Funny current (I_f) inhibitors for use in a method of treating and preventing heart failure in feline

FIELD OF THE INVENTION

The invention relates to the field of medicine, in particular to the field of veterinary medicine. The invention relates to the effect of funny current (I_f) inhibitors or a pharmaceutically acceptable salt thereof on the treatment of heart diseases, preferably related to heart failure (HF) in feline patients. It further relates to improving the quality of life and the general health condition as well as prolonging the life expectancy in feline patients suffering from heart failure and/ or heart failure due to one or more of the following etiologies HCM, DCM, RCM, UCM and / or ARVC.

BACKGROUND OF THE INVENTION

Feline heart failure is predominantly caused by different cardiomyopathies. The most common feline cardiomyopathy (CMP) is hypertrophic cardiomyopathy (HCM), followed by restrictive cardiomyopathy (RCM), unclassified cardiomyopathy (UCM), dilated cardiomyopathy (DCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC).

Typically cats with underlying cardiomyopathies remain clinically asymptomatic in the early stages of the disease until they are presented to the veterinarian because the disease has progressed and ventricular diastolic and/or systolic function is severely impaired resulting in heart failure.

Cats at this stage present either mild to moderate clinical symptoms with tachypnoea up to severe respiratory distress (dyspnoea) due to pulmonary oedema and/or pleural effusion requiring emergency treatment with oxygen therapy and intravenous diuretic and thoracocentesis in case of pleural effusion.

Elevated heart rate, especially in pet animals, may be treated with bradycardic agents such as for example calcium (Ca^{++}) channel blockers, beta-receptor blockers and other antiarrhythmic agents.

Known Ca^{++} channel blockers, which may be used for this purpose are diltiazem, verapamil, amlodipine and nifedipine.

Known beta-receptor blockers which may be used for this purpose are atenolol, bisoprolol, carvedilol, esmolol, sotalol, metoprolol or propanolol.

Beta-receptor blockers and calcium channel blockers are the most frequently used drugs in preclinical feline CMP. However, the use of these drugs remains controversial since a beneficial effect on disease progression or survival has not been demonstrated with either drug. In addition, it has been shown that the left atrial systolic and global function was significantly decreased by atenolol.

Known other antiarrhythmic agents, which may be used for this are adenosine, amiodarone, atropine, digoxin, isoproterenol, lidocaine, tocainide, mexiletine, phenytoin, procainamide, propafenone and quinidine, as for example sulfonates gluconates. Calcium channel blockers as well as beta blockers can be used as antiarrhythic agents as well.

In addition, also angiotensine-converting.enzyme inhibitors (ACE inhibitors), positive inotropes and anti-thrombotic agents are often administered to cats with heart failure. ACE inhibitors are used to reduce the activity of the renin-angiotensin-aldosterone system. Positive inotropes are used if the systolic function of the heart is decreased. Anti-thrombotic agents are administered in order to prevent the development of a thrombus or to dissolve it if it already exists.

Known ACE inhibitors, which may be used for this purpose are enalapril, ramipril, benzazepril, quinapril, perindopril, lisinopril, imidapril, zofenopril and trandolapril.

Known positive inotropes which may be used for this purpose are pimobendan, dopamine, dobutamine, epinephrine, norepinephrine, isoprenaline, digoxin, digitalis alkaloids, and theophylline.

Known anti-thrombotic agents which may be used for this purpose are antiplatelet drugs, such as clopidogrel, aspirin; anticoagulants, such as heparin, warfarin, low molecular weight heparin and thrombolytic drugs, such as streptokinase, tissue plasminogen activators.

So far known treatments in cats result in temporary relief of symptoms mainly with a diuretic drug to prevent further decompensation of the heart failure. However, all of these therapeutic regimens are only of supportive character and therefore limited.

The use of cilobradine or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment or prevention of heart failure is known from EP 1 534 296 B1.

However, there is a need for treating and preventing heart failure in feline, in particular cats, and to further to improve the morbidity, quality of life and long-term survival time, especially in feline, in particular cats, suffering from heart failure of any etiology.

The problem underlying the present invention was to provide a medication, which allows the treatment of heart failure in feline patients, in particular cats. Further, it was desired to find a way to improve quality of life and to reduce the risk of death in feline patients, preferably cats, in particular in those suffering from heart failure of any etiology.

DESCRIPTION OF THE INVENTION

Detailed Description of the Invention

Before the embodiments of the present invention it shall be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "a preparation" includes a plurality of such preparations. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the

art to which this invention belongs. All given ranges and values may vary by 1 to 5 % unless indicated otherwise or known otherwise by the person skilled in the art, therefore, the term "about" was omitted from the description. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are now described. All publications mentioned herein are incorporated herein by reference for the purpose of describing and disclosing the substances, excipients, carriers, and methodologies as reported in the publications which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

The solution to the above technical problem is achieved by the description and the embodiments characterized in the claims.

The invention relates to a funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for treating and/ or preventing of heart diseases, preferably related to heart failure (HF) in feline patients, preferably cats. Furthermore, the invention relates to a funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for improving quality of life and/ or improving general health condition and /or prolonging life expectancy in feline patients, in particular cats, suffering from HF.

The term "heart failure" as used herein relates to a condition in which a problem with the structure or function of the heart impairs its ability to supply sufficient blood flow to meet the body's needs, in particular any contractile disorder or disease of the heart. Clinical manifestations are as a rule the results of changes to the heart's cellular and molecular components and to mediators that drive homeostatic control. Heart failure is caused by different diseases of the heart. There are several main indications with different etiology that may result in heart failure such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restricted cardiomyopathy (RCM), unspecified cardiomyopathy (UCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC). Preferably these cardiomyopathies are classified according to Kittleson (Kittleson, Textbook of veterinary internal medicine, Eds. Ettinger, Feldman, Elsevier Saunders, Philadelphia. 2005, 1082). Thus, according to a further aspect the present invention relates to a funny current (I_f)

inhibitor or a pharmaceutically acceptable salt thereof for treating or preventing heart diseases, preferably HF due to one or more of the following etiologies HCM, DCM, RCM, UCM and / or ARVC. Thus, the invention also relates a funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for improving quality of life and/ or improving general health condition and /or prolonging life expectancy in feline patients, preferably cats, suffering from HF due to one or more of the following etiologies HCM, DCM, RCM, UCM and / or ARVC. The invention also relates to the management of heart failure in cats due to HCM, UCM, RCM, DCM, and/ or ARVC.

