DRUG PROFILE

CD-NP, a chimeric natriuretic peptide for the treatment of heart failure
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In development by Nile Therapeutics Inc, under license from the Mayo Foundation, CD-NP is a chimeric natriuretic peptide in which the 15-amino acid C-terminal tail of Dendroaspis natriuretic peptide is fused to the 22-amino acid human C-type natriuretic peptide. The rationale for its design was to create a peptide with the beneficial cardiovascular and renal effects of native natriuretic peptides, but without a clinically significant hypotensive response. CD-NP is able to bind to all three natriuretic peptide receptors (NPR-A, NPR-B and NPR-C) and, therefore, is unique in being able to increase cyclic guanosine monophosphate production downstream of both NPR-A and NPR-B. Animal studies and human trials demonstrated that CD-NP is safe and improves cardiovascular and renal function without inducing significant levels of hypotension. Preliminary data also suggest improved renal function in human heart failure patients. Ongoing clinical trials are needed to further validate CD-NP as an effective treatment option for heart failure.

Introduction
Heart failure (HF) can be viewed as a syndrome resulting from the progression of a number of cardiovascular diseases, leading to a progressive decline in cardiac function [1050846], [1070565]. HF has reached epidemic proportions in the developed world and is associated with significant morbidity and mortality in individuals diagnosed with the condition. For example, HF incidence approaches 10 in every 1000 of the population over 65 years of age. At 40 years of age, the lifetime risk of developing HF for both men and women is one in five. In 2005, HF mortality was 292,214 in the US and the estimated direct and indirect costs associated with HF in the US in 2009 were US $ 37.2 billion [1050846]. These figures have been increasing and are expected to continue to rise. This is largely because survival rates among individuals with underlying cardiovascular diseases (eg, coronary artery disease, hypertension and diabetes) are increasing, with many of these survivors ultimately developing HF [1050846], [1070565]. Current standards of care for HF include a variety of pharmaceuticals, such as β-blockers, ACE inhibitors, angiotensin II receptor blockers, aldosterone antagonists and diuretics [1070565]. While these pharmaceuticals are certainly of benefit, long-term prognosis remains poor in many individuals with HF [1070565]. This indicates that treatment for HF is currently inadequate in terms of meeting the burdens associated with this syndrome; therefore, there is a real need for new therapeutic strategies.

Natriuretic peptides (NPs), including atrial, brain, C-type and Dendroaspis NP (ANP, BNP, CNP and DNP, respectively), constitute a family of peptide hormones, which exert a number of effects in the cardiovascular

Therapeutic CD-NP

Originator Mayo Foundation

Licensee Nile Therapeutics Inc

Status Phase II Clinical

Indication Cardiac failure

Actions C-type natriuretic peptide ligand, Dendroaspis natriuretic protein ligand, Natriuretic peptide receptor A agonist, Natriuretic peptide receptor B agonist

Technologies Biological therapeutic, Infusion, Intravenous formulation, Protein chimeric

system [1068597], [1068628]. For example, ANP, BNP and DNP all reduce blood pressure by inducing natriuresis, diuresis and vasodilation, as well as by increasing endothelial permeability [1068597]. Conversely, CNP preferentially relaxes veins [1068631] and does not have an overt effect on natriuresis and diuresis; therefore, CNP does not alter blood pressure or enhance renal function to the same extent as the other NPs [1068635]. Additional effects of NPs include inhibition of the renin-angiotensin-aldosterone system (CNP exerts minimal effects compared with the other NPs), prevention of cardiac hypertrophy, antifibrotic effects and antiproliferative effects [1068597]. Within the NP family, CNP has the most potent antiproliferative and antifibrotic effects [1068636]. The production of all NPs is elevated in the setting of HF [1068628], [1068637].

