

COMPOUND AZD5462 FOR USE IN THE TREATMENT OF HEART FAILURE

The present specification claims benefit of priority to US patent application no. 63/519,654, filed 15 August 2023, and US patent application no. 63/555,454, filed 20 February 2024, the contents of which are hereby incorporated by reference in their entirety for all purposes.

Field

The present disclosure relates to dosing regimens and methods for treating subjects with heart failure, comprising administering Compound (I) or a pharmaceutically acceptable salt thereof, and pharmaceutical compositions comprising Compound (I) or a pharmaceutically acceptable salt thereof.

Background

Heart failure is associated with significant morbidity and mortality. It is characterized by complex tissue remodelling involving increased cardiomyocyte death and interstitial fibrosis.

Without being limited by theory, relaxin is understood to be a pleiotropic hormone that mediates systemic haemodynamic and renal adaptive changes during pregnancy. In pregnancy, relaxin mediates systemic hemodynamic and renal adaptive changes to meet the increased metabolic demands of gestation without causing cardiac damage and has a unique ability to reduce both systemic vascular resistance and renal resistance concomitantly. Without being bound by theory, if relaxin were to replicate these hemodynamic adaptations in the setting of heart failure, it could reduce myocardial demand and improve end-organ perfusion. Relaxin has also been shown to have anti-fibrotic properties and to have beneficial effects in heart failure including acute decompensated heart failure (ADHF). Relaxin activates a number of signalling cascades that have been shown to be beneficial in the setting of ischemia-reperfusion and heart

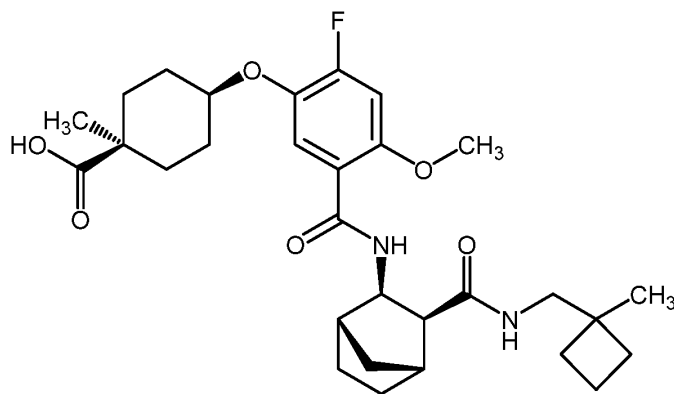
failure. These signalling pathways include activation of the phosphoinositide 3-kinase pathway and activation of the nitric oxide signalling pathway (Bathgate RA *et al.* (2013) *Physiol. Rev.* 93(1): 405-480; Mentz RJ *et al.* (2013) *Am. Heart J.* 165(2): 193-199; Tietjens J *et al.* (2016) *Heart* 102: 95-99; Wilson SS *et al.* (2015) *Pharmacology* 35: 315-327).

Clinical trials have been conducted using unmodified recombinant human Relaxin-2, serelaxin. Continuous intravenous administration of serelaxin to hospitalized patients improved markers of cardiac, renal, and hepatic damage and congestion (Felker GM *et al.* (2014) *J. Am. Coll. Cardiol.* 64(15): 1591-1598; Metra M *et al.* (2013) *J. Am. Coll. Cardiol.* 61(2): 196-206; Teerlink JR *et al.* (2013) *Lancet* 381(9860): 29-39). Serelaxin also yielded improvements in pulmonary artery pressures, cardiac output, and systemic and pulmonary vascular resistance, however, these results required a continuous infusion at 30 µg/kg/day, which was given for approximately 20 hours (Ponikowski *et al.*, (2014) *European Heart Journal* 35:431–441). Due to the rapid clearance of serelaxin from the patients' circulation, its therapeutic effects were limited, and the therapeutic effects rapidly disappeared once intravenous infusion stopped. Additionally, approximately one third of the patients experienced a significant drop in blood pressure (> 40 mm Hg) after receiving serelaxin intravenously, with the consequence that the infusion rate had to be reduced by half or even more.

The cognate receptor for human relaxin is RXFP1 and is a well-validated pharmacologically important GPCR family 1c member whose activation by the hormone relaxin is associated with hemodynamic, anti-fibrotic and anti-inflammatory properties (Halls ML *et al.*, (2015), *Pharmacol Rev.* 67(2): 389-440).

Small-molecule modulators of RXFP1 have been sought as relaxin mimetics. For example, Compound (I), also known as AZD5462 and (1S,4s)-4-(2-fluoro-4-methoxy-5-(((1S,2R,3S,4R)-3-(((1-methylcyclobutyl)methyl)carbonyl)bicyclo[2.2.1]heptan-2-

yl)carbamoyl)phenoxy)-1-methylcyclohexane-1-carboxylic acid, is a modulator of RXFP1 and is described in Example 1 of WO2022/122773A1.



Compound (I)

AZD5462 has entered Phase 1 and Phase 2b clinical studies (Clinicaltrials.gov Identifiers: NCT04994106, NCT05395117, NCT05395117 and NCT06299826) and may be useful in the treatment of disease states in which modulation of RXFP1 is beneficial, such as heart failure (HF). However, there remains a need to establish treatment regimens for patients with HF that utilise doses of Compound (I) that are efficacious, minimise adverse effects, and have other therapeutic benefits.

Summary

Disclosed herein are, in part, treatment regimens for the treatment of heart failure subjects using Compound (I) or a pharmaceutically acceptable salt thereof. The dosing regimen provided herein may improve quality of life for patients while retaining efficacy and minimizing side effects.

In one aspect, the present disclosure provides a method of treating a subject having heart failure, the method comprising administering to the subject from 5 mg to 360 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides Compound (I) or a pharmaceutically acceptable salt thereof for use in a method described herein.

In another aspect, the present disclosure provides a pharmaceutical composition comprising from 5 mg to 360 mg of Compound (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a pharmaceutical composition described herein for use in a method described herein.

Further aspects of the disclosure will be apparent to one skilled in the art from reading this specification.

Brief Description of the Drawings

Figure 1 shows ejection fraction (EF) change in non-human primates (NHP) following administration of AZD5462 at 0.25 mg/kg and 1 mg/kg (hollow circles) vs placebo (solid circles).

Figure 2 shows heart rate (HR) change in NHP following administration of AZD5462 at 0.25 mg/kg and 1 mg/kg (hollow circles) vs placebo (solid circles).

Figure 3 shows mean arterial pressure (MAP) change in NHP following administration of AZD5462 at 0.25 mg/kg and 1 mg/kg (hollow circles) vs placebo (solid circles).

Figure 4 shows end systolic volume (ESV) change in NHP following administration of AZD5462 at 0.25 mg/kg and 1 mg/kg (hollow circles) vs placebo (solid circles).

Figure 5 shows end diastolic volume (EDV) change in NHP following administration of AZD5462 at 0.25 mg/kg and 1 mg/kg (hollow circles) vs placebo (solid circles).

Figure 6 shows stroke volume (SV) change in NHP following administration of AZD5462 at 0.25 mg/kg and 1 mg/kg (hollow circles) vs placebo (solid circles).

Figure 7 shows systemic vascular resistance (SVR) change in NHP following administration of AZD5462 at 0.25 mg/kg and 1 mg/kg (hollow circles) vs placebo (solid circles).

Figure 8 shows a Phase 1 study design (Example 2).

Figure 9 shows the Mean Change from Baseline in Ambulatory Systolic Blood Pressure (mmHg) from Ambulatory Blood Pressure Monitoring during Part B of the Phase 1 study.

Figure 10 shows the Mean Change from Baseline in Ambulatory Diastolic Blood Pressure (mmHg) from Ambulatory Blood Pressure Monitoring during Part B of the Phase 1 study.

Figure 11 shows the Mean Change from Baseline in Ambulatory Heart Rate (beats/min) from Ambulatory Blood Pressure Monitoring during Part B of the Phase 1 study.

Figure 12 shows the Mean Change from Baseline in Ambulatory Pulse Pressure (mmHg) from Ambulatory Blood Pressure Monitoring during Part B of the Phase 1 study.

Figure 13 shows Geometric Mean Plasma Concentrations (nmol/L) of AZD5462 Versus Nominal Time Following Single Oral Dose Administration in Healthy Non-Japanese Participants – Part A of the Phase 1 study (Semi-logarithmic Scale).

Figure 14 shows Geometric Mean Plasma Concentrations (nmol/L) of AZD5462 Versus Nominal Time Following Single Oral Dose Administration in Healthy Non-Japanese Participants – Day 1, Part B of the Phase 1 study (Semi-logarithmic Scale).

Figure 15 shows Geometric Mean Plasma Concentrations (nmol/L) of AZD5462 Versus Nominal Time Following Multiple Twice Daily Oral Dose Administration in Healthy Non-Japanese Participants – Day 10, Part B of the Phase 1 study (Semi-logarithmic Scale).

Figure 16 shows change in renin levels from baseline in Part A (SAD) of the Phase 1 study.

Figure 17 shows change in renin levels from baseline in Part B (MAD) of the Phase 1 study.

Figure 18 shows change in serum creatinine levels from baseline in Part B (MAD) of the Phase 1 study.

Figure 19 shows change in eGFR from baseline in Part B (MAD) of the Phase 1 study.

Figure 20 shows the study flow chart for the Phase 1 food effect study described in Example 3.

Figure 21 shows the predicted eGFR exposure-response at steady state for AZD5462 QD dosing, based on Phase 1 data. Steady-state concentrations from dosing (oral, tablet) at 20 mg QD, 80 mg QD and 360 mg QD are shown as dashed lines.

Figure 22 shows the predicted renin exposure-response at steady state for AZD5462 QD dosing, based on Phase 1 data. Steady-state concentrations from dosing (oral, tablet) at 20 mg QD, 80 mg QD and 360 mg QD are shown as dashed lines. Shaded regions show 90 percent prediction intervals.

Figure 23 shows the predicted exposure-response for ESV, renin and SVR for average concentration at steady state, based on NHP HFrEF model data, for AZD5462 QD and BID dosing. Analysis was performed on geomean logged (y/y₀) normalized data at steady state up to week 26. Confidence intervals depict 90% CI. Steady-state concentrations (oral, tablet) from dosing at 20 mg QD, 40 mg QD, 100 mg QD and 360 mg QD are shown as dashed lines.

Detailed Description

Disclosed herein are methods involving low dose administration of Compound (I) or a pharmaceutically acceptable salt thereof to treat subjects with heart failure, and pharmaceutical compositions comprising Compound (I) or a pharmaceutically acceptable salt thereof for use in the methods described herein.

Compound (I)

Compound (I) may be prepared as described in Example 1 of WO2022/122773A1.

In one embodiment, Compound (I) or a pharmaceutically acceptable salt thereof is administered to the subject. In one embodiment, Compound (I) is administered to the subject. In one embodiment, a pharmaceutically acceptable salt of Compound (I) is administered to the subject.

In one embodiment, the pharmaceutical composition comprises Compound (I) or a pharmaceutically acceptable salt thereof. In one embodiment, the pharmaceutical composition comprises Compound (I). In one embodiment, the pharmaceutical composition comprises a pharmaceutically acceptable salt of Compound (I).

An example list of pharmaceutically acceptable salts can be found in the *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, P. H. Stahl and C. G. Wermuth, editors, Weinheim/Zürich: Wiley-VCH/VHCA, 2002. A suitable pharmaceutically acceptable salt of Compound (I) is, for example, an acid-addition salt or a base-addition salt. An acid addition salt of Compound (I) may be formed by bringing the compound into contact with a suitable inorganic or organic acid under conditions known to the skilled person. An acid addition salt may be formed using an inorganic acid, for example hydrochloric acid, hydrobromic acid, sulphuric acid or phosphoric acid. An acid addition salt may also be formed using an organic acid, for example trifluoroacetic acid, citric acid, maleic acid, oxalic acid, acetic acid, formic acid, benzoic acid, fumaric acid, succinic acid,

tartaric acid, lactic acid, pyruvic acid, methanesulfonic acid, benzenesulfonic acid or *para*-toluenesulfonic acid.

