The Multicomponent, Multitarget Therapy SUC in Cats with Chronic Kidney Disease: A Multicenter, Prospective, Observational, Nonrandomized Cohort Study

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Abstract
Background: We compared the natural multicomponent, multitarget therapy SUC (Solidago compositum ad us. vet., Ubichinon compositum and Coenzyme compositum, Heel GmbH, Baden-Baden, Germany) to the well-known angiotensin-converting enzyme inhibitor benazepril in a prospective, observational, nonrandomized, two-arm cohort study of cats with chronic kidney disease (CKD). The objective was to assess the tolerability and the effectiveness of SUC in cats with CKD. *Material and Methods*: One hundred thirty-six cats were screened for CKD, and 70 cats were eligible for the study. Thirty-three cats were assigned to the SUC treatment, and 35 cats received benazepril. All cats were diagnosed with CKD. The follow-up period was 168 days. Response was assessed as an improved or stable serum creatinine from baseline to the end of the study. Additionally, a clinical summary score, as measure of quality of life, was evaluated. *Results:* Serum creatinine remained close to baseline in both study groups with slightly improved values in the SUC group. The clinical summary score improved significantly in the SUC group on days 3, 7, 28, 56 and 112, but not on day 168. *Conclusions:* Within the limitations of the study, the results carry implications for the useful-

ness of SUC as an interesting new treatment option for feline CKD. The results indicate that SUC might be more effective if given at least twice weekly.

SUC zur Behandlung der chronischen Niereninsuffizienz der Katze nach dem Multicomponent-Multitarget-Prinzip: Eine multizentrische, prospektive, nichtrandomisierte Kohortenstudie

Schlüsselwörter
Katze · Chronische Niereninsuffizienz · Solidago compositum ad us. vet. · Ubichinon compositum · Coenzyme compositum

Zusammenfassung
Hintergrund: Es wurde die Multicomponent-Multitarget-Therapie SUC (Solidago compositum ad us. vet., Ubichinon compositum und Coenzym compositum, Heel GmbH, Baden-Baden, Deutschland) mit dem bekannten Angiotensin-Converting-Enzym-Inhibitor (ACEI) Benazepril in einer prospektiven, nichtrandomisierten, zweiarmigen Kohortenstudie an Katzen mit chronischer Nierenerkrankung (CNE) untersucht. Ziel war es, die Verträglichkeit und Wirksamkeit von SUC bei Katzen mit CNE zu beur-

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teilen. ***Material und Methoden:*** Einhundertsechsunddreißig Katzen mit Verdacht auf CNE wurden untersucht, bei 70 Katzen wurde eine CNE diagnostiziert und diese wurden in die Studie aufgenommen. Dreiunddreißig Katzen wurden mit SUC therapiert und 35 Katzen erhielten Benazepril. Der Beobachtungszeitraum betrug 168 Tage. Das Ansprechen auf die Therapie wurde definiert als ein verbessertes bzw. ein stabiles Serumkreatinin am Ende der Studie im Vergleich zum Ausgangswert. Zusätzlich wurde zur Bewertung der Lebensqualität der Katzen ein klinischer Summenscore erfasst. ***Ergebnisse:*** Das Kreatinin blieb in beiden Studiengruppen nahezu unverändert, mit geringgradig niedrigeren Werten in der SUC-Gruppe. Der klinische Summenscore verbesserte sich in der SUC-Gruppe im Vergleich zur Benazepril-Gruppe signifikant an den Tagen 3, 28, 56 und 112, nicht aber am Tag 168. ***Schlussfolgerungen:*** Die Ergebnisse zeigen, dass SUC eine neuartige und gut verträgliche Behandlungsalternative zu ACEIs bei Katzen mit leichter bis mittelschwerer CNE darstellt. Die Ergebnisse deuten darauf hin, dass eine zweimal wöchentliche Therapie mit SUC effektiver sein könnte als eine Dosierung einmal pro Woche.

Background

Chronic kidney disease (CKD) in cats is defined as a loss of kidney function [1]. CKD has been diagnosed with increasing numbers in recent decades [2, 3], and risk factors associated with the development of CKD have been identified [4]. Especially in cats, renal disorders are the number one cause for mortality in cats ≥5 years of age [5–8].

Symptoms of CKD are dependent on the severity of the disease. Common signs of CKD are lethargy, reduced appetite and consequently weight loss presuming a reduced quality of life [9]. In addition, polyuria/polydipsia, elevated creatinine concentrations, dehydration, proteinuria and lower urinary specific gravity (USG) are common [10].

The diagnostic workup should include complete blood count, serum chemistry, blood pressure and urine analysis with urine protein-to-creatinine ratio (UP/C) [10, 11]. A staging system for cats with CKD has been established by the International Renal Interest Society (IRIS) [12] (Table 1). The strongest predictors for survival are serum creatinine and UP/C [13].

CKD is an irreversible and progressive disease [14, 15], and the treatment aims to preserve kidney function and to maintain a good quality of life [10]. Treatment recommendations for feline CKD include dietary adjustments with protein and phosphate restriction, and management of potassium balance and anemia, as appropriate [16–20].

