A First-in-Human Study of AMG 986, a Novel Apelin Receptor Agonist, in Healthy Subjects and Heart Failure Patients

Winkle, Peter; Goldsmith, Steven; Koren, Michael J.; Lepage, Serge; Hellawell, Jennifer; Trivedi, Ashit; Tsirtsonis, Kate; Abbasi, Siddique A.; Kaufman, Allegra; Troughton, Richard

Published in:
Cardiovascular Drugs and Therapy

DOI:
10.1007/s10557-022-07328-w

Publication date:
2023

Cardiovascular Drugs and Therapy (2023) 37:743–755
https://doi.org/10.1007/s10557-022-07328-w

ORIGINAL ARTICLE

A First-in-Human Study of AMG 986, a Novel Apelin Receptor Agonist, in Healthy Subjects and Heart Failure Patients

Peter Winkle[1] · Steven Goldsmith[2] · Michael J. Koren[3] · Serge Lepage[4] · Jennifer Hellawell[5] · Ashit Trivedi[6] · Kate Tsirtsonis[7] · Siddique A. Abbasi[6] · Allegra Kaufman[6] · Richard Troughton[8] · Adriaan Voors[9] · Jean-Sebastien Hulot[10,11] · Erwan Donal[12] · Navid Kazemi[13] · Joel Neutel[14]

Accepted: 13 February 2022 / Published online: 23 April 2022

Abstract

Purpose AMG 986 is a novel apelin receptor (APJ) agonist that improves cardiac contractility in animal models without adversely impacting hemodynamics. This phase 1b study evaluated the safety/tolerability, pharmacokinetics, and pharmacodynamics of AMG 986 in healthy subjects and patients with heart failure (HF).

Methods Healthy adults (Parts A/B) and HF patients (Part C) aged 18–85 years were randomized 3:1 to single-dose oral/IV AMG 986 or placebo (Part A); multiple-dose oral/IV AMG 986 or placebo (Part B); or escalating-dose oral AMG 986 or placebo (Part C). Primary endpoint: treatment-emergent adverse events, laboratory values/vital signs/ECGs; others included AMG 986 pharmacokinetics, left ventricular (LV) function.

Results Overall, 182 subjects were randomized (AMG 986/healthy: $n=116$, placebo, $n=38$; AMG 986/HF: $n=20$, placebo, $n=8$). AMG 986 had acceptable safety profile; no clinically significant dose-related impact on safety parameters up to 650 mg/day was observed. AMG 986 exposures increased nonlinearly with increasing doses; minimal accumulation was observed. In HF with reduced ejection fraction patients, there were numerical increases in percent changes from baseline in LV ejection fraction and stroke volume by volumetric assessment with AMG 986 vs placebo (stroke volume increase not recapitulated by Doppler).

Conclusions In healthy subjects and HF patients, short-term AMG 986 treatment was well tolerated. Consistent with this observation, clinically meaningful pharmacodynamic effects in HF patients were not observed. Changes in ejection fraction and stroke volume in HF patients suggest additional studies may be needed to better define the clinical utility and optimal dosing for this molecule.

Trial Registration Number ClinicalTrials.gov NCT03276728.

Date of Registration September 8, 2017

Keywords AMG 986 · Heart failure · Apelin receptor agonist

Introduction

Heart failure (HF) is a common and debilitating disease, affecting an estimated 6.2 million US adults or ~ 2% of the US population [1]. Over the past several decades, a number of interventions designed to improve morbidity and mortality in HF have shown some success in reducing hospitalization rates and/or mortality in HF patients with reduced ejection fraction (HFrEF), including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, aldosterone antagonists, the angiotensin receptor-neprilysin inhibitor sacubitril, sodium-glucose cotransporter 2 inhibitors, the soluble guanylate cyclase stimulator vericiguat, the myosin activator omecamtiv mecarbil, the hyperpolarization-activated cyclic nucleotide–gated channel blocker ivabradine, and cardiac resynchronization [2–8]; however, morbidity and mortality rates remain high. In addition, available treatments are aimed at a diverse array of targets and often fail to control symptoms or restore quality of life, and until recently the subcategory of HF patients with preserved EF (HFpEF) has not been shown to derive clinical benefit

✉ Jennifer Hellawell
jhellawe@amgen.com

Extended author information available on the last page of the article

from available therapies, possibly due to the relative clinical heterogeneity of this population [6, 9–11].

The apelin receptor (APJ) is a member of the G protein–coupled receptor gene family that binds the apelin and ELABELA/Toddler/Apela (ELA) ligands and shares significant homology with the angiotensin II type 1 receptor [12–14]. APJ is ubiquitously expressed in endothelial and smooth muscle cells of the coronary and pulmonary vasculature as well as in the myocardium [15], and its expression is induced by a variety of pathophysiologic mechanisms in HF, including hypoxia, hyperreninemia, myocyte stretch, and hypoosmolality [16–18]. In preclinical models, the apelin-APJ axis negatively regulates angiotensin II-angiotensin II type I receptor (AT1R) action on vascular tone, leading to vasorelaxation, and also promotes cardiac contractility and aquaresis, attenuates ischemic injury, and contributes to neovascularization [19–24]. The amounts of AT1R, apelin/APJ, and its downstream plasminogen activator inhibitor-1 (PAI-1) are also thought to contribute to PAI-1-mediated thrombosis in patients with atrial fibrillation [25].

Additional preclinical data suggest that apelin may also be an attractive therapeutic target in other disease states that are often comorbid with HF, including age-associated sarcopenia and diabetes [26, 27]. Expression of APJ appears to be dynamic as HF progresses based on observations from nonclinical and clinical studies, which show that APJ is initially elevated in association with myocardial ischemia or HF, but decreased in advanced left ventricular (LV) hypertrophy and systolic dysfunction [28]. Furthermore, in a large transcriptional profiling study of patients with end-stage HF who underwent placement of LV assist devices and experienced myocardial recovery, APJ was the most significantly upregulated gene [29] and has thus been heralded as inducing "reverse heart failure."

Consistent with these observations, short-term IV administration of Pyr1(apelin)-13 has been shown to improve cardiac function acutely in murine and rodent models of HF, and in patients with HF [30–32]. More recently, short-term APJ agonism via IV administration of Pyr1(apelin)-13 during right heart catheterization has been reported to cause a reduction in pulmonary vascular resistance and concordant increase in cardiac output in patients with pulmonary arterial hypertension (PAH) [33–35]. Despite these observed salutary effects of IV apelin administration in both acute HF and PAH, the short half-life of apelin has historically restricted its use to infusion therapy. As new, longer half-life apelin analogs become available, it will be important to understand the effects of more prolonged APJ receptor occupancy and the resulting impact on designing optimal dosing paradigms.

AMG 986 is a first-in-class, novel, long-acting, small-molecule APJ agonist that binds APJ, and activates Gαi and β-arrestin with sub-nM potency [36]. The cardiovascular effects of AMG 986 in vivo have been studied in both rodent and canine models. In the ZSF1 rat (a model reproducing HFpEF), AMG 986 increased cardiac contractile reserve, EF, and stroke volume. Improvements in ventriculoarterial coupling were also observed in ZSF1 rats. In a canine HFrEF model (tachypacing), AMG 986 improved LV contractile function without affecting the heart rate. These preclinical findings support the hypothesis that AMG 986 would be beneficial in addressing the underlying pathophysiology of HF in patients with HFrEF or HFpEF. We conducted a phase 1b trial of AMG 986 in healthy subjects and patients with HF to assess its safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD).

Results

Subject Disposition

Subjects were enrolled at 13 study centers in 7 countries (Canada, France, Netherlands, New Zealand, Poland, Singapore, and the USA), and the study was conducted between August 2016 (first patient enrolled) and April 2019 (final patient follow-up). Overall, 88 healthy subjects were enrolled in Part A (22 and 66 in the pooled placebo group and pooled AMG 986 groups, respectively), 66 healthy subjects were enrolled in Part B (16 and 50 in the pooled placebo and pooled AMG 986 groups, respectively), and 28 patients with HF were enrolled in Part C (24 and 4 in the HFrEF and HFpEF groups, respectively). Further details regarding subject disposition are provided in Fig. 1. The study was terminated early and not all protocol-specified analyses were conducted, though no safety signals of concern were noted throughout the study.

