practices and in real-life field conditions as a control group. Both groups showed good compliance with only 2 velagliflozin cats and 1 insulin cat being excluded due to noncompliance. It remains possible that some cats and owners still prefer injection treatment over oral solutions.

The success data are based on the FAS group which, as predefined, had sufficient data in order to assess true efficacy of both treatment groups. Five velagliflozin cats had been excluded from analysis due to lack of follow-up data (n = 3 DKA; n = 2 noncompliance). Data S5 demonstrates that conclusions did not change with these 3 DKA cases included. Finally, for a case to be reported as a success, improvement had to be shown in at least 1 (thus not all) glycemic variable and 1 (thus not all) clinical sign.

A comparison of both efficacy and safety results with the SGLT2 inhibitor investigated previously should be cautioned against.[20] Despite the adverse effects and the efficacy seeming comparable, the current study is different in methodology and, crucially, provided the perspective of a control group. In addition, the current study included insulin-pretreated cats, as well as naïve diabetic cats.

A majority of owners reported pu/pd improved, which is also in line with studies in diabetic cats.[19,20] In people treated with

TABLE 10 Comparison of treatment groups on the basis of change from baseline using a restricted maximum likelihood-based mixed model repeated measures (MMRM) approach with baseline value of the endpoint in question as linear covariate, and treatment, visit, and visit by treatment interaction as fixed effects.

			Comparison velagliflozin group versus insulin group		
Variable	**Treatment history**		**Adjusted mean difference**	**95% confidence interval**	***P*-value**
Serum fructosamine change from baseline [µmol/L]	All	Day 7	−61.8	−104.8 to −18.8	.01
		Day 21	−107.3	−150.3 to −64.2	<.001
		Day 45	−103.2	−146.8 to −59.6	<.001
		Day 91	−63.5	−110.1 to −16.9	.01
	Pretreated	Day 7	−52.5	−122.5 to 17.4	.14
		Day 21	−88.7	−158.7 to −18.8	.01
		Day 45	−80.9	−152.9 to −8.9	.03
		Day 91	−22.3	−100.6 to 56.0	.57
	Naïve	Day 7	−56.5	−110.1 to −3.0	.04
		Day 21	−104.6	−158.2 to −51.0	<.001
		Day 45	−99.0	−153.2 to −44.9	<.001
		Day 91	−68.0	−125.1 to −10.9	.02
Mean BG change from baseline [mg/dL]	All	Day 7	−140.2	−182.6 to −97.9	<.001
		Day 21	−125.5	−168.1 to −82.9	<.001
		Day 45	−107.7	−151.2 to −64.2	<.001
		Day 91	−30.8	−77.6 to 16.0	.17
	Pretreated	Day 7	−161.2	−233.7 to −88.8	<.001
		Day 21	−162.6	−235.4 to −89.8	<.001
		Day 45	−147.8	−222.9 to −72.6	<.001
		Day 91	−30.9	−113.0 to 51.2	.46
	Naïve	Day 7	−130.3	−183.0 to −77.6	<.001
		Day 21	−102.3	−155.3 to −49.3	<.001
		Day 45	−82.7	−136.7 to −28.6	<.001
		Day 91	−30.1	−87.1 to 26.9	.30
Minimum BG change from baseline [mg/dL]	All	Day 7	−88.6	−129.8 to −47.3	<.001
		Day 21	−79.2	−120.7 to −37.6	<.001
		Day 45	−58.6	−101.1 to −16.0	.01
		Day 91	−47.5	−50.5 to 41.0	.84
	Pretreated	Day 7	−106.6	−180.5 to −32.6	.01
		Day 21	−88.9	−163.1 to −14.7	.02
		Day 45	−96.3	−172.8 to −19.9	.01
		Day 91	4.0	−79.8 to 87.8	.92
	Naïve	Day 7	−79.5	−129.9 to −29.1	.01
		Day 21	−70.1	−120.9 to −19.3	.01
		Day 45	−33.4	−85.3 to 18.5	.21
		Day 91	−5.5	−60.3 to 49.2	.84

Abbreviation: BG, blood glucose.