In addition, pharmacotherapy is often prescribed when proteinuria is present. For renal proteinuria angiotensin-converting enzyme inhibitors (ACEIs) are part of the standard of care in both cats and dogs [19, 21–24].

The combined treatment with Solidago compositum ad us. vet. (Heel GmbH, Baden-Baden, Germany), Ubichinon compositum (Heel GmbH, Baden-Baden, Germany) and Coenzyme compositum (Heel GmbH, Baden-Baden, Germany) with numerous ingredients (online suppl. Table 1, for all online suppl. material, see www.karger.com/doi/10.1159/000506698) has been developed as an integrative treatment for cats with CKD following a multicomponent, multitarget principle. In the following, the abbreviation SUC (Solidago ad us. vet., Ubichinon compositum and Coenzyme compositum) is being used. In most cats diagnosed with CKD, chronic tubulointerstitial nephritis and renal fibrosis are common findings on histology [25–27]. In humans, tubulointerstitial nephritis and renal fibrosis have been linked to cell senescence in kidney tissue [28, 29]. Senescent cells show expression of proinflammatory cyto- and chemokines causing inflammation, fibrosis and loss of function of organs [28]. Preventing the transition from normal to senescent cells has been linked to *Solidago virgaurea*, the main ingredient of Solidago compositum ad us. vet. [30]. Furthermore, compounds isolated from *S. virgaurea* are reported to have antimicrobial, analgesic, anti-inflammatory, spasmolytic and mild diuretic activity [31]. The diuretic activity of *S. virgaurea* has been linked to the inhibition of ACE comparable to the effect of benazepril [31]. ACE plays a pivotal role in the development of CKD causing glomerular hypertension resulting in glomerular damage and activation of proinflammatory and profibrotic pathways [32]. To summarize, *S. virgaurea* can reduce the inflammation of kidney tissue and protect organ function by preventing fibrosis. Ubichinon compositum and Coenzyme compositum can enhance mitochondrial respiration leading to reduced oxidative stress in the target tissue caused by an impaired mitochondrial respiratory system [33, 34]. There is a growing body of evidence that reduced respiratory capacity of mitochondria might be the cause or the consequence of chronic kidney disorders in patients [35–37].

Despite a lot of experience with the use of SUC, only a small number of studies are available showing effectiveness and tolerability of SUC in the cat [38–40]. The primary aim of this multicenter, prospective, two-armed, observational nonrandomized cohort study was to assess tolerability. The second aim was to show effectiveness of the treatment. In this clinical study, SUC was compared to the ACEI benazepril in cats with CKD. Additionally, quality of life was assessed by the owner and the treating veterinarian.
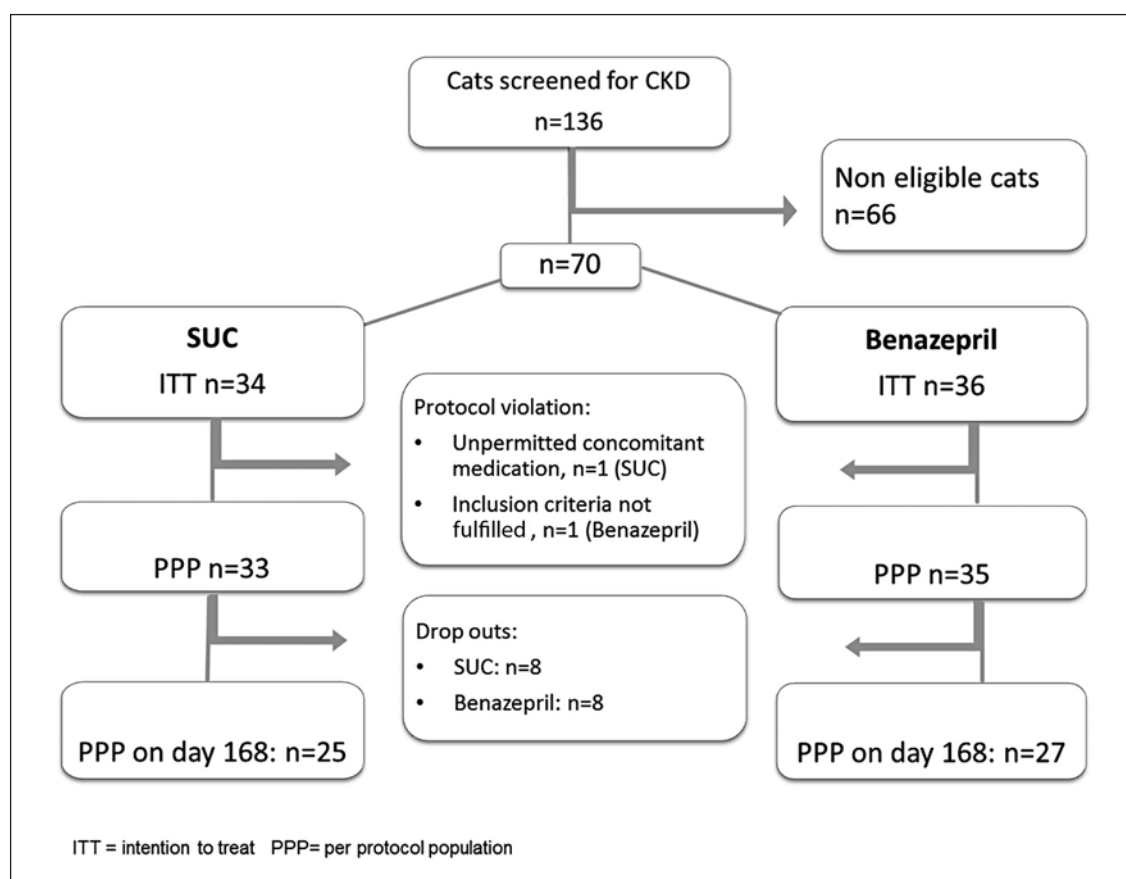
Fig. 1. Flowchart of the study.

