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OMECAMTIV MECARBIL

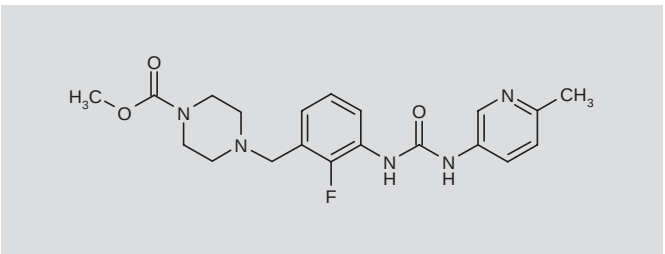
USAN

Cardiac Myosin Activator
Treatment of Heart Failure

AMG-423
CK-1827452
CK-452

4-[2-Fluoro-3-[3-(6-methylpyridin-3-yl)ureido]benzyl]piperazine-1-carboxylic acid methyl ester

InChI: 1S/C20H24FN5O3/c1-14-6-7-16(12-22-14)23-19(27)24-17-5-3-4-15(18(17)21)13-25-8-10-26(11-9-25)20(28)29-2/h3-7,12H,8-11,13H2,1-2H3,(H2,23,24,27)



$C_{20}H_{24}FN_5O_3$
Mol wt: 401.4347
CAS: 921625-14-1
EN: 405852

ABSTRACT

Positive inotropic agents are used in the treatment of heart failure. Intravenous inotropes (dopamine, dobutamine, milrinone) improve the hemodynamic and clinical status of acute decompensated chronic heart failure, but they also increase intracellular concentrations of Ca^{2+} and cAMP, leading to increased myocardial oxygen demands, hypotension, arrhythmias and mortality. In chronic heart failure, the limited benefits, complex pharmacology and narrow therapeutic window have relegated the use of digoxin. Cardiac myosin activators are a new class of inotropic agents that increase systolic ejection time at concentrations at which they do not modify the intracellular calcium or cAMP levels. Omecamtiv mecarbil is the first drug of this class. In animal models, healthy volunteers and phase II clinical trials in patients with stable chronic heart failure, it increased the systolic ejection time, fractional shortening, stroke volume and cardiac output without altering myocardial oxygen, thus improving cardiac efficiency. In this article, we review the preclinical and clinical pharmacological properties of omecamtiv mecarbil. The results of clinical trials suggest that omecamtiv mecarbil may represent an effective and probably safer alternative to conventional inotropics in the treatment of heart failure patients. The future development of this compound is also discussed.

SYNTHESIS**

Omecamtiv mecarbil is prepared as follows:

Cyanation of 3-chloro-2-fluoroaniline (I) with NaCN in the presence of $NiBr_2$ in NMP at 195-205 °C gives 3-amino-2-fluorobenzonitrile (II), which by treatment with $(i\text{-Bu})_2LiAlH_2$ and Rochelle salt in CH_2Cl_2 yields a mixture of 3-amino-2-fluorobenzaldehyde (III) and 2-fluoro-3-(iminomethyl)aniline (IV). This mixture of intermediates (III) and (IV) is submitted to reductive condensation with methyl piperazine-1-carboxylate (V) by means of $NaBH(OAc)_3$ in THF and the obtained aryl amine (VI) is finally coupled with 5-isocyanato-2-methylpyridine (VII) in refluxing acetone (1-3). Scheme 1.

BACKGROUND

Heart failure (HF) is a complex clinical syndrome arising from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. It represents a major and growing public health problem due to its high prevalence, high rates of in-hospital and post-discharge mortality and readmissions, and significant healthcare costs (4-6). Its prevalence in the general European population ranges from 0.4% to 2%, but increases rapidly with age, affecting 6-10% of people over the age of 65 years (6). The high and rapidly growing prevalence of HF translates into high hospitalization rates, being the single most common cause of hospitalization in patients over 65 years, and currently accounting for more than 1 million hospitalizations per year in both the U.S. and Europe (4-7). Moreover, the combination of aging of the population and improved survival after acute myocardial infarction has led to a rapid growth in the number of patients currently living with chronic HF, with a concomitant increase in the number of hospitalizations for decompensated HF. Furthermore, 35-50% of patients hospitalized

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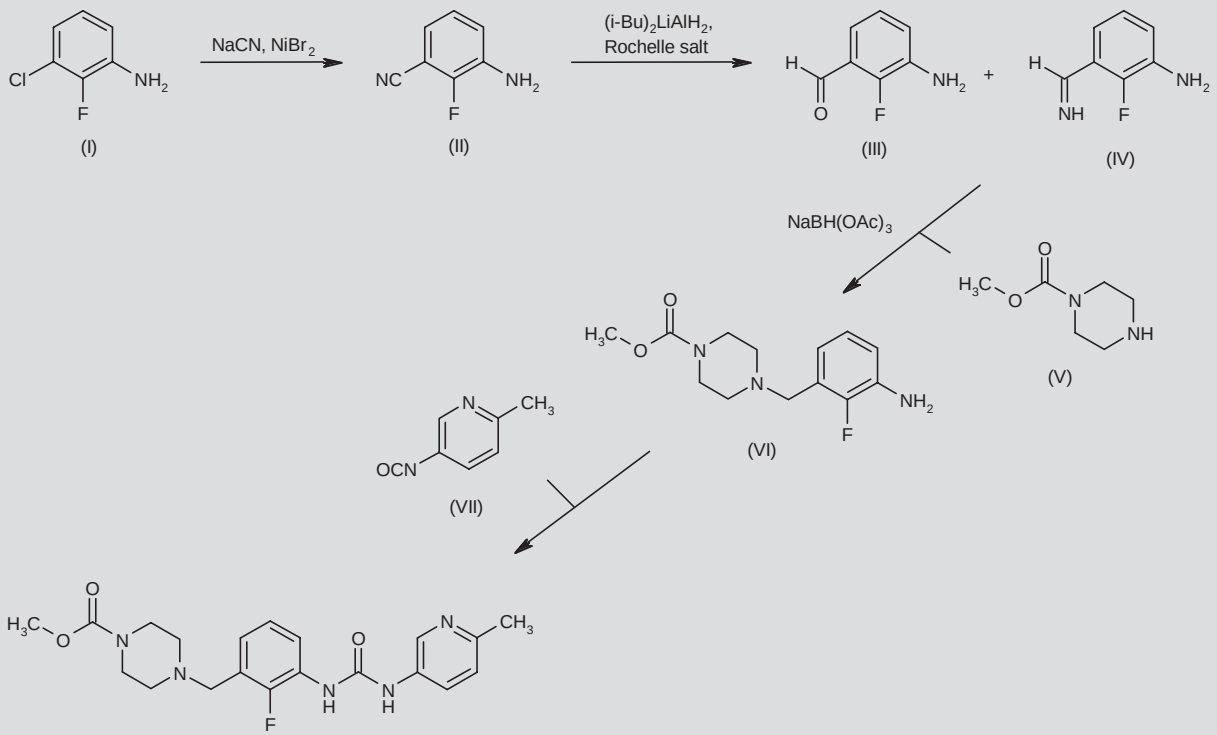
**Synthesis prepared by R. Pandian, R. Castañer.
Thomson Reuters, Provenza 388, 08025 Barcelona, Spain.

Scheme 1. Synthesis of Omecamtiv Mecarbil



with acute HF will be rehospitalized at least once within 12 months (4). The prognosis for HF is uniformly poor if the underlying problem cannot be rectified. Half of the patients with a diagnosis of HF will die within 5 years, and of patients with severe HF > 50% will die within 1 year. Finally, the direct health costs of HF treatment represent 1-2% of the healthcare budget costs in European countries, with hospital admissions for decompensated HF accounting for about 70% of this expenditure (8, 9). The estimated direct and indirect costs of HF in the U.S. for 2008 were $37.2 billion (7).