Demographic and Baseline Characteristics

Demographic and baseline clinical characteristics were well balanced across treatment groups in each of the 3 parts of the study and are summarized in Table 1.

Safety

No dose-limiting toxicities were observed in the study and there were no treatment-related trends observed in treatment-emergent adverse events (TEAEs) overall. Most TEAEs were reported as mild or moderate across both the AMG 986 and placebo groups. In Part A, 3 of 22 subjects (13.6%) in the pooled placebo group and 11 of 66 (16.7%) in the pooled AMG 986 group experienced TEAEs (Table 2). In Part B, 2 of 16 subjects (12.5%) in the pooled placebo group and 7 of 50 (14.0%) in the pooled AMG 986 group had TEAEs. Among patients with HFrEF

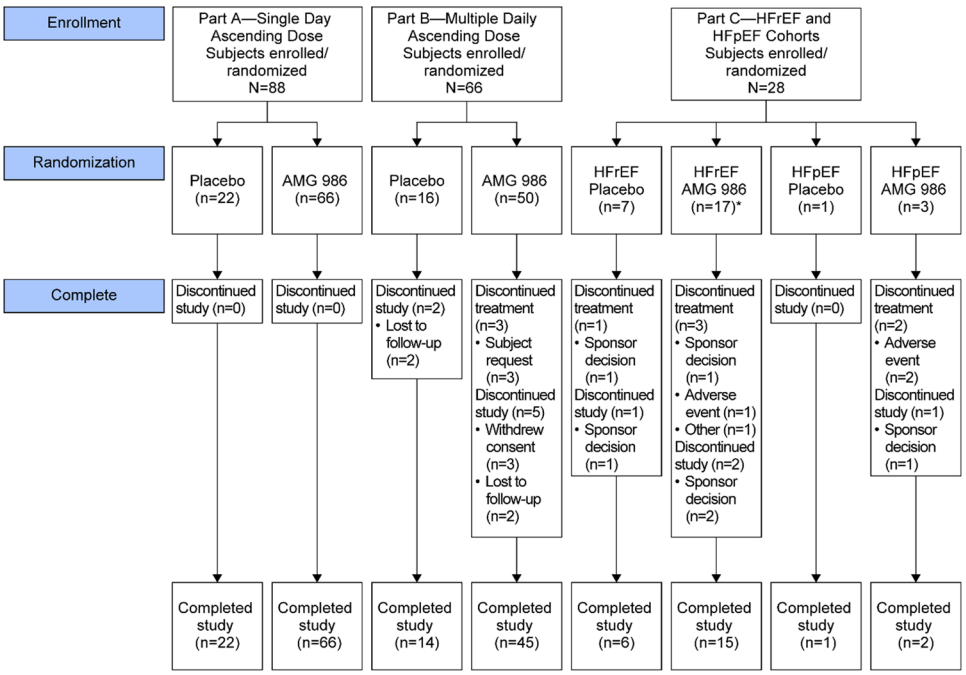

Fig. 1 Subject disposition in Parts A, B, and C (all enrolled subjects). *One of the 17 patients did not receive AMG 986. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; *N*, number of subjects in the analysis set; *n*, number of subjects with observed data

in Part C (Table 2), 2 of 7 patients (28.6%) in the placebo group and 6 of 16 (37.5%) in the AMG 986 group had TEAEs; 1 of 16 patients (6.3%) in the AMG 986 group had a TEAE of decreased white blood cell count, leading to withdrawal of AMG 986. This event was not associated with any additional safety findings, spontaneously resolved, and was deemed by the treating investigator to be unrelated to study treatment. Among patients with HFpEF in Part C, all 4 patients (1 in the placebo group and 3 in the AMG 986 group) had TEAEs (1 event each); 2 patients (66.7%) in the AMG 986 group had TEAEs (asthenia and pleuritic pain in 1 patient each) leading to withdrawal of AMG 986. The case of pleuritic pain, reported in a woman aged 70 years treated with AMG 986 (treatment assignment was unblinded in safety assessment) for 3 days, was categorized as a serious TEAE (Common Terminology Criteria for Adverse Events [CTCAE] grade 3). The event spontaneously resolved and was deemed by the treating investigator to be unrelated to the study treatment. No dose-related pattern in TEAEs was observed. No deaths were reported. Overall, AMG 986 had an acceptable safety profile, with the most common TEAEs being headache (reported in 5% of subjects), nausea (3%), dizziness (2%), and vomiting (2%). The corresponding values in the placebo group were 1 subject each for headache and dizziness (2%) and zero patients for nausea and vomiting. No notable differences between treatment groups were observed for vital signs or laboratory parameters (including standard parameters of renal function, chemistries, hematology, and coagulation).

PK Evaluation

The PK analysis set comprised AMG 986 plasma and urine samples from 144 subjects. In the IV single-daily ascending-dose (SAD) cohorts (Part A), mean drug C_{max} increased from 65 to 9580 ng/mL with increasing doses from 0.5 mg loading dose 1-h infusion to 60 mg loading dose 1-h infusion plus 360-mg maintenance dose 23-h infusion. In the IV multiple-daily ascending-dose (MAD) cohorts (Part B), mean C_{max} increased from 903 to 7970 ng/mL with increasing doses from 156 to 1548 mg over a total infusion of 96 h.

PK analysis revealed that across all per oral (PO) dosing cohorts, mean AMG 986 C_{max} increased from 334 to 18,400 ng/mL with increasing doses from 5 to 650 mg in SAD cohorts (Table 3). The time to reach maximal concentration (t_{max}) ranged from 1 to 2 h with no apparent dose-related trend, and terminal half-life ranged from 13.2 h (5-mg dose) to 21.0 h (650-mg dose), although there was no clear dose-related trend. Mean C_{max} increased from 407 to 22,300 ng/mL with increasing doses from 5 to 650 mg in MAD cohorts at day 7 (Table 4), and t_{max} ranged from 1 to 2 h with no apparent dose-related trend. Mean bioavailability decreased from 78 to 42% with increasing SAD doses from 5 to 650 mg. Repeated once-daily dosing resulted in minimal accumulation across dose groups. In patients with HF (Part C), mean AMG 986 C_{max} increased from 1030 to 7680 ng/mL with increasing doses from 10 to 100 mg (Table 5).

Dedicated clinical pharmacology studies were also conducted to evaluate the PK of AMG 986 in subjects with severe renal impairment, and to determine drug-drug interaction with a potent CYP3A4 and P-gp inhibitor