Material and Methods

Cats

A total of 136 client-owned cats >12 months suspected or known to have CKD were screened at 12 veterinary centers in Germany from 2012 to 2016. Seventy cats were eligible for the study (Fig. 1).

Inclusion Criteria

Cats of either sex were eligible for inclusion if owner informed consent was given. Cats with a body weight of 2.0–10 kg were included in the study. All cats had to be diagnosed with clinically stable CKD based on the criteria of the IRIS society. The IRIS stage includes serum creatinine, UP/C and blood pressure measurements (Table 1). The diagnosis of CKD was based on clinical history, physical examination and laboratory findings. The following criteria had to be met: serum creatinine concentration ≥2 and ≤5 mg/dL and USG ≤1.035. Cats with a clinical summary score of 10–15 were eligible for the study. Cats receiving a renal diet were eligible if they had received the diet for at least 4 weeks before enrollment in the study; also cats with diabetes mellitus or hyperthyroidism were eligible if the concomitant disease had been stable for at least 4 weeks.

Exclusion Criteria

Cats were not eligible for the study if they had a serum creatinine <2 and >5 mg/dL, a clinical summary score below 10 or above 15, bacterial urinary tract infection or received concomitant treatment within 14 days before enrollment with other ACEIs, diuret-

Table 1. IRIS stage from the International Renal Interest Society (IRIS)

IRIS stage	Creatinine, mg/dL	Comment
At risk	<1.6	Predisposing parameters
1	<1.6	Nonazotemic, some other renal abnormalities present
2	1.6–2.8	Mild renal azotemia
3	2.9–5.0	Moderate renal azotemia
4	>5.0	Risk of systemic clinical signs and uremic crisis

IRIS substage	UP/C value	Comment
1	<0.2	Nonproteinuric
2	0.2–0.4	Borderline proteinuric
3	>0.4	Proteinuric

IRIS substage	Systolic blood pressure, mm Hg	Comment
1	<140	Normotensive
2	140–159	Prehypertensive
3	160–179	Hypertensive
4	≥180	Severely hypertensive

Day 1-6	Day 7-14	Day 15-55	Day 56-168
Daily dosing	Dosing every other day	Dosing twice weekly	Dosing once weekly

Fig. 2. Dosing scheme of SUC during the study.

ics, nonsteroidal anti-inflammatory drugs, corticoids, nephrotoxic antibiotics, antiemetics or appetite stimulants. Cats treated with homeopathic or herbal remedies 28 days prior to study enrollment and for the duration of the study were excluded.

Study Design

This was a multicenter, prospective, observational, two-armed, nonrandomized, open-label cohort study conducted in 12 German veterinary practices between July 2012 and June 2016. The design and conduct of the study were in accordance with the Guidelines for Good Clinical Practice (GCP) VICH GL9 [41]. A contract research organization (Klifovet AG, Munich, Germany) was requested to design the study protocol. Suitable study sites were selected from a pool of investigators experienced in the conduct of GCP compliant clinical studies and in monitoring the active study phase according to GCP. The study sites were responsible for the data management and the reporting of the study results to Klifovet AG. Study sites were regarded suitable if they had experience in the use of the study medication, had enough patients to recruit the required number of cases and were equipped to collect the clinical data, for example cystocentesis.

Treatments

Cats were treated with either SUC or benazepril (Benefortin® Flavour 2.5 mg tablets; Boehringer Ingelheim Vetmedica GmbH, Ingelheim, Germany). Each participating center treated all cats with either SUC or benazepril. To ensure the correct treatment with either SUC or benazepril, the study sites that were familiar with benazepril treated all cats with benazepril and the study sites familiar with SUC used solely SUC. This design assured that veterinarians could not compare treatment results between groups to reduce the bias caused by the unblinded design of this observational study.

SUC is composed of numerous ingredients displayed in online supplementary Table 1. All components of SUC have dilutions in the range of 10^4–10^{10}. The components were mixed in equal parts, and a 3-mL solution was administered subcutaneously by the veterinarian at the first visit, followed by oral administration by the owner. Treatment was administered daily for the first week, every second day in the second week, twice weekly from day 21 to day 55, and then the dose was reduced to once weekly (Fig. 2). Benazepril was given at 0.5–1.0 mg/kg p.o. every 24 h as a 2.5-mg tablet according to the product label (cats with a body weight of 2.5–5 kg received 1 tablet, and cats with a body weight of >5 kg received 2 tablets). There was no standardization of cat diets and a renal diet was allowed if started ≥4 weeks prior to enrollment. Correction of dehydration by infusion was allowed within the study period, but infusion had to be discontinued at least 48 h before blood and urine sampling.