Although most cases of HF are associated with evidence of left ventricular (LV) systolic dysfunction, a large proportion of patients with chronic HF have diastolic HF as judged by preserved LV ejection fraction (< 40-50%) at rest (5, 6, 10). However, the distinction is somewhat arbitrary because most patients with HF have evidence of both systolic and diastolic dysfunction (4, 6). Therefore, the general goals of the treatment of HF are as follows (4, 5):

1) Relief of symptoms (dyspnea and/or fatigue) and signs. Breathlessness, ankle swelling and fatigue are the characteristic symptoms and signs of HF, but may be difficult to interpret, particularly in elderly patients, obese patients, women and patients with pulmonary disease. Peripheral edema, elevated venous pressure and hepatomegaly are the characteristic signs of congestion of systemic veins. Once a diagnosis of HF has been established, symptoms may be used to classify the severity of HF and should be used to monitor the effects of therapy.
2) Improve the hemodynamics (increase stroke volume and cardiac output, decrease pulmonary capillary wedge pressure).
3) Exert favorable effects on outcomes, including reductions in the duration of intravenous (i.v.) vasoactive therapy, patient's stay in-hospital, future readmissions and both short- and long-term mortality.
4) Preserve or improve renal function, prevent myocardial damage and manage other comorbidities that may cause/contribute to the progression of this syndrome.

Based on the framework that impaired cardiac contractility is a fundamental component of HF, drugs that increase cardiac contractility (e.g., positive inotropic agents) are used in the treatment of both acute and chronic HF. However, despite the fact that they increase cardiac output and improve end-organ perfusion, these drugs have been consistently associated with an increased mortality in patients with HF. Thus, there is an unmet need for new effective inotropic agents with a better safety profile than those currently used. In this article, we first analyze the mechanism of action, clinical uses, advantages and disadvantages of positive inotropic drugs in

patients with HF. Then, we review the basis for the development of a new group of positive inotropic agents, the so-called cardiac myosin activators, designed to improve systolic cardiac performance without increasing intracellular cyclic adenosine 3′,5′-monophosphate (cAMP) levels and free Ca^{2+} concentrations ($[Ca^{2+}]_i$). Finally, we shall describe the preclinical and clinical development of omecamtiv mecarbil, the first cardiac myosin activator and the clinical perspectives for this agent in the treatment of HF.

Conventional i.v. inotropic agents (e.g., sympathomimetics [dopamine, dobutamine, isoproterenol, norepinephrine] and phosphodiesterase PDE3 inhibitors [milrinone]) increase the cellular levels of cAMP and activate cAMP-dependent protein kinase A (PKA) and, ultimately, $[Ca^{2+}]_i$ (Fig. 1) (4, 6, 7, 11). Sympathomimetics increase cAMP production via direct activation of β_1-adrenoceptors and PDE3 inhibitors by blocking the enzyme that breaks down cAMP. PDE3 inhibitors increase cardiac contractility and produce arterial and venous vasodilatation, being preferred in patients with elevated LV filling pressures. Moreover, because their mechanism of action is independent of β-adrenoceptor activation, their hemodynamic effects are maintained in patients receiving β-blockers, being an alternative to dobutamine under these circumstances (4, 12).

Levosimendan exhibits a dual mechanism of action (11, 13, 14). It acts as a Ca^{2+} sensitizer, increasing cardiac contractility without altering Ca^{2+} transients. Levosimendan improves cardiac contractility by binding to the *N*-terminal domain of troponin C (TnC), stabilizes the conformation of the Ca^{2+}–TnC complex and increases the binding affinity of TnC for intracellular Ca^{2+} (Fig. 1). Since its inotropic effect is independent of β-adrenoceptor stimulation, levosimendan represents an alternative to β-adrenoceptor agonists in patients on β-blocker therapy. Moreover, it also produces pulmonary and systemic vasodilatation via adenosine triphosphate (ATP)-activated (resistance vessels) and Ca^{2+}-activated (K_{Ca}) and voltage-dependent (K_v) K^+ channels in vascular smooth muscle cells (11, 12, 14). In vitro and at concentrations much higher than those achieved in clinical use, levosimendan also exhibits PDE3-inhibitory effects. Initial studies demonstrated that levosimendan reduced arrhythmias and improved survival compared to placebo (CASINO, RUSSLAND) and dobutamine (CASINO, LIDO) (11-14). However, three recent trials