Therefore, in one embodiment the pharmaceutically acceptable salt is a hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, trifluoroacetic acid, citric acid, maleic acid, oxalic acid, acetic acid, formic acid, benzoic acid, fumaric acid, succinic acid, tartaric acid, lactic acid, pyruvic acid, methanesulfonic acid, benzenesulfonic acid or *para*-toluenesulfonic acid salt.

Compound (I) may form base addition salts. A base-addition salt of Compound (I) may be formed by bringing the compound into contact with a suitable inorganic or organic base under conditions known to the skilled person. For example, it may be possible to make an alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound with an alkali metal or alkaline earth metal hydroxide or alkoxide (e.g., an ethoxide or methoxide) or a suitably basic organic amine (e.g., a choline or meglumine) in an aqueous medium. Therefore, in one embodiment the pharmaceutically acceptable salt is a sodium, potassium, lithium, calcium, choline or meglumine salt.

Embodiments describing a mass of Compound (I) or a pharmaceutically acceptable salt thereof refer to the specified mass of Compound (I) or an equivalent molar amount of a pharmaceutically acceptable salt of Compound (I).

Dosing and Therapeutic Methods

The present disclosure provides methods of treating a subject with heart failure by administering to the subject from 5 mg to 360 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof.

The subject treated according to the methods described herein may be an animal, optionally a mammal. In one embodiment, the subject treated according to the methods described herein is a human.

Compound (I) or a pharmaceutically acceptable salt thereof may be administered to the subject orally or by injection, such as by intravenous, subcutaneous, or intramuscular injection. In some embodiments, Compound (I) or a pharmaceutically acceptable salt thereof is orally administered to the subject.

In some embodiments, Compound (I) or a pharmaceutically acceptable salt thereof is administered to the subject once daily (QD) or twice daily (BID).

In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof administered to the subject is from 5 mg to 360 mg per day, optionally from 10 mg to 360 mg per day, from 20 mg to 360 mg per day, from 30 mg to 360 mg per day, from 40 mg to 360 mg per day, from 50 mg to 360 mg per day, from 60 mg to 360 mg per day, from 70 mg to 360 mg per day, from 80 mg to 360 mg per day, from 90 mg to 360 mg per day, or from 100 mg to 360 mg per day. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof administered to the subject is from 10 mg to 100 mg per day, optionally from 20 mg to 100 mg per day, from 30 mg to 100 mg per day, from 40 mg to 100 mg per day, from 50 mg to 100 mg per day, from 60 mg to 100 mg per day, from 70 mg to 100 mg per day, from 80 mg to 100 mg per day, or from 90 mg to 100 mg per day. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof administered to the subject is from 20 mg to 80 mg per day, optionally from 30 mg to 80 mg per day, from 40 mg to 80 mg per day, from 50 mg to 80 mg per day, from 60 mg to 80 mg per day, or from 70 mg to 80 mg per day. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof administered to the subject is from 5 mg to 200 mg per day, optionally from 5 mg to 180 mg per day, from 5 mg to 150 mg per day, from

5 mg to 100 mg per day, from 5 mg to 90 mg per day, from 5 mg to 80 mg per day, from 5 mg to 70 mg per day, from 5 mg to 60 mg per day, from 5 mg to 50 mg per day, from 5 mg to 40 mg per day, from 5 mg to 30 mg per day, or from 5 mg to 20 mg per day. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof administered to the subject is from 10 mg to 200 mg per day, optionally from 10 mg to 180 mg per day, from 10 mg to 150 mg per day, from 10 mg to 100 mg per day, from 10 mg to 90 mg per day, from 10 mg to 80 mg per day, from 10 mg to 70 mg per day, from 10 mg to 60 mg per day, from 10 mg to 50 mg per day, from 10 mg to 40 mg per day, from 10 mg to 30 mg per day, or from 10 mg to 20 mg per day. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof administered to the subject is from 20 mg to 200 mg per day, optionally from 20 mg to 180 mg per day, from 20 mg to 150 mg per day, from 20 mg to 100 mg per day, from 20 mg to 90 mg per day, from 20 mg to 80 mg per day, from 20 mg to 70 mg per day, from 20 mg to 60 mg per day, from 20 mg to 50 mg per day, from 20 mg to 40 mg per day, or from 20 mg to 30 mg per day. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof administered to the subject is from 30 mg to 200 mg per day, optionally from 30 mg to 180 mg per day, from 30 mg to 150 mg per day, from 30 mg to 100 mg per day, from 30 mg to 90 mg per day, from 30 mg to 80 mg per day, from 30 mg to 70 mg per day, from 30 mg to 60 mg per day, from 30 mg to 50 mg per day, or from 30 mg to 40 mg per day. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof administered to the subject is from 40 mg to 200 mg per day, optionally from 40 mg to 180 mg per day, from 40 mg to 150 mg per day, from 40 mg to 100 mg per day, from 40 mg to 90 mg per day, from 40 mg to 80 mg per day, from 40 mg to 70 mg per day, from 40 mg to 60 mg per day, or from 40 mg to 50 mg per day. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof administered to the subject is about 5 mg per day, optionally about 10 mg per day, about 15 mg per day, about

20 mg per day, about 25 mg per day, about 30 mg per day, about 35 mg per day, about 40 mg per day, about 45 mg per day, about 50 mg per day, about 55 mg per day, about 60 mg per day, about 65 mg per day, about 70 mg per day, about 75 mg per day, about 80 mg per day, about 85 mg per day, about 90 mg per day, about 95 mg per day, about 100 mg per day, about 110 mg per day, about 120 mg per day, about 130 mg per day, about 140 mg per day, about 150 mg per day, about 160 mg per day, about 170 mg per day, about 180 mg per day, about 190 mg per day, or about 200 mg per day. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof administered to the subject is about 20 mg per day. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof administered to the subject is about 40 mg per day. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof administered to the subject is about 80 mg per day. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof administered to the subject is about 100 mg per day.

In some embodiments, Compound (I) or a pharmaceutically acceptable salt thereof is administered to the subject for one or more weeks, optionally two or more weeks, three or more weeks, four or more weeks, six or more weeks, eight or more weeks, eight or more weeks, ten or more weeks, twelve or more weeks, sixteen or more weeks, twenty or more weeks, twenty four or more weeks, or twenty eight or more weeks.

In some embodiments, Compound (I) or a pharmaceutically acceptable salt thereof is administered to the subject chronically.

In some embodiments, the heart failure is chronic heart failure (CHF). In some embodiments, the heart failure is acute heart failure (AHF).

In some embodiments, the heart failure is heart failure with preserved ejection fraction (HFpEF). In some embodiments, the heart failure is heart failure with ejection fraction $\geq 41\%$ (HF with EF $\geq 41\%$). In some embodiments, the heart failure is heart failure

with mid-range ejection fraction (HFmrEF). In some embodiments, the heart failure is heart failure with reduced ejection fraction (HFrEF). In some embodiments, the heart failure is heart failure with ejection fraction $\leq 35\%$ (HF with EF $\leq 35\%$).

In some embodiments, the subject has received treatment for the heart failure for ≥ 4 weeks, optionally ≥ 1 month, prior to treatment with Compound (I) or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has received standard of care (SoC) treatment for the heart failure for ≥ 4 weeks, optionally ≥ 1 month, prior to treatment with Compound (I) or a pharmaceutically acceptable salt thereof.

In some embodiments, the subject has an estimated glomerular filtration rate (eGFR) of ≥ 30 mL/min/1.73m² prior to treatment. In some embodiments, the subject has an eGFR of ≥ 45 mL/min/1.73m² prior to treatment. In some embodiments, the subject has an eGFR of ≥ 60 mL/min/1.73m² prior to treatment.

In some embodiments, the subject has a Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ TSS) of ≤ 75 prior to treatment.

In some embodiments, the subject has an elevated level of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) prior to treatment. In some embodiments, the subject has NT-proBNP > 400 pg/mL prior to treatment. In some embodiments, the subject has NT-proBNP > 300 pg/ml and sinus heart rhythm prior to treatment. In some embodiments, the subject has NT-proBNP > 900 pg/ml and atrial fibrillation prior to treatment.

In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof causes no significant change in blood pressure of the subject. This may be no significant change (e.g. percentage change) relative to baseline blood pressure of the subject (i.e. pre-administration) and/or as compared to placebo. In some embodiments, no significant change in blood pressure of the subject means no more than a 20% change relative to baseline blood pressure of the subject. In

some embodiments, the blood pressure is systolic blood pressure. In some embodiments, the blood pressure is diastolic blood pressure.

In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof causes no significant change in resting heart rate of the subject. This may be no significant change (e.g. percentage change) relative to resting heart rate of the subject (i.e. pre-administration) and/or as compared to placebo. In some embodiments, no significant change in resting heart rate of the subject means no more than a 20% change relative to baseline resting heart rate of the subject.

In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in end systolic volume (ESV) of the subject as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in ESV in the subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, or at least 40%, as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of about 20 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in ESV in the subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, or at least 40%, as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of about 40 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in ESV in the subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, or at least 40%, as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of about 80 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in ESV in the subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, or at least 40%, as compared to

baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of about 100 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in ESV in the subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, or at least 40%, as compared to baseline levels, e.g., after 24 weeks of treatment.

In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in ejection fraction (EF) in the subject as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration of Compound (I) or a pharmaceutically acceptable salt thereof, increases EF in the subject by 1% to 30% as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration of Compound (I) or a pharmaceutically acceptable salt thereof increases EF in the subject by at least 5%, at least 10%, at least 20%, at least 25%, or at least 30%, as compared to baseline levels e.g., after 24 weeks of treatment. In some embodiments, administration of about 20 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof increases EF in the subject by at least 5%, at least 10%, at least 20%, at least 25%, or at least 30%, as compared to baseline levels e.g., after 24 weeks of treatment. In some embodiments, administration of about 40 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof increases EF in the subject by at least 5%, at least 10%, at least 20%, at least 25%, or at least 30%, as compared to baseline levels e.g., after 24 weeks of treatment. In some embodiments, administration of about 80 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof increases EF in the subject by at least 5%, at least 10%, at least 20%, at least 25%, or at least 30%, as compared to baseline levels e.g., after 24 weeks of treatment. In some embodiments, administration of about 100 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof increases EF in the subject by at least 5%, at least 10%, at least 20%, at least 25%, or at least 30%, as

compared to baseline levels e.g., after 24 weeks of treatment. In some embodiments, the administration of Compound (I) or a pharmaceutically acceptable salt thereof increases EF by at least 25% in the subject, e.g., after 24 weeks of treatment. In one embodiment, EF is left ventricular ejection fraction (LVEF).

In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in renin in the subject as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in renin in the subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, or at least 60%, as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of about 20 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in renin in the subject by at least 10%, at least 15%, at least 20%, at least 25%, or at least 30%, as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of about 40 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in renin in the subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, or at least 40%, as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of about 80 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in renin in the subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%, as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of about 100 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in renin in the subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least

40%, at least 45%, at least 50%, or at least 60%, as compared to baseline levels, e.g., after 24 weeks of treatment.

In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in systemic vascular resistance (SVR) of the subject as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in SVR in the subject by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, or at least 30%, as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of about 20 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in SVR in the subject by at least 5%, as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of about 40 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in SVR in the subject by at least 5%, or at least 10%, as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of about 80 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in SVR in the subject by at least 5%, at least 10%, or at least 15%, as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of about 100 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in SVR in the subject by at least 5%, at least 10%, at least 15%, or at least 20%, as compared to baseline levels, e.g., after 24 weeks of treatment.