Table 1 Baseline demographic and clinical characteristics for Parts A, B, and C

	Part A			Part B		
	Placebo pooled (*N* = 22)	AMG 986 pooled (*N* = 66)	All subjects (*N* = 88)	Placebo pooled (*N* = 16)	AMG 986 pooled (*N* = 50)	All subjects (*N* = 66)
Men, *n* (%)	22 (100)	59 (89.4)	81 (92.0)	16 (100)	49 (98.0)	65 (98.5)
Ethnicity, *n* (%)						
Hispanic/Latino	6 (27.3)	22 (33.3)	28 (31.8)	1 (6.3)	5 (10.0)	6 (9.1)
Not Hispanic/Latino	16 (72.7)	44 (66.7)	60 (68.2)	15 (93.8)	45 (90.0)	60 (90.9)
Race, *n* (%)						
Asian	3 (13.6)	6 (9.1)	9 (10.2)	6 (37.5)	11 (22.0)	17 (25.8)
Black	5 (22.7)	16 (24.2)	21 (23.9)	5 (31.3)	17 (34.0)	22 (33.3)
Native Hawaiian/other Pacific Islander	0	0	0	0	1 (2.0)	1 (1.5)
White	11 (50.0)	35 (53.0)	46 (52.3)	5 (31.3)	18 (36.0)	23 (34.8)
Other	1 (4.5)	8 (12.1)	9 (10.2)	0	3 (6.0)	3 (4.5)
Mean (SD) age, y	37.2 (9.4)	39.5 (9.8)	38.9 (9.7)	36.9 (10.0)	37.4 (9.8)	37.3 (9.8)
Mean (SD) weight, kg	83.1 (13.2)	81.4 (11.9)	81.8 (12.2)	81.5 (12.6)	79.4 (12.7)	79.9 (12.6)
Mean (SD) height, cm	176.21 (7.15)	174.10 (8.04)	174.63 (7.84)	177.43 (7.86)	176.76 (8.24)	176.92 (8.09)
Mean (SD) BMI, kg/m^2	26.66 (3.43)	26.83 (2.89)	26.78 (3.01)	25.68 (3.12)	25.32 (3.28)	25.40 (3.22)
Part C	Placebo PO		AMG 986 10 + 30 + 100 mg PO		All patients	
	HFrEF (*N* = 7)	HFpEF (*N* = 1)	HFrEF (*N* = 16)	HFpEF (*N* = 3)	HFrEF (*N* = 23)	HFpEF (*N* = 4)
Men, *n* (%)	4 (57.1)	0	13 (81.3)	1 (33.3)	17 (73.9)	1 (25.0)
Ethnicity, n (%)						
Hispanic/Latino	1 (14.3)	0	0	0	1 (4.3)	0
Not Hispanic/Latino	6 (85.7)	1 (100)	16 (100)	2 (66.7)	22 (95.7)	3 (75.0)
Race, *n* (%)						
Asian	2 (28.6)	0	2 (12.5)	0	4 (17.4)	0
Black	2 (28.6)	0	6 (37.5)	2 (66.7)	8 (34.8)	2 (50.0)
White	3 (42.9)	1 (100)	8 (50.0)	0	11 (47.8)	1 (25.0)
Other	0	0	0	1 (33.3)	0	1 (25.0)
Mean (SD) age, years	61.6 (10.1)	73.0 (NA)	65.4 (6.4)	69.0 (1.0)	64.3 (7.7)	70.0 (2.2)
Mean (SD) weight, kg	88.8 (2.8)	79.0 (NA)	83.7 (13.1)	82.9 (11.0)	85.3 (11.2)	81.9 (9.2)
Mean (SD) height, cm	168.26 (5.17)	162.50 (NA)	169.44 (7.82)	162.00 (9.54)	169.08 (7.02)	162.13 (7.79)
Mean (SD) BMI, kg/m^2	31.55 (2.53)	29.69 (NA)	29.26 (3.97)	31.83 (3.01)	29.96 (3.70)	31.30 (2.68)
Mean (SD) LVEF, %	33.30 (8.42)	NA	28.38 (6.48)	NA	NA	NA

Per eligibility criteria, all heart failure with reduced ejection fraction (HFrEF) patients were in New York Heart Association class II/III and were treated with stable, optimal HFrEF therapy, including at least a β-blocker and a renin–angiotensin–aldosterone system (RAAS) inhibitor

HFpEF heart failure with preserved ejection fraction; *LVEF* left ventricular ejection fraction; *N* number of subjects in the safety analysis set; *n* number of subjects with observed data; *NA* not available or not applicable; *PO* oral

(itraconazole). The results of these studies demonstrate that AMG 986 PK is similar in healthy subjects and subjects with renal impairment [37]. Furthermore, AMG 986 PK is altered in presence of itraconazole [38]. Collectively, these findings support the enrolment of heart failure patients with renal impairment to clinical trials of AMG 986 without the need for dose adjustments and suggest that potent CYP3A4 inhibitors should be administered with caution in future studies of AMG 986.

PD Evaluation

No PD assessment for apelin-like effects was conducted in the healthy volunteer ascending-dose portions of the study (Parts A and B). No trends were observed in safety measures of blood pressure and heart rate though detailed exposure–response analyses of these data were not performed. The PD evaluation was performed for patients in Part C based on echocardiographic assessments collected on days

Table 2 Summary of treatment-emergent adverse events in Parts A, B, and C

Subjects, *n* (%)	Part A		Part B		Part C			
					Placebo PO		AMG 986 10 + 30 + 100 mg PO	
	Placebo pooled (*N* = 22)	AMG 986 pooled (*N* = 66)	Placebo pooled (*N* = 16)	AMG 986 pooled (*N* = 50)	HFrEF (*N* = 7)	HFpEF (*N* = 1)	HFrEF (*N* = 16)	HFpEF (*N* = 3)
All TEAEs	3 (13.6)	11 (16.7)	2 (12.5)	7 (14.0)	2 (28.6)	1 (100)	6 (37.5)	3 (100)
Serious TEAE	0	0	0	0	0	0	0	1 (33.3)
TEAE leading to discontinuation of AMG 986	0	0	0	0	0	0	1 (6.3)	2 (66.7)
Fatal TEAE	0	0	0	0	0	0	0	0

HFpEF heart failure with preserved ejection fraction; *HFrEF* heart failure with reduced ejection fraction; *N* number of subjects in the safety analysis set (randomized and dosed subjects); *n* number of subjects with observed data; *PO* per oral; *TEAE* treatment-emergent adverse event

Table 3 Mean AMG 986 pharmacokinetic parameter estimates following a single oral administration in healthy subjects: Part A

Mean PK parameter, (% CV)	AMG 986					
	5 mg	30 mg	100 mg	200 mg	400 mg	650 mg
t_{max}, h[A]	1.0	1.5	1.0	2.0	1.5	1.0
C_{max}, ng/mL	334 (22)	1850 (33)	5760 (24)	12,200 (34)	16,200 (33)	18,400 (35)
$t_{½,z}$, h	13.2 (32)	19.9 (65)	17.0 (33)	17.7 (24)	19.7 (49)	21.0 (37)
AUC_{∞}, h • ng/mL	2550 (34)	13,100 (25)	35,400 (5)	88,700 (33)	102,000 (53)	169,000 (61)
F, %	78	63	66	83	42	42

[A]Median values reported

Values are reported to 3 significant figures except for time to maximal concentration (t_{max}), which was rounded to 2 significant figures

AUC_{∞} area under plasma concentration–time curve from time 0 to ∞; *CV* coefficient of variation; *F* bioavailability (average of *F* values calculated against all IV formulations); *h* hour; *PK* pharmacokinetic; $t_{½,z}$ terminal half-life

1, 4, 8, 11, 15, 18, 21, and 30. Mean relative changes from baseline in LVEF and LV stroke volume (method of disks [MoD]/volumetric assessment) were greater in patients with HFrEF receiving AMG 986 versus patients receiving placebo (Figs. 2 and 3). Of note, patients randomized to AMG 986 had a lower baseline mean LVEF than those randomized to placebo (Fig. 4). In individual HFrEF patients, both increases and decreases in LVEF were inconsistently observed in patients randomized to AMG 986 and placebo. In addition, no dose effect during the 2 dose escalations was observed, and mean LVEF did not return to pretreatment levels in the AMG 986-treated group at the day-30 time point, which should have represented a near-complete washout of study drug based on the observed elimination half-life of ~ 18 h. By Doppler assessment, the mean relative change from baseline in LV stroke volume in patients with HFrEF fluctuated above and below 0% over time in patients receiving AMG 986 or placebo (Fig. 5). There were no clear dose-related trends over time, and a high degree of variability was observed. There were no discernible treatment-related differences in selected measures of diastolic function, including left atrial volume indexed, intraventricular relaxation time, and E/e' ratio. LV strain and strain rate were not assessed in this study. Mean levels of N-terminal prohormone B-type natriuretic peptide (NT-proBNP), a biomarker of ventricular wall stress with both diagnostic and prognostic implications in HF, also did not change appreciably over time (Fig. 6).