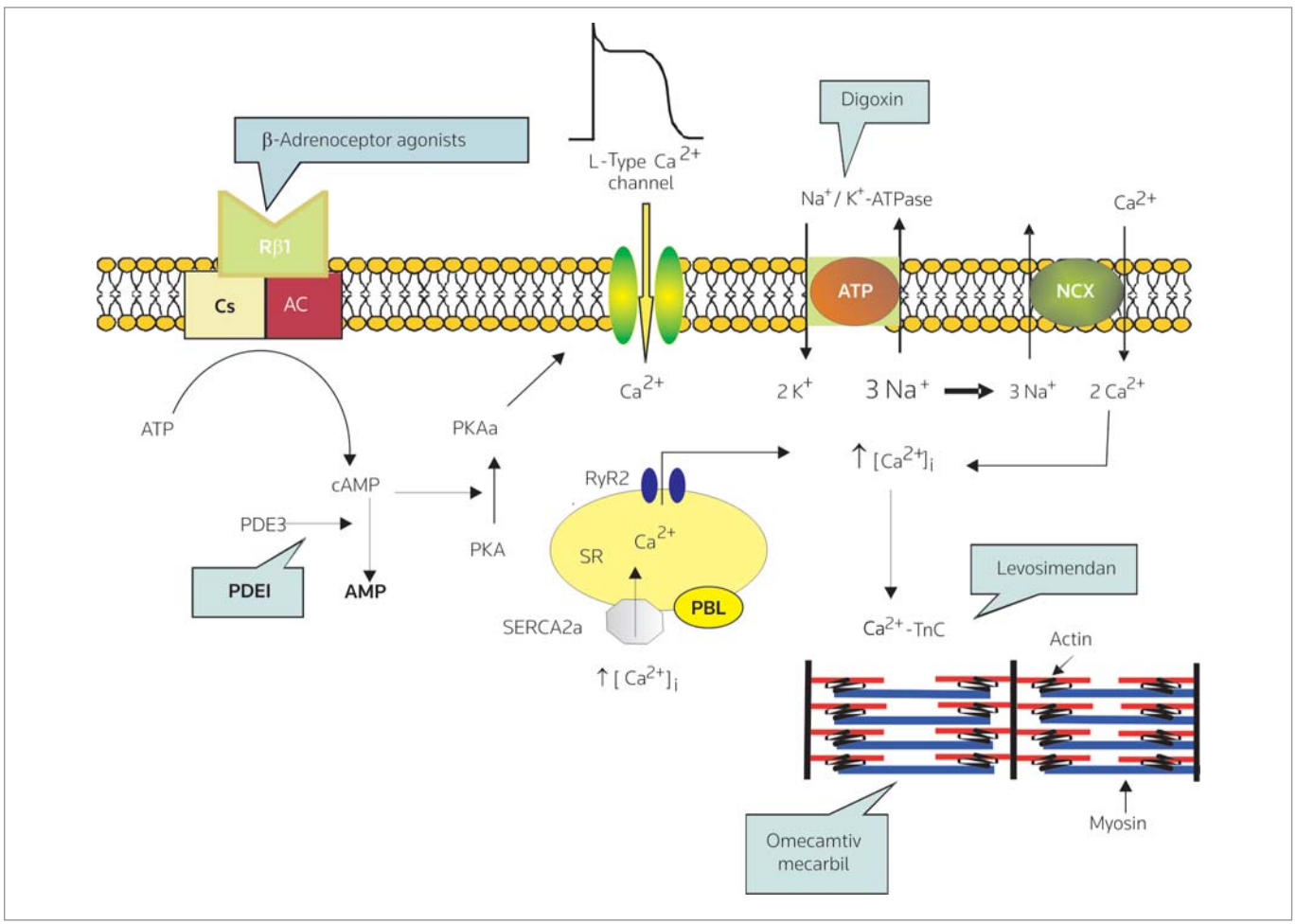


Figure 1. Mechanism of action of positive inotropic agents. AC, adenylate cyclase; ATP, adenosine-5'-triphosphate; G_s, Gs protein; Rβ1, β1-adrenoceptor; PBL, phospholamban; PDE3, phosphodiesterase type 3; PDEI, PDE3 inhibitor; PKA, protein kinase A; RyR2, ryanodine receptor; SERCA2a, sarcoplasmic reticulum Ca^{2+}-ATPase; SR, sarcoplasmic reticulum; TnC, troponin C.

found that levosimendan improved clinical status but failed to reduce mortality as compared with placebo (REVIVE) and dobutamine (SURVIVE) (11). Moreover, in these trials levosimendan was associated with a lower incidence of worsening of HF and a higher incidence of hypotension and cardiac arrhythmias (atrial fibrillation, ventricular ectopy and ventricular tachycardia). Thus, new clinical trials are needed to define the effect of levosimendan on survival in patients with severe HF.

Twenty years ago, digoxin was regarded along with diuretics as the first-line therapy for systolic HF. Digoxin inhibits membrane-bound α-subunits of the Na^+/K^+-ATPase. This inhibition increases the intracellular Na^+ concentration, which in turn increases $[Ca^{2+}]_i$ via the Ca^{2+}/Na^+ exchanger, resulting in the positive inotropic effect of digoxin (Fig. 1) (15). However, the very narrow therapeutic window, the numerous drug interactions and the limited benefits found in the large Digitalis Investigation Group (DIG) trial (10) (where digoxin therapy improved ventricular function and patient well-being and reduced hospital admissions for worsening HF, but had no effect on mortality) have cast major doubts on its clinical use in HF patients in sinus rhythm (16, 17).

Recent evidence suggests that the benefits of digoxin may be related to inhibition of Na^+/K^+-ATPase in noncardiac tissues, such as vagal afferent fibers (where it produces an improvement in baroreceptor function that inhibits the sympathetic nervous system) and the kidneys (where digoxin reduces the tubular reabsorption of Na^+ and suppresses renin secretion), and to inhibition of the neurohumoral activation. In fact, digoxin reduces serum levels of norepinephrine, atrial natriuretic factor, angiotensin II and vasopressin and plasma renin activity (16). Furthermore, all these clinical, hemodynamic and neurohumoral effects appeared at low doses of digoxin, resulting in a serum digoxin concentration (SDC) of < 1 ng/mL. Interestingly, a retrospective analysis of the DIG trial found that digoxin at an SDC between 0.5 and 0.9 ng/mL reduced mortality and hospitalizations in HF patients, including those with preserved systolic function, while at a higher SDC digoxin reduced HF hospitalizations but had no effect on mortality or all-cause hospitalizations (18, 19).

In the ADHERE registry, 9.7% of patients hospitalized for acute HF syndromes in the U.S. received an i.v. inotrope and, in general, they tended to have more severe HF, including higher blood urea nitrogen levels, lower blood pressure and lower LV ejection fraction (20). In the EuroHeart Failure Survey II, which described the management of acutely hospitalized HF patients in Europe, the most commonly used inotropics were dopamine (11%), dobutamine (10%) and levosimendan (4%). Digitalis was given in 27% of patients on admission and in 31% at discharge (10).

Positive inotropic drugs are indicated in patients with low systolic blood pressure (< 120 mmHg) or low output states, in the presence of signs of peripheral hypoperfusion (cold, clammy skin, decreased renal function, impaired mentation) with or without congestion or pulmonary edema refractory to diuretics and vasodilators at optimal doses (4-6). Inotropes can also be used to stabilize patients at risk of progressive hemodynamic collapse or as a "bridge" until other life-saving therapy (coronary revascularization, mechanical circulatory support, ventricular assist devices or cardiac transplantation) can be undertaken (4, 6, 12). In a small number of end-stage patients in whom other therapies are not appropriate, inotropics may be considered as a palliative option of end-of-life care. Presently, there is no evidence that patients with HF with preserved systolic function benefit from positive inotropic agents.

Chronic oral therapy with digoxin is recommended in patients with HF and impaired systolic function who are in sinus rhythm and continue to have signs and symptoms despite standard therapy that includes angiotensin-converting enzyme (ACE) inhibitors (or angiotensin receptor blockers) and β-blockers (4-6, 21). Digoxin is prescribed routinely in patients with HF and chronic atrial fibrillation to slow rapid ventricular rate in addition to or prior to a β-blocker; β-blockers are usually more effective when added to digoxin in controlling the ventricular response, particularly during exercise (6, 22). In the DIG ancillary trial the use of digoxin was associated with a trend toward a reduction in hospitalizations resulting from worsening HF, but had no effect on mortality (23). However, in two other studies, digoxin use was associated with an increase in mortality (24, 25).

An ideal inotropic agent for treating HF should reduce signs and symptoms, improve LV function, reduce systemic and pulmonary vascular resistance and exert a favorable or neutral effect on mortality, without increasing heart rate or myocardial oxygen consumption (MVO_2), decreasing blood pressure and coronary perfusion (particularly in patients with coronary artery disease), worsening renal function and producing cardiac arrhythmias or myocardial damage (apoptosis, necrosis) (4-6, 11).

Although short- or long-term use of inotropic drugs may improve hemodynamic parameters and relieve symptoms in patients with HF, their benefits are counteracted by serious adverse events, including an increase in heart rate, contractility and MVO_2, neurohumoral activation, proarrhythmia, intracellular Ca^{2+} overload (which increases wall tension and induces cardiac arrhythmias and myocyte cell death) and hypotension, especially at high doses, which reduces coronary perfusion (11, 12, 20, 26). A meta-analysis of 21 trials found that, compared with placebo, i.v. administration of β_1-adrenoceptor agonists and PDE3 inhibitors improved symptoms and hemodynamics but tended to increase mortality in patients with HF (27). In another meta-analysis of 21 clinical trials, treatment with PDE3 inhibitors improved symptoms and hemodynamics but increased cardiac death, sudden death and arrhythmias in patients with chronic HF (28). Consequently, the chronic use of phosphodiesterase inhibitors should be avoided in HF patients.

The underlying etiology of acute HF is also important in determining long-term survival. Viable and not contracting (hybernating) myocardium is present in up to 60% of patients with acute HF syndromes and chronic ischemia (29). This hibernating myocardium is at risk for injury in patients with HF because of increased LV filling pressures, hypotension and neurohormonal activation (30).