SGLT2 inhibitors, frequent urination, thirst, volume depletion, and orthostatic hypotension have been reported, although they are only rarely deemed clinically important, nor lead to treatment discontinuation.[30] Exogenous insulin treatment directly ensures adequate cellular glucose uptake, whereas SGLT2 inhibitors would only indirectly, through recovery of endogenous insulin production, do so. Because such recovery might need time or be (initially) insufficient, especially initial improvement of clinical signs such as pu/pd and polyphagia could be affected. Also, comparison of improvement rates in pu/pd and polyphagia through calculation of 95% confidence intervals did not demonstrate a statistical difference between the 2 groups (Data S5). It is also encouraging to

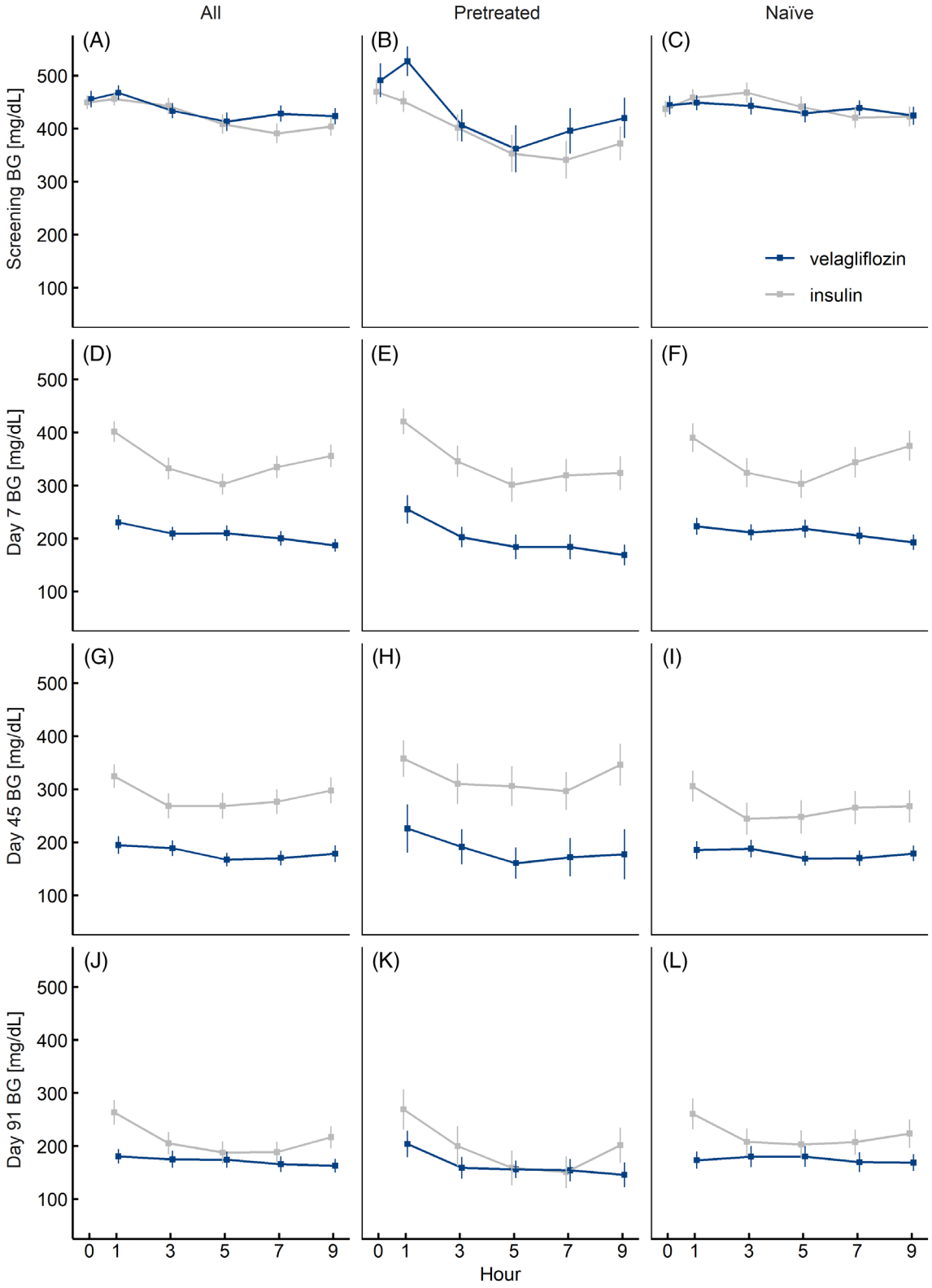

FIGURE 5 Mean blood glucose for each time point of the blood glucose (BG) curves in the full analysis set, and in the subgroups of naïve and pretreated cats. Error bars represent mean ± standard deviation (SD).

see that use of velagliflozin was associated with an increase of number of cats with optimal BCS and decrease of cats with suboptimal BCS (Figure 3). The study design, without specific sample size calculation beyond that for the composite success variable, renders the absence of a difference in BCS improvement between the 2 groups vulnerable to a type 2 error. Ideally, exact measurements

TABLE 11 Quality of life changes according to owners during the trial.