The degree of the heart disease in feline patients, preferably in cats, in particular heart failure or heart failure due to HCM, UCM, RCM, DCM, ARVC is classified by the ISACHC classification scheme. According to the invention the ISACHC classes as adopted from the definition of the International Small Animal Cardiac Health Council (ISACHC) classification scheme:

In feline patients, in particular in cats, heart failure is classified based on result of history, physical examination and further examinations such as for example echocardiographic examination and if deemed necessary thoracic radiographic examination.

Class I A: Asymptomatic cats

Evidence of a heart murmur without clinical signs and without_echocardiographic evidence of cardiac structural changes.

Class I B: Asymptomatic cats

Evidence of a heart murmur without clinical signs but with_echocardiographic evidence of cardiac structural changes without enlargement of cardiac.

Class II: Mild to moderate heart failure

Echocardiographic evidence of CMP and mild to moderate heart failure: Evidence of mild to moderate clinical symptoms for heart failure (i.e. shortening of breath/ tachypnoea, mild respiratory distress/dyspnoea). Here, treatment (i.e. with a diuretic as defined herein, e.g. furosemide) is necessary to control clinical symptoms, but is possible at home.

Class III A: Advanced heart failure but outpatient therapy possible

Echocardiographic evidence of CMP and advanced heart failure: with clinical signs that are immediately obvious like respiratory distress (dyspnoea), or hypoperfusion at rest. Outpatient therapy is possible; hospitalization is not required.

Class III B: Advanced heart failure requiring hospitalization
Echocardiographic evidence of CMP showing advanced clinical signs of heart failure which requires treatment at the hospital (i.e. iv (intravenous) furosemide, oxygen supplementation).

Thus, as an example a cat that for example belongs to class III A or B is improving in health or in symptoms enough for it to reach a better ISACH class such as class II or either class IA or class IB, in particular compared to non-treated cats. The same is valid for a cat being classified according the ISACH scheme to belong to class II is improving in symptoms for it to be graded as class IA or class IB, in particular compared to non-treated cats.

According to another aspect of the invention, cats suffering from heart disease can also be classified with a score of 1, 2 or 3 using a 4 point score adapted from the ISACHC:

Score 1: heart disease associated with no clinical signs but detectable (auscultation, echocardiography and radiography).

Score 2: Clinical signs of heart failure evident and adversely affect the quality of life. Typical signs include dyspnea/tachypnea, pulmonary congestion, weakness/lethargy, anorexia, exercise intolerance.

Score 3: Clinical signs of advance heart failure immediately obvious. These clinical signs could have included respiratory distress, marked ascites/pulmonary congestion, profound exercise intolerance or hypoperfusion at rest.

Score 4: Severe cases: subject is moribund, sufferes from cardiogenic shock or acute posterior paresis/paralysis. Hospitalization is mandatory.

Thus, as an example a cat that for example belongs to score 3 or 4 is improving in health and/ or in symptoms enough for it to reach a better ISACHC score such as score 2 or 3 respectively, in particular compared to non-treated cats.

The term "quality of life" as used herein relates also to a tendency of a better quality of life (QoL) when treated with a funny current (I_f) inhibitor, in particular cilobradine versus placebo treated cats. For the purpose of the present invention the cat's quality of life is assessed, in particular by owners, in general as described by Freeman et al. 2010 (Freeman LM, Rush JE, Oyama MA. Development and Evaluation of a Quality of Life Questionnaire for Cats with Cardiac Disease. J Vet Intern Med 2010; 24: 674). The change, in particular the improvement of the quality of life, is measured with the following grading system: 0 (not at all/none), 1 (very little/very few), 2 (little/few), 3 (moderately/some), 4 (much/many) and 5 (very much/a lot). The assessment further includes an evaluation of a development of and/ or changes in breathing difficulties, tiredness/ fatique, fainting/ collapsing, eating habits, drinking habits, behaviour in general, behaviour regarding using litter box, personality, and hospitalisation.

The cat's quality of life can also be assessed by the owner on a daily base. The change is measured with the following grading system: 1 (better), 2 (equal), 3 (worse). The assessment refers to the overall perception of the owner including all his/her impressions.

Thus, the method for improving the quality of life as mentioned herein in particular relates to an increase in one of the grading systems as described above. As an example the invention relates to improving quality of life in feline patients being grade 3 or 4 to grade 2 or 3 respectively after the administration as described herein, in particular compared to non-treated cats.

Furthermore, the ease of administration also contributes to the quality of life of the animal in need of such treatment as the treatment can only be really successful when it is possible to administer the pharmaceutical composition for the treatment the herein described heart diseases to the feline, preferably cat. Thus an additional assessment can be made with regard to ease of administration, the majority of the time, whether it was mostly uncomplicated to give, difficult to give or often not possible to give a pharmaceutical composition comprising a funny current (I_f) inhibitor, in particular cilobradine and other excipients and/ or vehicles. In

addition the owner is asked if the medication was given in the majority of time with the application syringe directly into the mouth or with a small amount of food.

In addition, the demeanour of the feline, in particular a cat, is in particular assessed by veterinarians, by evaluating how active, listless or depressed the feline, in particular cat, is. An assessment of the overall control of the heart disease is also included as poor, fair, good or excellent.

The term "improving general health condition" as used herein relates to findings during clinical examination, results of the laboratory measurements, assessment of echocardiography, ECG, X-ray parameters, blood pressure measurement, dose of administered medication as well as the cat's behavior. Thus, in order to evaluate the improvement of the general health condition of a feline patient, preferably at least two examinations have to be performed, in particular before and after administration as described herein. As an example the general health condition of a feline patient is improved if the findings during clinical examination, results of the laboratory measurements, assessment of echocardiography, ECG, X-ray parameters, dose of administered medication as well as the cat's behavior show a beneficial effect of the administration as described herein, in particular compared to non-treated cats.