Although baseline contractile function is depressed, the hybernating myocardium retains its responsiveness to dobutamine. However, both in animal models and in patients with hibernating myocardium, the increase in cardiac contractility and MVO_2 without a previous restoration of coronary blood flow can result in a supply and demand mismatch, deplete myocardial energy stores and exacerbate the underlying myocardial ischemia; these changes lead to increased

myocardial apoptosis, promote and/or accelerate the progression of HF and increase the incidence of ventricular arrhythmias (11, 31, 32). This explains why in several randomized clinical trials inotropic drugs that increase intracellular cAMP levels increased in-hospital and post-discharge mortality, particularly in patients with coronary artery disease (20, 26-28, 33, 34). In a post hoc analysis of the OPTIME-CHF trial, which randomized patients with systolic dysfunction and decompensated HF not requiring i.v. inotropic therapy to receive 48-72 h of i.v. milrinone or placebo, milrinone-treated patients with coronary artery disease tended to have significantly worse outcomes (days hospitalized from cardiovascular causes within 60 days and the composite of death or rehospitalization), particularly those who developed drug-related hypotension (33); in contrast, outcomes in nonischemic patients treated with milrinone tended to be improved.

Concerns about the efficacy and safety of presently available inotropics have stimulated the development of new inotropic agents, possibly with a cAMP-independent mechanism of action, that improve cardiac output and relieve HF symptoms without inducing Ca^{2+} overload or increasing MVO_2 and mortality rates or inducing proarrhythmic effects. For the 500,000 patients who are admitted each year both in Europe and in the U.S. with decreased LV systolic function, as well as the half million patients undergoing cardiac surgery and others requiring inotropic support, the potential value of a safe i.v. agent is large.

Excitation–contraction coupling is the process by which cardiac membrane depolarization activates the contraction of the heart (11, 35, 36). During the contractile process a molecular interaction takes place between the thin (actin) and thick (myosin) filaments of the sarcomeres, which is triggered by the rise in $[Ca^{2+}]_i$ and driven by the energy derived from ATP hydrolysis. Myosin is a hexamer composed of two heavy chains and two pairs of myosin light chains. The myosin heavy chains contain in their globular head the ATPase domain (which cleaves ATP to produce energy) and the actin-binding site, through which the contractile force is transduced. The thin filaments contain three different types of proteins: actin, tropomyosin and troponin (Tn) complex. Actin is a globular protein arranged as a chain of repeating units, forming two strands of an α helix carried on a tropomyosin molecule that functions as a backbone. Tropomyosin is a rod-shaped protein that interacts with adjacent tropomyosin molecules in a head-to-tail manner, forming continuous strands that lie into the depth of the groove formed by the two actin strands. Attached to tropomyosin at regular intervals is the Tn complex made up of three subunits: TnC, which contains the Ca^{2+}-binding subunits that regulate contraction, troponin-T (TnT), which attaches the troponin complex to tropomyosin, and troponin-I (TnI), which in concert with tropomyosin regulates the interactions between actin and myosin. Troponin and tropomyosin regulate the interaction between myosin and actin in a Ca^{2+}-sensitive manner. At low $[Ca^{2+}]_i$ (during the diastole) TnI binds tightly to actin in a conformation that keeps tropomyosin in a position along the actin filament, where it inhibits the interaction between actin and myosin and thereby suppresses its ATPase activity. During the systole, $[Ca^{2+}]_i$ rises, Ca^{2+} binds to the *N*-terminus of TnC and this binding induces a conformational change in the troponin complex, such that both TnI and tropomyosin move away from the myosin binding sites on the actin, thereby making them accessible to the myosin globular heads. When Ca^{2+} is removed from TnC, the troponin complex resumes its inactivated position, thereby inhibiting myosin–actin binding.

According to the cross-bridge theory for muscle contraction, the movement of actin among the myosin filaments is accomplished by the repetitive attachment and detachment of myosin heads (myosin cross-bridges) to and from actin filaments (11, 35, 36). During the process ATP is hydrolyzed. Molecular events begin during the diastole, when a molecule of ATP binds with high affinity to the myosin head, which rapidly dissociates the myosin heads from actin, producing muscle relaxation (Step 1). Myosin ATPase rapidly hydrolyzes myosin-bound ATP (Step 2) to adenosine diphosphate (ADP) and organic phosphate (Pi), which remain tightly bound to the myosin head, yielding a ternary complex (myosin–ADP–Pi) that increases the affinity for actin. During this step, the energy of ATP hydrolysis is transferred to the myosin head, causing a shape change so that the myosin head is cocked and placed in line with its binding site on the actin filament (Step 3). When $[Ca^{2+}]_i$ increases and the binding site on the actin filament becomes available, the actin–myosin–ADP–Pi complex undergoes an activation step (the slowest step of the cycle), which converts this complex to a high-affinity actin–*myosin–Pi–ADP complex (Step 4), so that a cross-bridge is formed causing the release of Pi. This release produces a conformational change of the myosin cross-bridge, so that the myosin head flexes, pulling the 10-nm actin filaments towards the center of the sarcomere (power stroke, Step 5). The combination of Steps 4 and 5 is referred to as the "strongly bound state time", as the myosin is strongly bound to actin throughout these steps (35). Finally, ADP dissociates from the myosin head (Step 6), which causes the dissociation of the myosin head from the actin filament and myosin returns to its original configuration. At this time a new molecule of ATP binds to the myosin head and the cycle is repeated. ATP can also by hydrolyzed without producing mechanical work, but if an actin-independent Pi release takes place no force-generating (power) stroke is produced, i.e., ATP hydrolysis is wasted.

There are three aspects of this cycle of particular interest. First, the key events underlying the cross-bridge cycle can be explained by changes in the molecular configuration of the myosin head that alternates between two major molecular configurations: a weakly binding conformation that predominates when ATP is bound to the head and a strongly binding conformation which predominates when the products of ATP hydrolysis (ADP and Pi) are released and explains why the power stroke is initiated (35). Second, the total cycle time is limited by Step 4 and is determined by how fast the low-affinity actin–*myosin–Pi–ADP complex is converted to the high-affinity actin–*myosin–Pi–ADP complex. Finally, force generation depends on the number of cross-bridges reacting with the thin filament and the duration of the reaction between the cross-bridge and the thin filament (36). The total number of available cross-bridges is determined by how fast the weakly bound actin–*myosin–Pi–ADP complex is converted to the strongly bound actin–*myosin–Pi–ADP complex and triggers the release of Pi (Step 4) (35). Thus, an agent that increases this rate-limiting step in the cardiac cycle while inhibiting the nonproductive hydrolysis of ATP would allow more myosin heads to be active during each heart beat and would be expected to improve myocardial efficiency.

Omecamtiv mecarbil (formerly CK-1827452) is a member of a diaryl urea family of cardiac myosin activators that represent a novel class

of inotropic agents that directly stimulate the activity of the myosin ATPase in the cardiac sarcomere. The kinetic analysis of the myosin cycle demonstrated that omecamtiv mecarbil accelerated the transition rate of myosin from the weakly to the strongly bound state (actin–*myosin–Pi–ADP) of the cycle and increased the release of Pi from the myosin head in a concentration-dependent manner, e.g., productive ATP hydrolysis. Interestingly, this activation is specific for cardiac myosin, since omecamtiv mecarbil had no detectable activity against myosins from skeletal or smooth muscle or nonmuscle (37), occurred in membrane-free sarcomeric protein preparations and was independent of the sarcomeric regulatory proteins (37, 38). However, omecamtiv mecarbil did not affect the rate of release of myosin from the strongly bound state, as ADP release rate is not increased, the rates of ATP binding or any other step of the contractile cycle. Thus, omecamtiv mecarbil reduced the time spent in the weakly bound state and prolonged the duration of the reaction of the cross-bridge with the thin filament in its force-generating reaction, which may underlie its ability to improve cardiac contractility. This explains why the positive inotropic effect of omecamtiv mecarbil is accompanied by an increase in the time to peak tension and in the systolic ejection time (SET), indicating an increasing duration of contraction. Furthermore, omecamtiv mecarbil decreased the rate of actin-independent Pi release from actin-bound myosin, thus reducing nonproductive (wasteful) ATP hydrolysis (37-41). It is interesting to note that all these changes occurred in the absence of changes in Ca^{2+} transient or in intracellular cAMP levels (39, 42).