Treatment	Quality of Life	Screening N (%)	Day 3 N (%)	Day 7 N (%)	Day 21 N (%)	Day 45 N (%)	Day 91 N (%)
Velagliflozin group (n = 54)	Poor	5 (9.3)	…	…	…	…	…
	Fair	21 (38.9)	…	…	…	…	…
	Good	16 (29.6)	…	…	…	…	…
	Very good	8 (14.8)	…	…	…	…	…
	Excellent	3 (5.6)	…	…	…	…	…
	Not known	1 (1.9)	…	…	…	…	…
	Change from baseline						
	Improved	…	22 (40.7)	28 (51.9)	37 (68.5)	39 (75.0)	38 (80.9)
	Same	…	31 (57.4)	26 (48.1)	16 (29.6)	11 (21.2)	9 (19.1)
	Worsened	…	…	…	1 (1.9)	2 (3.8)	…
	Not known	…	1 (1.9)	…	…	…	…
Insulin group (n = 62)	Poor	11 (17.7)	…	…	…	…	…
	Fair	20 (32.3)	…	…	…	…	…
	Good	22 (35.5)	…	…	…	…	…
	Very good	7 (11.3)	…	…	…	…	…
	Excellent	2 (3.2)	…	…	…	…	…
	Change from baseline						
	Improved	…	21 (33.9)	30 (48.4)	34 (54.8)	39 (66.1)	37 (74.0)
	Same	…	39 (62.9)	30 (48.4)	25 (40.3)	17 (28.8)	11 (22.0)
	Worsened	…	2 (3.2)	2 (3.2)	3 (4.8)	3 (5.1)	2 (4.0)

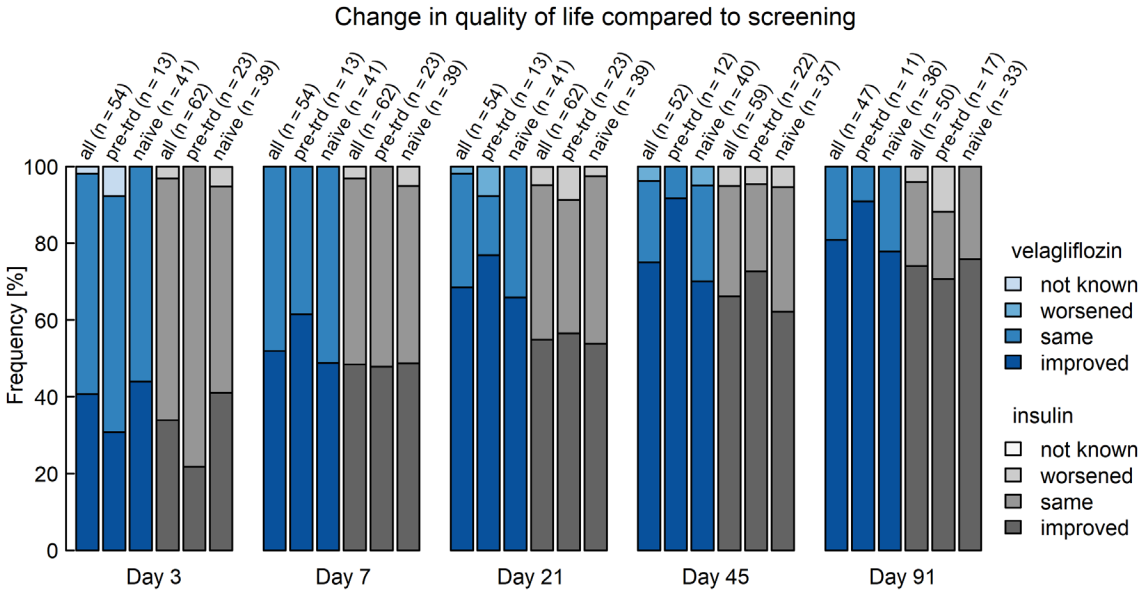

FIGURE 6 Change compared with screening in quality of life in all cats, and in the subgroups of naïve and insulin-pretreated (pre-trd) cats in the velagliflozin and insulin groups.

of volume drunk and urinated had been taken to substantiate this and guard against observation and recall bias (although practically not feasible in field studies). Nevertheless, the owners' observations could relate to the expected improvement of endogenous insulin production in cats due to a rapid decrease in glucotoxicity,[16,17] resulting in a decrease of total amount of circulating BG (as evidenced by all glycemic variables) and thus a decrease in net urine glucose output, (paradoxically) reducing osmotic diuretic effect. Studies on the effect of SGLT2 inhibitors on beta-cell function in diabetic cats are currently unavailable.