In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in eGFR of the subject as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof

results in an increase in eGFR of the subject by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, or at least 6%, as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of about 20 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in eGFR of the subject by at least 1%, or at least 2%, as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of about 40 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in eGFR of the subject by at least 1%, or at least 2%, as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of about 80 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in eGFR of the subject by at least 1%, at least 2%, or at least 3%, as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of about 100 mg per day of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in eGFR of the subject by at least 1%, at least 2%, at least 3%, or at least 4%, as compared to baseline levels, e.g., after 24 weeks of treatment.

In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in stroke volume (SV) in the subject as compared to baseline levels, e.g., after 24 weeks of treatment.

In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in serum creatinine in the subject as compared to baseline levels, e.g., after 24 weeks of treatment.

In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in 6-minute walking distance (6MWD) of the subject as compared to baseline levels, e.g., after 24 weeks of treatment.

In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ TSS) of the subject as compared to baseline levels, e.g., after 24 weeks of treatment.

In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in maintenance or improvement in New York Heart Association Functional Class (NYHA FC) of the subject as compared to baseline levels, e.g., after 24 weeks of treatment. In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an improvement in New York Heart Association Functional Class (NYHA FC) of the subject as compared to baseline levels, e.g., after 24 weeks of treatment.

In some embodiments, administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in the subject as compared to baseline levels, e.g., after 24 weeks of treatment.

In some embodiments, changes (e.g., increases or decreases) in biomarker levels or patient outcomes following administration of Compound (I) or a pharmaceutically acceptable salt thereof are relative to baseline (pre-administration) measures, and may be placebo-corrected.

In some embodiments, the changes (e.g., increases or decreases) in biomarker levels or patient outcomes following administration of Compound (I) or a pharmaceutically acceptable salt thereof are measured after 1-24 weeks of treatment, optionally after 24 weeks of treatment.

In some embodiments, there is provided Compound (I) or a pharmaceutically acceptable salt thereof for use in any of the methods described herein.

In some embodiments, there is provided Compound (I) or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for use in any of the methods described herein.

Pharmaceutical Compositions

In some embodiments, the methods for treating subjects with heart failure described herein may comprise administration of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and from 5 mg to 360 mg of Compound (I) or a pharmaceutically acceptable salt thereof. Such pharmaceutical compositions also form an embodiment of the present disclosure.

The one or more excipient(s) selected for inclusion in such a pharmaceutical composition will depend on factors such as the mode of administration and the form of the composition provided. Pharmaceutically acceptable excipients are known in the art, see for instance Remington's Pharmaceutical Sciences (by Joseph P. Remington, 18th ed., Mack Publishing Co., Easton, PA), and *Handbook of Pharmaceutical Excipients*, Sixth edition, Pharmaceutical Press, edited by Rowe, Ray C; Sheskey, Paul J; Quinn, Marian, both of which are incorporated by reference herein in their entirety.

Pharmaceutically acceptable excipients may function as, for example, adjuvants, diluents, carriers, stabilisers, flavourings, colorants, fillers, binders, disintegrants, lubricants, glidants, thickening agents and coating agents. As persons skilled in the art will appreciate, certain pharmaceutically acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the composition and what other excipients are present in the composition.

The pharmaceutical compositions may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), or for parenteral

administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing). The compositions may be obtained by conventional procedures well known in the art. Compositions intended for oral use may contain additional components, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

In one embodiment, the pharmaceutical composition comprises from 5 mg to 360 mg of Compound (I) or a pharmaceutically acceptable salt thereof, optionally from 10 mg to 360 mg, from 20 mg to 360 mg, from 30 mg to 360 mg, from 40 mg to 360 mg, from 50 mg to 360 mg, from 60 mg to 360 mg, from 70 mg to 360 mg, from 80 mg to 360 mg, from 90 mg to 360 mg or from 100 mg to 360 mg. In one embodiment, the pharmaceutical composition comprises from 5 mg to 180 mg of Compound (I) or a pharmaceutically acceptable salt thereof, optionally from 10 mg to 180 mg, from 20 mg to 180 mg, from 30 mg to 180 mg, from 40 mg to 180 mg, from 50 mg to 180 mg, from 60 mg to 180 mg, from 70 mg to 180 mg, from 80 mg to 180 mg, from 90 mg to 180 mg or from 100 mg to 180 mg. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof in the pharmaceutical composition is from 10 mg to 100 mg, optionally from 20 mg to 100 mg, from 30 mg to 100 mg, from 40 mg to 100 mg, from 50 mg to 100 mg, from 60 mg to 100 mg, from 70 mg to 100 mg, from 80 mg to 100 mg, or from 90 mg to 100 mg. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof in the pharmaceutical composition is from 20 mg to 80 mg, optionally from 30 mg to 80 mg, from 40 mg to 80 mg, from 50 mg to 80 mg, from 60 mg to 80 mg, or from 70 mg to 80 mg. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof in the pharmaceutical composition is from 5 mg to 180 mg, optionally from 5 mg to 150 mg, from 5 mg to 100 mg, from 5 mg to 90 mg, from 5 mg to 80 mg, from 5 mg to 70 mg, from 5 mg to 60 mg, from 5 mg to 50 mg, from 5 mg to 40 mg, from 5 mg to 30 mg, or from 5 mg to 20 mg. In some embodiments, the

amount of Compound (I) or a pharmaceutically acceptable salt thereof in the pharmaceutical composition is from 10 mg to 180 mg, optionally from 10 mg to 150 mg, from 10 mg to 100 mg, from 10 mg to 90 mg, from 10 mg to 80 mg, from 10 mg to 70 mg, from 10 mg to 60 mg, from 10 mg to 50 mg, from 10 mg to 40 mg, from 10 mg to 30 mg, or from 10 mg to 20 mg. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof in the pharmaceutical composition is from 20 mg to 180 mg, optionally from 20 mg to 150 mg, from 20 mg to 100 mg, from 20 mg to 90 mg, from 20 mg to 80 mg, from 20 mg to 70 mg, from 20 mg to 60 mg, from 20 mg to 50 mg, from 20 mg to 40 mg, or from 20 mg to 30 mg. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof in the pharmaceutical composition is from 30 mg to 180 mg, optionally from 30 mg to 150 mg, from 30 mg to 100 mg, from 30 mg to 90 mg, from 30 mg to 80 mg, from 30 mg to 70 mg, from 30 mg to 60 mg, from 30 mg to 50 mg, or from 30 mg to 40 mg. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof in the pharmaceutical composition is from 40 mg to 180 mg, optionally from 40 mg to 150 mg, from 40 mg to 100 mg, from 40 mg to 90 mg, from 40 mg to 80 mg, from 40 mg to 70 mg, from 40 mg to 60 mg, or from 40 mg to 50 mg. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof in the pharmaceutical composition is about 5 mg, optionally about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, or about 180 mg. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof in the pharmaceutical composition is about 20 mg. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof in the pharmaceutical composition is about 40 mg. In some

embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof in the pharmaceutical composition is about 80 mg. In some embodiments, the amount of Compound (I) or a pharmaceutically acceptable salt thereof in the pharmaceutical composition is about 100 mg.

In one embodiment, the pharmaceutical composition is suitable for oral administration. In one embodiment, the pharmaceutical composition is in the form of one or more tablets. In one embodiment, the pharmaceutical composition is in the form of two tablets. In one embodiment, the pharmaceutical composition is in the form of a single tablet. In one embodiment, the one or more tablets are film-coated tablets.

In one embodiment, the pharmaceutical composition is administered to the subject once daily (QD) or twice daily (BID). In one embodiment, the pharmaceutical composition is administered to the subject once daily (QD). In one embodiment, the pharmaceutical composition is administered to the subject twice daily (BID).

In one embodiment, the pharmaceutical composition is administered to the subject orally.

In one embodiment, the pharmaceutical composition is a single tablet and is administered to the subject orally, once daily.

In one embodiment, the pharmaceutical composition is a single tablet and is administered to the subject orally, twice daily.

Kits

A kit comprising a pharmaceutical composition of the disclosure may be provided. The kit may comprise a package containing a pharmaceutical composition of the disclosure and instructions. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of

manufacture, use or sale for human administration. In some embodiments the instructions comprise instructions for using the pharmaceutical composition in any of the methods described herein.

Exemplary Dosing Regimens

In some embodiments, a tablet comprising Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising from 20 mg to 180 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising from 20 mg to 150 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising from 20 mg to 100 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising from 20 mg to 80 mg of Compound (I) is administered orally to the subject once daily.

In some embodiments, a tablet comprising about 20 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 25 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 30 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 35 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 40 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 45 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 50 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 55 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 60 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a

tablet comprising about 65 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 70 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 75 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 80 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 85 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 90 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 95 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 100 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 110 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 120 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 130 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 140 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 150 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 160 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 170 mg of Compound (I) is administered orally to the subject once daily. In some embodiments, a tablet comprising about 180 mg of Compound (I) is administered orally to the subject once daily.

In some embodiments, a tablet comprising Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising from 10 mg to 100 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a

tablet comprising from 10 mg to 50 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising from 20 mg to 40 mg of Compound (I) is administered orally to the subject twice daily.

In some embodiments, a tablet comprising about 10 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 15 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 20 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 25 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 30 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 35 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 40 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 45 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 50 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 55 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 60 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 65 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 70 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 75 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 80 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 85 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising

about 90 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 95 mg of Compound (I) is administered orally to the subject twice daily. In some embodiments, a tablet comprising about 100 mg of Compound (I) is administered orally to the subject twice daily.

Definitions

As used herein, the articles "a" and "an" may refer to one or to more than one (e.g. to at least one) of the grammatical object of the article.

"About" and "approximately" are used interchangeably herein and mean an acceptable degree of variation for the quantity measured given the nature or precision of the measurements based on pharmaceutical formulation.

Embodiments provided herein as "comprising" one or more features may also be considered as disclosure of the corresponding embodiments "consisting of" such features.

As used herein, the term "heart failure" includes acute heart failure, chronic heart failure (CHF) and acute decompensated heart failure (ADHF). The term "heart failure" also includes more specific diagnoses such as heart failure with preserved ejection fraction (HFpEF), heart failure with ejection fraction $\geq 41\%$ (HF with EF $\geq 41\%$), heart failure with mid-range ejection fraction, or heart failure with reduced ejection fraction (HFrEF). This also includes heart failure due to hypertrophic cardiomyopathy or dilated cardiomyopathy.

The term "pharmaceutically acceptable" as used herein means approved by a regulatory agency of the Federal or a state government, or listed in the U.S. Pharmacopeia, European Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

The term "treatment" refers to the amelioration and/or elimination of one or more symptoms or causes of the target disease or condition. In some embodiments, this involves modulating the levels of one or more biological markers or functions, e.g., as

compared to a diseased state, e.g., to within a non-diseased range (as compared against a healthy cohort).

Concentrations, amounts, volumes, percentages, and other numerical values may be presented herein in a range format. It is to be understood that such range format is used merely for convenience and brevity and should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of the range but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. It is to be understood that ranges include the range endpoints unless explicitly stated otherwise.

The above embodiments and below Examples are to be understood as illustrative and nonlimiting. Further embodiments are envisaged. It is to be understood that any feature provided in relation to any one embodiment may be used alone, or in combination with other features provided, and may also be used in combination with one or more features of any other of the embodiments, or any combination of any other of the embodiments. Furthermore, equivalents and modifications not provided above may also be employed without departing from the scope of the disclosure, which is defined in the accompanying claims.

Other examples and variations are within the scope of the disclosure, as set out in the appended claims. All documents cited herein are each entirely incorporated by reference herein, including all data, tables, figures, and text presented in the cited documents.