Study Duration and Evaluation

Cats were observed for 168 days. Clinical examinations were performed at the screening visit, at baseline (day 0) and on days 3, 7, 28, 56, 112 and 168, respectively, within a time window of ±1 day

until day 7 and ±3 days afterwards. Blood pressure was measured noninvasively at the screening visit, and on days 56 and 168 if possible. At each time point, 5 measurements were taken, and a mean blood pressure was calculated. Urine was collected at screening and on days 7, 28, 56, 112 and 168 to determine UP/C and USG. Cystocentesis was the preferred method at all time points. Additionally, complete blood count and blood chemistry were done at the screening visit and on days 7, 28, 56, 112 and 168. Response was assessed as a decreased or stable serum creatinine compared to baseline. Clinical parameters were recorded at each visit.

Clinical Summary Score

Quality of life was assessed at each visit using a clinical summary score according to Mizutani et al. [22] on a scale from 1 to 4 for each variable. The clinical summary score included 5 variables such as general behavior, appetite, vomiting, dehydration and fur condition. The sum of all values from the 5 variables was calculated and displayed as clinical summary score, with 5 being the lowest value and 20 the highest. A high value is indicative of a markedly reduced quality of life. General behavior was graded as: 1 = normal activity, 2 = slight asthenia (slight weakness), 3 = moderate asthenia (moderate weakness) and 4 = coma. Appetite was graded as 1 = good appetite, 2 = slightly reduced appetite (>50% of normal food intake), 3 = markedly reduced appetite (<50% of normal food intake) and 4 = complete anorexia. Vomiting was graded as no difference in frequency = 1, not daily but more frequent than usual = 2, vomiting once daily = 3, and vomiting more than once a day was graded as 4. Dehydration was graded from 1 to 4 with 1 for no dehydration and 4 indicating severe dehydration. Fur condition was graded as 1 = normal, 2 = some tangles, reduced grooming, 3 = dull, tangles, infrequent grooming, and 4 = dull and greasy fur, no grooming.

Overall Therapeutic Effectiveness

The overall therapeutic effectiveness was graded as 1 = marked improvement, 2 = slight improvement, 3 = unchanged to 4 = deterioration and was assessed by the veterinarian and the owner on the last study day.

Safety data were collected throughout the study. All suspected adverse events were reported according to standard pharmacovigilance protocols. Treatment compliance was assessed by collecting and counting remaining tablets and ampoules at the end of the study.

Statistical Methods

The study was designed as a prospective, reference-controlled, nonrandomized observational study. Standard statistical methods were employed using SAS 9.3. Baseline data were compared between groups using the Wilcoxon test for interval data, Mantel-Haenszel test for ordinal data and Fisher's exact test for binary data.

For the comparison between treatments, changes from baseline and differences between the groups were calculated. Statistical comparisons were conducted with ANOVA, Mantel-Haenszel test and Fisher's exact test as appropriate. For all comparisons, two-

Table 2. Demographic data at baseline (per-protocol population)

Characteristic	Benazepril group (n = 35)	SUC group (n = 33)	p value for difference between groups
Age (mean ± SD), years	14.1±3.1	12.8±3.4	0.086
Weight (mean ± SD), kg	4.3±1	4.3±1.1	0.937
Male sex, n (%)	19 (54)	22 (67)	0.33
Castrated, n (%)	35 (100)	33 (100)	n.a.
Previously diagnosed with CKD, n (%)			0.82
≥1 year ago	8 (23)	7 (21)	
<1 year ago	17 (49)	14 (43)	
No	10 (29)	12 (36)	
On renal diet, n (%)	14 (40)	14 (42)	1.0
Concomitant illness, n (%)	13 (37)	4 (12)	0.025
Currently under treatment for other conditions, n (%)	11 (31)	4 (12)	0.08
Blood pressure (mean ± SD), mm Hg	156.8±13.9	156.4±15.2	0.92
Renal variables (means ± SD)			
Serum creatinine, mg/dL	2.52±0.56	2.75±0.68	0.13
USG	1,023.1±6.3	1,020.1±6.5	0.13
UP/C	0.28±0.2	0.16±0.2	0.02
Clinical summary score	10.7±0.9	10.8±1.0	0.74

sided 95% confidence limits were calculated. A p value <0.05 was considered statistically significant.

At baseline UP/C was noticeably lower in the SUC group, comparison of UP/C was performed with ANOVA adjusted for propensity scores – based on creatinine and UP/C at baseline.

The noninferiority of SUC to benazepril was assessed on the response variable change from baseline in serum creatinine. The limit for the lower boundary of the 95% confidence interval for the differences between the treatment groups at 168 days was compared to 0.6 mg/dL, which was considered within the magnitude of change without clinical relevance and also represents half the difference in serum creatinine between IRIS stages 2 and 3 [12].

One aim of the study was to show noninferiority of SUC to benazepril therapy, and for this purpose, the effectiveness variables were analyzed in the per-protocol population. An additional intention-to-treat analysis was performed to evaluate the robustness of the results.