The term "prolonging life expectancy" is also referred to and encompasses "long-term survival time" or "reducing cardiac mortality or morbidity", which as used herein relates to the superiority of funny current (I_f) inhibitor, in particular cilobradine, to placebo, in particular non-treatment, in cats with heart failure, meaning that the cats have a higher life span following an administration as described herein, in particular on a regular daily basis.

Cardiac mortality is further defined to be an event when a spontaneous death occurs during the study period, where no other clinical cause could be identified despite the knowledge of the underlying cardiac disease. Cardiac morbidity is further defined to be an event when a progression of the cardiac disease occurs which requires rescue therapy. Rescue therapy is given to a cat in the event of cardiac morbidity. Furthermore, cardiac morbidity is defined as progression of the cardiac disease with adjunct worsening of clinical symptoms (e.g. worsening of respiratory signs) when one of the following criteria below is met: The cat

requires diuretic treatment, preferably furosemide, with dosages above the upper dose limit of 10 mg/kg per day to control clinical symptoms (e.g. dyspnoea) of heart failure; the cat requires additional treatment, such as angiotensine-converting.enzyme inhibitors, Ca-channel bockers, β-receptor blocker, nitroglycerine, diuretics other than furosemide or other antiarrhythmic drugs because of worsening of clinical symptoms (e.g. dyspnoea, lethargy) and either worsening of echocardiographic examination parameters (e.g. significantly decreased FS, left atrium size enlargement) compared to baseline assessment or worsening of creatinine blood levels > 440 µmol/L (> 5.0 mg/dl) or development of clinically significant electrolyte imbalances (i.e. hypokaliaemia, hyponatriaemia); the cat develops a thromboembolic event; the cat develops more than two relapsing episodes of acute congestive heart failure (ISACHC class IIIB) requiring hospitalization necessitating oxygen therapy and/or iv (intravenous) diuretic medication; the cat needs to have more than 2 repeated thoracocentesis. The assessment is based on the following hypothesis H0 and HA: H0 - No superiority of treatment with cilobradine to placebo control versus; HA - Superiority of treatment with cilobradine to placebo control. As an example the invention relates to prolonging life expectancy in feline patients, if the life span of the cat is prolonged in comparison to non-treated cats or if the assessment meets the requirements for the HA criterion as mentioned above, or a similar requirement.

"Funny current (I_f) inhibitors", also referred to as "I_f channel blockers" herein relate to a I_f inhibitor including pharmaceutically acceptable salts thereof, which selectively block hyperpolarization-activated cyclic nucleotide-gated channels (HCN) in cardiac conductive tissue, channels responsible for the transmembrane current known as I_f. It is through blockade of this current that I_f channel blockers are assumed to produce their specific bradycardic effect. HCN channels are widely distributed in the nervous system and in the eye they mediate the current known as I_h. The effect of zatebradine and cilobradine on the I_h channel has also been investigated (Neuroscience, Vol. 59(2), pp. 363-373, 1994 for zatebradine, and British Journal of Pharmacology, Vol. 125, pp. 741-750, 1998 for cilobradine). The results have suggested that I_h can also be blocked by these compounds. Since I_h has been described in the different neurones of the visual signal processing system, the effect on I_h current has been suggested to be an explanation for possible side-effects (visual disturbances) of some I_f blockers. Cilobradine in particular reduces the heart rate in the sino-atrial node of the heart by selective blockade of I_f channels ("funny channel") through a direct interaction with

predominantly HCN4 channels. This blockage is potent and has a dosage and voltage dependency. Because of the high selectivity to the I_f current, effects on vasomotor tone or myocardial contractility and lusitropy are not observed at therapeutically relevant doses in healthy cats. The negative chronotropic effect of cilobradine leads to a reduction of myocardial oxygen demand, prolongation of the diastolic interval and increased stroke volume with a subsequent increase of myocardial oxygen supply.

Preferred funny current (I_f) inhibitors are cilobradine, anilidine, zatebradine and ivabradine, preferably cilobradine and zatebradine, even more preferred is cilobradine.

Cilobradine (3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one) and its hydrochloride salt, are disclosed for example in EP-B-0 224 794 and its US counterpart US 5,175,157. As already mentioned cilobradine is also known to have a favourable activity in the treatment or prevention of heart failure (see EP-B-1 534 296). Cilobradine, zatebradine and alinidine are also known to have a favourable activity in the treatment and induction of the regression of idiopathic hypertrophic cardiomyopathy (HCM), ischemic cardiomyopathy and valvular hypertrophic heart diseases (see WO 01/78699)

Anilidine [2-(N-allyl-2,6-dichloro-anilino)-2-imidazolidine], is disclosed for example in US 3,708,485, and ivabradine 3-[3-[[[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl]methylamino]propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one and its hydrochloride salt, is disclosed for example in EP-B-534859.

Zatebradine [1-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on-3-yl)-3-[N-methyl-N-(2-(3,4-dimethoxy-phenyl)-ethyl)-propane], is disclosed in for example in EP-B-0 065 229 and its US counterpart US 5,516,773. Zatebradine is known to have a favourable activity in the treatment of cardiac insufficiency (see EP-B-0 471 388).

Ivabradine is especially known to have a favourable activity in the treatment of myocardial disorders (from EP-B-534859 or US 5,296,482). The administration of ivabradine in cats with subclinical HCM is described by Riesem et al. (Riesen, Schober, smith, Otoni, Xiaobai, Bonagura; AJVR, Vol.73, No. 2: Effects of ivabradine on heart rate and left ventricular

function on healthy cats and cats with hypertrophic cardiomyopathy). Here, a significant heart rate reduction was observed in both healthy and subclinical HCM cats. The negative chronotropic effect showed dose-dependency in the healthy cats.

The term "patient" as used herein relates to feline patients, preferably cats, even more preferred domestic cats, in particular to feline suffering from heart failure, even more preferred to cats suffering from heart failure. According to another embodiment of the invention the feline patients suffer from heart failure due to one or more of the following etiologies HCM, DCM, RCM, UCM and / or ARVC.