Discussion

This was a phase 1b study of AMG 986, a first-in-class, novel, small-molecule APJ agonist that has been shown in animal models to bind and activate APJ to improve cardiac contractility without adversely impacting blood pressure and heart rate [36]. Overall, AMG 986 exhibited an acceptable safety and tolerability profile that was similar to that seen in subjects receiving a placebo. There were no deaths in the study.

The PK analysis showed that AMG 986 exposures increased nonlinearly with increasing doses across all dosing cohorts and oral bioavailability was 40–80%. Mean AMG

Table 4 Mean AMG 986 plasma pharmacokinetic parameters following multiple oral administrations in healthy subjects: Part B

Mean PK parameter (% CV)	Day 1						Day 7					
	AMG 986											
	5 mg	30 mg	100 mg	200 mg	400 mg	650 mg	5 mg	30 mg	100 mg	200 mg	400 mg	650 mg
t_{max}, h[A]	2.0	1.0	1.0	1.5	1.5	1.5	2.0	1.5	1.0	1.0	1.0	1.5
C_{max}, ng/mL	368 (19.7)	1990 (17.1)	9550 (27)	9230 (37.6)	17,500 (16.2)	24,000 (37.8)	407 (20.3)	1740 (23.4)	10,100 (34.5)	8300 (36.3)	19,000 (42.0)	22,300 (51.5)
AUC_{24}, h • ng/mL	2490 (27.8)	10,300 (22.4)	54,700 (39.2)	50,700 (17.6)	101,000 (22.8)	112,000 (21.6)	2910 (22.1)	11,200 (25.3)	62,800 (50.6)	50,600 (15.6)	115,000 (31.6)	110,000 (35.7)

[A]Median values reported

Values are reported to 3 significant figures except for time to maximal concentration (t_{max}), which was rounded to 2 significant figures

AUC_{24} area under plasma concentration–time curve from time 0 to 24 h postdose; *CV* coefficient of variation; *h* hour; *PK* pharmacokinetic

986 exposures demonstrated minimal accumulation and a reasonable half-life. Of note, the exposures observed in Part C were equivalent to the predicted EC50 based on the preclinical models.

LVEF and stroke volume (MoD/volumetric assessment) appeared to increase in patients with HFrEF receiving AMG 986 vs placebo and these increases were noted throughout the 3-week dosing period, but there were no consistent differences with respect to LV stroke volume when measured by the Doppler method. The Doppler and volumetric methods of measuring stroke volume have their respective strengths and limitations [39]. While the Doppler method is arguably technically easier and more consistent, a significant error can be introduced to technical issues (e.g., differences in transducer angle and acoustic windows) that are challenging to control in an international phase 1 study conducted across multiple sites. Advantages of volumetric assessment include correcting for shape distortions and less geometrical assumptions; however, apex foreshortening is common, along with endocardial dropout. Because the volumetric assessment of stroke volume is derived from the same volumetric measurements that are used to calculate LVEF, it is perhaps not surprising that this method more closely mirrored the PD effects observed on LVEF. However, the lack of a clear dose–response within the range of doses tested and the inconsistency of findings across the echocardiographic measures explored, as well as the failure to return to baseline levels after washout of AMG 986, raise questions about how to interpret these findings. It is also possible that differences in mean baseline LVEF may have produced a regression artifact that affected the LVEF findings. Generally, despite analyzing these data with the assistance of two independent blinded echocardiography core laboratories, we are unable to definitively explain these discrepancies.

Given the pleiotropic and dynamic effects of apelin modulation observed in preclinical and clinical studies, it is possible that the sample size and duration and modality of dosing may have been insufficient in this study to cause a meaningful and detectable PD effect. Although short-term dynamic effects have previously been described with apelin agonism in similarly sized studies of both HF and pulmonary hypertension, those studies involved treatment with IV infusions of Pyr-apelin-13—the natural ligand of APJ—and not oral formulations like AMG 986 [32, 35].

PK modeling predictions of human maximal AMG 986 exposures at the starting dose of 5 mg were anticipated to approximate the target concentration associated with cardiovascular function improvement in the dog model [36]. Although there was an observed trend of decreasing dose-normalized exposures in MAD groups, the exposures achieved would have been expected to correlate with meaningful PD effects. Moreover, because the role of apelin in HF biology has been observed to be dynamic, it is possible

Table 5 Mean AMG 986 plasma pharmacokinetic parameters following multiple ascending oral doses in patients with heart failure: Part C

Dose	t_{max}, h[A]	C_{max}, ng/mL	$C_{predose}$, ng/mL	$C_{min,24}$, ng/mL	AUC_{24}, h • ng/mL
10 mg	1.0	1030 (36.6)	0.00 (NR)	126 (98.5)	9550 (38.8)
30 mg	2.0	2850 (39.6)	257 (157.0)	343 (76.6)	26,600 (27.1)
100 mg	2.0	7680 (59.8)	941 (129.6)	1290 (126.7)	77,500 (76.4)

[A]Median values reported

Values are reported to 3 significant figures except for time to maximal concentration (t_{max}) and % coefficient of variation (CV), which are presented as 2 significant figures and 1 decimal place, respectively

AUC_{24} area under plasma concentration–time curve from time 0 to 24 h postdose; $C_{min,24}$ concentration at 24 h postdose; $C_{predose}$ predose concentration at days 1 (0 h), 8 (168 h), and 15 (336 h); *h* hours; *NR* not reported

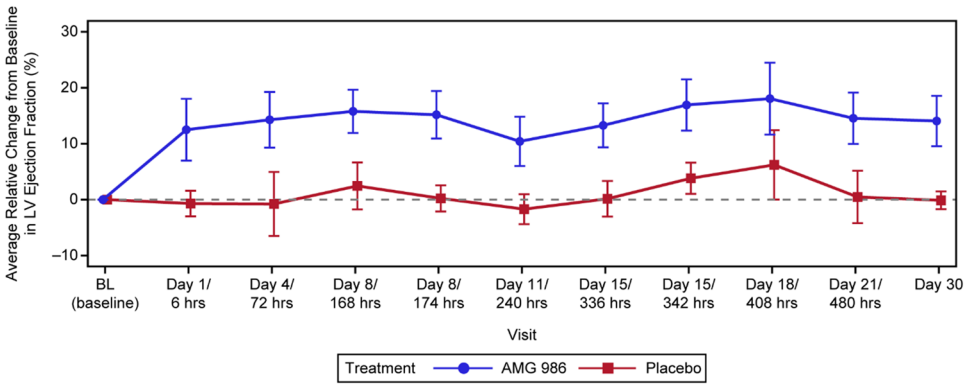

Fig. 2 Mean relative change from baseline in left ventricular (LV) ejection fraction by visit in Part C for the heart failure with reduced ejection fraction (HFrEF) group. Error bars represent ± SEM. hrs, hours

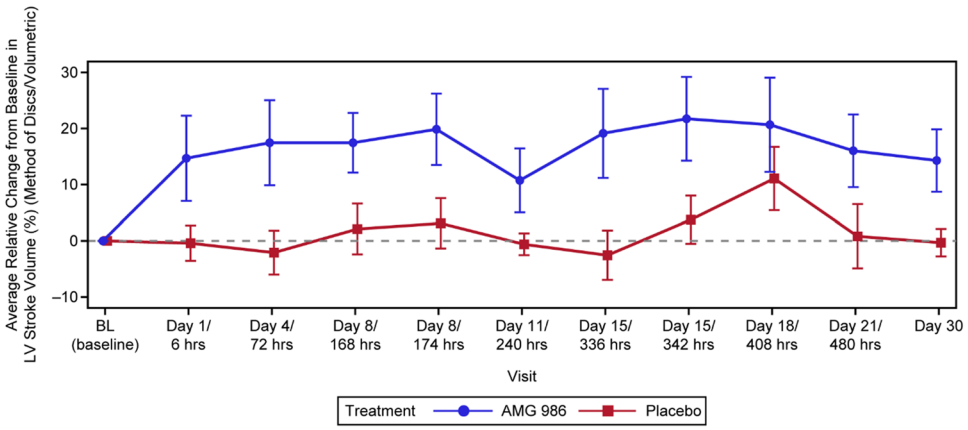

Fig. 3 Mean relative change from baseline in left ventricular (LV) stroke volume (method of disks [MoD]/volumetric assessment) by visit in Part C for the HFrEF (heart failure with reduced ejection fraction) group. Error bars represent ± SEM. hrs, hours