NPs elicit their effects by binding to specific cell surface receptors, denoted NP receptor A, B or C (NPR-A, NPR-B or NPR-C) [1068597], [1068638]. NPR-A and NPR-B are

guanylyl cyclase receptors that increase cytosolic levels of cyclic guanosine monophosphate (cGMP) upon binding of an NP. NPR-A binds ANP, BNP and DNP, whereas NPR-B preferentially binds CNP. Most of the beneficial effects of NPs in HF have been attributed to the NPR-A and NPR-B guanylyl cyclase receptors [1068640]. The NPR-C receptor, which can bind all NPs, is not linked to a particulate (membrane bound) guanylyl cyclase enzyme. Although NPR-C is commonly classified as a clearance receptor, numerous studies have demonstrated that this receptor is associated with the activation of inhibitory G-proteins [1068638], and some of the functional effects associated with this signaling pathway have been elucidated [1068639]. The role of NPR-C in cardiovascular disease is not well understood. In addition to internalization following the binding to NPRs, NPs are degraded by a circulating neutral endopeptidase (NEP), which is an important determinant of NP half-life [1068597].

The concept of using NPs for the treatment of HF is not new. For example, anaritide (a form of ANP lacking the three N-terminal amino acids of full-length ANP), carperitide (full-length ANP) and nesiritide (recombinant human BNP) have all been tested (reviewed in [1068597] and [1068640]). Nesiritide is currently approved for the treatment of acute decompensated HF in the US and Canada [1070580]; however, its use has been limited because it can cause inappropriate levels of hypotension in some patients, which may result in impaired renal perfusion [1068808]. Another factor that has negatively impacted nesiritide as a HF treatment is the publication of two meta-analyses suggesting that the compound is associated with worsening renal function and higher incidences of death compared with non-inotropic therapies, such as diuretics and vasodilators [597378], [633690]. However, it is important to note that not all studies support this conclusion [857563], [1068814]. Indeed, several clinical trials had previously demonstrated that nesiritide improved hemodynamic and renal function and that it was more effective than standard treatments (eg, nitroglycerin), which helped form the basis of the initial application for approval [444959]. To help address some of these contradictory results regarding the effects of nesiritide, a large, phase III, placebo-controlled, multicenter clinical trial, called ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure), was recruiting approximately 7000 patients with acute decompensated HF (ClinicalTrials.gov identifier: NCT00475852).

Among the new candidates for acute HF therapy, CD-NP is a novel synthetic NP being developed by Nile Therapeutics Inc (under license from the Mayo Foundation) in an attempt to enhance the favorable NP effects while minimizing the hypotensive effects of native NPs, such as ANP or BNP [1068640]. CD-NP is a fusion peptide in which the 15-amino acid tail of DNP has been attached to the 22-amino acid human CNP [1046052]. CNP was chosen as a key component for a chimeric NP because it increases cGMP via NPR-B activation (rather

than NPR-A) and relaxes veins more effectively than arteries [1068635]. This means that CNP can reduce the load on the heart (because of specific venodilation) without inducing significant hypotension; however, the limited capacity of native CNP to enhance renal function (possibly because of the lack of a C-terminal extension, a unique feature among NPs, as well as an increased susceptibility to degradation by NEP) impairs its usefulness as a HF treatment.

DNP was originally discovered in the venom of the Green Mamba snake [1068646], but it is also present in the circulation and myocardium of mammals, including humans [1068628], [1068649]. The C-terminal extension of DNP is 15 amino acids in length, which is the longest of any known NP (ANP, BNP and CNP have C-terminal extensions of 5, 6 and 0 amino acids, respectively). This unique structural characteristic may reduce the ability of NEP (which is highly expressed in the kidney) to degrade DNP in comparison to other NPs [467671]. DNP can bind both NPR-A and NPR-C [815707], [1068653] and elicits potent natriuretic and vasodilatory responses [1068649]. The rationale for developing CD-NP was to create a peptide that combines the beneficial venodilatory and cardiac (antifibrotic) effects of CNP with the renal-enhancing properties of DNP, while avoiding the hypotensive effects of native NPs, such as ANP or BNP.