Thus, according to the invention the funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine is used for treating and/ or preventing heart diseases, preferably heart failure (HF) in feline patients, preferably cats. Thus according to the invention the funny current (I_f) inhibitors or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine is used for treating and/ or preventing heart diseases, preferably heart failure (HF) due to one or more of the following etiologies HCM, DCM, RCM, UCM and / or ARVC in feline patients, preferably cats.

According to the invention the feline patient, preferably a cat, is additionally monitored with regard to its overall well-being and mortality. Administration of an I_f-channel blocker to a feline patient, in particular to cats, preferably results in not just the treatment and/ or prevention of heart failure but also to an improved quality of life and general health condition and to a prolonged life expectancy.

Thus, according to a further aspect of the invention it is found by the inventors that the use of a funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine, improves the quality of life of feline patients in particular cats, preferably suffering from HF, and/ or from heart failure (HF) due to one or more of the following etiologies HCM, DCM, RCM, UCM and / or ARVC.

Furthermore, the inventors have found that a funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine, also improves the general health condition of feline patients, in particular cats, preferably suffering from HF heart failure (HF) and/ or HF due to one or more of the following etiologies HCM, DCM, RCM, UCM and / or ARVC in feline patients, preferably in cats.

According to a further aspect of the invention the inventors find that the use of a funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine, prolongs the life expectancy of feline patients, in particular cats, preferably suffering from HF and/ HF due to one or more of the following etiologies HCM, DCM, RCM, UCM and / or ARVC in feline patients, in particular cats.

The term "effective amount" as used herein means an amount sufficient to achieve an alleviation of heart failure in a patient when a funny current (I_f) inhibitor is administered at a dosage as described herein. The progress of the therapy can be monitored by standard cardiologic diagnosis, for example, by echocardiography, cardiac catheterization, or cardiac MRI, X-ray, ECG, cardiac biomarkers or cardiac magnetic resonance imaging. The progress of the therapy can also be monitored by clinical symptoms as well as quality of life related parameters as defined above/ herein. Furthermore the effective amount also gives the patient, preferably feline patients, even more preferred cats, an improved quality of life and/ or improved general health condition and /or prolonged life expectancy. This progress and improvement of well-being obtained by the therapy can be monitored by the pet owner as well as veterinarian.

Dosage

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the patient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the renal and hepatic function of the patient, and the effect desired.

A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the disorder. By way of general guidance, the dosage per administration of the active ingredient, preferably of a funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine, when used for the treatment and/ or prevention of heart failure, will range from 0.01 mg/ kg bodyweight to 1.0 mg/ kg bodyweight per administration, preferably 0.02 to 0.8 mg/kg bodyweight, more preferred from 0.04 to 0.6 mg/ kg bodyweight, even more preferred from 0.06 mg/ kg to 0.4 mg/ kg bodyweight, 0.08 mg/ kg to 0.3 mg/ kg bodyweight, most preferred from 0.1 mg/ kg bodyweight to 0.3 mg/ kg bodyweight or 0.1 to 0.2 mg/ kg bodyweight per administration. These dosages should be administered once or twice per day. The treatment is advisable in clinically apparent cases, both in acute as well as in chronic settings. The administration of said dosages preferably also results in one, two or all of the following conditions: an improved quality of life, improved general health condition as well as a prolonged life expectancy.

Thus according to a further aspect of the present invention relates to a use of a funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine for the preparation of a medicament/ pharmaceutical composition for the treatment and/ or prevention of a patient, preferably a feline patient, in particular a cat, suffering from heart failure. According to another aspect, the invention provides the use of a funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even

more preferred cilobradine for the preparation of a medicament/pharmaceutical composition for the treatment of a patient, preferably a feline patient, in particular a cat, suffering from heart failure due to one or more of the following etiologies HCM, DCM, RCM, UCM and / or ARVC. This use preferably also results in one, two or all of the following conditions: an improved quality of life, improved general health condition as well as a prolonged life expectancy in feline patients, in particular cats, suffering from heart failure and/ or heart failure due to one or more of the following etiologies HCM, DCM, RCM, UCM and / or ARVC.

Preferably the funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine is used for treating and/ or preventing heart failure in a feline patient, in particular a cat, wherein the dosage to be administered is in the range from 0.01 to 2 mg/kg bodyweight per day, preferably in the range from 0.02 to 1.5 mg/kg bodyweight per day, even more preferred in the range from 0.05 to 1 mg/kg bodyweight per day, even more preferred in the range from 0.07 to 0.7 mg/kg bodyweight per day, most preferred in the range from 0.09 to 0.5 mg/kg bodyweight per day, in particular 0.1 to 0.3 mg/ kg bodyweight per day or 0.1 mg/kg to 0.2 mg/kg bodyweight per day.

Preferably the funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine is used for treating and/ or preventing heart failure due to one or more of the following etiologies HCM, DCM, RCM, UCM and / or ARVC in a feline patient, , wherein the dosage to be administered is in the range from 0.01 to 2 mg/kg bodyweight per day, preferably in the range from 0.02 to 1.5 mg/kg bodyweight per day, even more preferred in the range from 0.05 to 1 mg/kg bodyweight per day, even more preferred in the range from 0.07 to 0.7 mg/kg bodyweight per day, most preferred in the range from 0.09 to 0.5 mg/kg bodyweight per day, in particular in the range from 0.1 to 0.3 mg/ kg bodyweight per day or in the range from 0.1 mg/kg to 0.2 mg/kg bodyweight per day.

Administration

The compounds of this invention can be administered in an oral dosage forms as tablets, capsules (each of which may include sustained release or timed release formulations), pills,

powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. According to the invention funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine, is to be administered orally or parenterally.

The funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine, is administered once, twice or three times per day, preferably once or twice, even more preferred once per day.

The funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

Combined use

Preferably, the funny current (I_f) inhibitor such as cilobradine is administered in combination with a second active therapeutic agent. Preferably, such second active therapeutic agent is a diuretic. Preferably such diuretic is a loop diuretic, e.g. furosemide, bumetanide, ethacrynic acid or toresmide; or thiazide diuretic, e.g. chlorotiazide, hydrochlorothiazide, metolazone; or potassium-sparing diuretics, e.g. spironolactone, eplerenone, triamterene or amiloride. Most preferably, such diuretic is furosemide and such potassium-sparing diuretic is spironolactone. The diuretic, in particular the loop diuretic, e.g. furosemide should be administered in a dose of 0.5 to 5 mg/ kg once or twice daily. It may well be that diuretic, e.g. furosemide can be completely withdrawn once the patient has been stabilized.