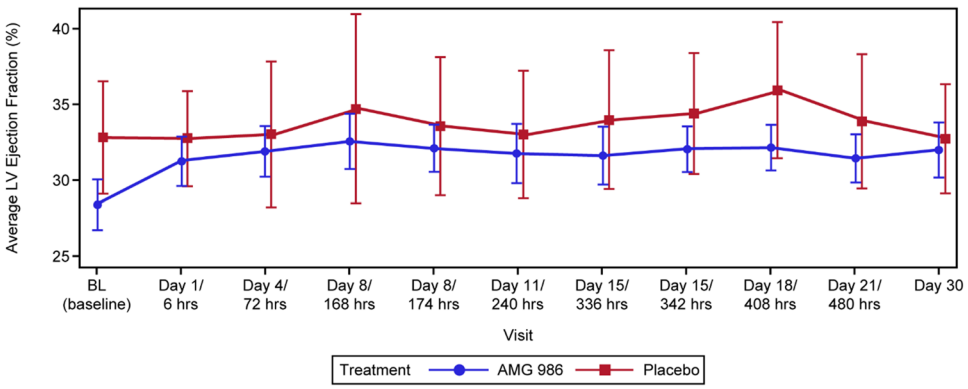

Fig. 4 Mean left ventricular (LV) ejection fraction for the heart failure with reduced ejection fraction (HFrEF) group by visit in Part C. Error bars represent ± SEM. hrs, hours

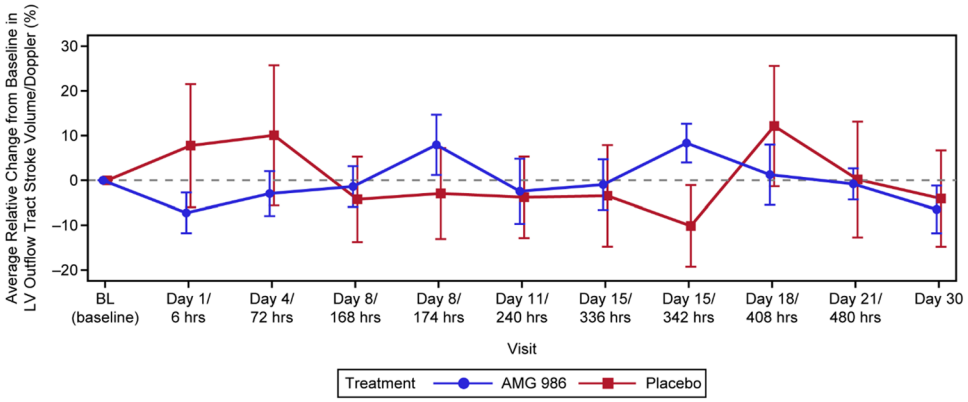

Fig. 5 Mean relative change from baseline in left ventricular (LV) stroke volume (Doppler assessment) by visit in Part C for the heart failure with reduced ejection fraction (HFrEF) group. Error bars represent ± SEM.. hrs, hours

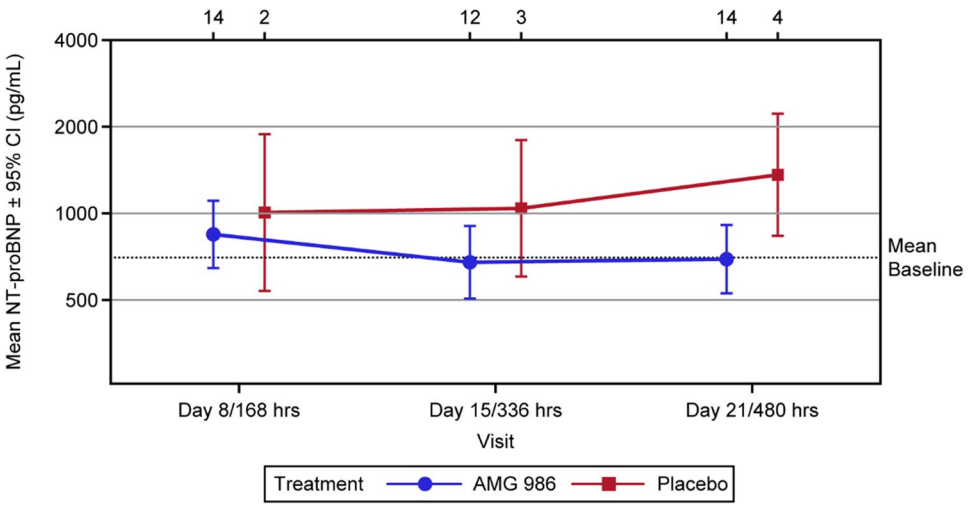

Fig. 6 Baseline-adjusted mean levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) in Part C for patients with heart failure with reduced ejection fraction (HFrEF). Dotted line represents mean NT-proBNP for all patients pretreatment (baseline); values above data points indicate the number of patients with available data at each time point; error bars represent 95% CIs. CI, confidence interval; hrs, hours

that pharmacologic attenuation of this target led to adaptive downstream effects such as interference with receptor dimerization and subsequent downstream signaling cascades. In addition, the doses chosen for Part C in HF patients were based on modeling from nonclinical data and extrapolation of benefit observed in a small clinical study using the short-acting APJ agonist Pyr 1(apelin13) [32]. Although no differences between treatment groups were observed in vital signs as a safety signal in Parts A and B, no detailed exposure–response assessments for apelin-like activity (e.g., heart rate and blood pressure effects) were performed to evaluate the translatability of the animal data and durability of effect over time or to validate the choice of doses for Part C. Thus, although numeric differences are noted in EF and SV between AMG 986 and placebo patients, the lack of dose–response may be due to having tested a relatively narrow dose range.

Alternatively, the lack of a robust response in HF patients may be due to the well-recognized large variability inherent in studying small populations of HF patients. There may exist a subset of HF patients with more prominent dysregulation of the apelin axis in whom targeted attenuation of APJ signaling by AMG 986 may be more clinically effective. In addition, as HF is a heterogeneous and complex condition, PD effects observed in early phases of drug development do not always correlate with demonstrated clinical benefit in later phases of development. Indeed, a disconnect between the results of early-phase and registrational phase 3 trials of drugs for HF has been observed numerous times in the past (e.g., with the levosimendan, tezosentan, tolvaptan, rolofylline, and nesiritide programs) [40]. As such, it is possible that the PD effects observed in the present study did not capture the true biologic and possible clinical benefits of AMG 986 in HF, or that apelin is a more suitable therapeutic target in other disease states, such as sarcopenia, diabetes, or PAH.