BDM (2,3-butanedione-2-monoxime) and blebbistatin inhibit myosin activity by uncoupling myosin–actin cross-bridge contractility from the Ca^{2+} transient. At high concentrations, these inhibitors inhibited cross-bridge formation and decreased cardiac contractility without altering the Ca^{2+} transients. Omecamtiv mecarbil reversed the inhibitory effects of BDM and blebbistatin on the contractility of isolated cardiac myocytes, which confirmed its role as a direct myosin activator (40, 43).

PRECLINICAL PHARMACOLOGY

In isolated rat ventricular myocytes omecamtiv mecarbil increased cardiac contractility (EC_{20} = 200 nM) and fractional shortening and prolonged the time to peak contraction in a concentration-dependent manner (44). The increase in the time to peak contraction is a hallmark of cardiac myosin activators and indicates that they increases the amplitude and duration of myocyte contraction (39). These effects were not associated with significant changes in Ca^{2+} transients at concentrations up to 10 μM in Fura-2-loaded myocytes, in diastolic length or in cellular cAMP levels (40, 41, 43, 44). Moreover, combination of omecamtiv mecarbil with a β-adrenoceptor agonist (isoproterenol) resulted in an additive increase in contractility, with no further change in Ca^{2+} transient, confirming that the mechanism of action of omecamtiv mecarbil is independent of the activation of the cAMP/PKA pathway (40, 41). In addition, omecamtiv mecarbil increased myocyte fractional shortening even in the presence of propranolol (1 μM), which completely inhibited the contractile response to isoproterenol (20 μM) (41). Furthermore, omecamtiv mecarbil had no effect on the sarcoplasmic reticulum (SR) Ca^{2+}-ATPase pump, SR Ca^{2+} content, phosphorylation of phospholamban, caffeine-induced Ca^{2+} transients or on the Na^+/Ca^{2+} exchanger, and did not inhibit PDE3 activity in isolated rat ventricular myocytes or human platelets (40, 41, 43, 44). Finally, omecamtiv mecarbil produced a similar increase in cardiac contractility in ventricular myocytes isolated from normal rats and rats with HF following ligation of the left coronary artery, while, due to chronic neurohumoral activation, the contractile response to isoproterenol was significantly decreased in myocytes from infarcted animals.

The effects of omecamtiv mecarbil were studied in anesthetized Sprague-Dawley rats and conscious dogs and cardiac function was assessed using two-dimensional guided M-mode echocardiography and simultaneous pressure measurements.

In the rat model, i.v. infusion of omecamtiv mecarbil (0.25-2.5 mg/kg/h) significantly increased LV fractional shortening in a dose-dependent manner (from 107.8 ± 4.6% to 120.4 ± 4.3% after a 30-min infusion at 1.2 mg/kg/h) and decreased the systolic diameter (from 96.8 ± 3.6% to 90.9 ± 4.3%), without changes in diastolic diameter, blood pressure or heart rate. In rats with HF induced by ligation of the left anterior descending coronary artery, omecamtiv mecarbil (0.25-1.2 mg/kg/h) increased the LV fractional shortening in a dose-dependent manner (from 95.4 ± 8.0% to 111.4 ± 6.3% after a 30-min infusion at 1.2 mg/kg/h) and decreased the systolic diameter (from 101.6 ± 2.9% to 92.0 ± 2.6%) (40, 43).

In normal dogs, i.v. infusion of omecamtiv mecarbil (0.03-1 mg/kg/h) increased LV fractional shortening and stroke volume in a dose-dependent manner without changes in mean arterial pressure (43, 45). At 0.5 mg/kg/h i.v., omecamtiv mecarbil increased LV fractional shortening and stroke volume and modestly reduced heart rate, while cardiac output, maximum rate of rise of LV pressure (dP/dt_{max}), total peripheral resistance and mean blood pressure were only slightly changed. In dogs with severe HF induced by occlusion of the left anterior descending artery and continuous rapid ventricular pacing (240 bpm for 5-6 weeks), omecamtiv mecarbil (0.5 mg/kg by bolus, then 0.5 mg/kg/min for 3-5 h) significantly increased SET (20% change from baseline), LV fractional shortening (30-40%), systolic LV wall thickening (30-40%), stroke volume (20-25%) and cardiac output (45%) (37, 39, 43-46). These changes were accompanied by a decrease in left atrial pressure, LV end-diastolic pressure, total peripheral resistance and heart rate. However, there were no significant changes in arterial blood pressure, LV systolic pressure, dP/dt_{max}, coronary blood flow, coronary sinus O_2 content, MVO_2 or diastolic function. Since stroke work increased over 60% in the context of no increase in MVO_2, it resulted in a 25-30% increase in cardiac efficiency. Furthermore, these hemodynamic effects were maintained following i.v. infusion of omecamtiv mecarbil (0.25 mg/kg/h) for 72 h (45).

In conscious dogs with severe LV hypertrophy and HF, omecamtiv mecarbil (0.2 mg/kg/h) also increased LV SET and systolic wall thickening, fractional shortening and stroke volume, while it reduced LV end-diastolic pressure, mean left atrial pressure and heart rate (45, 46). Interestingly, omecamtiv mecarbil did not modify endo/epicardial myocardial blood flow ratio, coronary sinus O_2 content or MVO_2.

All these in vitro and in vivo findings demonstrated that omecamtiv mecarbil produced a greater improvement in LV function (e.g., increase in stroke volume and cardiac output) in dogs with HF than in normal dogs. Unlike other inotropic agents (β-adreno-

ceptor agonists and PDE3 inhibitors), which generally increased LV dP/dt_{max} and MVO_2 and shortened LV SET, omecamtiv mecarbil increased systolic function by increasing SET without altering the dP/dt_{max}, and improved overall systolic function without changes in MVO_2, which resulted in an increase in cardiac efficiency. The improvement in LV function persisted after 72-h i.v. infusion of omecamtiv mecarbil and in the presence of β-blocking agents. These findings provided support for the potential clinical benefit of omecamtiv mecarbil in the treatment of HF and clearly encouraged the study of this drug in patients with HF.

SAFETY

In the first-in-human study (CY 1111), omecamtiv mecarbil at concentrations at or below the maximum tolerated dose (MTD; 0.5 mg/kg/h for 6 h) was well tolerated when compared to placebo and there was no dose-related increase in the overall incidence of adverse events (47-49). At 0.5 mg/kg/h mean systolic blood pressure decreased by 11.3 and 7.4 mmHg, respectively, in standing and supine volunteers, but no dose-dependent changes in heart rate, P-R, Q-T or $Q\text{-}T_c$ intervals were reported (47). Omecamtiv mecarbil was clinically well tolerated at 0.625 mg/kg/h for 6 h, but too few volunteers received this dose to define it according to protocol as the MTD. For the patients who were tolerant of all study drug infusions, no consistent pattern of adverse events with either dose or duration of infusion emerged. By design, the study found doses that were not well tolerated. The omecamtiv mecarbil infusions were terminated early due to symptoms of chest tightness, lightheadedness, palpitations and feeling hot in two volunteers treated at 1.0 mg/kg/h and in one of two volunteers treated at 0.75 mg/kg/h. In these subjects, signs of intolerability included tachycardia (~150 bpm) and electrocardiographic changes. In one volunteer treated with 1 mg/kg/h a transient increase in cardiac-specific TnI and TnT was observed, but creatine kinase levels remain unchanged. Subsequent electrocardiograms (ECGs) and echocardiograms returned to normal in this subject and cardiac magnetic resonance imaging enhanced by gadolinium, a sensitive test for myocardial injury, detected no cardiac abnormality. These side effects are most likely due to an excessive prolongation of the SET, leading to decreased diastolic coronary perfusion and diastolic filling, and resolved rapidly with discontinuation of the drug infusion. However, it is important to note that no "off-target" adverse effects were noted even at these extreme doses.