Thus, according to a further aspect the present invention relates to the combined use of a funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even

more preferred cilobradine with a diuretic, preferably a loop diuretic e.g. furosemide for the treatment of a feline patient, in particular a cat, suffering from heart failure. Preferably, funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine and adiuretic, in particular the loop diuretic, e.g. furosemide are administered at the dosages described herein.

According to a further aspect the present invention relates to a two phase combination therapy for the treatment of a patient suffering from heart failure comprising in the first phase the administration of a funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine in combination with a diuretic, in particular the loop diuretic, e.g. furosemide, and in the second phase the administration of the funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine, without using loop diuretic, e.g. furosemide. Preferably, the funny current (I_f) inhibitor such as cilobradine and a diuretic, in particular the loop diuretic, e.g. furosemide, are administered at the dosages described herein.

According to a further aspect the present invention relates to the combined use of a funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine, with one or two or more pharmaceutically active compounds selected from the group consisting of calcium channel blocker, a ß-adrenoreceptor antagonists, positive inotropes, ACE inhibitors, anti-thrombotic agents and antiarrythmic agents, for the treatment and/ or prevention of a patient, preferably feline patient, even more preferred a cat, suffering from heart failure. In another aspect, the invention relates to a funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof, in particular cilobradine, zatebradine, anilidine or ivabradine, preferably cilobradine or zatebradine, even more preferred cilobradine with one or two or more pharmaceutically active compounds selected from the group consisting of calcium channel blocker, a ß-adrenoreceptor antagonists, positive inotropes, ACE inhibitors, antithrombotic agents and other antiarrythmic agents for the treatment and/ or prevention of a patient, preferably feline patient, even more preferred a cat, suffering from

heart failure due to one or more of the following etiologies HCM, DCM, RCM, UCM and / or ARVC. The above described combined uses are also useful for one, two or all of the following conditions: improvement of the quality of life, improvement of general health condition as well as a prolongation of life expectancy in feline patients, in particular cats, suffering from heart failure and/ or heart failure due to one or more of the following etiologies HCM, DCM, RCM, UCM and / or ARVC. Further, the invention relates to the management of heart failure in cats due to HCM, UCM, RCM, DCM, ARVC in conjunction with concomitant therapy, such as for example with diuretics, in particular loop diuretics such as furosemide, as needed.

In a different aspect, one subject of the invention pertains to pharmaceutical compositions comprising cilobradine ((+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on), cilobradine hydrochloride ((+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on hydrochloride), zatebradine (1-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on-3-yl)-3-[N-methyl-N-[(2-(3,4-dimethoxyphenyl)ethyl]amino]-propane), or alinidine (2-(N-allyl-2,6-dichloro-anilino)-2-imidazoline) for use in a method for the treatment of a heart disease of an animal, preferably a mammal, more preferred a predominantly carnivorous mammal, even more preferred feline, most preferred a cat.

In line with the explanations above, cilobradine or cilobradine hydrochloride are preferred, more preferred is cilobradine hydrochloride, wherein , it is particularly preferred to use multi-layered particles for the treatment of heart diseases, especially heart failure, of cats (feline), e.g. by incorporation into a respective medical formulation.
Preferred is the use of liquid pharmaceutical compositions with a final concentration of the active ingredient of 0.5 to 5 mg/ml, preferred 0.75 to 4 mg/ml, more preferred 0.5 to 3 mg/ml.

The invention thus further provides the funny current (I_f) inhibitor or the pharmaceutically acceptable salt thereof for use in a method as described herein, wherein the funny current (I_f) inhibitor is selected from zatebradine (1-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on-3-yl)-3-[N-methyl-N-[(2-(3,4-dimethoxyphenyl)ethyl]amino]-propane), 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)piperidin-3-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-

benzazepin-2-on, its enantiomer cilobradine ((+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on) or alinidine (2-(N-allyl-2,6-dichloro-anilino)-2-imidazoline), mostly preferred cilobradine hydrochloride ((+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on hydrochloride).

Also, the invention thus provides the funny current (I_f) inhibitor or the pharmaceutically acceptable salt thereof for use in a method as described herein, wherein the funny current (I_f) inhibitor or the pharmaceutically acceptable salt thereof is contained in a pharmaceutical composition in overall liquid form, comprising the funny current (I_f) inhibitor or the pharmaceutically acceptable salt thereof in a final concentration of 0.5 to 5 mg/ml, preferred 0.75 to 4 mg/ml, more preferred 0.5 to 3 mg/ml.

The invention thus also provides the use of a funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for preparing a medicament, as described herein, wherein the funny current (I_f) inhibitor is selected from zatebradine (1-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on-3-yl)-3-[N-methyl-N-[(2-(3,4-dimethoxyphenyl)ethyl]amino]-propane), 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)piperidin-3-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on, its enantiomer cilobradine ((+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on) or alinidine (2-(N-allyl-2,6-dichloro-anilino)-2-imidazoline), mostly preferred cilobradine hydrochloride ((+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on hydrochloride).

Also, the invention thus provides the use of a funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for preparing a medicament, as described herein, wherein the funny current (I_f) inhibitor or the pharmaceutically acceptable salt thereof is contained in a pharmaceutical composition in overall liquid form, comprising the funny current (I_f) inhibitor or the pharmaceutically acceptable salt thereof in a final concentration of 0.5 to 5 mg/ml, preferred 0.75 to 4 mg/ml, more preferred 0.5 to 3 mg/ml.

The invention thus also provides a method of

- treating or preventing heart failure and/ or
- improving the quality of life and/ or
- improving general health condition and /or
- prolonging life expectancy

in a feline patient, preferably a cat, as described herein, wherein the funny current (I_f) inhibitor is selected from zatebradine (1-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on-3-yl)-3-[N-methyl-N-[(2-(3,4-dimethoxyphenyl)ethyl]amino]-propane), 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)piperidin-3-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on, its enantiomer cilobradine ((+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on) or alinidine (2-(N-allyl-2,6-dichloro-anilino)-2-imidazoline), mostly preferred cilobradine hydrochloride ((+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on hydrochloride).