Results

Study Populations

The 12 participating practices enrolled a total of 70 cats, with 36 cats in the benazepril group and 34 cats in the SUC group (intention-to-treat population). The per-protocol population consisted of 68 cats, 35 in the benazepril cohort, and 33 in the SUC cohort. Reasons for exclusion from the study were nonfulfillment of inclusion criteria in the benazepril group ($n = 1$), and therapy with an ACEI in the SUC group ($n = 1$). Three cats with USG = 1.036 (2 in the SUC group, 1 in the benazepril group) were included as a protocol deviation, because all other criteria were fulfilled. Fifty-two cats (76%) completed the study, with 27 cats in the benazepril group and 25 cats in the SUC group. The raw data sets of the study are available in online supplemental Table 2.

In both treatment arms, 8 cats terminated the study prematurely. In the benazepril group 2 cats were euthanized because of CKD, having increased serum creatinine and UP/C values within the study period, and 1 cat terminated the study prematurely because of worsened CKD. One cat in the SUC arm was euthanized due to worsening of CKD, and 1 cat diagnosed with hypertension in need of hypertensive treatment was excluded from the study. All additional reasons for dropouts were not related to CKD in both treatment arms. In the benazepril group cats were excluded due to the following reasons: pancreatitis, purulent otitis, bacterial cystitis and withdrawal of owner consent, and in the SUC group cats were excluded because of an adenocarcinoma, death of unknown cause, withdrawal of owner consent and nonfulfillment of inclusion criteria.

In this observational study, cats were not randomized to either treatment arm. Comparing cats in the benazepril and the SUC group showed that age, weight, gender, clinical summary score, serum creatinine and USG were not statistically different at baseline, but both groups differed statistically when comparing UP/C (Table 2). To correct for this difference, a propensity score was used to assure comparability of both groups.

At the screening visit (per-protocol population) 22 cats in the SUC group were in IRIS stage 2 and 11 cats in IRIS stage 3. In the benazepril group 27 cats were in stage 2 and 8 cats in stage 3. IRIS stage and substages are displayed in Table 3.

Table 3. IRIS stage and substage of per-protocol population at baseline

Iris stage	Creatinine, mg/dL	SUC $n = 33$	Benazepril $n = 35$
1	<1.6	0	0
2	1.6–2.8	22	27
3	2.9–5.0	11	8
4	>5.0	0	0
IRIS substage	UP/C value	$n = 33$	$n = 35$
1	<0.2	19	8
2	0.2–0.4	12	22
3	>0.4	2	5
IRIS substage	Systolic blood pressure, mm Hg	$n = 25$	$n = 34$
1	<140	4	4
2	140–159	15	13
3	160–179	6	13
4	≥180	0	4

Renal Variables

Overall, serum creatinine remained close to baseline values during the study in both groups (Fig. 3). At the end of the study serum creatinine increased by only 0.05 mg/dL in the SUC group and 0.21 mg/dL in the benazepril group (Fig. 3, $p = 0.49$).

The change in serum creatinine to baseline did not reach statistical significance showing noninferiority of both treatment arms taking into account the noninferiority margin of 0.6 mg/dL with the upper boundary of the 95% confidence interval being 0.3 mg/dL.

In the SUC group 65% of all cats had a stable or decreased serum creatinine within the study period, with up to 70% of cats with decreased serum creatinine in IRIS stage 3. Comparing both groups, there was no statistically significant difference in the number of cats progressing to a higher IRIS stage ($p = 0.78$, SUC group: 9 cats, benazepril group: 8 cats). Results were independent whether cats received renal diet or not ($n = 14$ cats in both treatment arms).

Clinical Summary Score

The clinical summary score showed a rapid improvement of the cats in the SUC group within 3 days. The clinical summary score was significantly improved compared to the benazepril group on days 3 ($p = 0.015$), 7 ($p = 0.0022$), 28 ($p = 0.0024$), 56 ($p < 0.0001$) and 112 ($p = 0.0043$), but not on day 168 (Fig. 4). Several variables, for example general behavior, appetite score and vomiting, showed a sta-

tistically significant improvement in the SUC group compared to the benazepril group at certain time points. Body weight was stable in both groups during the study period.

Overall therapeutic effectiveness scores were assessed by the owners and veterinarians. The scores for effectiveness of both treatments did not differ, with slightly better values in the SUC group not reaching significance. Veterinarians rated SUC as overall effective in 72% of cats and benazepril treatment was considered overall effective in 68% of the cats. Owners evaluated SUC as overall effective in 70% of cases and benazepril as effective in 65%.

Compliance

Compliance of the owners to adhere to the study protocol was high with over 90% compliance in both treatment arms.

Tolerability

Both treatment regimens were well tolerated, 12/36 cats in the intention-to-treat population in the benazepril group (33%), and 8/34 cats in the SUC group (24%) had ≥1 adverse event reported. Five cats in each group had ≥1 severe adverse event. Two cats in the benazepril group were euthanized because of the CKD, and 1 cat was euthanized due to a CKD-unrelated reason. In the SUC group 1 cat died of unknown cause, and 1 cat was euthanized because of the CKD. There were no statistically significant differences between the groups in the frequency of any of these events.