Synthesis

During the development of CD-NP, two peptides were initially synthesized. First, the 15-amino acid C-terminal tail of DNP (PSLRDPRPNAPSTSA) was prepared. CD-NP was then synthesized as a chimera of human CNP and the DNP peptide C-terminal tail (GLSKGCFGLKLDRIGSMSGLGCPSLRDPRPNAPSTSA). Both of these peptides were prepared using solid-phase methods and the identity of the peptides was confirmed by electrospray ionization mass spectrometry analysis [1046052].

Preclinical development
In vitro
Because CD-NP incorporates structural elements of both CNP and DNP, it is important to know which NPR(s) CD-NP displays affinity towards. This has been assessed in detail by Dickey *et al* [1068653] using human embryonic kidney (HEK) 293 cells heterologously expressing human NPRs. In these experiments, the production of cGMP downstream of NPR-A and NPR-B was measured (whole-cell and membrane assays) and competition binding experiments for NPR-A and NPR-C were performed. Importantly, these HEK293 cells do not express endogenous NPRs, thus ensuring that any NP-dependent increase in cGMP levels results from the activation of the stably expressed receptor. Results demonstrated that CD-NP was able to bind to and/or activate all three NPRs. Specifically, CD-NP induced cGMP production in HEK293 cells stably expressing NPR-A with an EC_{50} value of 723 nM versus 10.8 nM for ANP and 28.4 nM for

BNP. Notably, saturating concentrations of CD-NP did not produce as much cGMP as saturating concentrations of ANP, indicating that CD-NP acts as a partial agonist of NPR-A. In similar experiments performed on cells expressing NPR-B, CD-NP demonstrated an EC_{50} value of 202 nM versus 38 nM for CNP. The 15-amino acid DNP tail was also assayed singly and exhibited no ability to stimulate NPR-A or NPR-B [1068653]. Binding affinity data are incomplete, but [125I]ANP competition binding experiments have revealed that it takes approximately 1000-fold more CD-NP than ANP to compete for [125I] ANP binding to NPR-A. Importantly, however, CNP and the C-terminal tail of DNP were unable to compete for [125I]ANP binding to NPR-A, which demonstrates that CD-NP, but not CNP, can act as an NPR-A agonist [1068653]. At the time of publication, similar binding affinity data using NPR-B were not available.

To study the ability of CD-NP to bind to NPR-C, a binding assay experiment was performed in which the ability of CD-NP, ANP and CNP to compete for bound [125I]ANP in cells expressing NPR-C was measured [1068653]. Comparable concentrations of CD-NP, ANP and CNP were able to block [125I]ANP binding confirming that CD-NP, like native NPs, binds to NPR-C. Together these experiments demonstrated that CD-NP can bind to all three NPRs and increase cGMP production via both NPR-A and NPR-B [1068653].

The functional effects of CD-NP have also been examined *in vitro* using isolated canine glomeruli and cultured human fibroblasts in order to assess renal function [1046051] and antifibrotic activity [1046064], respectively. In isolated glomeruli, CD-NP (10^{-5} M) enhanced cGMP production by an approximately 8-fold greater extent compared with CNP at the same concentration. This effect of CD-NP was blocked in the presence of the NPR-A antagonist A-71915 [1046051]. Together these data indicate that, unlike native CNP, CD-NP possesses the capacity to increase renal function by activating NPR-A and increasing cGMP production.

The antifibrotic and antiproliferative effects of CD-NP were studied in cultured human fibroblasts expressing all three NPRs [1046064]. In non-CD-NP preincubated fibroblasts, the application of TGFβ1 (10 ng/ml) for 48 h significantly ($p < 0.0001$) enhanced the production of collagen type I. This pro-fibrotic response was reduced by 20% in fibroblasts that were preincubated with CD-NP (10^{-6} M) for 30 min [1046064]. Similar results were obtained when cultured fibroblasts were treated with the pro-fibrotic and hypertrophic cytokine cardiotrophin-1 [1046050], [1046052]. CD-NP increased the production of cGMP in the cultured human fibroblasts to a similar extent to CNP [1046052].