TABLE 12 Occurrence of hypoglycemic events until Day 91 by treatment (SAF).

Variable	Velagliflozin group		Insulin group		Total	
	F	N (%)	*F*	N (%)	*F*	N (%)
Total number of animals	…	61 (100)		66 (100)		127 (100)
Any hypoglycemic event	11	8 (13.1)	67	35 (53.0)	78	43 (33.9)
Nonclinical hypoglycemic event	11	8 (13.1)	62	34 (51.5)	73	42 (33.1)
Clinical hypoglycemic event	…	…	5	5 (7.6)	5	5 (3.9)

Note: % denotes percent of animals with at least 1 event in category; *F* denotes number of events.
Abbreviations: N, number of animals with at least 1 event in category, SAF, safety assessment group.

TABLE 13 Urine culture findings during postscreening visits in Safety Group of velagliflozin- and Caninsulin-treated cats with differentiation according to urine collection technique.

	Urine sampling technique	Velagliflozin		Caninsulin	
		F	N (%)	*F*	N (%)
Total number of animals	…	…	61 (100.0)	…	66 (100.0)
Positive culture	Any	29	19 (31.1)	28	18 (27.3)
	Cystocentesis	19	13 (21.3)	17	11 (16.7)
	Free catch	10	7 (11.5)	11	8 (12.1)

Note: Definition of a positive culture was growth of >1000 CFU/mL for cystocentesis samples and >100 000 CFU/mL for free catch samples. % denotes percent of animals with at least 1 event in category. *F* denotes number of events.
Abbreviations: CFU, colony forming unit; N, number of animals with at least 1 event in category.

Human studies and 1 study suggesting an improvement in insulin sensitivity in obese nondiabetic cats are promising.[13-15,18]

Polyphagia did not consistently improve in all velagliflozin group cats. Given that SGLT2 inhibitors promote urinary excretion of an energy source, their use has been associated with reduction in body weight (which is often desirable) in people.[13-15] The cats in the current study did not suffer, however, from undesirable changes in body condition. The persistent polyphagia in some cats might therefore represent an appropriate compensatory mechanism and was not seen as a negative impact on QoL according to owners. Interestingly, there was considerable success in improving diabetic neuropathy associated plantigrade/palmigrade stance in the velagliflozin group. This might be attributable to the induced rapid and constant glucose lowering effect. The small number of cases with this clinical presentation prohibited meaningful statistical comparison and this finding could be skewed by the fact that 11% of insulin-treated cats had a moderate plantigrade stance versus 4% of velagliflozin-treated cats.

The number of statistical comparisons as part of this clinical trial was limited to prevent an inflated Type I error. Nevertheless, the limited analysis on the more easily quantifiable glycemic variables showed significant differences in favor of velagliflozin for early time points, and as early as 1 week after treatment start. It is speculated that early intervention and sustained glucose reduction throughout the day helps reduce the mal-effects of glucotoxicity on beta-cells and thus preserve beta-cells in line with several studies, including ones in cats.[15-17] All velagliflozin cats were recommended to be transitioned back to insulin injection treatment after conclusion of the study, given the lack of availability of a licensed product at the time. The occurrence of possible diabetic remission in this group of cats was not systematically monitored and recorded. Although prospective evaluation is warranted, remission rates could be in line with the rates reported for insulin studies, approximately 1 in 3 cats, or be higher given the effective reduction of glucotoxicity.[6,7,16,17,29,30]