In a phase IIa trial (CY 1121) assessing escalating doses of omecamtiv mecarbil in patients with stable HF, the drug was well tolerated in the first two cohorts. Heart rate increased, but blood pressure remained unchanged (50-52). The safety data from the first four cohorts suggested that the drug was well tolerated, with no serious adverse events reported in patients exposed to the intended range of plasma concentrations. However, five patients were discontinued from the trial: two patients had signs and symptoms associated with clinical intolerance due to excessive concentrations of omecamtiv mecarbil (> 1300 ng/mL) and increased troponin levels; in one hypertensive patient (baseline blood pressure: 182/116 mmHg) an asymptomatic increase in TnI levels was discovered following completion of infusion; one patient presented local contractile dysfunction on the echocardiogram, and one patient a $Q\text{-}T_c$ > 500 ms during infusion (baseline $Q\text{-}T_{cF}$ = 493 ms) (53). Additionally, three serious adverse events were reported, including a non-S-T elevation myocardial infarction in the setting of a drug overdose, a case of septicemia in the setting of a diabetic foot ulcer and one case of pneumonia.

In the CY 1011 trial, both i.v. and oral formulations of omecamtiv mecarbil were well tolerated, and there were no serious adverse events. A total of 25 adverse events were reported; most of them were mild in severity, although three volunteers were withdrawn from the study (54). No serious adverse events, changes in ECG, vital signs or laboratory tests were observed (55).

In the CY 1221 trial assessing low and high doses of omecamtiv mecarbil, of the 94 patients treated, a total of 19 patients experienced 29 adverse events (photopsia, infusion-site pain and dyspnea) at any time during the trial: 5 patients on placebo, 2 patients on the lower dose and 12 patients on the higher dose of omecamtiv mecarbil. Overall, 23 of 29 were reported as mild in severity, 4 as moderate and 2 as severe (56); 14 of the 29 were reported as unrelated to treatment, 8 as possibly related and 7 of 29 as probably related to treatment. No other clinically important changes were observed on vital signs, ECGs and cardiac biomarkers as compared to placebo. Two severe adverse events occurred in the same patient receiving the higher dose. This patient tolerated the infusion of omecamtiv mecarbil while at rest uneventfully but experienced persistent angina and S-T depression during the third exercise treadmill testing (ETT), which persisted for several minutes into the recovery period. Cardiac catheterization identified a severe stenosis of the proximal left anterior descending coronary artery and the patient was successfully treated with a coronary stent. Troponin I (but not creatine kinase CK-MB) levels were elevated after percutaneous transluminal coronary angioplasty (PTCA), prompting the second serious adverse event (i.e., postprocedural myocardial infarction); however, troponin levels became normal 19 h after the PTCA procedure. Both serious adverse events were reported as unrelated to treatment by the investigator. Thus, the safety profile of omecamtiv mecarbil seems quite promising compared with other inotropic agents, and no evidence of proarrhythmia has been reported.

CLINICAL STUDIES

Cytokinetics has performed five phase I clinical trial in healthy volunteers.

A double-blind, randomized, placebo-controlled, dose-escalation study (CY 1111) enrolled 34 healthy volunteers who received a 6-h double-blind infusion of ascending doses of omecamtiv mecarbil (5, 15, 25, 62.5, 125, 250, 500, 625, 750 and 1000 μg/kg/h) or placebo each week for 4 weeks. Each treatment sequence consisted of three ascending omecamtiv mecarbil doses and a placebo infusion randomized into each treatment sequence on 4 separate days 1 week apart. The low dose of each subsequent cohort was the high dose from the prior cohort; modifications of the dosing schedule were made as the MTD was reached (39, 47-49). Echocardiograms were performed at baseline, 1, 3, 6, 7, 8, 10 and 24 h and were paired with coincidently measured plasma concentrations of omecamtiv mecarbil. A total of 484 observations were analyzed. The primary objective was to determine the MTD and plasma concentrations of omecamtiv mecarbil after 6 h of infusion. Secondary objectives included evaluation of its pharmacodynamics (assessed by echocardiography), pharmacokinetics, safety and tolerability. At the MTD of 0.5

mg/kg/h for 6 h (peak plasma concentrations [C_{max}] = 905 μg/mL, range 497-1242 μg/mL), omecamtiv mecarbil significantly increased indices of LV systolic function (ejection fraction 6.8%, fractional shortening 9.2%) and this increase was associated with an 84-ms mean prolongation of SET. Moreover, these effects remained even in the presence of a β-blocker, and at the end of the 6-h infusion at the MTD mean standing and supine systolic blood pressure fell 11.3 and 7.4 mmHg, respectively, versus placebo. These findings demonstrated that, as previously found in preclinical studies, omecamtiv mecarbil increased LV systolic function by directly increasing SET rather than contraction velocity. In fact, unlike conventional inotropes, omecamtiv mecarbil did not decrease isovolumetric contraction time nor increase LV dP/dt_{max}. At doses up to and above the MTD, there were no changes versus placebo in heart rate or electrocardiographic P-R, Q-T or Q-T_c intervals. There was a linear dose-related relationship between the plasma concentrations and the changes in SET (r^2 = 0.97), LV fractional shortening (r^2 = 0.93) and ejection fraction (r^2 = 0.90) (49). The prolongation of the SET was the most sensitive marker of drug effect and this effect was well correlated with the increases in LV ejection fraction and LV fractional shortening. The close relationship between omecamtiv mecarbil plasma concentrations, prolongation of the SET and improvements in LV function suggested that the effect on cardiac function after dosing with this drug may be reliably observed and predictable.

A single-center phase I trial which progressed from a single-blind, single-dose phase to a randomized, double-blind, placebo-controlled, multiple-dose phase was designed to evaluate the safety, tolerability and pharmacokinetics of an oral formulation (capsules) of omecamtiv mecarbil administered both as a single oral dose and as multiple oral doses of 10 and 30 mg to steady state in healthy men and women. The secondary objective of this study was to evaluate the pharmacokinetics of omecamtiv mecarbil after a single oral dose and after multiple oral doses to steady state and to compare the pharmacokinetic parameters between healthy men and women. Omecamtiv mecarbil was well tolerated, with no drug-related serious adverse events. Dose proportionality between the 10- and 30-mg dose levels was observed both after single and multiple doses to steady state and no differences were observed between men and women (55).

A single-center, randomized, open-label, four-way crossover phase I trial (CY 1011) was designed to compare the bioavailability of an oral liquid and a capsule formulation of omecamtiv mecarbil (both at 0.125 mg/kg) versus a reference i.v. infusion (0.125 mg/kg administered at a constant rate over 1 h) and to determine the bioavailability of the capsule formulation in fed (after a standard high-fat breakfast) and fasted states relative to the liquid dose (54). Oral absorption was rapid for the liquid and the capsule formulations in fasted volunteers, reaching C_{max} values after 0.5 and 1 h, respectively. Food delayed the rate of absorption (median time to C_{max} = 3 h) in four of seven subjects, without a substantial effect on overall bioavailability or AUC. Absolute oral bioavailability of omecamtiv mecarbil was approximately 100% for all three formulations, suggesting that there is no first-pass metabolism and that the drug may have a low susceptibility for pharmacokinetic interactions with drugs metabolized via cytochrome P450 enzymes in the liver and small intestine. The data suggest that there is relatively little variability in oral absorption between subjects and that predictable plasma levels can be obtained with the oral formulation. Moreover, these data, together with those from healthy volunteers who received i.v. omecamtiv mecarbil, support drug dosing both i.v. and orally without requiring adjustment for patient weight. Because omecamtiv mecarbil was found to be rapidly absorbed, modified-release formulations should be developed to reduce the rate of drug absorption without significantly affecting the overall bioavailability.