Aside from the above-stated technical and biologic difficulties inherent in early drug development in heart failure, the main limitation of this study is the small number of subjects studied over a relatively short duration of dosing. In accordance with FDA guidance, this phase I first-in-human study was focused primarily on assessing the safety, tolerability, PK, and PD of AMG 986. As such, the study was accordingly limited to less than 100 participants dosed up to the limits of contemporaneous preclinical toxicology

coverage. While cohorts of subjects with a given disease are often studied in phase I studies, most subjects are otherwise healthy so as to avoid confounding of assessment of safety, tolerability, PK, and PD attributable to study drug. As a chronic and heterogenous condition that often develops over years, extrapolation of clinical effect in heart failure in the confines of a phase I study was particularly challenging. In addition, the small number of HFpEF subjects recruited makes it especially difficult to draw conclusions in this population. There were no drugs specifically approved for the treatment of HFpEF at the time this study was designed and conducted so the role of apelin modulation on top of approved background therapies, such as sacubitril/valsartan and SGLT2 inhibitors, is unknown. Although subject-level data on medical history was collected for this study, granular data on specific etiology of heart failure and adjudication thereof was not captured for this phase I study due to practical limitations. Indirect assessments of hemodynamics were captured on serial echocardiograms performed throughout the study and these results are described in the manuscript. Invasive hemodynamic measurements via right heart catheterization were also not performed in this phase I study as the risks of this procedure had to be balanced against the need to first establish safety and tolerability in humans.

There is an unmet need for effective therapies to reduce the high hospitalization and mortality rates associated with HF, as well as the prospect that AMG 986 may have proven effective both in patients with HFrEF and those with HFpEF. Given the recognized limitations of the first-in-human study and our evolving understanding of APJ biology, APJ modulation remains a viable therapeutic target in other disease states.

In this phase 1b trial, AMG 986 administered PO or IV in single or multiple-daily doses was safe and well tolerated in healthy subjects and patients with HF. However, the apelin axis remains an attractive therapeutic target despite the limitations of this study and additional research may be warranted to better understand the therapeutic potential of APJ.

Methods

Study Design

This was a phase 1b, multicenter, randomized, placebo-controlled, double-blind, once-daily (Part A), and multiple-daily (Part B) ascending-dose study in healthy adult men and women aged 18–55 years, in which subjects received AMG 986 by IV infusion or PO administration in a fasted state. In Part C of the study, patients aged 18–85 years with HFrEF or HFpEF received ascending doses of AMG 986 or placebo by once-daily PO administration for 21 days (Fig. 7).

Part A was a randomized, parallel-group, double-blind, once-daily, ascending-dose study consisting of 11 cohorts of healthy subjects (5 IV infusion and 6 PO cohorts). Within each cohort, 8 subjects were to be randomized to receive AMG 986 or corresponding placebo in a 3:1 ratio. Starting doses of 0.5 mg by IV infusion lasting 1 h and 5 mg PO were planned. Part B was a randomized, parallel-group, double-blind, MAD study consisting of 8 planned cohorts of healthy subjects (2 IV infusion cohorts and 6 PO cohorts). Within each cohort, 8 subjects were to be randomized to receive AMG 986 or corresponding placebo in a 3:1 ratio. In Part C, up to 40 patients—20 with HFrEF and 20 with HFpEF—were to be randomized to receive AMG 986 or corresponding placebo in a 3:1 ratio (15 AMG 986 and 5 placebo). AMG 986 patients were to receive once-daily 10 mg PO for the first 7 days, 30 mg PO for the next 7 days, and 100 mg PO for the last 7 days.

Inclusion and Exclusion Criteria

Parts A and B of the study enrolled healthy subjects with no history or evidence of clinically relevant medical disorders, aged 18–55 years. Key eligibility criteria for Part C included a confirmed diagnosis of New York Heart Association class II–III HF for ≥ 3 months with stable condition for ≥ 4 weeks, LVEF $\leq 40\%$ for HFrEF and $\geq 50\%$ for HFpEF (confirmed by echocardiography, radionuclide ventriculography, cardiac magnetic resonance imaging, or contrast ventriculography within 12 months prior to randomization), and baseline NT-proBNP ≥ 250 pg/mL. All patients in Part C were in receipt of concomitant medication and this is reported in Supplementary Table 1. A complete list of inclusion and exclusion criteria is provided in the Supplementary Text.

Study Outcomes

The primary endpoints were the incidences of TEAEs and clinically significant changes in physical examinations, laboratory values (including hematologic parameters and measures of hepatic and renal function; see Supplementary Table 2 for complete list), vital signs, and ECGs. Secondary endpoints included the following PD parameters: changes over time from baseline in key echocardiographic parameters of LV systolic and diastolic function, and serum levels of NT-proBNP in healthy subjects and HF patients, as well as additional echocardiographic measures (changes in ventriculoarterial coupling and global strain) in HF patients only. The schedule for echocardiograms assessments for Part C is provided in Fig. 8. Additional secondary endpoints included pharmacokinetic (PK) characterization of AMG 986 after IV infusion and PO administration in healthy subjects and HF patients.

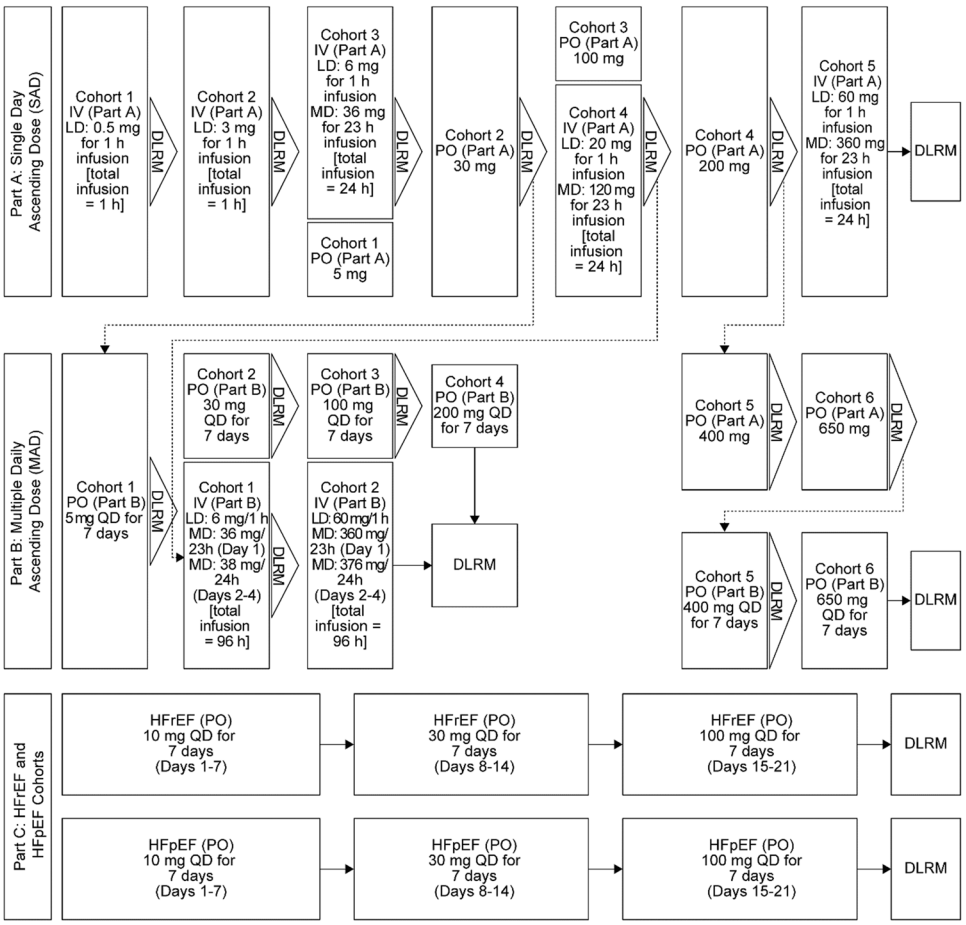

Fig. 7 Study design: AMG 986 administration schema. Subjects were given AMG 986 at the specified dosages or corresponding placebo. DLRM, dose level review meeting; h, hour; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LD, loading dose; MAD, multiple-daily ascending dose; MD, maintenance dose; PO, oral; QD, once daily; SAD, single-daily ascending dose