In vivo
In anesthetized dogs, CD-NP (10, 50 and 100 ng/kg/min, iv 30-min infusion) exhibited dose-dependent effects on cardiorenal parameters [736656], [1046049], [1046050],

[1046052]. All three doses of CD-NP reduced pulmonary capillary wedge pressure (PCWP; from 6.4 at baseline to 5.2, 4.4 and 3.6 mmHg after treatment with 10, 50 and 100 ng/kg/min, respectively; $p < 0.05$ versus baseline for all doses) and right atrial pressure (RAP) was reduced at doses of 50 and 100 ng/kg/min (from 1.0 to -0.03 and -0.4 mmHg; $p < 0.05$ for both doses). These cardiac unloading measures were only associated with very small reductions in mean arterial pressure (MAP), even at the 100-ng/kg/min dose (from 137 to 118 mmHg). A decrease in heart rate was also observed (from 130 to 119 bpm at 100 ng/kg/min; $p < 0.05$) [1046049], [1046052].

Despite a modest reduction in MAP, the high dose of CD-NP increased glomerular filtration rate (GFR; from 37 to 55 ml/min; $p < 0.05$), natriuresis (urinary sodium excretion increased from 48 to 462 μEq/min; $p < 0.05$) and diuresis (urine flow increased from 0.7 to 1.7 ml/min; $p < 0.05$), and decreased proximal and distal fractional sodium reabsorption without changes in renal blood flow (from 240 to 253 ml/min). The medium and high doses of CD-NP increased both plasma and urinary cGMP ($p < 0.05$ from baseline), whereas the medium and low doses of CD-NP reduced plasma renin activity ($p < 0.05$). Renal parameters and cGMP changes returned towards baseline during recovery from CD-NP application [1046049], [1046052]. When these effects of CD-NP were directly compared with BNP, CD-NP (50 ng/kg/min) increased GFR whereas an equimolar dose of BNP had no effect ($p < 0.05$ between groups). Notably, CD-NP was less hypotensive than BNP ($p < 0.05$ between groups) [736656], [1046050], [1046052], [1046070]. Interestingly, the 15-amino acid DNP tail peptide was able to induce significant natriuretic and diuretic responses in this canine model, which was attributed to a reduction in proximal fractional sodium reabsorption in the kidneys [1046052].

A similar study investigated the hemodynamic, renal and hormonal parameters at four time points (pre-infusion [baseline], 30- and 60-min during infusion and post-infusion) in anesthetized dogs administered with CD-NP (50 ng/kg/min, iv 75-min infusion) or an equimolar dose of CNP (29.3 ng/kg/min, iv 75-min infusion) [848713], [1068686]. The effects of CD-NP were maximal at the 60-min infusion time point and were returning towards baseline at post-infusion. At the maximal-effect time point, CD-NP significantly ($p < 0.001$) increased plasma cGMP, urinary cGMP excretion and urine sodium excretion compared with CNP. In the hemodynamic analysis, the effects of CD-NP in reducing PCWP, RAP and pulmonary arterial pressure were more pronounced than with CNP. Mean blood pressure was unchanged in either group [848713]. In an analysis of the renin-angiotensin-aldosterone system (an important regulator of blood pressure), CD-NP (at 60-min during infusion) significantly suppressed plasma renin activity (from 6.1 at baseline to 1.1 ng/ml/h; $p < 0.01$) and angiotensin II levels (from 16.6 to 4.4 pg/ml; $p < 0.01$) compared with modest decreases observed with CNP (from 3.9 to 3.4 ng/ml/h and 16.4 to 14.1 pg/ml, respectively). CD-NP non-significantly

reduced plasma aldosterone levels from baseline (21.6 to 14.3 ng/dl), whereas there was no decrease with CNP (18.7 to 26.7 ng/dl) [1068686].

The ability of CD-NP (100 ng/kg/min, iv) to induce cardiac unloading, natriuresis, diuresis and enhance GFR was evaluated in a canine model of chronic HF induced by rapid ventricular pacing [1046062]. All parameters improved (p < 0.05) from baseline. Specifically, CD-NP decreased RAP (from 3 at baseline to 2 mmHg) and PCWP (from 11 to 9 mmHg) along with a modest reduction in MAP (109 to 100 mmHg). GFR (from 30 to 54 ml/min) and renal blood flow (185 to 226 ml/min) were both increased in conjunction with a significant natriuretic (urinary sodium excretion increased from 5.2 to 96 μEq/min) and diuretic (urine flow increased from 0.1 to 1.3 ml/min) response. These effects of CD-NP occurred in association with increases in plasma (from 16 to 36 pmol/ml) and urine (no data available) cGMP and a reduction in plasma renin activity (from 17 to 5 ng/ml/h) [1046062].