Also, the invention thus provides a method of

- treating or preventing heart failure and/ or
- improving the quality of life and/ or
- improving general health condition and /or
- prolonging life expectancy

in a feline patient, preferably a cat, as described herein, wherein the funny current (I_f) inhibitor or the pharmaceutically acceptable salt thereof is contained in a pharmaceutical composition in overall liquid form, comprising the funny current (I_f) inhibitor or the pharmaceutically acceptable salt thereof in a final concentration of 0.5 to 5 mg/ml, preferred 0.75 to 4 mg/ml, more preferred 0.5 to 3 mg/ml.

EXAMPLES

The following examples serve to further illustrate the present invention; but the same should not be construed as a limitation of the scope of the invention disclosed herein.

Example 1

Formulation of a compound for the treatment of a heart disease

This example aims at the formulation of compound (+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on hydrochloride in liquid form.

For the production of multi-layered particles for incorporation into a liquid dosage form, a three-step process was applied which process is summarized in table 1.

Table 1: Flow chart for the production of multi-layered particles according to the invention, comprising (+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on hydrochloride as active ingredient.

step	**starting material**	**Coating**	**result**
1	inert core particles	drug layering with pharmaceutically active ingredient and HPMC / magnesium stearate	IR pellets
2	IR pellets	seal coating with PVP K 30 / Talc / colloidal siliciumdioxide	SC (seal coated) pellets
3	SC pellets	taste masking coating with EC / HPMC / magnesium stearate / colloidal siliciumdioxide	final multi-layered particle

Step 1: Drug layering

Like in example 1 microcrystalline cellulose particles with an average diameter of 100 µm were used as starting material and layered with active ingredient and binder, using water as solvent. The layer material consisted of 66.6% (w/w) of the pharmaceutically active ingredient, 31.7% (w/w) HPMC (Pharmacoat ® 606; see example 1) and 1.7% (w/w) magnesium stearate, dispersed in purified water to yield approx. 19% solids in the spraying liquid.

The resulting composition of the produced IR pellets is given in table 2.

Table 2: Composition of IR pellets comprising (+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on hydrochloride

Component	Amount [% (w/w)]
inert core particles (Cellets ® 100)	80.94
pharmaceutically active ingredient	12.70
HPMC (Pharmacoat ® 606)	6.04
Magnesium stearate	0.32

Step 2: Seal coating

The IR pellets produced in step 1 were further processed in the same apparatus by spraying the seal coating onto the IR pellets. The material for the seal coating was composed of PVP K 30 (commercially available by the provider BASF, Ludwigshafen, Germany, under the trade name Kollidon ® 30 / talc, at a weight-percent ratio of 75.4 : 22.5, dispersed in a 94:6 mixture (m/m) of acetone and ethanol. 0.5% (w/w) of a highly disperse (colloidal) silicium dioxide (Aerosil ® 200, commercially available from Evonik) was added by an additional (intermediate step) to the seal coated material after the application of the PVP K 30 / talc mixture and drying of the organic solvent.

The total composition of the SC (seal coated) pellets yielded in this step (cilobradine seal coated pellets) is given in table 3.

Table 3: Composition of SC pellets comprising (+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on hydrochloride

Component	Amount [% (w/w)]
IR pellets comprising the pharmaceutically active ingredient	76.54
PVP K 30 (Kollidon ® 30)	17.67

Talc	5.29
colloidal silicium dioxide (Aerosil ® 200)	0.5

Step 3: Final coating (taste masking coating)

The SC pellets produced in step 2 were further processed in the same apparatus by spraying the final coating onto the SC pellets. The material for the final taste and/or odor masking coating was composed of EC / HPMC / magnesium stearate at a weight-percent ratio of 55.2 : 23.8 : 19.8 (the ratio of EC / HPMC in the film coating being about 70:30). For this purpose, EC, HPMC and magnesium stearate were dispersed in a 1:1 mixture (v/v) of methanol and dichloromethane, and sprayed onto the SC pellets.

The coating was applied to a thickness of 75% based on the initial amount of SC pellets.

Like in step 2, 0.5% of the colloidal silica of Aerosil ® 200 were added to the final product before sieving.

The chosen EC was Ethocel ® 45 cps STD Premium, commercially available from Dow Chemical, Schwalbach, Germany. The chosen HPMC for this layer was Methocel ® E5 Premium LV, commercially available from Dow Chemical. Aerosil ® 200 was provided by Evonik.

The overall composition of the final multi-layered particles is given in table 4.

Table 4: Composition of final multi-layered particles comprising (+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on hydrochloride

Component	**Amount [% (w/w)]**
SC pellets comprising the pharmaceutically active ingredient	56.86
EC	23.86

HPMC	10.25
Magnesium stearate	8.54
colloidal silicium dioxide (Aerosil ® 200)	0.5

Table 5 discloses the detailed overall composition of taste masked multi-layered particles comprising (+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on hydrochloride, as produced according to steps 1-3 of this example, along with the assumed physicochemical function of the respective material.

Table 5: Detailed composition of final multi-layered particles comprising (+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on hydrochloride

Component	**Amount [% (w/w)]**	**Function**
inert core particles (Cellets ® 100)	35.23	Carrier
pharmaceutically active ingredient cilobradine (calculated as hydrochloride)	5.53	Drug layer
HPMC	2.63	
Polyvinylpyrrolidone K 30	10.05	Seal coating
Talc	3.01	
Ethylcellulose	23.86	Final coating (taste masking)
HPMC	10.25	
Magnesium stearate	8.68	
colloidal silicium dioxide (Aerosil ® 200)	0.78	Reduction of electrostatic charging in seal coating and final coating

Dissolution experiments

The multi-layered particles produced in this example were tested with respect to their dissolution properties in the same way as the particles according to example 1, again at the two different pH values of 6.8 and 1. Measured values are the total percentage of released material after the respective time, normalized to the theoretical drug content.

The result is given in table 6.