Diabetic ketoacidosis is a rare, but dangerous, complication of the use of SGLT2 inhibitors in humans.[30-34] Stand-alone SGLT2 inhibitor treatment relies on sufficient residual endogenous insulin production capacity. In the absence of endogenous insulin, a metabolic switch to DKA is possible. Decreased insulin concentrations result in increased lipolysis in adipose tissue, which provides more substrate for ketogenesis in the liver. In addition, a decrease in insulin (or an increase in glucagon, or both) increases ketogenesis in hepatocytes. Finally, controversy exists over whether SGLT2 inhibitors stimulate or inhibit the secretion of glucagon, thus influencing ketogenesis.[31-36] Nevertheless, no relevant increases in blood beta-hydroxy-butyrate was noted in 5 diabetic cats treated with a SGLT2 inhibitor in a recent report.[19] In people, evidence exists that DKA cases were directly triggered by SGLT2 inhibitors,[31] with other evidence suggesting the involvement of other factors.[32] In addition, in cats, many factors unrelated to SGLT2 inhibitors can induce DKA, with 1 study suggesting that as many as 14% of diabetic cats presenting to a veterinary teaching hospital will suffer from an episode of DKA.[37] Human Type 2 DM is usually treated earlier in the disease process compared with cats; this could therefore be associated with lower DKA rates; 1 study reported 521 patients with DKA during 370 454 person-years of follow-up while receiving a SGLT2 inhibitor.[34] The risk also varied depending on type of employed SGLT2 inhibitor. The event rate for presumed DKA in the current study was nevertheless low, despite also including insulin-pretreated diabetic cats. As in many people, all cases were euglycemic. Notably, dipsticks were

used to screen for ketones in the current study; the use of serum instead of urine or blood beta-hydroxy-butyrate could potentially have picked up more presumed DKA cases. Euglycemic DKA would represent a novel concept for most veterinarians and if SGLT2 inhibitors become more widely used in future, education on the management of cases suffering from this is warranted. Overall, further study of DKA risk is warranted, as well as strategies to mitigate this risk, especially because DKA is potentially fatal and expensive to treat. Such strategies might include frequent screening for presence of ketones by owner with or without veterinary team especially in the 1st week after the start of treatment (~75% of presumed DKA cases occurred within the 1st week); exercising additional caution when there are other risk factors for DKA (eg, any condition associated with inappetence or dehydration); and education of owners and attending clinicians on euglycemic DKA in ill diabetic cats being treated with this type of medication. Fortunately, prompt stopping of velagliflozin, treatment of DKA and start of insulin treatment resolved DKA successfully in all cats in which treatment was allowed.

Given that SGLT2 inhibitors can partially cross-react to SGLT1 receptors in the gastrointestinal tract, the relatively frequent occurrence of loose feces and diarrhea was not unexpected.[35] The frequency of this adverse effect can vary according to type of SGLT2 inhibitor. For the vast majority feces changes were temporary and according to the owners, this did not impede QoL of their cat, nor did they seemingly affect their ability to maintain a good BCS. Dose decreases were not allowed as part of the study protocol. Dose decreases could help, which can be easily implemented, given that velagliflozin is an oral solution. Dietary interventions could also be considered for this purpose. These findings seem comparable to the situation with bexagliflozin.[19,20]

Finally, female genital mycotic urinary tract infections have been speculated to form a complication of SGLT2 inhibitor use in human type 2 DM.[38-40] In the current study, incidence of positive urine culture was comparable for both the velagliflozin and insulin group. For both groups, this was higher than reported,[41,42] which might relate to the study's more intense monitoring schedule, as well as sampling techniques and transport times. Whether this should prompt more frequent screening is debatable, especially given the veterinary profession's increasing understanding that subclinical bacteriuria does not always need to be treated. Screening at times of clinical signs of a urinary tract infection, as recommended in recent literature,[25] seems prudent or with signs compatible with a possible pyelonephritis. As mentioned earlier, it remains probably inappropriate to compare the incidence of possible urinary tract infections to another SGLT2 inhibitor study,[20] given the absence of the control group as well as differing methodology.

In conclusion, q24h oral velagliflozin proved safe and effective as a stand-alone treatment in naïve and pretreated diabetic cats. More studies are indicated on various aspects of this novel treatment modality, including exact effect on consumed water and volume of urination, as well as how to mitigate any possible small risk for euglycemic DKA. Given its positive effect on QoL, its oral q24h administration, its rapid and robust effect on glycemic variables, and no records of clinical hypoglycemia, velagliflozin provides a desirable additional treatment option for diabetic cats simplifying current management strategies.

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CONFLICT OF INTEREST DECLARATION

Boehringer Ingelheim Animal Health initiated and funded this study and will market the studied drug in the future. All authors received remuneration for their work during the study.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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

Internal ethics approval process. Study was conducted according to Good Clinical Practice (VICH GCP GL09, 2000); study was approved by national bodies of the 3 countries in which it was conducted.

HUMAN ETHICS APPROVAL DECLARATION

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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