Examples

Example 1: Evaluation of chronic efficacy of AZD5462, in cynomolgus monkey (*Macaca fascicularis*) with heart failure and reduced left ventricular ejection fraction (LVEF)

The chronic efficacy of AZD5462 on cardiac function was evaluated in obese and aged cynomolgus monkeys (*Macaca fascicularis*). The cynomolgus monkey is selected as the test species of choice over other lower mammalian species because of its close relationship to humans, both phylogenetically and physiologically. Old cynomolgus monkeys fed with high fat diet for at least 2 years share risk factors with patients susceptible to cardiovascular disease and develop metabolic syndrome which can characteristically progress to heart failure and reduced LVEF. The effect of AZD5462 on LVEF was evaluated when administered by subcutaneous (SC) injection at different dose levels for 73 weeks. From a pool of approximately 100 obese and aged cynomolgus monkeys aged 12–20 years with a body weight of 6–13 kg that had been fed a high-fat diet for at least 2 years; 36 monkeys were identified by 2D echocardiographic screening for LVEF between 30–60%. Healthy monkeys of this age weigh 5–8 kg and have an LVEF of 70–75%, and therefore LVEF below 60% represents an HFrEF model. Identified animals were selected and randomly assigned to 2 treatment groups with 8 monkeys each, and a vehicle group with 20 monkeys. The dosing period consisted of once daily subcutaneous administrations of AZD5462 at dose levels of 0.25, and 1 mg/kg (QD).

Cardiac functional measurements by 2D echocardiography were determined 10 times during the entire study period, at baseline week -2 and at week 5, 9, 13, 17, 21, 25, 29, 37, 41, 45, 49, 54, 57, 61, 65, and 69 of the dosing periods. Parameters included LVEF (%) were based on apical two- and four-chamber views and the biplane method. HDO (High Definition Oscillometry) was used to measure parameters including mean arterial pressure (MAP) and heart rate (HR). Systemic vascular resistance (SVR) was calculated

using the following formula: MAP/CO, where MAP was measured by HDO and the Cardiac Output (CO) was derived from the 2D Echo measurement.

AZD5462 was able to improve LVEF at weeks 5, 9, 13, 17, 21, 25, 29, 37, 41, 45, 49, 54, 57, 61, 65, and 69 in both AZD5462 dose levels compared with vehicle control, without affecting heart rate or blood pressure (Figures 1, 2 and 3).

Figure 1 shows the improvement of LVEF in cynomolgus monkey (*Macaca fascicularis*) with heart failure and reduced LVEF treated with AZD5462. Figure 2 shows that HR is not affected in cynomolgus monkey (*Macaca fascicularis*) with heart failure and reduced LVEF after treatment with AZD5462. Figure 3 shows that MAP is not affected in cynomolgus monkey (*Macaca fascicularis*) with heart failure and reduced LVEF after treatment with AZD5462. Figure 4 shows the change in End Systolic Volume (ESV) after treatment with AZD5462. Figure 5 shows the change in End Diastolic Volume (EDV) after treatment with AZD5462. Figure 6 shows the change in Stroke Volume (SV) after treatment with AZD5462. Figure 7 shows the change in Systemic Vascular Resistance (SVR) after treatment with AZD5462. In Figures 1 to 7, hollow circles indicate administration of AZD5462, and solid circles indicate administration of placebo.

Example 2: Phase 1 (Ph1) Study in Healthy Volunteers

A Phase 1, single ascending dose (SAD) and multiple ascending dose (MAD) study in healthy participants was conducted to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of AZD5462 (ClinicalTrials.gov identifier NCT04994106).

In Part A of the study (SAD), cohorts of participants were randomized to receive single oral doses of AZD5462 (20 mg, 80 mg, 400 mg, 750 mg, and 1000 mg) or placebo. In Part B (MAD), participant cohorts were randomized to receive a single oral dose of AZD5462 on days 1 and 10, and twice-daily (BID) oral doses (40 mg, 120 mg, 250 mg, and 500 mg each dose) from days 2 to 9, or placebo. The study design is shown in Figure 8.

Each Part included at least one cohort of participants of Japanese descent.

AZD5462 was administered as a 10 mg/mL oral solution.

The study endpoints were as follows:

Primary endpoint

- Safety and tolerability of AZD5462 following single and multiple ascending oral dose administration

Secondary endpoint

- Single-dose and steady-state pharmacokinetics of AZD5462 following oral administration

Exploratory endpoints

- Change from baseline in plasma/serum renin concentration
- Creatinine clearance (eGFR) averaged over 24 hours
- Change from baseline in 24-hour ambulatory blood pressure monitoring measurements (MAD study only)

Inclusion Criteria

- Healthy male and female (of non-childbearing potential) participants aged 18 to 50 years of age and healthy participants of Japanese descent, 20 to 50 years of age, with suitable veins for cannulation or repeated venipuncture
- Female participants must have a negative pregnancy test at the Screening Visit
- Have a body mass index between 18 and 32 kg/m² inclusive and weigh at least 50 kg and no more than 105 kg inclusive
- For cohorts comprised solely of participants of Japanese descent, a participant will be considered of Japanese descent only if both parents and all grandparents are Japanese

Exclusion Criteria

- History of any clinically important disease or disorder

- History or presence of gastrointestinal, hepatic or renal disease or any other condition known to interfere with absorption, distribution, metabolism or excretion of drugs
- Any clinically important illness, medical/surgical procedure or trauma within 4 weeks of the first administration of study drug
- Any clinically important abnormalities in clinical chemistry, hematology or urinalysis results
- Any positive result on Screening for serum hepatitis B surface antigen, hepatitis C antibody, and Human immunodeficiency virus
- Abnormal vital signs
- Any clinically important abnormalities in rhythm, conduction or morphology of the resting electrocardiogram (ECG) and any clinically important abnormalities in the 12 lead ECG
- History of severe allergy/hypersensitivity or ongoing clinically important allergy/hypersensitivity, or history of hypersensitivity to drugs with a similar chemical structure or class to AZD5462
- Use of any prescribed or nonprescribed medication including antacids, analgesics (other than paracetamol/acetaminophen), herbal remedies, mega dose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during the 2 weeks or 5 half-lives of the medication, whichever is longer, prior to the first administration of study drug
- Has received another new chemical entity (defined as a compound which has not been approved for marketing) within 30 days (or 5 half-lives, whichever is the longest) of the first administration of study drug in this study

- Clinical signs and symptoms consistent with Coronavirus disease 2019, eg, fever, dry cough, dyspnea, sore throat, fatigue, or confirmed infection by appropriate laboratory test within the last 4 weeks prior to Screening or on admission

Results

All randomized participants completed the SAD study and 36 out of 42 completed the MAD study. Participant disposition and baseline characteristics are shown in Table 1.

Table 1

	Overall (N = 98)	
	Part A – SAD (N = 56)	Part B – MAD (N = 42)
Completed study, n (%)	56 (100)	36 (85.7)
Age, years, median (range)	39.0 (20–50)	35.0 (25–50)
Male, n (%)	53 (94.6)	41 (97.6)

Safety

Table 2 provides a summary of adverse events observed in the Phase 1 study. In summary:

- There were no major safety and tolerability concerns up to the highest dose (1000 mg SAD, 500 mg BID MAD).
- No deaths, other serious adverse events (AEs) or any other significant AEs occurred. Three patients discontinued treatment owing to AEs in the MAD study (dizziness with 120 mg BID, supraventricular tachycardia with 250 mg BID and a positive COVID-19 test).
- AEs appeared to be more common with AZD5462 than with placebo (approximately 40% vs 20%), with no clear relationship to dose.
 - Most AEs were mild or moderate in intensity, with exception of one AE in the MAD study being reported as severe (dizziness).

- No clinically relevant trends in 12-lead electrocardiograms or clinical laboratory results.

Table 2 – Summary of adverse events

	Part A – SAD (N = 56)		Part B – MAD (N = 42)	
	Pooled AZD5462 (n = 42)	Pooled placebo (n = 14)	Pooled AZD5462 (n = 32)	Pooled placebo (n = 10)
Any AE, n (%)	12 (28.6)	1 (7.1)	14 (43.8)	2 (20.0)
Any serious AE, n (%)	0	0	0	0
AE leading to discontinuation, n (%)	0	0	3 (9.4)	0
Treatment-related AEs, n (%)	8 (19.0)	1 (7.1)	8 (25.0)	1 (10.0)
AEs, n (%)				
Gastrointestinal disorders	3 (7.1) ^a	1 (7.1)	4 (12.5) ^b	1 (10.0)
Nausea	1 (2.4) ^c	1 (7.1)	2 (6.3) ^d	0
Vomiting	1 (2.4) ^c	0	2 (6.3) ^d	0
Diarrhoea	1 (2.4) ^c	0	Not reported	Not reported
Abdominal pain	1 (2.4) ^e	0	1 (3.1) ^f	0
Headache	3 (7.1) ^g	0	2 (6.3) ^h	0
Device site dermatitis	3 (7.1) ⁱ	0	0	1 (10.0)
Orthostatic heart rate response increase ^j	1 (2.4) ^k	0	2 (6.3) ^l	0

^a80 mg cohort, n = 1; 750 mg cohort, n = 1; 400 mg Japanese descent cohort, n = 1. ^b120 mg BID cohort, n = 1; 250 mg BID cohort, n = 1; 500 mg BID cohort, n = 1; 500 mg Japanese descent cohort, n = 1. ^c400 mg Japanese descent cohort, n = 1. ^d120 mg BID cohort, n = 1; 250 mg BID cohort, n = 1. ^e80 mg cohort, n = 1. ^f500 mg BID Japanese descent cohort, n = 1. ^g400 mg cohort, n = 1; 1000 mg cohort, n = 2. ^h40 mg BID cohort, n = 1; 120 mg BID cohort, n = 1. ⁱ400 mg cohort, n = 1; 400 mg Japanese descent cohort, n = 1; 1000 mg cohort, n = 1. ^jIncluded as an AE of interest. ^k750 mg cohort, n = 1. ^l40 mg BID cohort, n = 1; 500 mg BID Japanese descent cohort, n = 1.

Vital signs

Vital signs (supine systolic and diastolic BP, orthostatic BP, HR, temperature, and respiratory rate) were evaluated during the study.

In Part A, all vital sign measurements were measured with the participant in supine position and after 5-minute supine rest, before any blood draws. Blood pressure was measured in triplicates (within a total of 5 minutes) and the mean of the measurements were used. Measurements were done pre-dose, 20 minutes, 40 minutes, 1 hour, 2 hours, and 12 hours post-dose (Day 1); 24 hours post-dose (Day 2); and 48 hours post-dose (Day 3).

In Part B, all vital sign measurements were measured after 5 minutes rest in supine position, before any blood collection. Blood pressure was measured in triplicates (within a total of 5 minutes) and the mean of the measurements were used. Vital signs were measured pre-morning dose and 20 minutes, 40 minutes, 1, 2, and 12 hours post-morning dose.

A trend in systolic and diastolic BP decrease and a trend in HR increase were observed. No AEs of hypotension were reported. No other clinically relevant trends were observed for vital signs. There were no AEs related to vital signs reported.

Ambulatory blood pressure monitoring (ABPM)

Participants in Part B participated in 24-hour ABPM assessments, including mean 24-hour systolic and diastolic blood pressure (BP) and heart rate (HR). There was a trend for dose-dependent reduction in daytime and overall 24 h systolic and diastolic BP. No clear trend in HR was observed given the CIs and lack of dose dependence. There were no clear effects on pulse pressure. Figure 9 presents the ambulatory systolic BP. Figure 10 presents the ambulatory diastolic BP. Figure 11 presents the ambulatory HR. Figure 12 presents the ambulatory pulse pressure.

No major safety and tolerability concerns were identified in this study in doses up to the highest dose given (1000 mg Part A [SAD] and 500 mg BID Part B [MAD]). Overall, AZD5462 was generally well-tolerated and there were no major safety concerns.

