A Phase I, Randomized, Double-Blind, Placebo Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 986 in Healthy Subjects and Heart Failure Patients

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To evaluate the safety and tolerability of ascending multiple PO doses of AMG 986 in heart failure patients (Part C).* To characterize AMG 986 pharmacokinetics (PK) after IV infusion and oral administrationin heart failure patients.* To characterize...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON46755

Source
ToetsingOnline

Brief title
20150183

Condition

- Heart failures

Synonym
cardiac insufficiency, Heart failure

Research involving
Human

Sponsors and support

Primary sponsor: Amgen
Source(s) of monetary or material Support: Amgen

Intervention

Keyword: cardiovascular, heart failure, Patients, trials

Outcome measures

Primary outcome

Subject incidence of treatment-emergent adverse events.

* Subject incidence of clinically significant changes in physical examinations,

vital signs,

laboratory safety tests, and electrocardiograms (ECGs).

Secondary outcome

AMG 986 PK parameters including, but not limited to, maximum observed

concentration

(Cmax), the time of maximum observed concentration (tmax), area under the

concentration-time curve (AUC), and oral bioavailability.

* Changes over time from baseline in echocardiographic parameters of left

ventricular

systolic and diastolic functions (left ventricular ejection fraction, fraction

shortening, stroke

volume, wall thickening, end-systolic and end-diastolic volumes and indexes,

septal and

lateral e*, E/A ratio, E/e* ratio, E wave deceleration time, left atrial volume

index) in

heart failure patients, as well as changes in ventriculo-arterial coupling and

global strain in heart failure patients

Study description

Background summary

AMG 986 is a novel apelin receptor (APJ) small molecule agonist that binds and activates APJ receptor to improve cardiac function by increasing cardiac contraction and
relaxation, by improving cardiac reserve, and by decreasing systemic vascular resistance without a significant impact on heart rate and myocardial oxygen consumption. AMG 986 is being developed as a potential treatment for heart failure

Study objective

To evaluate the safety and tolerability of ascending multiple PO doses of AMG 986 in heart failure patients (Part C).
* To characterize AMG 986 pharmacokinetics (PK) after IV infusion and oral administration
in heart failure patients.
* To characterize the pharmacodynamic (PD) effects of AMG 986 in heart failure patients.

Study design

This study is a randomized, placebo-controlled, double-blind, single day ascending dose (SDAD) study (Part A), a multiple daily ascending dose (MDAD) study (Part B), in
healthy subjects, and a MDAD study (Part C) in heart failure patients. In Parts A and B of the
study, healthy volunteers will receive AMG 986 by continuous IV infusion or by oral administration
in a fasted state. IV Infusions will be divided into an initial loading dose (LD) for the first hour
followed immediately by a maintenance dose (MD). In Part C of the study, patients with heart
failure and either reduced (HFrEF) or preserved (HFpEF) ejection fraction will receive MDAD of
IP by once daily oral administration for 21 days.

All available safety and laboratory data will be reviewed in an unblinded fashion by the members
of the Dose Level Review Meeting (DLRM) prior to the first dose administration of IP at the higher
dose level. For study Part A, PK assessments will be part of each DLRM. For study Parts B and
C, vital signs, and all available PK and PD data will also be reviewed at the DLRM. All cohorts in
Part B will enroll sequentially after review of safety data at the previous dose level. Both cohorts
in Part C (HFrEF cohort and HFpEF cohort) will enroll concurrently after completion of study Part
B.
Based on emerging safety and tolerability data and upon assessment by the Principal Investigator
(PI), Medical Monitor and Global Safety Officer (DLRM members), cohorts may be removed or
additional cohorts may be added. Subject numbers within each cohort may also be increased or
decreased based on the decision from the DLRM. Doses to be administered within each cohort
may be higher or lower than the last. Dosing of any subject shall not exceed the highest planned
IV and PO cohorts.
Please Note that the Netherlands will only participate in Part C of the protocol.

Intervention

Blood sampling, Echocardigram, ECG

Study burden and risks

Potential risks associated with IP in this study are outlined in Section 2 of the protocol and in the informed consent. Bloodsampling will be the most invasive assessment done in this study.There are risks associated with the procedures which are outlined in section 7 of the protocol and the informed consent.

Contacts

Public
Amgen

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4800DH Breda 4800DH Breda
NL
Scientific
Amgen

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Criteria for HFrEF- Patients between the ages of 18 and 85 years with stable NYHA class II or III chronic HF in sinus rhythm on optimal therapy and a left ventricular ejection fraction of < 40% and NT-proBNP level of > 250 pg/mL.
* Criteria for HFpEF- Patients between the ages of 18 and 85 years with stable NYHA class II or III chronic HF, in sinus rhythm on optimal standard of care therapy with a left ventricular ejection fraction of > 50% and NT-proBNP level of > 250 pg/mL.

Exclusion criteria

*Heart rate * 100 beats per minute after 5 minutes of rest or an untreated symptomatic bradyarrhythmia within 1 month prior to enrollment.
*Severe uncorrected valvular heart disease, or hypertrophic obstructive cardiomyopathy, active myocarditis, constrictive pericarditis, or clinically significant congenital heart disease.
*Estimated glomerular filtration rate (eGFR)
within the screening period of less than 30 mL/min/1.732m2 as calculated using the Modification of Diet in Renal Disease (MDRD) formula.

*For subjects in Part C of the study: Systolic blood pressure > 160 mm Hg or < 100 mm Hg, or diastolic blood pressure > 110 mm Hg or < 60 mm Hg, assessed on 2 separate occasions prior to enrollment.
*For subjects in Part C of the study: Troponin I > ULN if there is also evidence of an acute cardiovascular event.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-11-2018
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AMG 986
Generic name:	AMG 986

Ethics review

Approved WMO

Date:	01-11-2017
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	06-03-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-04-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-05-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-05-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-09-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-09-2018

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-002940-34-NL
ClinicalTrials.gov	NCT03276728
CCMO	NL63274.100.17