Finally, CD-NP (dose unspecified, osmotic pump for 2 weeks) was also studied in a rat model of myocardial infarction induced by coronary artery ligation [1046057]. Myocardial infarction decreases ejection fraction, increases left ventricular mass and increases collagen content in the myocardium. At 3 weeks post-infarction, aldosterone (15 versus 39.4 dl/ml with vehicle control; p = 0.036) and heart weight/body weight ratio (p < 0.0005 versus control) were reduced, while MAP (105 versus 92 mmHg; p = 0.0047) and renal blood flow (7.0 versus 4.8 ml/min; p = 0.0443) were increased in the CD-NP-treated group compared with vehicle controls. Furthermore, the CD-NP group displayed lower collagen content in the left ventricle (3.5 versus 5.0%; p < 0.05) as well as in the renal cortex (1.3 versus 3.5%; p = 0.002) and medulla (1.2 versus 19.0%; p = 0.0006). Proteinuria was also reduced by CD-NP treatment (2.5 versus 9.6 mg/day; p < 0.0001), while ejection fraction, GFR, diuresis and natriuresis were similar between groups [1046057].

Toxicity
No toxicity data had been reported from the preclinical studies of CD-NP at the time of publication.

Metabolism and pharmacokinetics
At the time of publication, the $t_{1/2}$ of CD-NP had not been reported, but it was presumed to be longer than CNP, which had a $t_{1/2}$ of approximately 2.5 min [1068635]. CNP has no C-terminal extension and is the NP that is most susceptible to degradation by NEP, whereas DNP, which has the longest C-terminal extension, has been identified to be resistant, or even insensitive, to degradation by NEP [467671]. Accordingly, it has been suggested that the presence of a long C-terminal extension will make CD-NP less prone to being metabolized and increase its $t_{1/2}$ [1046052].

Interestingly, infusion of CD-NP can alter circulating levels of endogenous NPs. For example, CD-NP increased circulating BNP during infusion when compared with CNP (40 versus 18 pg/ml; p < 0.001) in anesthetized dogs [848713], [1068686]. The greater increase in BNP following CD-NP infusion strongly supports a longer $t_{1/2}$ for CD-NP when compared with CNP. Definitive measurements of CD-NP $t_{1/2}$ are needed.

Clinical development
Phase I
A phase I, first-in-human, dose-escalation clinical trial (NCT00482937; NIL-CDNP-CT001) evaluated the effects of increasing doses of CD-NP (iv 4-h infusion) in healthy volunteers (n = 22) [1046054], [1046059]. The trial consisted of two stages: an open-label, ascending-dose arm (stage 1) to determine the MTD of CD-NP, and a randomized, double-blind, placebo-controlled arm (stage 2) to investigate the effects of CD-NP on cGMP production, MAP and renal function. Stage 1 dosing was originally scheduled to ascend from 10 to 300 ng/kg/min with dose escalation to stop if predetermined events took place, including the development of clinically significant hypotension or the occurrence of arrhythmias. Volunteers (three cohorts of four participants each) were treated with 10 and 25 ng/kg/min before a dose of 17.5 ng/kg/min was tested and determined to be the MTD (see *Side effects and contraindications* section for further details) [1046059].