Table 6: Drug release from multi-layered particles comprising (+)-3-[(N-(2-(3,4-dimethoxyphenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on hydrochloride finally coated with EC/HPMC 70:30 at pH 1 and pH 6.8 (mean, n≥3; visualized in figure 4)

Time [min]	**% released at pH 1**	**% released at pH 6.8**
0	0.0	0.0
5	19.4	7.2
10	25.6	9.4
30	53.4	16.7
45	72.9	23.2
60	87.2	30.9
90	103.4	48.3

According to these data, the dissolution from EC/HPMC coated pellets is delayed, therefore providing efficient taste and/or odor masking of the bitter drug (+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on hydrochloride. This could be verified by acceptance tests with laboratory cats with the derived completely formulated liquid composition prepared as described below.

Usually, EC/HPMC films show a sustained release behaviour that is independent of pH. In this case, however, the product surprisingly showed a slower release at pH 6.8 which is favourable with regards to the invention, i.e. providing efficient taste masking in the oral

cavity and a faster release in the acidic stomach. This may be explained by the lipophilicity profile of the active substance cilobradine HCl, which is slightly more lipophilic at neutral pH values. This, together with the coating applied, may have led to a slower release.

Liquid pharmaceutical composition

In order to prepare a liquid pharmaceutical composition, the final multi-layered particles comprising the active ingredient ciloradine prepared in the way explained above were incorporated into an oily liquid. This liquid consisted of a mixture of Medium chain triglycerides (Miglyol ® 821, bought from Sasol, Hamburg, Germany), a hydrophilic colloidal silicium dioxide (Aerosil ® 200, Evonik), a hydrophobic colloidal silicium dioxide (Aerosil ® R972, Evonik) and meat flavor, at the weight ratios listed in table 7.

Table 7: Liquid pharmaceutical composition comprising multi-layered particles comprising (+)-3-[(N-(2-(3,4-dimethoxy-phenyl)ethyl)-piperidin-3-(S)-yl)-methyl]-(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-on hydrochloride

Component	**Amount [% (w/w)]**
medium chain triglycerides (Miglyol ® 821)	93.23
hydrophilic colloidal silicium dioxide (Aerosil ® 200)	4.44
hydrophobic colloidal silicium dioxide (Aerosil ® R972)	1.82
meat flavor	0.51

The multi-layered particles as produced according to step 3 were suspended in the mentioned liquid composition to an amount of about 3.8% (w/v), resulting in a concentration of 2 mg/ml of the pharmaceutically active ingredient (calculated as hydrochloride).

It has been found that the composition of the oily solvent, especially the mixture of hydrophilic and hydrophobic colloidal silica, ensures an appropriate viscosity behaviour of the suspension that remains more or less unchanged over the storage period. During storage, the suspension exhibits a high viscosity, preventing sedimentation of the suspended

cilobradine pellets. If shaken, the viscosity of the suspension is transiently lowered so that it can easily be applied via a syringe-like oral dispenser.

Example 2

TREATMENT OF CATS SUFFERING FROM HF DUE TO HCM

A blinded, controlled, randomised, efficacy field study was conducted with HCM cats receiving cilobradine (initial dose: 0.2 mg/kg po. twice daily) or placebo (dose: 0.0 mg/kg po. twice daily) for 85 days. The dose of cilobradine could be adjusted during the study (dose range 0.1-0.5 mg/kg per-oral twice daily). The administration of furosemide was allowed in both groups. All cats were hospitalised in the first week of the study (study days 1-6) and they were allowed to go home afterwards (study days 7-85).

Cats with a diagnosis of HCM were included in the study. The diagnosis of HCM was established by using echocardiography showing global, regional or segmental thickness of the interventricular septum and/or left ventricular free-wall in diastole greater than 6 mm. Further inclusion criteria were:

Systolic blood pressure less than 170 mmHg

Serum thyroxine (T4) was normal

Body weight was higher than 2 kg.

The owner provided a signed informed consent for the animal to enter the study. Cats that suffered from heart disease with a score of 1, 2 or 3 using a 4 point score adapted from the ISACHC:

Score 1: heart disease associated with no clinical signs but detectable (auscultation, echocardiography and radiography)

Score 2: Clinical signs of heart failure evident and adversely affect the quality of life. Typical signs include dyspnea/tachypnea, pulmonary congestion, weakness/lethargy, anorexia, exercise intolerance

Score 3: Clinical signs of advance heart failure immediately obvious. These clinical signs could have included respiratory distress, marked ascites/pulmonary congestion, profound exercise intolerance or hypoperfusion at rest.

Score 4: Severe cases: subject was moribund, suffered from cardiogenic shock or acute posterior paresis/paralysis. Hospitalization was mandatory.

Cats having one or more of the following criteria were excluded:

The cat had received one or more of the following pretreatments: Calcium channel blockers, e.g. diltiazem, angiotensin converting enzyme inhibitors, β-blockers, acetylsalicylic acid, digitales glycosides.(Cats pre-treated with furosemide alone were allowed to be included in either of the groups if they matched all inclusion criteria above)

Elevated serum T4 level.

Elevated serum blood urea nitrogen (BUN) levels higher than 90 mg/dL or elevated serum creatinine levels higher than 3 mg/dL.

Systolic arterial blood pressure greater than or equal to 170 mmHg.

Dilated cardiomyopathy (DCM)

Suffered from heart disease with a score of 4 (adapted ISACHC score) or with no documented episode of heart failure (score 2 or 3) within 30 days before enrolment.

Fixed aortic stenosis.

Were pregnant or lactating queens

Were nursing kittens.

Body weight less than 2 kg.

Sinus bradycardia (heart rate less than 120 bpm at consultation).

The cat's quality of life was assessed on a daily base using the following grading system: 1 (better), 2 (equal), 3 (worse). As displayed in figure 1, the quality of life of the cat, which received cilobradine showed an almost continuous improvement (black trapeze). On the other hand, the quality of life of the cat, which received placebo (open circle) became worse or did not change throughout the whole study period, see figure 1.

The heart rate of the cat receiving cilobradine reduced throughout the study, whereas the heart rate of the cat receiving placebo increased (see table 8).