Discussion

The results of the current study showed that the multicomponent, multitarget combination SUC is noninferior to the commonly used ACEI benazepril for the treatment of cats with CKD of mild to moderate severity, with similar effects on laboratory parameters indicative of disease progression. Review of the current literature showed that most tested drugs are noninferior compared to benazepril [21–24, 42–45] (Table 4). Some of the indicated studies included a placebo group to confirm effectivity of their study drug [22, 23, 42, 45, 46]. Mizutani et al. [22] and Takenaka et al. [45] showed an increase in serum creatinine within the treatment time of 180 days in the placebo group, showing the progressive course of the disease. In the present study, a placebo group was not included due to ethical constraints and because it is widely accepted that renal function in affected cats decreases over time with increasing serum creatinine levels. The observation time of the cats in this study was in accordance with previously published data [22–24, 42, 45] and within this time frame serum creatinine was reduced on days 28, 56 and 112 in the SUC group (Fig. 3) but not in the bena-
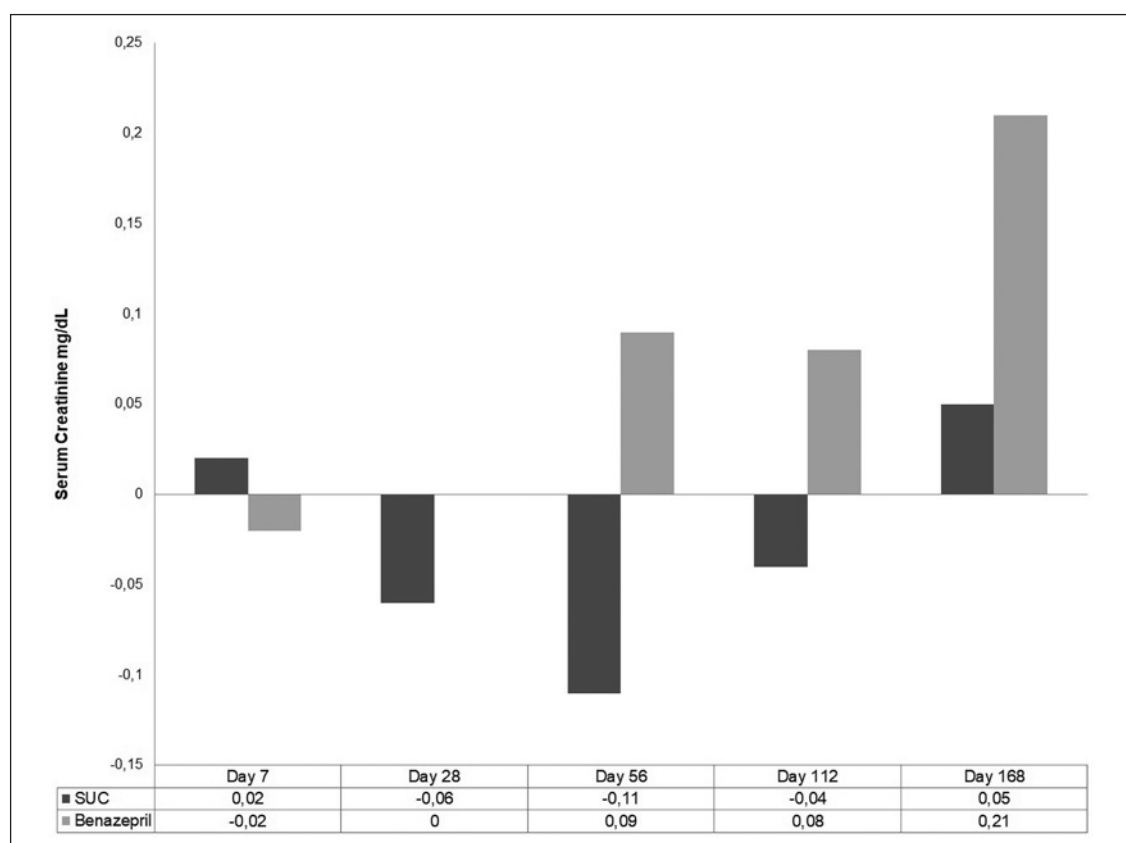
Fig. 3. Change in serum creatinine from baseline. Differences in serum creatinine between groups were not statistically significant at any time point. In the SUC group (■), serum creatinine was reduced until day 112.