Because the immediate-release formulation of the drug was rapidly absorbed, several modified-release formulations were developed to reduce the rate of drug absorption without significantly affecting the overall bioavailability. A single-center, two-part, open-label phase I trial assessed the pharmacokinetics and relative bioavailability of three different oral modified-release formulations of omecamtiv mecarbil as compared to the immediate-release formulation in 12 healthy male subjects. The secondary objective of the trial was to determine whether there is an effect of food on the pharmacokinetics of these formulations. The single-dose pharmacokinetics of one formulation in both the fasted and fed states demonstrated a reduced C_{max} as compared to the immediate-release formulation, without a substantial effect on overall bioavailability (55). This prototype modified-release oral formulation of omecamtiv mecarbil (undisclosed) has been selected to proceed forward into further clinical testing.

Three randomized, double-blind, placebo-controlled phase II trials analyzed the pharmacokinetics, efficacy and safety of i.v. omecamtiv mecarbil in patients with stable HF and of i.v. and oral omecamtiv mecarbil in patients with ischemic cardiomyopathy and angina.

A multicenter, double-blind, randomized, placebo-controlled, dose-escalating pharmacokinetic and pharmacodynamic phase IIa clinical trial (NCT00624442, CY 1121) evaluated the safety and tolerability of omecamtiv mecarbil administered as an i.v. infusion in five cohorts of patients with a clinical diagnosis of HF, LV ejection fraction < 40%, normal sinus rhythm and stable drug regimen, including ACE inhibitors or angiotensin AT_1 receptor blockers, β-blockers and diuretics, if necessary (50-53). Patients with cardiovascular hospitalization within 6 weeks of entry or Canadian Cardiovascular Society (CCS) class III or IV angina were excluded. The primary objectives were to evaluate the safety and tolerability of omecamtiv mecarbil administered as an i.v. infusion to patients with stable HF and to assess the drug's effect on pharmacodynamic response (LV ejection fraction, fractional shortening and SET). Secondary outcomes were to determine the pharmacokinetics of omecamtiv mecarbil in this population and to establish a relationship between the plasma concentrations and pharmacodynamic effects of the drug (as assessed by echocardiography). Cohorts of one to four patients underwent four treatment periods, receiving three infusions of escalating active doses and a placebo infusion randomized into the dose escalation sequence to maintain blinding. Each of the four infusions was given at least 1 week apart. Loading and maintenance doses were modeled on the basis of the pharmacokinetic data derived from the previously described CY 1111 study. Patients received a loading infusion to rapidly achieve a target plasma concentration of omecamtiv mecarbil during the first hour, followed by slower infusions intended to maintain that plasma concentration during the remainder of treatment. Cohorts 1 and 2 studied a range of omecamtiv mecarbil plasma concentrations from 90 ng/mL in the lowest dose regimen

in cohort 1 to 650 ng/mL in the highest dose regimen in cohort 2. The duration of infusion was 2 h in both cohorts (the second hour at half of the respective infusion rates). Cohorts 3-5 were designed to gain experience across the same range of plasma concentrations but with infusion durations of 24 h (cohorts 3 and 4) and 72 h (cohort 5). Overall, in 45 patients, a total of 151 treatment periods were initiated. Across the range of plasma concentrations evaluated, the pharmacokinetics of omecamtiv mecarbil were generally linear with respect to dose. Following a 1-h loading infusion of omecamtiv mecarbil and a 1-h maintenance infusion of 0.125/0.0625, 0.25/0.125, 0.5/0.25, 0.75/0.375 and 1/0.5 mg/kg/h, C_{max} values of 93, 177, 331, 578 and 613 ng/mL, respectively, were obtained (52). Following a 1-h loading and 23-h maintenance infusion of 0.25/0.125/0.025, 0.5/0.25/0.05 and 1/0.5/0.1 mg/kg/h, mean C_{max} values of 183, 271 and 600 ng/mL, respectively, were reported.

Omecamtiv mecarbil significantly increased SET, stroke volume, cardiac output, fractional shortening and LV ejection fraction in a concentration-dependent manner. More specifically, at plasma concentrations > 100 ng/mL omecamtiv mecarbil significantly increased SET and fractional shortening, at concentrations > 200 ng/mL it increased stroke volume and heart rate started to decrease, and at > 300 ng/mL it increased cardiac output, while LV end-systolic and -diastolic volumes started to decrease, possibly due to unloading of the ventricle (51, 52). At plasma concentrations > 400 ng/mL, increases in stroke volume and cardiac output appeared to plateau in association with a concentration-dependent decline in heart rate (53, 57). Despite the increase in SET, the proportion of the cardiac cycle dedicated to ejection remained relatively constant, due to the decline in heart rate and LV end-systolic volume at high doses. However, blood pressure remained unchanged.

There was a statistically significant correlation between increasing omecamtiv mecarbil plasma concentrations and the increase in systolic function (Doppler-derived SET, fractional shortening, stroke volume and ejection fraction) and the decreases in LV end-systolic and end-diastolic volumes. The effects of omecamtiv mecarbil on SET and stroke volume appeared to be persistent over a 24-h period. With 72 h of infusion, decreases in LV volumes appeared sustained. In patients with reduced stroke volumes (< 50 mL) at baseline omecamtiv mecarbil produced a significant, dose-dependent increase in systolic LV function (SET, stroke volume, cardiac output, fractional shortening and ejection fraction) which was generally greater than that in patients with greater stroke volumes at baseline (57). Moreover, there were statistically significant correlations between increasing omecamtiv mecarbil plasma concentrations and decreases in LV end-systolic and end-diastolic volumes, as well as in heart rate. These findings support further clinical trials in a larger patient population, and translation of this novel and unique mechanism into higher-risk populations with HF.

The dose-limiting effect of omecamtiv mecarbil is believed to be related to excessive prolongation of the SET, which can limit diastolic coronary flow and ventricular filling, producing myocardial ischemia. Therefore, it is of interest to investigate whether symptom-related exercise capacity in HF patients with ischemic cardiomyopathy and angina was deleteriously affected by omecamtiv mecarbil at pharmacologically active concentrations (56). A double-blind, randomized, placebo-controlled phase IIa trial (NCT00682565, CY 1221) evaluated low- and high-dose regimens of omecamtiv mecarbil, each including both i.v. and oral formulations, in 94 patients with ischemic cardiomyopathy and angina, an LV ejection fraction of ≤ 35% and NYHA class II-III. Patients in the low-dose cohort received a 20-h i.v. infusion of omecamtiv mecarbil (24 mg/h for 2 h and then 6 mg/h for 18 h) to target a maximum plasma concentration of 295 ng/mL, or placebo; patients then received an oral immediate-release formulation (12.5 mg t.i.d.) for 7 days to target a maximum plasma concentration of 184 ng/mL. Patients in the high-dose cohort received a 20-h i.v. infusion of omecamtiv mecarbil (2 h at 48 mg/h plus 18 h at 11 mg/h) to target a maximum plasma concentration of 550 ng/mL, or placebo; patients then received an oral immediate-release formulation (25 mg t.i.d.) for 7 days with a target plasma concentration of 368 ng/mL, or placebo. The primary endpoint was to assess the effect of i.v. omecamtiv mecarbil on symptom-limited exercise tolerance, defined as stopping exercise during the third ETT due to angina at a stage earlier than the shorter of two baseline ETTs. Secondary outcomes were: a) to assess the tolerability of omecamtiv mecarbil administered t.i.d. to steady state as an immediate-release, blend-in-capsule oral formulation to outpatients; and b) to assess plasma concentrations of omecamtiv mecarbil at trough and 1 h after dosing with omecamtiv mecarbil administered t.i.d. to steady state as an immediate-release, blend-in-capsule oral formulation to outpatients. During screening, patients underwent two symptom-limited ETTs and the shorter of these two ETTs was defined as the baseline. A third ETT was performed during the final 2 h of the maintenance infusion. In each cohort, patients whose symptom-limited exercise tolerance during the infusion did not deteriorate relative to baseline received either omecamtiv mecarbil or placebo administered orally for 7 days. Omecamtiv mecarbil plasma levels were determined during the infusions, as well as before and 1 h after the final oral dose. The primary safety endpoint occurred in 1 patient receiving placebo (n = 29) and in no patients receiving omecamtiv mecarbil at either low (n = 34) or high (n = 34) doses; 52% and 50% of patients, respectively, exercised to stage 4 or above during ETT on low- and high-dose omecamtiv mecarbil, compared to 41% in the placebo group. Thus, it can be concluded that in HF patients with ischemic cardiomyopathy and angina who theoretically could be most vulnerable to the possible deleterious consequences of SET prolongation, omecamtiv mecarbil did not adversely affects exercise capacity at concentrations that improve cardiac function.