In stage 2 of the trial, an additional 10 volunteers were randomized to receive CD-NP (17.5 ng/kg/min; n = 6) or placebo (n = 4) [1046054], [1046059]. CD-NP increased plasma cGMP (~ 7-fold from baseline; p < 0.01), urine cGMP (~ 2-fold from baseline; p < 0.01) and urinary sodium excretion (~ 2-fold from baseline; p < 0.05) in association with an increase in urine flow (increase in mean urine flow 1.2 ml/min; p < 0.05 from baseline), while no response was observed in all parameters in the placebo cohort. A small reduction in MAP (from 85 to 82 mmHg; p < 0.05 from baseline) was observed in the CD-NP group, but GFR was not significantly altered (mean increase of 2 ml/min from baseline); both parameters did not differ from placebo. CD-NP significantly suppressed mean aldosterone levels in the plasma compared with baseline (from 21.9 to 9.5 ng/dl; p < 0.001), whereas the change with placebo was non-significant (from 20.3 to 13.6 ng/dl). Mean plasma angiotensin II levels were not significantly altered from baseline, although there were trends towards decreases in both CD-NP (from 29.2 to 23.0 ng/l) and placebo (23.3 to 19.8 ng/l) groups [1046078]. Intriguingly, CD-NP was also demonstrated to increase heart rate by 25 to 30% from baseline levels; the significance of this change was still under investigation at the time of publication [1046059].

A phase Ib, non-randomized, open-label, uncontrolled, multicenter, ascending-dose clinical trial (NCT00557661; NIL-CDNP-CT002) evaluated the effects of CD-NP (3 to 30 ng/kg/min, iv 24-h infusion) in patients (n = 20)

diagnosed with congestive HF (left ventricular ejection fraction [LVEF] ≤ 40% and New York Heart Association [NYHA] functional class II or III) within 6 months prior to enrolment. A dose of 20 ng/kg/min was the MTD [969577], [1046061].

At doses of 3, 10 and 20 ng/kg/min, CD-NP reduced MAP by a mean of 2.2, 8.9 and 13.2 mmHg, respectively, from baseline. At the same respective doses, treatment with CD-NP reduced serum creatinine (a biomarker of renal function) levels by 10, 10 and 7% from baseline levels, which correlated with significant increases in creatinine clearance: 10 (p = 0.01), 9 (p = 0.02) and 7% increase compared with baseline. In addition, levels of cystatin C (another biomarker of renal function) were also significantly reduced from baseline: 5 (p = 0.05), 9 (p = 0.05) and 4% reductions at 3, 10 and 20 ng/kg/min, respectively. The effect of CD-NP on diuresis was similar to that observed with furosemide, a common diuretic used frequently in the management of HF patients. The average total urine volume during the 3-, 10- and 20-ng/kg/min infusions of CD-NP was 2738 ml. By comparison, during the 24-h period prior to CD-NP infusion, in which patients received standard doses of furosemide, the average total urine volume was 2217 ml [969577], [1046061].

At the time of publication, a phase Ib, double-blind, placebo-controlled, single-center clinical trial (NCT00620308; 07-005523) assessing the effects of CD-NP (20 ng/kg/min plus another dose level yet to be disclosed, iv 4-h infusion) in patients (expected n = 27) with stable chronic HF (LVEF ≤ 40% documented within the last 2 years, and NYHA functional class I to III symptoms) was recruiting participants. The primary endpoint of the trial was to evaluate the renal, neurohumoral and non-invasive hemodynamic physiologic parameters within the first 24 to 36 h post-treatment and at follow-up visits on days 9 and 30 [929697].

Phase II

A phase IIa, open-label, ascending-dose, sequential-group, multicenter clinical trial (NCT00699712; NIL-CDNP-CT003) evaluated CD-NP (3 and 10 ng/kg/min plus two higher doses undisclosed at the time of publication, iv 8-h infusion) in patients (expected total n = 30) with stabilized acute HF, receiving standard-of-care HF medications. In interim data from the first cohort, 11 patients were administered 3 ng/kg/min CD-NP followed by a 14-h washout period before receiving a 10 ng/kg/min infusion [952085].