Fig. 4. Clinical summary score as indicator of quality of life. Mean summary score of all clinical and behavioral variables at baseline and during follow-up visits (days 3, 7, 28, 56, 112, 168). The dashed line displays values of the clinical summary score of the benazepril group, and the solid line displays the values for the SUC group. Horizontal lines represent standard errors. Higher scores indicate reduced quality of life; * $p < 0.05$: statistically significant difference between groups.
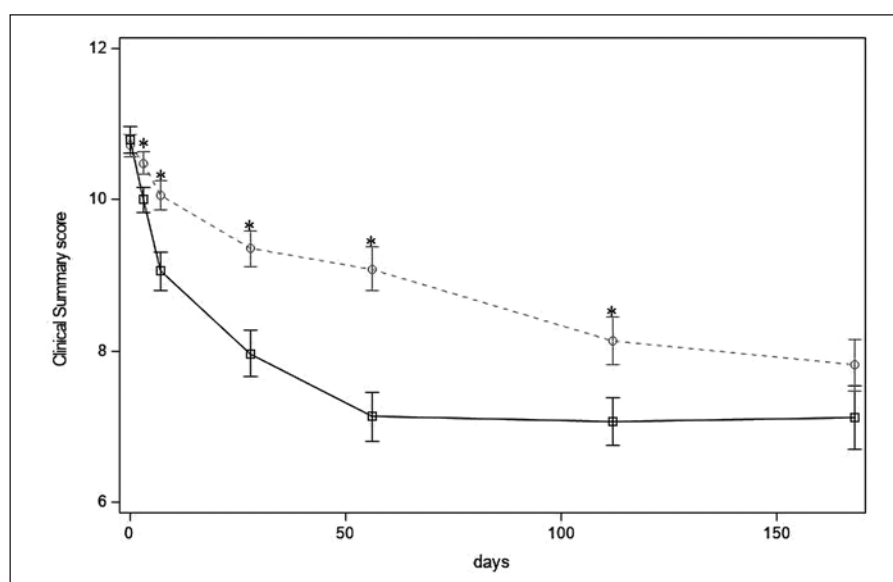
zepril group. The quality of life, an important parameter, was assessed by King et al. [46] and Mizutani et al. [22]; in both studies, no improvement of quality of life was seen. In the present study, treatment with SUC showed a significant improvement of the quality of life on days 3, 7, 28, 56 and 112, but not on day 168.

Taking the results from the relevant literature together (Table 4), benazepril is still standard of care in cats with

Table 4. Review of literature on therapeutic interventions in feline CKD

Authors	Therapy	n	IRIS stage	Design	Raw data available	Statistic	Observation time, days	Parameter	Sign.
Brown et al. [42], 2001	Benazepril, 0.25–0.5 mg/kg Benazepril, 0.5–0.1 mg/kg Benazepril, 1.0–2.0 mg/kg Placebo	8 8 8 8	n.a.	Randomized, monocentric, induced CKD	No	Multivariate	180	Blood pressure GFR	Yes[1] Yes[1]
King et al. [46], 2006	Benazepril Placebo	96 96	Stages 2–4	Randomized, double-blinded, multicenter (23 centers)	No	Multivariate, repeated measure	900	Survival UP/C QL (clinical score)	No Yes[1] No
Mizutani et al. [22], 2006	Benazepril Placebo	33 28	Stages 2–4	Randomized, double-blinded, multicenter (numbers not stated)	No	Repeated measure	180	Serum Crea UP/C Survival QL (Clinical Score)	No Yes[1] No No
Watanabe and Mishina [23], 2007	1. Induced CKD, benazepril 2. Spontaneous CKD, benazepril, no treatment	5 6 5	n.a. Stages 2–3	Part 1: n.a. Part 2: monocentric	No	Univariate Univariate	21 168	Blood pressure Serum crea. Serum phos. Blood pressure	Yes[1] Yes[1] No n.a.
Rishniw et al. [43], 2011	Azodyl (synbiotic) Psyllium husk (prebiotic, control)	5 5	Stages 2–4	Randomized, double-blinded, multicenter (numbers not stated)	No	Univariate	60	Serum crea. Serum BUN	No No
Hanzlicek et al. [44], 2014	Chinese rhubarb Benazepril Chinese rhubarb + benazepril	9 9 8	Stages 2–3	Randomized, monocentric	No	Multivariate, repeated measure	660	Serum crea. UP/C Blood pressure	No No No
Sent et al. [24], 2015	Telmisartan Benazepril	112 112	Stages 2–4	Randomized, investigator-blinded, multicenter (48 centers)	No	Multivariate	180	UP/C	Yes[2]
Takenaka et al. [45], 2018	Beraprost sodium Placebo	36 38	Stages 2–3	Randomized double-blinded, multicenter (22 centers)	No	Multivariate, repeated measure	180	Serum crea. Serum BUN QL (clinical score)	Yes[3] Yes[3] Yes[3]
Own data, 2020	SUC Benazepril	33 35	Stages 2–3	Observational, multicenter (12 centers)	Yes[a]	Multivariate	168	Serum crea. UP/C QL (clinical score) Blood pressure	No No Yes[4] No

n, number of cats; sign., significant (in favor of 1 = benazepril, 2 = telmisartan, 3 = beraprost or 4 = SUC); n.a. not assessed; CKD, chronic kidney disease; GFR, glomerular filtration rate; UP/C, urine protein-to-creatinine ratio; QL, quality of life; serum crea., serum creatinine; serum phos., serum phosphate; serum BUN, serum blood urea nitrogen; SUC, Solidago compositum ad us. vet., Ubichinon compositum, Coenzyme compositum. [a] See supplementary Table 2.

CKD, even though telmisartan has recently shown greater effects on UP/C [24].

Cats treated with SUC showed a rapid improvement of the clinical summary score presuming a better quality of life as early as day 3 after starting treatment for CKD. The difference in the clinical summary score compared to benazepril was statistically significant at all time points except on day 168. The slight reduction in the clinical summary score in the SUC group at the end of the study might have been caused by the reduced treatment frequency at this time point in the SUC group. The dose was reduced to once weekly on day 56 and this dosing regimen might not be sufficient to protect feline kidney tissue. The clinical summary score has been influenced by the fact that veterinarians and owners were not blinded to the treatment. To reduce the bias caused by unblinded design and nonrandomization, each participating study center treated all cats with either benazepril or SUC. Therefore, study centers could not compare treatment effects between groups.