Pharmacokinetics

Pharmacokinetic data from the study is presented in Table 3 to Table 6. In summary:

- AZD5462 was rapidly absorbed with a median time to maximum plasma concentration between 0.53 hours (range, 0.50–1.00) and 1.75 hours (0.53–2.23) across all cohorts.
- Plasma AZD5462 concentration declined in a biphasic manner, and had a geometric mean terminal half-life of 3.6–6.3 hours across Japanese and non-Japanese participants in the SAD cohorts.
- Exposure to AZD5462 increased more than proportionately with dose.
- Semi-logarithmic plots of geometric mean AZD5462 plasma concentration versus time for non-Japanese participants for Parts A and B are presented in Figure 13 (Part A), Figure 14 (Part B, Day 1) and Figure 15 (Part B, Day 10)

In Table 3 to Table 6 below, N = number of participants in the PK analysis set; n = Number of participants included in analysis; n = N for all parameters unless specified; Gmean = Geometric mean; gCV = Geometric coefficient of variance (%); Max = Maximum; Min = Minimum; τ = 12 hours.

Table 3 - Plasma Pharmacokinetic Parameters for AZD5462 Following Single Oral Dose Administration in Healthy Non-Japanese Participants – Part A

Parameter (Units)	Statistic	Dose				
		20 mg	80 mg	400 mg	750 mg	1000 mg
N = 6	n					
AUCinf	Gmean	0.6602	3.181	42.96	90.23	186.8

($\mu\text{mol}\cdot\text{h/L}$)	(gCV%) Min–Max	(40.08) 0.419-1.18	(54.95) 1.91-6.18	(44.87) 26.5-75.3	(13.63) 72.1-102	(34.94) 116-270
AUClast ($\mu\text{mol}\cdot\text{h/L}$)	Gmean (gCV%) Min–Max	0.6427 (39.67) 0.407-1.13	3.138 (55.25) 1.88-6.08	42.89 (44.87) 26.5-75.1	90.08 (13.79) 71.7-102	186.6 (34.99) 116-270
Cmax ($\mu\text{mol/L}$)	Gmean (gCV%) Min–Max	0.2575 (39.73) 0.158-0.463	1.935 (58.59) 0.979-3.68	19.92 (46.15) 9.57-28.2	36.21 (16.43) 30.1-43.9	58.74 (19.02) 48.1-77.2
tmax (h)	Median Min–Max	1.02 0.50-1.50	0.55 0.52-1.18	0.84 0.53-1.50	0.94 0.52-2.00	1.75 0.53-2.23
tlast (h)	Median Min–Max	10.02 6.00-12.00	14.04 12.02-24.37	36.03 24.05-36.13	48.05 24.05-48.08	42.13 24.27-48.20
t _{1/2} (h)	Gmean (gCV%) Min–Max	1.623 (49.82) 1.02-3.51	3.585 (67.84) 1.73-7.29	4.894 (36.90) 3.09-7.80	6.320 (80.15) 2.71-15.5	5.474 (74.10) 2.27-15.5
CL/F (L/h)	Mean (gCV%) Min–Max	55.62 (40.08) 31.2-87.6	46.17 (54.95) 23.8-77.1	17.09 (44.87) 9.75-27.7	15.26 (13.63) 13.5-19.1	9.827 (34.94) 6.80-15.8
Vz/F (L)	Gmean (gCV%) Min–Max	130.3 (20.96) 88.7-158	238.8 (75.58) 100-799	120.7 (66.61) 43.5-259	139.2 (89.80) 54.6-428	77.60 (99.91) 27.2-317
CLR (L/h)	Gmean (gCV%) Min–Max	0.01642 (91.11) 0.00510-0.0406	0.01602 (195.0) 0.00250-0.0591	0.02326 (66.85) 0.0101-0.0579	0.03665 (31.06) 0.0244-0.0589	0.01797 (160.5) 0.00390-0.0772

Table 4 - Plasma Pharmacokinetic Parameters for AZD5462 Following Single Oral Dose Administration in Healthy Japanese and Non-Japanese Participants – Part A

Parameter (Units)	Statistic	400 mg		750 mg	
		Japanese	Non-Japanese	Japanese	Non-Japanese
N = 6	n				
AUCinf ($\mu\text{mol}\cdot\text{h/L}$)	Gmean (gCV%) Min–Max	49.03 (16.87) 36.1-58.3	42.96 (44.87) 26.5-75.3	124.6 (29.62) 82.4-192	90.23 (13.63) 72.1-102
AUClast ($\mu\text{mol}\cdot\text{h/L}$)	Gmean (gCV%) Min–Max	48.96 (16.85) 36.0-58.2	42.89 (44.87) 26.5-75.1	124.5 (29.62) 82.4-192	90.08 (13.79) 71.7-102
Cmax ($\mu\text{mol/L}$)	Gmean (gCV%) Min–Max	20.51 (26.47) 15.9-28.2	19.92 (46.15) 9.57-28.2	50.76 (13.08) 42.2-60.1	36.21 (16.43) 30.1-43.9
tmax (h)	Median Min–Max	0.64 0.50-3.02	0.84 0.53-1.50	1.29 0.62-2.00	0.94 0.52-2.00
tlast (h)	Median Min–Max	24.11 16.07-48.05	36.03 24.05-36.13	36.10 24.00-48.15	48.05 24.05-48.08
t _{1/2}	Gmean	3.586	4.894	4.693	6.320

(h)	(gCV%) Min–Max	(57.26) 2.42-10.3	(36.90) 3.09-7.80	(44.12) 2.93-7.15	(80.15) 2.71-15.5
CL/F (L/h)	Gmean (gCV%) Min–Max	14.98 (16.87) 12.6-20.4	17.09 (44.87) 9.75-27.7	11.05 (29.62) 7.17-16.7	15.26 (13.63) 13.5-19.1
Vz/F (L)	Gmean (gCV%) Min–Max	77.50 (50.37) 50.2-188	120.7 (66.61) 43.5-259	74.82 (21.60) 59.3-96.7	139.2 (89.80) 54.6-428
CLR (L/h)	Gmean (gCV%) Min–Max	0.02638 (84.05) 0.00624-0.0422	0.02326 (66.85) 0.0101-0.0579	0.03416 (42.82) 0.0193-0.0694	0.03665 (31.06) 0.0244-0.0589

Non-Japanese Participants – Part A (SAD)

AZD5462 was rapidly absorbed following single oral administration with a median t_{max} of 0.55 h to 1.75 h post-dose and an overall range of 0.50 h to 2.23 h post-dose with no apparent trend with dose.

The increase in systemic exposure to AZD5462 with dose was supraproportional for C_{max} , AUC_{inf} , and AUC_{last} with slopes of 1.381 (90% CI: 1.304, 1.457), 1.438 (90% CI: 1.354, 1.523) and 1.445 (90% CI: 1.361, 1.529), respectively and corresponding 90% CI that did not span unity.

Japanese Participants – Part A (SAD)

AZD5462 was rapidly absorbed following single oral administration with a median t_{max} of 0.64 h to 1.29 h post-dose and an overall range of 0.50 h to 3.02 h post-dose with no apparent trend with dose.

The increase in systemic exposure to AZD5462 with dose was supraproportional for C_{max} , AUC_{inf} and AUC_{last} with slopes of 1.441 (90% CI: 1.099, 1.784), 1.484 (90% CI: 1.090, 1.878) and 1.485 (90% CI: 1.091, 1.879), respectively and corresponding 90% CI that did not span unity.

There appeared to be no difference in peak (C_{max}) and total (AUC_{inf} and AUC_{last}) exposure between Japanese and non-Japanese participants following a 400 mg single

dose. The GLSM ratio was 102.94% (90% CI: 70.55%, 150.22%) for C_{max}, 114.12 (90% CI: 81.20%, 160.37%) for AUC_{inf} and 114.16% (90% CI: 81.24%, 160.42%) for AUC_{last}. At the 750 mg dose level, there appeared to be no difference in peak exposure, however total exposure was higher in Japanese participants compared to non-Japanese participants. The GLSM ratio was 140.17% (90% CI: 7.31%, 2688.50%) for C_{max}, 138.12% (90% CI: 108.99%, 175.04%) for AUC_{inf} and 138.25% (90% CI: 109.04%, 175.29%) for AUC_{last}.

Table 5 - Plasma Pharmacokinetic Parameters for AZD5462 Following Single or Multiple Twice Daily Oral Dose Administration in Healthy Non-Japanese Participants – Part B

Parameter (Units)	Statistic	Dose							
		Day 1				Day 10			
		40 mg	120 mg	250 mg	500 mg	40 mg	120 mg (n = 5)	250 mg (n = 6)	500 mg
N = 6 ^a	n								
AUC _τ (μmol*h/L)	Gmean (gCV%) Min–Max	1.252 (25.82) 0.842-1.74	6.276 (36.33) 4.18-11.8	17.51 (20.91) 12.2-21.4	63.95 (44.42) 38.6-139	1.391 (34.82) 0.980-2.18	6.697 (31.69) 4.71-9.82	23.22 (17.53) 17.3-28.4	91.18 (41.33) 56.1-185
AUC _{inf} (μmol*h/L)	Gmean (gCV%) Min–Max	1.256 (25.84) 0.843-1.74	6.415 (36.88) 4.24-12.1	17.83 (21.43) 12.4-22.2	64.67 (44.62) 39.1-141	NA	NA	NA	NA
AUC _{last} (μmol*h/L)	Gmean (gCV%) Min–Max	1.229 (25.52) 0.833-1.72	6.362 (36.90) 4.21-12.0	17.76 (21.23) 12.4-22.0	64.56 (44.58) 39.0-141	1.389 (34.88) 0.971-2.18	6.935 (33.03) 4.82-10.1	24.01 (17.55) 18.1-29.3	93.62 (41.64) 58.1-191
C _{max} (μmol/L)	Gmean (gCV%) Min–Max	0.5667 (29.79) 0.419-0.812	4.289 (40.95) 3.16-9.10	11.72 (14.75) 9.07-14.4	26.40 (36.08) 15.7-43.4	0.7112 (57.28) 0.349-1.56	4.116 (29.59) 2.90-6.16	15.78 (13.60) 12.4-17.9	33.35 (24.88) 21.7-45.8
t _{max} (h)	Median Min–Max	1.03 0.53-1.50	0.66 0.52-1.02	0.53 0.50-1.00	0.87 0.55-3.00	0.69 0.28-1.20	0.55 0.50-0.55	0.54 0.52-1.13	1.07 0.50-1.58
t _{last} (h)	Median Min–Max	8.01 7.98-8.07	19.84 8.02-23.87	23.78 23.75-23.92	23.73 23.72-23.80	12.03 8.00-16.03	24.02 16.00-36.02	36.02 24.00-36.05	36.01 24.08-36.25
t _{1/2z} (h)	Gmean (gCV%) Min–Max	1.325 (11.69) 1.18-1.55	3.073 (65.79) 1.21-5.47	3.979 (15.28) 3.27-4.98	2.991 (18.22) 2.34-3.85	2.216 (49.05) 1.19-3.48	6.149 (84.64) 3.11-21.3	9.004 (45.23) 4.68-16.5	6.101 (60.19) 2.37-10.4
CL/F (L/h)	Gmean (gCV%) Min–Max	58.46 (25.84) 42.1-87.1	34.35 (36.88) 18.3-52.0	25.74 (21.43) 20.6-36.9	14.19 (44.62) 6.51-23.5	52.81 (34.82) 33.7-74.9	32.90 (31.69) 22.4-46.8	19.77 (17.53) 16.2-26.5	10.07 (41.33) 4.97-16.4
V _z /F (L)	Gmean (gCV%) Min–Max	111.8 (29.15) 73.5-154	152.3 (62.86) 73.2-305	147.7 (19.40) 117-212	61.25 (49.38) 30.1-130	168.8 (35.99) 118-266	291.8 (77.42) 181-921	256.8 (54.53) 129-502	88.62 (72.56) 43.0-245
CLR	Gmean					0.02222	0.04528	0.03223	0.02876