At 8 h post-infusion, 3 ng/kg/min of CD-NP reduced PCWP by 2.9 mmHg from baseline (p = 0.02). PCWP was further reduced after the 10-ng/kg/min infusion following the washout period, achieving statistical significance (p = 0.02) by 2 h post-infusion. In patients who completed both doses of CD-NP (n = 9), there was a significant overall reduction in PCWP of 5.4 mmHg (p = 0.002) from baseline. A trend toward decreasing RAP and increasing

cardiac output was also reported, although data were non-significant. CD-NP dose-dependently increased urine outflow, with urine output of 48 and 93 ml/h during the 3- and 10-ng/kg/min infusions, respectively (both p = 0.01 from the pre-dose baseline period). There was no effect on serum creatinine levels during the infusion periods [952085].

At the time of publication, a phase II, randomized, single-blind, placebo-controlled, parallel-assignment, multicenter clinical trial (NCT00839007; NIL-CDNP-CT005) of CD-NP (three doses undisclosed at the time of publication, iv 72-h infusion) was recruiting patients (expected n = 40) with acute decompensated HF and renal insufficiency. Endpoints included safety and tolerability, symptom relief and assessment of biomarkers of HF and renal function [1030977].

Side effects and contraindications

In the dose-escalating stage of the first-in-human phase I clinical trial, CD-NP was well tolerated without serious side effects [1046059]. At a dose of 25 ng/kg/min, two out of four volunteers developed symptomatic hypotension after a diuretic response. Additional adverse events documented at this dose of CD-NP were flushing, dizziness, tachycardia, paresthesia and dyspnea. These events generally occurred transiently. Measurements of anti-CD-NP and CD-NP antibodies suggested immunogenicity was not an issue. In stage 2 of this trial, three out of six volunteers receiving the predetermined MTD of CD-NP (17.5 ng/kg/min) developed asymptomatic orthostatic hypotension [1046059].

CD-NP was reported to be well-tolerated at doses up to 20 ng/kg/min in the phase Ib clinical trial in patients with congestive HF. As in the first-in-human trial, dose escalation in this trial was limited by symptoms of hypotension, which were observed at a dose of 30 ng/kg/min [969577]. In the phase IIa clinical trial, no hypotension or clinically significant blood pressure reductions had been observed in patients receiving up to 10 ng/kg/min CD-NP [952085].

Patent summary

Ondrej Lisy and John C Burnett of the Mayo Foundation claimed the chimeric NPs BD-NP (Mayo Foundation) and CD-NP in the international patent application WO-00144284. Corresponding granted US patents US-06407211 and US-07384917 are both due to expire in December 2019, while US-06818619 has been extended under US154 to July 2020; the granted European equivalent patent, EP-01242452, will expire in December 2020.

In June 2009, Lisy and Burnett claimed the use of chimeric natriuretic polypeptides for inhibiting cardiac remodeling, with particular emphasis on CD-NP, in WO-2009149161. At the time of publication, regional patents for this application were pending grant.

Current opinion

The use of NPs for the therapeutic treatment of HF holds great promise. The expression of all NPs is significantly upregulated in HF and animal studies have confirmed that this is a compensatory, protective response [1068597]. In fact, quantifying the circulating levels of BNP has prognostic and diagnostic value when assessing the progression of heart disease [1068689]. Although considered to be cardioprotective, the increase of NPs in HF is commonly characterized by altered NP function as a consequence of changes in biological activity and increased renal resistance to NPs [1068690], [1068691]. Such findings form a strong basis for the development and use of exogenous NPs in the treatment of HF patients.

The approval of nesiritide for the treatment of acute decompensated HF was based on initial clinical trials demonstrating that exogenous BNP application improved ventricular function in HF patients [456352]; however, as discussed above, nesiritide has since been associated with a significant hypotensive response. The novel design of CD-NP was developed to circumvent this induction of hypotension. The use of CNP as the backbone of CD-NP is logical for a number of reasons. As outlined above, CNP more effectively relaxes veins compared with arteries and also exhibits the most potent antifibrotic effects within the NP family. Also of potential importance is a recent report demonstrating that a significant portion of the cGMP produced in normal and failing hearts is the result of NPR-B activation [1068692]. Because CD-NP activates both NPR-A and NPR-B, this synthetic peptide may augment cGMP production more effectively than compounds such as nesiritide, which only increases cGMP via NPR-A activation. Although CNP itself does not have significant renal-enhancing properties, the addition of the 15-amino acid DNP C-terminal tail appears to confer this important property to CD-NP. Therefore, CD-NP is a multifunctional peptide that elicits its effects by binding to all NPRs.