In humans, ACEIs have a pivotal role in the treatment of kidney disease [47].

Benazepril is a common ACEI for the treatment of feline CKD, and studies have supported its effectiveness in the therapeutic management of cats with renal insufficiencies [21–24]. However, concerns about adverse side effects and the known negative pharmacodynamic interactions might limit the applicability. Therefore, SUC has evolved to be a complementary treatment option for feline CKD [38–40] that is well tolerated with high acceptance by owner and cat with improved quality of life.

The goal of CKD treatment is to improve quality of life in the affected cats and to slow down the progression of renal fibrosis to end-stage renal failure [16]. It was not expected to see a tremendous improvement of serum creatinine by either treatment in this study because renal fibrosis cannot be converted into normal renal tissue bringing back normal renal function. Effectiveness of CKD treatment is characterized by stabilizing or slightly improving serum creatinine values [22, 23]. Interestingly, serum creatinine values improved during the study when SUC was given at least twice weekly (until day 55) with a stable UP/C during the study period. This effect was lost on day 112, when SUC was given only once weekly. This change in serum creatinine might indicate a dose-response relationship of SUC. On one hand, these findings might indicate that *S. virgaurea* slowed down tissue fibrosis as demonstrated in a fibroblast culture [30] to a certain extent if given at least twice weekly and that this protective effect might have been lost by underdosing SUC. On the other hand, it is possible that SUC might not have a long-term effect on the progressive course of CKD in cats. Also, for benazepril it was shown earlier that lowering the dose results in a diminished effect on the course of CKD [42].

Taking the results from the clinical summary score and serum creatinine together, it can be concluded that SUC is a new treatment option that should be given at least twice weekly. But the short follow-up time, the number of cats in the study and the dosing regimen might be the reason that the difference in the results between both treatment groups did not favor SUC. To answer these questions a larger placebo-controlled, double-blinded study with an adapted dosing regimen should be done.

The clinical summary score as measure of quality of life did not fully reflect the change in renal parameters such as serum creatinine. Serum creatinine was not significantly reduced by either treatment, but the clinical summary score showed a significant improvement of the quality of life in the SUC group. This finding was consistently seen throughout the study period suggesting an effect of the SUC treatment. This effect might partly be explained by the number of cats (n = 20) with improved serum creatinine in the SUC group during the study. In addition, the beneficial effect on clinical behavior was also seen in previous field studies with SUC [38–40].

Observational and unblinded studies are difficult to analyze because of different population characteristics. In this study there was no statistically significant difference between groups when comparing serum creatinine. Serum creatinine is the most important prognostic indicator for severity of the disease [12]. In addition, UP/C is an important prognostic indicator, and to correct for significant differences in UP/C between both groups at baseline the propensity score was used. Comparing both groups with the propensity score no significant difference in serum creatinine at any time point was detected showing noninferiority of either treatment arm.

Eight cats in the benazepril group did not show proteinuria (UP/C <0.2) at baseline (Table 3). Nowadays, the recommended treatment would not include benazepril for these cats, but at the time the study was designed, this was the standard of care for cats with CKD [24].

SUC is designed to act on multiple different targets to protect renal tissue, therefore it can be recommended at any stage of disease independently of proteinuria to protect kidney tissue from further damage. Interestingly, even 70% of cats in IRIS stage 3 treated with SUC had a decreased serum creatinine and consequently an improved quality of life showing that SUC can be started at any time independently of IRIS stage, and treatment should be given at least twice a week in the maintenance phase to protect renal tissue from further damage. A larger study with greater statistical power would be needed to confirm these findings and to find the best dosing scheme for SUC.

Conclusions

In summary, this observational pilot study indicates that the effectiveness of the multitarget, multicomponent therapy SUC was noninferior to that of the commonly used ACEI benazepril for the treatment of mild to moderate feline CKD over a follow-up period of 168 days. Within the limitations of the study, the results carry implications for the usefulness of SUC as an interesting new treatment option for feline CKD. There is also evidence that the dosing frequency of SUC plays a pivotal role in protecting kidney tissue to stabilize this fatal disease in cats. Further studies, including possible use as add-on therapy and comparisons with newer treatment options seem appropriate.

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Statement of Ethics

All owners gave their informed consent for their cats to be included in the study. The design and conduct of the study were in accordance with the guidelines for GCP VICH GL9 [20].

Disclosure Statement

U.B. has no competing interest to declare. G.B. is an employee of CRO Klifovet AG, who received consultancy fees from Heel GmbH. P.K. has received consultancy fees from Heel GmbH. E.R. is an employee of Heel GmbH.

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Author Contributions

U.B. analyzed and interpreted the data. G.B. designed the study and analyzed the data. P.K. interpreted the data and was instrumental in preparing the manuscript. E.R. designed the study, interpreted the data and contributed to the writing of the manuscript. All authors read and approved the final paper.

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