(L/h)	(gCV%) Min–Max	NA	NA	NA	NA	(54.47) 0.0101- 0.0411	(16.97) 0.0354- 0.0566	(68.75) 0.0146- 0.0750	(61.32) 0.0110- 0.0458
Rac AUC	Gmean (gCV%) Min–Max	NA	NA	NA	NA	1.111 (28.52) 0.806-1.68	1.040 (15.51) 0.832-1.24	1.371 (14.94) 1.05-1.57	1.426 (7.309) 1.33-1.63
Rac Cmax	Gmean (gCV%) Min–Max	NA	NA	NA	NA	1.255 (61.26) 0.564-2.73	0.9167 (31.58) 0.677-1.44	1.363 (26.27) 0.861-1.78	1.263 (14.60) 1.06-1.58
TCP AUC	Gmean (gCV%) Min–Max	NA	NA	NA	NA	1.107 (28.52) 0.801-1.67	1.020 (15.61) 0.814-1.23	1.351 (15.13) 1.04-1.55	1.410 (7.602) 1.31-1.62

^a N = 7 for 250 mg cohort

Table 6 - Plasma Pharmacokinetic Parameters for AZD5462 Following Single or Multiple Twice Daily Oral Dose Administration in Healthy Japanese and Non-Japanese Participants – Part B

Parameter (Units)	Statistic	Day 1		Day 10	
		500 mg		500 mg	
N = 7 ^a	n	Japanese	non-Japanese	Japanese (n = 5)	non-Japanese
AUC _τ (μmol*h/L)	Gmean (gCV%) Min–Max	75.55 (32.72) 52.6-145	63.95 (44.42) 38.6-139	102.1 (13.91) 83.0-118	91.18 (41.33) 56.1-185
AUC _{inf} (μmol*h/L)	Gmean (gCV%) Min–Max	76.41 (32.96) 52.8-147	64.67 (44.62) 39.1-141	NA	NA
AUC _{last} (μmol*h/L)	Gmean (gCV%) Min–Max	76.30 (32.97) 52.8-147	64.56 (44.58) 39.0-141	105.6 (15.68) 84.6-129	93.62 (41.64) 58.1-191
C _{max} (μmol/L)	Gmean (gCV%) Min–Max	36.71 (21.80) 29.6-56.0	26.40 (36.08) 15.7-43.4	43.57 (17.53) 36.0-57.5	33.35 (24.88) 21.7-45.8
t _{max} (h)	Median Min–Max	1.07 0.40-1.58	0.87 0.55-3.00	0.62 0.53-1.27	1.07 0.50-1.58
t _{last} (h)	Median Min–Max	23.73 23.70-23.85	23.73 23.72-23.80	35.97 23.95-36.03	36.01 24.08-36.25
t _{1/2,z} (h)	Gmean (gCV%) Min–Max	3.047 (16.02) 2.51-3.79	2.991 (18.22) 2.34-3.85	9.012 (65.11) 4.24-18.6	6.101 (60.19) 2.37-10.4
CL/F (L/h)	Gmean (gCV%) Min–Max	12.01 (32.96) 6.26-17.4	14.19 (44.62) 6.51-23.5	8.993 (13.91) 7.80-11.1	10.07 (41.33) 4.97-16.4
V _z /F (L)	Gmean (gCV%) Min–Max	52.82 (43.48) 22.6-72.9	61.25 (49.38) 30.1-130	116.9 (60.69) 54.1-209	88.62 (72.56) 43.0-245
CLR	Gmean			0.02638	0.02876

(L/h)	(gCV%) Min–Max	NA	NA	(73.44) 0.00927-0.0465	(61.32) 0.0110-0.0458
Rac AUC	Gmean (gCV%) Min–Max	NA	NA	1.431 (22.55) 1.06-1.79	1.426 (7.309) 1.33-1.63
Rac Cmax	Gmean (gCV%) Min–Max	NA	NA	1.305 (12.22) 1.09-1.47	1.263 (14.60) 1.06-1.58
TCP AUC	Gmean (gCV%) Min–Max	NA	NA	1.414 (22.48) 1.05-1.78	1.410 (7.602) 1.31-1.62

^a N= 6 for Non-Japanese participants

Non-Japanese participants – Part B (MAD)

AZD5462 was rapidly absorbed following single and multiple twice daily oral administration with a median t_{max} of 0.53 h to 1.07 h post-dose and an overall range of 0.28 h to 3.00 h post-dose. There was no apparent trend with dose or day.

There was a decrease in apparent clearance (CL/F) with increasing dose. Geometric mean CL/F values ranged between 10.07 L/h and 58.46 L/h.

The increase in systemic exposure to AZD5462 at steady state with dose was supraproportional for C_{max} and AUC_τ, with slopes of 1.558 (90% CI: 1.429, 1.688) and 1.644 (90% CI: 1.522, 1.766), respectively and corresponding 90% CI that did not span unity.

There appeared to be no evidence of time-dependence in PK at the lower (40 mg and 120 mg) dose levels following multiple twice daily oral administration. The geometric mean AUC ratios (steady state AUC_τ over first dose AUC_{inf}) were 110.70% (90% CI: 87.95%, 139.934%) and 102.26% (90% CI: 88.39%, 118.32%) at the 40 mg and 120 mg dose levels, respectively.

At the higher (250 mg and 500 mg) dose levels, the geometric mean AUC ratios (steady state AUC_τ over first dose AUC_{inf}) were 133.63% (90% CI: 118.01%, 151.32%) and 140.98% (90% CI: 132.44%, 150.06%). This could potentially suggest time-dependence in PK following multiple BID oral administration at these dose levels.

Japanese participants– Part B (MAD)

AZD5462 was rapidly absorbed following single and multiple twice daily oral administration with a median t_{max} of 0.62 h to 1.07 h post-dose and an overall range of 0.40 h to 1.58 h post-dose. There was no apparent trend with day.

The geometric mean AUC ratio (steady state AUC_{τ} over first dose AUC_{inf}) was 133.60% (90% CI: 100.99%, 176.74%). This could potentially suggest time-dependence in PK following multiple twice daily administration at the 500 mg dose level.

There appeared to be a trend towards higher peak but similar total exposure in Japanese participants compared to non-Japanese participants following single or multiple twice daily dosing at the 500 mg dose level. The GLSM ratios on Day 1 were 139.05% (90% CI: 104.64%, 184.76%) for C_{max} , 118.15% (90% CI: 81.43%, 171.42%) for AUC_{inf} and 118.19% (90% CI: 81.46%, 171.46%) for AUC_{last} . The GLSM ratios on Day 10 were 130.65% (90% CI: 102.75%, 166.11%) for C_{max} and 111.96% (90% CI: 79.37%, 157.95%) for AUC_{τ} .

Pharmacodynamics – Renin and creatinine

- Plasma renin levels increased dose-dependently in participants receiving multiple doses of AZD5462 (**Figures 16 and 17**).
- Serum creatinine levels decreased in a dose-dependent manner corresponding to an increase in estimated glomerular filtration rate (eGFR) in participants receiving multiple doses of AZD5462 (**Figures 18 and 19**).

Example 3: A Randomized, 6-period, 6-treatment, Single-Dose, Crossover Study to Assess the Pharmacokinetics of AZD5462 Film-coated Tablet Formulation, to Assess the Relative Bioavailability of AZD5462 Film-coated Tablet Formulation vs Oral Solution, and to Assess the Influence of Food on the Pharmacokinetics of AZD5462 in Healthy Participants (Clinicaltrials.gov Identifier NCT05512806)

This study was an open-label, randomized, 6-period, 6-treatment, single-dose, crossover study in healthy participants, performed at a single study center. A total of 16 healthy male and female participants of non-childbearing potential were randomized in this study. Each participant received 6 single-dose treatments of AZD5462 across 6 treatment periods according to 1 of 4 treatment sequences (ADBCEF, BACDFE, CBDAEF, and DCABFE):

- Treatment A: 60 mg of AZD5462 film-coated tablet (3 × 20 mg tablet; fasted state).
- Treatment B: 60 mg of AZD5462 film-coated tablet (3 × 20 mg tablet; fed state).
- Treatment C: 180 mg of AZD5462 film-coated tablet (1 × 180 mg tablet; fasted state).
- Treatment D: 180 mg of AZD5462 oral solution (10 mg/mL; fasted state).
- Treatment E: 720 mg of AZD5462 film-coated tablet (4 × 180 mg tablet; fasted state).
- Treatment F: 720 mg of AZD5462 film-coated tablet (4 × 180 mg tablet; fed state).

Treatments A, B, C, and D were administered during Periods 1 to 4, and Treatments E and F were administered during Periods 5 and 6.

There was a 2-day washout between Periods 1 and 2, Periods 3 and 4, and Periods 4 and 5 (ie, 48 hours [h] between the single doses of AZD5462). The duration of the washout was based on the estimated $t_{1/2}$ of AZD5462, which was estimated to be approximately 5 h. The washout between Periods 2 and 3 was 3 days. After 48 h between the single doses of AZD5462, an additional day was included as buffer day, in consideration of participant's tolerance to the study procedures. The washout between Periods 5 and 6 was up to 5 days (ie, up to 120 h between the single doses of AZD5462) because AZD5462 at 720 mg could affect CYP3A4 activity via time-dependent inhibition and/or

induction. Since pre-clinical data indicated that CYP3A4 plays an important role in the elimination of AZD5462, the washout period needed to be extended to ensure that the enzyme activity returned to baseline to avoid the risk of carry-over effects.

The study comprised:

- A Screening Period of maximum 28 days.
- Six Treatment Periods during which participants were residents at the study center from Day -1 until Day 17.

A Follow-up Phone Call on Day 21 ($\pm$ 1 day) to record adverse events (AEs) and concomitant medication.

The Study Flow Chart is shown in Figure 20.

AZD5462 Administered Under Fasted Conditions (Treatments A, C, D, and E)

AZD5462 was administered after an overnight fast of at least 10 h. The dose of AZD5462 film-coated tablet was administered with approximately 240 mL of water. The dose of AZD5462 oral solution was administered with water, the total volume administered (AZD5462 oral solution and water) was approximately 240 mL.

Participants were allowed to drink water freely until 1 hour before dosing to prevent dehydration. Water was allowed ad libitum from 2 h after dosing, and a standard meal was given 4 h after dosing.

AZD5462 Administered Under Fed Conditions (Treatments B and F)

AZD5462 was administered with approximately 240 mL of water after a high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) test meal had been consumed.

Following an overnight fast of at least 10 h, participants had to start the ingestion of the test meal 30 minutes prior to dosing of AZD5462. Participants had to finish this meal within

30 minutes or less. The participants had to finish at least 75% of the meal to proceed with dosing.

No fluids, except for fluids included in the test meal, were allowed apart from water, which could be given until 1 hour prior to dosing and resumed 2 h after dosing.

Study Objectives:**Primary Objectives:**

- To characterize the pharmacokinetics (PK) of a film-coated tablet of AZD5462 at 3 dose levels by assessment of AUC_{inf}, AUC_{last}, and C_{max} of AZD5462.
- To evaluate the effect of a high-fat, high-calorie meal, in comparison to fasting conditions, on the PK of AZD5462 after a single oral dose at 2 dose levels by assessment of AUC_{inf}, AUC_{last}, and C_{max} of AZD5462.
- To evaluate the relative bioavailability of the film-coated tablet vs oral solution formulation by assessment of AUC_{inf}, AUC_{last}, and C_{max} of AZD5462.

Secondary Objectives:

- To further assess the safety and tolerability of single doses of AZD5462 in healthy participants.

Inclusion Criteria:

- Provision of signed and dated, written informed consent prior to any study specific procedures.
- Healthy male and female participants aged 18 to 55 years at screening and admission with suitable veins for cannulation or repeated venipuncture.
- Female participants must have a negative pregnancy test at screening and on admission to the study center, must not be lactating and must be of non-

childbearing potential confirmed at screening by fulfilling one of the following criteria:

1. Postmenopausal defined as amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and Follicle-stimulating hormone (FSH)/Luteinizing hormone (LH) levels in the postmenopausal range.
 2. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.
- Male participant must adhere to the contraception methods details.
 - Have a Body mass index (BMI) between 18 and 32 kg/m² inclusive and weigh at least 50 kg and no more than 105 kg inclusive at screening.