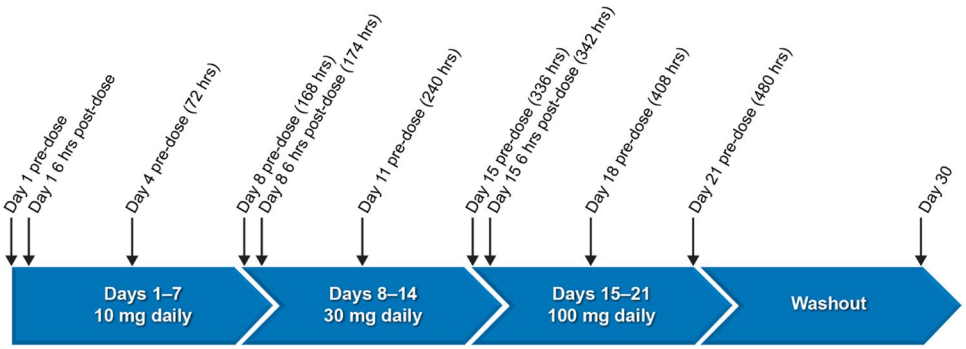

Fig. 8 Schedule for echocardiographic assessments in Part C. hrs, hours

Sample Size Calculation

The sample size for all parts of the study was based on practical considerations and was consistent with the number of subjects enrolled in similar studies. Approximately 152 healthy subjects (8 per cohort in 19 cohorts for Parts A and B) and up to 40 HF patients in Part C were expected to be enrolled. For safety considerations, with up to 144 subjects receiving AMG 986 (114 healthy and 30 HF), it was estimated that there would be a 99.94% chance of detecting a TEAE with a true incidence rate of ≥ 5%; a rare TEAE with a true incidence rate of 1% would be estimated to have a 76.48% chance of being detected. Although the sample size for this phase 1b study was driven primarily by feasibility, measurable hemodynamic effects of IV apelin have been reported in both HF and PAH patients with sample sizes of just 24 and 19, respectively [32, 35]. This study was terminated early due to a business decision by the sponsor; therefore, enrollment in the HFpEF group was not completed.

Statistics

Descriptive statistics were provided for selected demographics, baseline characteristics, safety and PK data, and selected echocardiographic measures. For PD data, summary measures were determined and a relationship to increasing dose of AMG 986 was explored. The statistical model included the actual dose of AMG 986 and the baseline value of the measurement. To assess the precision of the PD value, the standard error of the mean was calculated by dividing the standard deviation by the square root of the sample size. As is typical of early-phase safety and PK studies, the sample size was not selected for statistical inference of PD endpoints. Thus, the PD analyses presented indicate trends in effect and are hypothesis-generating only.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10557-022-07328-w.

Acknowledgements Employees of Amgen were involved in the study design, collection, analysis and interpretation of data, writing of the report, and decision to submit the article for publication. We would like to thank the investigators, clinical staff, and patients who participated in this study. Medical writing and editorial support was provided by Eric Justice of BioScience Communications, New York, New York, USA (on behalf of Amgen), and Liam Gillies, PhD, funded by Amgen.

Author Contribution JH: study design, study oversight, data collection, analysis and interpretation of data, writing of the report; AT: analysis and interpretation of data, writing of the report; KT: analysis and interpretation of data, writing of the report; SAA: analysis and interpretation of data, writing of the report; AK: study design, study oversight, data collection, analysis and interpretation of data, writing of the report; all other authors (external clinical PIs): enrollment of human subjects, analysis and interpretation of data, writing of the report.

Funding This study was sponsored by Amgen Inc.

Data Availability Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: http://www.amgen.com/datasharing.

Code Availability Not applicable

Declarations

Ethics Approval This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Independent ethics committees and regulatory agencies (as appropriate) approved the study protocol before the study was initiated.

Consent to Participate All subjects provided their written informed consent to participate.

Consent for Publication All authors have approved the decision to submit the manuscript for publication.

Conflict of Interest P. Winkle has no competing interests to declare. S. Goldsmith has no competing interests to declare. M.J. Koren is an employee of a company that received research grants and consulting fees from Amgen. S. Lepage has no competing interests to declare. J. Hellawell, A. Trivedi, K. Tsirtsonis, and S.A. Abbasi are employees and shareholders of Amgen. A. Kaufman is a former employee and shareholder of Amgen. R. Troughton has received grant funding from American Regent, Amgen, Bayer, Merck, and Roche Diagnostics, and personal fees from Merck and Roche Diagnostics. A. Voors has received research support and/or consulting fees from Amgen, AstraZeneca, Bayer AG, Boehringer Ingelheim, Cytokinetics, Merck, MyoKardia, Novartis, Novo Nordisk, and Roche Diagnostics. The Assistance Publique–Hôpitaux de Paris, which employs J.-S. Hulot, has received research grants from BioSerenity, Novo Nordisk, Sanofi, and Servier. J.-S. Hulot has also received speaker, advisory board, and consultancy fees from Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Novartis, and Novo Nordisk. E. Donal has had research facilities provided by and received fees from Abbott and General Electric Healthcare. N. Kazemi has no competing interests to declare. J. Neutel has no competing interests to declare. All authors reviewed this manuscript in draft form, provided critical input during the development process, and approved its submission for publication.

References

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: a report from theAmerican Heart Association. Circulation. 2020. https://doi.org/10.1161/cir.0000000000000757.
2. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure with reduced ejection fraction. N Engl J Med. 2020. https://doi.org/10.1056/nejmoa1915928.
3. Cleland JG, Daubert J-C, Erdmann E, et al. The effectof cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005. https://doi.org/10.1056/nejmoa050496.
4. Krum H, Teerlink JR. Medical therapy for chronic heart failure. Lancet. 2011. https://doi.org/10.1016/s0140-6736(11)61038-6.
5. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019. https://doi.org/10.1056/nejmoa1911303.
6. Ponikowski P, Voors AA, Ankeret SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology ESC. Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016. https://doi.org/10.1093/eurheartj/ehw128.
7. Teerlink JR, Diaz R, Felker GM, et al. Cardiac myosin activation-with omecamtiv mecarbil in systolic heart failure. N Engl J Med. 2021. https://doi.org/10.1056/nejmoa2025797.
8. Yancy CW, Jessup M, Bozkurt B, et al. ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;2017. https://doi.org/10.1161/cir.0000000000000509.
9. Cohen-Solal A, Logeart D. Is the glass half full or half emptyafter PARAGON-HF? Cardiovasc Res. 2020. https://doi.org/10.1093/cvr/cvz326.
10. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med. 2019. https://doi.org/10.1056/nejmoa1908655.

11. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021. https://doi.org/10.1056/NEJMoa2107038.
12. Chng SC, Ho L, Tian J, Reversade B. ELABELA: a hormone essential for heart development signals via the apelinreceptor. Dev Cell. 2013. https://doi.org/10.1016/j.devcel.2013.11.002.
13. O'Dowd BF, Heiber M, Chan A, et al. A human gene that shows identity with the gene encoding the angiotensin receptor is located on chromosome 11. Gene. 1993. https://doi.org/10.1016/0378-1119(93)90495-o.
14. Tatemoto K, Hosoya M, Habata Y, et al. Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. Biochem BiophysRes Commun. 1998. https://doi.org/10.1006/bbrc.1998.9489.
15. Kleinz MJ, Skepper JN, Davenport AP. Immunocytochemical localisation of the apelin receptor, APJ, to human cardiomyocytes, vascular smooth muscleand endothelial cells. Regul Pept. 2005. https://doi.org/10.1016/j.regpep.2004.10.019.
16. Eyries M, Siegfried G, Ciumas M, et al. Hypoxia-induced apelin expression regulates endothelial cell proliferation and regenerativeangiogenesis. Circ Res. 2008. https://doi.org/10.1161/circresaha.108.179333.
17. O'Carroll AM, Lolait SJ. Regulation of rat APJ receptor messenger ribonucleic acid expression in magnocellular neurones of theparaventricular and supraopric nuclei by osmotic stimuli. J Neuroendocrinol. 2003. https://doi.org/10.1046/j.1365-2826.2003.01044.x.
18. Parikh VN, Liu J, Shang C, et al. Apelin and APJ orchestrate complex tissue-specificcontrol of cardiomyocyte hypertrophy and contractility in the hypertrophy-heart failure transition. Am J Physiol HeartCirc Physiol. 2018. https://doi.org/10.1152/ajpheart.00693.2017.
19. Ashley E, Powers J, Chen M, et al. Theendogenous peptide apelin potently improves cardiac contractility and reduces cardiac loading in vivo. CardiovasRes. 2005. https://doi.org/10.1016/j.cardiores.2004.08.018.
20. Berry MF, Pirolli TJ, Jayasankar V, et al. Apelin has in vivo inotropic effects on normal and failing hearts. Circulation . 2004. https://doi.org/10.1161/01.cir.0000138382.57325.5c.
21. Cheng X, Cheng XS, Pang CCY. Venous dilator effect ofapelin, an endogenous peptide ligand for the orphan APJ receptor, in conscious rats. Eur J Pharmacol. 2003. https://doi.org/10.1016/s0014-2999(03)01821-1.
22. Dalzell JR, Rocchiccioli JP, Weir RA, et al. The emergingpotential of the apelin-APJ system in heart failure. J Card Fail. 2015. https://doi.org/10.1016/j.cardfail.2015.03.007.
23. Salcedo A, Garijo J, Monge L, et al. Apelin effects in human splanchnic arteries. Role of nitric oxide and prostanoids. Regul Pept. 2007. https://doi.org/10.1016/j.regpep.2007.06.005.
24. Tatemoto K, Takayama K, Zou MX, Kumaki I, Zhang W, Kumano K, et al. The novel peptide apelin lowers blood pressure via a nitric oxidedependentmechanism. Regul Pept. 2001. https://doi.org/10.1016/s0167-0115(01)00236-1.
25. Cheng Hai, Chen Yuhan, Li Xueling, et al. Involvement of Apelin/APJ Axis in Thrombogenesis in Valve Heart Disease Patients with Atrial Fibrillation. Int Heart J. 2019;60:145–50.
26. Hu H, He L, Li L, Chen L. Apelin/APJ system as a therapeutic target in diabetes and its complications. Mol Genet Metab. 2016. https://doi.org/10.1016/j.ymgme.2016.07.012.
27. Vinel C, Lukjanenko L, Batut A, et al. The exerkine apelinreverses age-associated sarcopenia. Nat Med. 2018. https://doi.org/10.1038/s41591-018-0131-6.
28. Chandrasekeran B, Dar O, McDonagh T. The role of apelin in cardiovascular function and heart failure. Eur JHeart Fail. 2008. https://doi.org/10.1016/j.ejheart.2008.06.002.
29. Chen MM, Ashley EA, Deng DXF, et al. Novel role for the potent endogenous inotrope apelin in human cardiac dysfunction. Circulation. 2003. https://doi.org/10.1161/01.cir.0000091235.94914.75.
30. Boal F, Timotin A, Roumegoux J, et al. Apelin-13administration protects against ischaemia/reperfusion-mediated apoptosis through the FoxO1 pathway in high-fatdiet induced obesity. Br J Pharmacol. 2016. https://doi.org/10.1111/bph.13485.
31. Chun HJ, Ali ZA, Kojima Y, et al. Apelin signaling antagonizes Ang II effects in mouse models of atherosclerosis. J Clin Invest. 2008. https://doi.org/10.1172/jci34871.
32. Japp AG, Cruden NL, Barnes G, et al. Acute cardiovascular effects of apelin in humans: potential role in patients with chronic heart failure. Circulation. 2010. https://doi.org/10.1161/circulationaha.109.911339.
33. Maguire JJ, Kleinz MJ, Pitkin SL, Davenport AP. [Pyr1]apelin-13 identified as the predominant apelin isoform in the human heart: vasoactive mechanisms and inotropic action in disease. Hypertension. 2009. https://doi.org/10.1161/hypertensionaha.109.134619.
34. Zhong JC, Zhang ZZ, Wang W, McKinnie SMK, Vederas JC, Oudit GY. Targeting the apelin pathway as a novel therapeutic approach for cardiovascular diseases. Biochim Biophys Acta Mol Basis Dis. 2017. https://doi.org/10.1016/j.bbadis.2016.11.007.
35. Brash L, Barnes GD, Brewis MJ, et al. Short-term hemodynamic-effects of apelin in patients with pulmonary arterial hypertension. JACC Basic Trans Sci. 2018. https://doi.org/10.1016/j.jacbts.2018.01.013.
36. Ason B, Chen Y, Guo Q, et al. Cardiovascular response to small-molecule APJ activation. JCI Insight. 2020. https://doi.org/10.1172/jci.insight.132898.
37. Trivedi A, Mather O, Vega S, Simiens MA, Hellawell J, Lee E. Effect of severe renal impairment on the safety, Tolerability, and Pharmacokinetics of AMG 986. Accepted for publication in Clinical Drug Investigation 2022.
38. Trivedi A, Mather O, Vega S, Hutton S, Hellawell J, Lee E. A phase 1 open-label study to evaluate the effect of food and concomitant itraconazole administration on the Pharmacokinetics of AMG 986 in Healthy Subjects. Accepted for publication in Clinical Pharmacology in Drug Development. 2022. https://doi.org/10.1002/cpdd.1074.
39. Luis SA, Chan J, Pellikka PA. Echocardiographic assessment of left ventricular systolic function: an overview of contemporary techniques, including speckle-tracking echocardiography. Mayo Clin Proc. 2019. https://doi.org/10.1016/j.mayocp.2018.07.017.
40. Butler J, Hamo CE, Udelson JE, et al. Reassessing phase II heart failure clinical trials: Consensus recommendations. Circ Heart Fail. 2017. https://doi.org/10.1161/circheartfailure.116.003800.

Authors and Affiliations

Peter Winkle[1] · Steven Goldsmith[2] · Michael J. Koren[3] · Serge Lepage[4] · Jennifer Hellawell[5] · Ashit Trivedi[6] · Kate Tsirtsonis[7] · Siddique A. Abbasi[6] · Allegra Kaufman[6] · Richard Troughton[8] · Adriaan Voors[9] · Jean-Sebastien Hulot[10,11] · Erwan Donal[12] · Navid Kazemi[13] · Joel Neutel[14]

[1] Anaheim Clinical Trials, 2441 W La Palma Ave, Anaheim, CA 92801, USA

[2] Hennepin Healthcare and the University of Minnesota, 715 S 8 St, Minneapolis, MN 55415, USA

[3] Jacksonville Center for Clinical Research, 4085 University Blvd S #1, Jacksonville, FL 32216, USA

[4] Department of Medicine, Université de Sherbrooke, 3001, 12e Avenue Nord, Sherbrooke, Québec J1H 5N4, Canada

[5] Amgen Inc., 1120 Veterans Blvd, South San Francisco, CA 94080, USA

[6] Amgen Inc., One Amgen Center Dr, Thousand Oaks, CA 91320, USA

[7] Amgen Limited, 1 Uxbridge Business Park, Sanderson Rd, Uxbridge UB8 1DH, UK

[8] Department of Medicine, Christchurch Heart Institute, University of Otago, PO Box 4345, Christchurch 8140, New Zealand

[9] Department of Cardiology (AB31), University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands

[10] Université de Paris, INSERM, PARCC, F-75006 Paris, France

[11] CIC1418 and DMU CARTE, AP-HP, Hôpital Européen Georges-Pompidou, F-75015 Paris, France

[12] Universitaire Rennes, Centre Hospitalier Universitaire de Rennes, INSERM, LTSI – UMR 1099, 2 rue Henri Le Guilloux 35033, 35000 Rennes, France

[13] Palm Research Center, Inc., 9280 W Sunset Rd, Suite 306, Las Vegas, NV 89148, USA

[14] Orange County Research Center, 14351 Myford Rd, Suite B, Tustin, CA 92780, USA