Some questions remain regarding the effects and mechanisms of action of CD-NP. For example, in phase I clinical trials, it was noted that a modest level of hypotension did occur upon administration of CD-NP, albeit much less than BNP [1046059]. Furthermore, 50% of patients receiving the MTD of CD-NP developed asymptomatic orthostatic hypotension. This hypotension was attributed to a reduction in intravascular volume downstream of the natriuretic/diuretic effects of CD-NP; however, the possible role of venodilation and/or vasodilation in this effect should be determined. Although it is thought that CNP preferentially relaxes veins, studies have documented the ability of CNP to dilate coronary arteries [1068693], possibly by activating the NPR-C receptor [1068695], [1068696]. Therefore, studies directly evaluating the effects of CD-NP on isolated arteries from different vascular beds and vascular smooth muscle cells are warranted.

Phase I clinical trials also documented an increase in heart rate following administration of CD-NP [1046059]. Heart rate is a major determinant of cardiac output and pump function and the increase in heart rate may serve to maintain cardiac output, or prevent it from decreasing too profoundly, when stroke volume is altered following a change in cardiac loading conditions. CNP can affect heart rate by altering ionic currents in the sinoatrial node in a mouse model [1068699], which could increase myocardial perfusion in conjunction with the effect on coronary artery tone mentioned previously. Whether CD-NP causes coronary artery dilation and/or alters myocardial perfusion is not known and should be investigated.

Additional clarification of the effects of the C-terminal DNP extension is also needed. Specifically, it is unclear why infusion of the 15-amino acid tail of DNP on its own induced natriuretic and diuretic effects in the dog [1046052], but does not appear to bind to or activate any NPR [1068653]. It has been suggested that the DNP C-terminal tail peptide may interfere with the ability of NEP to degrade NPs, but this has not been tested and should be clarified.

Finally, some of the *in vitro* effects of CD-NP, particularly the positive effects on cardiac fibrosis demonstrated in human cardiac fibroblasts, remain to be validated in humans *in vivo*. Although these anti-fibrotic effects are very exciting, it is possible that CD-NP will not be as effective in humans who may not receive prolonged continuous CD-NP intravenous infusion, particularly if they are not admitted to a hospital. Indeed, the issue of CD-NP administration methods and protocols is an important one. It is unknown whether CD-NP will be promoted for outpatient use, as has been suggested for nesiritide. The effects of CD-NP should be directly compared with nesiritide in human trials because both drugs target a similar patient population. This would permit a more rigorous assessment of the hemodynamic effects of CD-NP in comparison with BNP.

Overall, the available data from animal studies and small phase I and II clinical trials support the assertion that CD-NP elicits beneficial hemodynamic and renal effects, with only minor coincident hypotension. Furthermore, the peptide appears safe and without serious complications when used at appropriate doses. Phase II trials in patients with stable acute HF and acute decompensated HF are currently ongoing or recruiting participants. The results of these clinical trials are needed in order to progress towards larger phase III trials and to establish the utility of this promising HF treatment.

Deals
Nile Therapeutics Inc
By May 2007, Nile Therapeutics was developing CD-NP, which was identified at the Mayo Foundation for Medical Education and Research [800883].

Development status

Developer	Country	Status	Indication	Date	Reference
Nile Therapeutics Inc	Russian Federation	Phase II	Cardiac failure	11-JUL-08	924778
Nile Therapeutics Inc	US	Phase II	Cardiac failure	04-AUG-09	1030977
Nile Therapeutics Inc	Germany	Phase II	Cardiac failure	04-AUG-09	1030977
Nile Therapeutics Inc	Israel	Phase II	Cardiac failure	04-AUG-09	1030977
Mayo Foundation	US	Discontinued	Cardiac failure	31-MAY-07	800883

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Inventors Simari RD, Pan S, Burnett JC, Chen HH.

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