Exclusion Criteria:

- History of any clinically significant disease or disorder which may either put the participant at risk because of participation in the study, or influence the results or the participant's ability to participate in the study.
- Any of the below conditions:
 1. Systemic sclerosis.
 2. Moderate to severe valvular disease.
 3. Hypertrophic obstructive cardiomyopathy.
 4. Restrictive cardiomyopathy.
 5. Gilbert's syndrome.
 6. History of vascular or left ventricular aneurysms, or prior dissections.
 7. Any history of joint hypermobility, Marfan's Syndrome, or any connective tissue disorder.

- History or presence of gastrointestinal, hepatic or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.
- Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of Investigational medicinal product (IMP).
- Any laboratory values with the following deviations at screening, or admission to the study center:
 1. Total bilirubin > Upper limit of normal (ULN).
 2. Alanine aminotransferase > 1.5 × ULN.
 3. Aspartate aminotransferase > 1.5 × ULN.
 4. Estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73m², as assessed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.
 5. White blood cell count < 3.5 k/uL and > ULN.
 6. Hemoglobin < Lower limit of normal (LLN).
- Any clinically significant abnormalities in clinical biochemistry, hematology, or urinalysis results.
- Any clinically significant abnormal findings in vital signs after 5 minutes supine rest, at screening or admission defined as any of the following:
 1. Systolic Blood pressure (BP) < 90 mmHg or ≥ 140 mmHg.
 2. Diastolic BP < 50 mmHg or ≥ 90 mmHg.
 3. Heart rate < 50 bpm or > 90 bpm.
- Any clinically important abnormalities in rhythm, conduction or morphology of the resting 12-lead Electrocardiogram (ECG) at screening or admission.
 1. Prolonged QTcF > 450 ms.
 2. Shortened QTcF < 340 ms.

3. Family history of long QT syndrome.
 4. PR(PQ) interval shortening < 120 ms (PR > 110 ms but < 120 ms is acceptable if there is no evidence of ventricular pre-excitation).
 5. PR(PQ) interval prolongation (> 240 ms) intermittent second (Wenckebach block while asleep is not exclusive) or third-degree AV block, or AV dissociation.
 6. Persistent or intermittent complete BBB. Participants with Intraventricular conduction delay (IVCD) with QRS < 120 ms are acceptable if there is no evidence of eg, ventricular hypertrophy, or pre-excitation.
- Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody, and Human immunodeficiency virus (HIV) antibody.
 - Known or suspected history of drug abuse.
 - Has received another new chemical entity within 30 days of the first administration of IMP in this study.
 - Plasma donation within 1 month of screening or any blood donation/loss > 500 mL during the 3 months prior to screening.
 - History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, or history of hypersensitivity to drugs with a similar chemical structure or class to AZD5462.
 - Current smokers or those who have smoked or used nicotine products within the 3 months prior to screening.
 - Positive screen for drugs of abuse, alcohol, or cotinine at screening or on each admission to the study center prior to the first administration of the IMP.
 - Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks prior to the first administration of IMP.

- Use of any prescribed or non-prescribed medication including antacids, analgesics, herbal remedies, megadose vitamins, and minerals during the 2 weeks or 5 half-lives of the medication, whichever is longer, prior to the first administration of IMP.
- Known or suspected history of alcohol or drug abuse or excessive intake of alcohol.
- Excessive intake of caffeine-containing drinks or food.
- Participants who have previously received AZD5462.
- Any ongoing or recent minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions, and requirements.
- Participants who are vegans or have medical dietary restrictions.
- Participants who cannot communicate reliably with the Principal Investigator (PI).
- Vulnerable participants, eg, kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.
- Clinical signs and symptoms consistent with Coronavirus disease 2019 (COVID-19), or confirmed infection by appropriate laboratory test within the last 4 weeks prior to screening or on admission.

A summary of the PK results from the study is presented in Table 7.

Table 7 - Summary statistics of AZD5462 PK Parameters

Parameter (Unit)	Summary Statistic	AZD5462 (N=16)					
		Treatment A	Treatment B	Treatment C	Treatment D	Treatment E	Treatment F
AUC _{inf} (h*µmol/L)	gMean	1.984	2.038	5.253 ^a	12.47 ^a	13.92 ^b	35.16
	(gCV%)	28.25	33.65	28.79	17.84	38.35	26.19

AUC _{inf} /D (h*μmol/L/mg)	gMean (gCV%)	0.03306 28.25	0.03397 33.65	0.02918 ^a 28.79	0.0693 ^a 17.84	0.01933 ^b 38.35	0.04884 26.19
AUC _{last} (h*μmol/L)	gMean (gCV%)	1.818 29.91	1.997 34.29	4.723 35.32	12.66 19.62	13.04 36.86	33.24 30.63
AUC _{last} /D (h*μmol/L/mg)	gMean (gCV%)	0.03030 29.91	0.03328 34.29	0.02624 35.32	0.07034 19.62	0.01811 36.86	0.04617 30.63
C _{max} (μmol/L)	gMean (gCV%)	0.3818 40.72	0.4480 45.72	0.8923 41.26	9.174 29.06	2.864 53.22	7.327 34.56
C _{max} /D (μmol/L/mg)	gMean (gCV%)	0.006363 40.72	0.007467 45.72	0.004957 41.26	0.05096 29.06	0.003978 53.22	0.01018 34.56
t _{max} (h)	Median (Min, Max)	3.01 (1.02-5.02)	3.04 (0.77-6.27)	3.00 (0.67-5.00)	0.67 (0.33-0.73)	1.98 (0.67-4.20)	3.45 (1.50-6.02)
t _{1/2λz} (h)	gMean (gCV%)	6.576 138.5	2.727 49.16	10.75 ^a 72.43	5.747 ^a 77.13	16.46 ^b 66.20	18.91 72.67
MRT _{inf} (h)	gMean (gCV%)	7.798 72.49	5.393 27.93	9.828 ^a 38.75	2.390 ^a 22.47	12.93 ^b 64.64	9.575 74.78
λ _z (h)	gMean (gCV%)	0.1054 138.5	0.2541 49.16	0.06445 ^a 72.43	0.1206 ^a 77.13	0.04212 ^b 66.20	0.03666 72.67
CL/F (L/h)	gMean (gCV%)	55.54 28.25	54.05 33.65	62.91 ^a 28.79	26.5 ^a 17.84	94.96 ^b 38.35	37.6 26.19
V _z /F (L)	gMean (gCV%)	526.9 126.4	212.7 50.59	976.2 ^a 66.67	219.7 ^a 85.02	2254 ^b 59.54	1026 92.91
V _{ss} /F (L)	gMean (gCV%)	433.1 73.86	291.4 38.33	618.3 ^a 43.44	63.33 ^a 32.37	1228 ^b 62.06	360 88.65
C _{last} (μmol/L)	gMean (gCV%)	0.009362 42.31	0.007977 36.49	0.01355 63.87	0.009121 42.99	0.03378 95.61	0.02991 90.38
t _{lag} (h)	Median (Min, Max)	0.33 (0-1.95)	0 (0-1.02)	0.33 (0-0.67)	0 (0-0)	0 (0-0.38)	0 (0-0.98)

^a Number of participants used in analysis of geometric mean parameter was 15.

^b Number of participants used in analysis of geometric mean parameter was 13.

gCV% = geometric coefficient of variation; gMean = geometric mean; Max = maximum; Min = minimum; n = number of participants in analysis; N = number of participants in the PK analysis set; PK = pharmacokinetic.

Statistical assessment of dose proportionality in AZD5462 exposure when administered as a film-coated tablet in the fasted state is presented in Table 8. Between the 60 mg and 720 mg dose levels in the fasted state (Treatments A, C, and E), exposure increased in an apparent less than dose-proportional manner with the slope estimates for AUCinf, AUClast, and Cmax of 0.7837, 0.7904, and 0.8123, respectively.

Table 8 - Assessment of Dose Proportionality in AZD5462 (PK Analysis Set)

	n	Slope		Intercept		Coefficient of Determination
		Estimate	90% CI	Estimate	90% CI	
Cmax (μmol/L)	48	0.8123	(0.7103, 0.9142)	-4.304	(-4.835, -3.755)	0.7910
AUClast (h*μmol/L)	48	0.7904	(0.7116, 0.8692)	-2.608	(-3.032, -2.183)	0.8572
AUCinf (h*μmol/L)	44	0.7837	(0.7054, 0.8621)	-2.485	(-2.900, -2.070)	0.8676

Results are analyzed using the power model approach with the logarithm of PK parameters AUCinf, AUClast, and Cmax as the dependent variables and the logarithm of the dose as the independent variable: $([AUCinf \text{ or } Cmax] = \alpha * \text{dose}^\beta)$. Only the data for the participants receiving Treatment A (film-coated tablet 60 mg AZD5462, fasted), Treatment C (film-coated tablet 180 mg AZD5462, fasted), and Treatment E (film-coated tablet 720 mg AZD5462, fasted) are included.

CI = confidence interval; n = number of data points used in analysis.

Statistical comparison of key PK parameters (food effect) is presented in Table 9. At the 60 mg dose level, the GLSM PK parameter ratios were all close to one and the CIs spanned the value of 1, suggesting that food intake did not affect the exposure to AZD5462 at this dose level. At the 720 mg dose level, food intake increased the AUCinf, AUClast, and Cmax by 2.51-, 2.55-, and 2.56-fold, respectively.

Table 9 - Statistical Comparison of Key PK Parameters – Food Effect (PK Analysis Set)

	Comparison	n	Geometric LS Mean	Comparison of Treatment Groups	
				Ratio	90% CI
C _{max} (μmol/L)	Treatment B (fed) vs Treatment A (fasted)	16 vs 16	0.4480 vs 0.3818	1.174	(0.9669, 1.424)
	Treatment F (fed) vs Treatment E (fasted)	16 vs 16	7.327 vs 2.864	2.558	(2.108, 3.105)
AUC _{inf} (h*μmol/L)	Treatment B (fed) vs Treatment A (fasted)	16 vs 16	2.038 vs 1.984	1.028	(0.9062, 1.165)
	Treatment F (fed) vs Treatment E (fasted)	16 vs 13	35.16 vs 14.03	2.506	(2.192, 2.865)
AUC _{last} (h*μmol/L)	Treatment B (fed) vs Treatment A (fasted)	16 vs 16	1.997 vs 1.818	1.098	(0.9645, 1.251)
	Treatment F (fed) vs Treatment E (fasted)	16 vs 16	33.24 vs 13.04	2.549	(2.238, 2.902)

Results are assessed using an ANOVA model with fixed effect for treatment, period, and sequence, and random effect for participants within sequence. Least squares geometric means for AUC_{inf}, AUC_{last}, and C_{max} are calculated and presented. Least squares means and differences with their associated CI are back transformed to original scale to get geometric LS means and geometric mean ratios with their respective CI. ANOVA = analysis of variance; CI = confidence interval; LS = least squares; n = number of participants in analysis.

Statistical comparison of relative bioavailability of AZD5462 film-coated tablet versus oral solution is presented in Table 10. The bioavailability of AZD5462 following administration of the film-coated tablet (Treatment C) was lower than following administration of the oral solution (Treatment D). Based on the GLSM ratios, AZD5462 AUC_{inf}, AUC_{last}, and C_{max} for the film-coated tablet were approximately 40%, 37%, and 9.7% of the respective parameter values for the oral solution.