Table 8

Heart rate (beats per minutes)					
	SD 0	**SD 7**	**SD 28**	**SD 56**	**SD 84**
Cilobradine cat	152	120	144	124	210
Placebo cat	156	230	210	190	186

The reduction of the interventricular septal thickness in systole was considerably greater in the cat, which received cilobradine compared to the cat, which received placebo (see table 9).

Table 9

Interventricular septal thickness in systole (mm)		
	SD 0	**SD 84**
Cilobradine cat	11.7	7.5
Placebo cat	12.3	10.0

Furthermore, right heart enlargement was assessed by X-ray using the following scoring system:

Score 1: normal size

Score 2: mild enlargement

Score 3: moderate enlargement

Score 4: severe enlargement

Mild enlargement of the right side of the heart was observed using X-ray in the cat receiving placebo at the end of the study. In contrast, the right side of the heart was normal in the cat receiving cilobradine throughout the study (see table 10).

Table 10

Right heart enlargement (score)		
	SD 0	**SD 84**
Cilobradine cat	1	1
Placebo cat	1	2

EXAMPLE 3

Cilobradine showed a half-life of 10.1-13.9 h in healthy male subjects after once daily po. Administration for 7 days (see table 11 and table 12). Cilobradine chloride salt was administered at a dose of 5, 10 and 20 mg per subject in form of capsules. This is equal to a

dose of 0.07, 0.14 and 0.28 mg/kg cilobradine chloride salt assuming a body weight of 70 kg. In contrast, cilobradine showed a half-life of 2.53-3.52 h in healthy cats after once daily po. administration for 4 days. Cilobradine hydrochloride was administered at a dose of 0.1 mg/kg and 0.3 mg/kg as a suspension. Interestingly, a dose dependent heart rate reduction was observed in both humans and cats over 9 h following the administration of the above mentioned cilobradine doses. There are some differences between cats and humans in terms of pharmacokinetics of cilobradine. This might be related to differences in absorption, metabolisation, distribution or excretion.

In summary, although similar pharmacodynamic features were observed in humans and cats, this was not in line with the observed different pharmacokinetic features between cats and humans.

Table 11

Human			
Dose of cilobradine chloride salt (mg/subject)	5	10	20
Dose of cilobradine chloride salt (mg/kg)*	0.07	0.14	0.28
Half-life (h)	13.9	13.0	10.1

* assuming 70 kg body weight

Table 12

Cat		
Dose of cilobradine hydrochloride (mg/kg)	0.1	0.3
Half-life (h)	3.52	2.53

Overall from the above described examples, it can be concluded that a cat suffering from heart failure, which has been treated with cilobradine show a clear improvement in its quality of life and its general health condition with very low administration dose, despite the fact that the half-life is significantly shorter in cats compared to humans.

EXAMPLE 4

The pharmacodynamic profile of cilobradine hydrochloride was characterised at two dose levels administered by the oral route, once and twice daily, in the conscious cat. The study involved 2 groups of 3 male European Short Hair cats weighing between 4.15 kg and 4.75 kg on the day of the first treatment.

Each cat was dosed with cilobradine hydrochloride once (sid) and twice (bid) daily successively at 0.1 or 0.3 mg/kg in a cross over-design. Each treatment was separated by an interval of 24 hours (sid) or 12 hours (bid). A washout period of 7 days was scheduled between the 2 dosing periods.

Cats were previously instrumented with telemetric transmitters for heart rate measurements. Telemetric measurements were recorded for 15 seconds every 5 minutes at a sampling rate of 500 Hz on D-2, D-1, from D0 up to D9 and from D16 up to D25 except for D4 and D20 during blood sampling.

Under the experimental conditions adopted, cilobradine hydrochloride administered orally at the doses of 0.1 and 0.3 mg/kg per day, induced a dose-dependent bradycardia.

BRIEF DESCRIPTION OF DRAWING

Figure 1 illustrates the quality of life of cats receiving cilobradine (black trapeze) or placebo (open circle).

CLAIMS

1. A funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for use in a method for

- treating or preventing heart failure and/ or
- improving the quality of life and/ or
- improving general health condition and /or
- prolonging life expectancy

in feline patients.

2. The funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for the use in a method according to claim 1, wherein the feline patients suffering from heart failure due to HCM, DCM, RCM, UCM and / or ARVC.

3. The funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for the use according to claim 1 or 2, wherein the funny current (I_f) inhibitor is selected from the group consisting of cilobradine, zatebradine, anilidine and ivabradine.

4. The funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for the use according to any one of claims 1 to 3, wherein the funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof is to be utilized in oral or parenteral form.

5. The funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for the use according to any one of claims 1 to 4, wherein the funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof is prepared as a medicament in a form to be used in a dosage of 0.01 to 2 mg per kg bodyweight per day.

6. The funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for the use according to claim 5, wherein the medicament is a solid or liquid formulation.

7. The funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for the use according to claim 6, wherein the medicament is a solid formulation which comprises

0.001 to 0.2 mg of the inhibitor or the pharmaceutically acceptable salt thereof per mg of the solid formulation.

8. The funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for the use according to claim 6, wherein the medicament is a liquid formulation which comprises 0.1 to 20 mg of the inhibitor or the pharmaceutically acceptable salt thereof per mg of the liquid formulation.

9. The funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for the use according to any one of claims 1 to 8, wherein the funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof is to be administered in a daily dosage of 0.01 to 2 mg/kg bodyweight.

10. The funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for the use according to any one of claims 1 to 9, wherein funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof is to be administered together with diuretics (combination therapy).

11. The funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for the use in a method according to claim 7, wherein the diuretic is administered in a dosage of 0.5 to 10 mg/kg bodyweight once or twice daily.

12. Use of a funny current (I_f) inhibitor or a pharmaceutically acceptable salt thereof for preparing a medicament for

- the treatment or prevention of heart failure and/ or
- improving the quality of life and/ or
- improving general health condition and /or
- prolonging life expectancy

in a feline patient.

13. The use according to claim 12 for improving the quality of life and/ or general health condition and /or prolonging life expectancy in feline patients suffering from HF due to HCM, DCM, RCM, UCM and / or ARVC.