In another open-label, multicenter phase IIa trial (NCT00748579, CY 1124) the primary objective was to evaluate the effects of omecamtiv mecarbil on myocardial efficiency, defined as the ratio of ventricular performance to MVO_2, in 18 patients with symptomatic HF (NYHA class II or greater) and LV ejection fraction < 35%, in sinus rhythm and with a clinical indication for left/right heart catheterization (58). The secondary outcome was to evaluate the effects of omecamtiv mecarbil on ventricular performance, MVO_2, pressure–volume relationships, SET and invasively measured hemodynamics, including filling pressures and cardiac output. Patients were enrolled in two cohorts. In cohort 1, eight patients underwent an i.v. infusion of omecamtiv mecarbil (30 min at 54 mg/h followed by a 1-h maintenance dose at 21 mg/h), to reach an estimated (based on data from the CY 1111 trial) median plasma level of 280 ng/mL (range: 126-445 ng/mL). In cohort 2, 12 patients received a loading dose of 72 mg/h for ≤ 1 h, followed by

1 h at 36 mg/h, to achieve a mean plasma level of 560 ng/mL (range: 242-888 ng/mL). No further data were available at the time of publication.

A randomized, open-label, parallel-assignment, multiple-dose phase II trial (NCT00941681) is being performed in patients with stable heart failure. The primary objective is to evaluate the steady-state pharmacokinetics of a modified- and an immediate-release oral formulation of omecamtiv mecarbil in 32 patients with stable HF. The secondary objective is to evaluate the safety and tolerability of both formulations when dosed to steady state in these patients. Patients are enrolled in three cohorts. In cohort 1, patients will receive a modified-release (50 mg b.i.d.), cohort 2 an immediate-release (37.5 mg t.i.d.) and cohort 3 a modified-release formulation (100 mg b.i.d.) of omecamtiv mecarbil for 10 days.

Cytokinetics continues enrolling patients in an ongoing open-label, nonrandomized phase IIa trial to evaluate an i.v. formulation of omecamtiv mecarbil in patients with stable HF undergoing clinically indicated coronary angiography in the cardiac catheterization laboratory, and a fourth phase IIa trial is under way to evaluate and compare the oral pharmacokinetics of a modified-release and an immediate-release formulation of omecamtiv mecarbil in patients with stable heart failure (59).

DRUG INTERACTIONS

The primary objective of another single-center, open-label, sequential, parallel-group phase I trial was to evaluate the effect of ketoconazole (a potent inhibitor of cytochrome P450 CYP3A4) at steady state on the pharmacokinetics of a single oral dose of omecamtiv mecarbil in 16 male volunteers who were classified as extensive (EM) or poor metabolizers (PM) on the basis of their CYP2D6 genotype. The secondary objectives were to evaluate the pharmacokinetic parameters of omecamtiv mecarbil administered alone in subjects with PM as compared to subjects with EM genotype for CYP2D6 and the effects of diltiazem (a moderate inhibitor of CYP3A4) at steady state in another 8 healthy male volunteers with the EM genotype. Ketoconazole reduced the clearance and increased the area under the plasma concentration versus time curve (AUC; 50%), as well as the half-life of omecamtiv mecarbil (from 22 to 27 h) in EM, although the C_{max} was unaffected (65 ng/mL vs. 67 ng/mL) (56). Diltiazem increased the half-life of omecamtiv mecarbil from 18 to 20 h but did not modify the C_{max} or AUC values when both drugs were coadministered. Additional data from this trial comparing the pharmacokinetics of omecamtiv mecarbil in subjects with the EM versus the PM genotype for CYP2D6 are expected. Thus, it was concluded that no clinically meaningful drug–drug interactions with either ketoconazole or diltiazem were identified in either EM or PM via 2D6.

FUTURE DIRECTIONS

Omecamtiv mecarbil represents the first compound of a new class of inotropic agents, the cardiac myosin activators. Omecamtiv mecarbil increased cardiac myosin ATPase activity and accelerated the transition of the actin–myosin complex from the weakly to the strongly bound state, while it inhibited nonproductive ATP hydrolysis. As a result, it improved systolic cardiac function, increasing SET, fractional shortening and stroke volume at concentrations at which it did not modify $[Ca^{2+}]_i$, cAMP levels or MVO_2, which indicated that omecamtiv mecarbil improved myocardial efficiency. Results obtained in animal models, in healthy volunteers and in patients with stable HF and ischemic cardiomyopathy suggested that omecamtiv mecarbil may represent a safe and effective therapeutic alternative to conventional positive inotropic agents (e.g., dobutamine and milrinone) to improve cardiac function in patients with systolic HF, with no evidence of arrhythmias or ischemia at therapeutic doses. The drug was rapidly absorbed, presented 100% oral bioavailability and its half-life supported the development of a modified-release formulation as an oral therapy for chronic HF. Moreover, clinical trials found a linear dose-dependent relationship between drug concentration and the duration of systolic ejection, a measure of the mechanism of action. Finally, several phase IIa studies are under way in different subsets of patients and a phase III clinical program is under development.

However, because of the novelty of its mechanism of action and the lack of phase III clinical trials, there is no information on the long-term efficacy and safety (hospitalizations and mortality rates) of omecamtiv mecarbil in patients with chronic (NYHA class III-IV) HF, acute HF syndromes with different comorbidities (i.e., hypertension, diabetes, renal insufficiency, abnormalities in cardiac rhythm, valvular or pericardial disease) or familial cardiomyopathies. There are no comparative studies with conventional i.v. inotropes (dobutamine, milrinone, levosimendan), its effects on sarcomeric Ca^{2+} binding, neurohumoral activation, apoptosis or other signaling pathways involved in the pathogenesis of HF are unknown, and the pharmacokinetic profile (including active metabolites) in patients with hepatic or renal insufficiency, as well as potential interactions with other drugs commonly used in patients with HF, are unknown. Therefore, at the present time it is difficult to predict the possible role of omecamtiv mecarbil in patients with HF. A complete phase III program is required to answer all these and other questions in order to confirm the efficacy and safety shown in phase I and II clinical trials. Certainly, we have an unmet need for safer and more effective positive inotropic drugs than those that we currently prescribe in our outpatients with acute or chronic systolic HF.

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DISCLOSURE

The authors state no conflicts of interest.

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