Table 10 - Statistical Comparison of Relative Bioavailability of AZD5462 Between Film-coated Tablet Versus Oral Solution (PK Analysis Set)

	Comparison	n	Geometric LS Mean	Comparison of Treatment Groups	
				Ratio	90% CI
C _{max} (μmol/L)	Treatment C (tablet) vs Treatment D (solution)	16 vs 16	0.8923 vs 9.174	0.09727	(0.08013, 0.1181)
AUC _{inf} (h*μmol/L)	Treatment C (tablet) vs Treatment D (solution)	15 vs 15	5.142 vs 12.78	0.4024	(0.3532, 0.4586)
AUC _{last} (h*μmol/L)	Treatment C (tablet) vs Treatment D (solution)	16 vs 16	4.723 vs 12.66	0.3730	(0.3276, 0.4248)

Results are assessed using an ANOVA model with fixed effect for treatment, period and sequence and random effect for participants within sequence. Least squares geometric means together for AUC_{inf}, AUC_{last}, and C_{max} are calculated and presented. LS means and differences with their associated CI are back transformed to original scale to get geometric LS means and geometric mean ratios with their respective CI. ANOVA = analysis of variance; CI = confidence interval; LS = least squares; n = number of participants in analysis.

Example 4: Phase 2B (Ph2b) study design for AZD5462

A draft protocol for a proposed Ph2b study protocol is summarised below.

A Ph2b study will be conducted to evaluate administration of 20 mg QD, 80 mg QD and 360 mg QD of AZD5462 vs placebo in patients with heart failure, including patients with HFrEF and patients with HFpEF. Participants will receive a once daily oral dose of AZD5462 in tablet form.

Outcome measures may include one or more of:

- Change from baseline in End Systolic Volume (ESV)
- Change from baseline in End Diastolic Volume (EDV)
- Change from baseline in Stroke Volume (SV)

- Change from baseline in Ejection fraction (EF)
- Change from baseline in systemic vascular resistance (SVR)
- Change from baseline in serum creatinine
- Change from baseline in renin
- Change from baseline in eGFR (estimated glomerular filtration rate)
- Change from baseline in 6-minute walking distance (6MWD)
- Change from baseline in Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ TSS)
- Change from baseline in New York Heart Association Functional Class (NYHA FC)
- Change from baseline in N-terminal prohormone of brain natriuretic peptide (NT-proBNP)

The outcome measures may be assessed after a treatment period of 24 weeks as compared to placebo.

The dose selection of AZD5462 for the proposed Ph2b study of 20 mg QD, 80 mg QD and 360 mg QD (oral, tablet) was based on parameters including efficacy, pharmacokinetic, pharmacodynamic, and safety data from the studies described in Examples 1 to 3. For example, the dose selection takes into account the increase in renin observed at 40 mg BID and projected efficacy at lower doses such as 20 mg QD, trends towards an undesired reduction in blood pressure at 500 mg BID, and food effect at higher doses of AZD5462. In addition, using concentration-response relationships for ejection fraction, end systolic volume, and systemic vascular resistance from the NHP HFrEF model (Example 1), and pharmacokinetic data and biomarker data from the SAD/MAD study (Example 2), it is predicted that the dose range selected in the Ph2b study will enable characterization of the dose-response for these parameters (Figures 21 to 23).

Translation of concentration-response/dose-response effects on these parameters from NHP to human is made by taking differences in target potency, pharmacokinetics and plasma protein binding into account. Based on this analysis, 0.25 mg/kg QD dosing in the NHP study was found to correspond approximately to a human 20 mg QD (oral, tablet) dose, and 1 mg/kg QD dosing in the NHP study was found to correspond approximately to a human 80 mg QD (oral, tablet) dose.

Example 5: Phase 2B (Ph2b) study design for AZD5462

A Ph2B study of AZD5462 will be performed according to the protocol summarised below.

Overall Design Synopsis

This is a Phase IIb randomised, double-blind, placebo-controlled, multi-centre, dose-ranging study to evaluate the efficacy, safety, and pharmacokinetics (PK) of AZD5462 on top of standard of care in 2 cohorts of participants with heart failure (HF): Cohort A and Cohort B. The study will be conducted as a parallel 2 cohort study. Participants in each cohort will be separately randomised 1:1:1:1 at Visit 2 to receive a once-daily (OD) oral dose of AZD5462 tablets or placebo for 24 weeks. The study will be conducted in approximately 50 sites across an estimated 12 countries.

Brief Summary

The purpose of this study is to measure efficacy and safety of AZD5462 compared to placebo in adult participants with HF. The study will include 3 periods and approximately 12 study visits:

- Screening period of up to 4 weeks, with at least one study visit;
- Treatment period of 24 weeks, with 8 study visits;
- Follow-up period of 4 weeks, with 3 study visits.

Number of Participants

Approximately 220 participants in Cohort A and 140 participants in Cohort B will be randomised to achieve 188 evaluable participants in Cohort A and 120 evaluable participants in Cohort B.

Study Arms and Duration

The study will have 2 cohorts (Cohorts A and B) each with 4 treatment arms:

- AZD5462 20 mg, oral, OD;
- AZD5462 80 mg, oral, OD;
- AZD5462 360 mg, oral, OD;
- Placebo, oral, OD.

The expected total duration of the study is 29 to 32 weeks, depending on the length of the Screening period. The study endpoints include, but are not limited to:

Primary Outcome Measures

- Cohort A and B: Change from Baseline in Cardiac Function [Time Frame: From Baseline to Week 25] to evaluate the effect of AZD5462 after 24 weeks of treatment in participants with HF.

Secondary Outcome Measures

- Cohort A and B: Change from Baseline in Cardiac Function [Time Frame: From Baseline to Week 13 and Week 25] to evaluate the effect and dose response of AZD5462 after 12 and 24 weeks of treatment in participants with HF.
- Cohort A and B: Change from Baseline in cardiac function parameters [Time Frame: From Baseline to Week 13 and Week 25] to evaluate the effect of

AZD5462 on echocardiographic markers related to structural, systolic and diastolic function after 12 and 24 weeks of treatment in participants with HF.

- Cohorts A and B: Change from Baseline in Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OSS) [Time Frame: From Baseline to Weeks 3, 5, 13, and 25] to evaluate the effect of AZD5462 on HF health status in participants with HF.
- Cohorts A and B: Change from Baseline in New York Heart Association Functional Class (NYHA FC) [Time Frame: Baseline and Week 25] to evaluate the effect of AZD5462 on HF health status in participants with HF.
- Cohorts A and B: Percentage Change from Baseline in cardiac biomarkers [Time Frame: From Baseline to Weeks 5, 13, and 25] to evaluate the effect of AZD5462 on biomarkers of cardiac function in treatment participants with HF.
- Cohorts A and B: Plasma Concentration of AZD5462 [Time Frame: Day 15 (Week 3), Day 29 (Week 5) and 85 (Week 13)] to evaluate the PK of AZD5462 after repeat OD oral dosing in participants with HF.
- Cohorts A and B: Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) [Time Frame: From Baseline to Week 29 (Day 197)] to evaluate the safety and tolerability of AZD5462 as compared to placebo in participants with HF.

Inclusion Criteria

- Participant must be 18 years (or the legal age of consent in the jurisdiction in which the study is taking place) to 85 years of age, inclusive, at the time of signing the ICF.
- Participants must have a pre-existing diagnosis of HF NYHA FC II to IV.

- Participants must be on stable HF standard of care medication for at least 4 weeks prior to Screening.
- Minimum body mass index (BMI) of 18 kilograms per meter square (kg/m^2) at Screening.
- For female participants, the participant must not be pregnant or lactating and must be of non-childbearing potential.
- All male participants should refrain from fathering a child or donating sperm until 3 months after the final study Follow-up Visit. Non-sterilised male participants should avoid fathering a child either by true abstinence or use of a condom for all sexual intercourse with a female partner of childbearing potential from the first dose until 3 months after the final Follow-up Visit.

Exclusion Criteria

- Historical or current evidence of a clinically significant disease or disorder including, but not limited to:
 - Myocardial infarction, stroke, transient ischaemic attack, coronary artery bypass grafting, or percutaneous coronary intervention within 12 weeks prior to Screening or transcatheter structural heart interventions or cardiac valve surgery within 6 months prior to Screening.
 - Sarcoidosis, restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, or hypertrophic (obstructive) cardiomyopathy.
 - History of untreated clinically significant valve disease or a Screening confirmation of severe aortic stenosis, severe mitral stenosis, moderate or severe aortic insufficiency or severe mitral insufficiency.
 - Amyloidosis, Fabry disease, or haemochromatosis.

- Pericardial disease (i.e., visually significant white pericardium on echocardiogram).
- Known coagulation disorders.
- Current diagnosis of active hepatitis.
- Severe pulmonary disease that is not expected to improve over time, as assessed by the investigator.
- Decompensated HF or any cardiopulmonary hospitalisation within 4 weeks prior to Screening.
- History of active malignancy within 2 years, except for fully excised or treated basal cell carcinoma, or ≤ 2 squamous cell carcinomas of the skin and participants who are under investigation for breast or cervical cancer, including participants with a pap smear of grade ≥ 3 .
- History of hypersensitivity to drugs with a similar chemical structure or class to AZD5462 or any component of AZD5462 drug product.
- Known history of drug or alcohol abuse within 24 months of Screening.
- Cardiac ventricular arrhythmia that requires treatment.
- History of or anticipated heart transplant.
- Current or planned bi-ventricular assist device implantation.
- Any planned highly invasive cardiovascular procedure (e.g., coronary revascularisation, ablation of atrial fibrillation/flutter etc).
- Positive hepatitis C antibody, hepatitis B virus surface antigen or hepatitis B virus core antibody at Screening.
- Known to have historically tested positive for Human immunodeficiency virus.

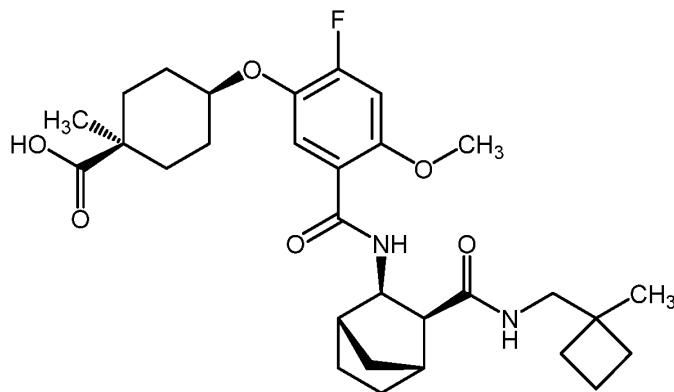
Rationale

As noted in Example 4, the dose selection of AZD5462 for the Ph2b study of 20 mg QD, 80 mg QD and 360 mg QD (oral, tablet) was based on parameters including efficacy, pharmacokinetic, pharmacodynamic, and safety data from the studies described in Examples 1 to 3. For example, the dose selection takes into account the increase in renin observed at 40 mg BID and projected efficacy at lower doses such as 20 mg QD, trends towards an undesired reduction in blood pressure at 500 mg BID, and food effect at higher doses of AZD5462. In addition, using concentration-response relationships for ejection fraction, end systolic volume, and systemic vascular resistance from the NHP HFrEF model (Example 1), and pharmacokinetic data and biomarker data from the SAD/MAD study (Example 2), it is predicted that the dose range selected in the Ph2b study will enable characterization of the dose-response for these parameters (Figures 21 to 23).

Translation of concentration-response/dose-response effects on these parameters from NHP to human is made by taking differences in target potency, pharmacokinetics and plasma protein binding into account. Based on this analysis, 0.25 mg/kg QD dosing in the NHP study was found to correspond approximately to a human 20 mg QD (oral, tablet) dose, and 1 mg/kg QD dosing in the NHP study was found to correspond approximately to a human 80 mg QD (oral, tablet) dose.

Claims

1. A method of treating a subject having heart failure, the method comprising administering to the subject from 5 mg to 360 mg per day of Compound (I)



Compound (I)

or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein Compound (I) or a pharmaceutically acceptable salt thereof is Compound (I).
3. The method of claim 1 or claim 2, wherein the amount of Compound (I) or a pharmaceutically acceptable salt thereof administered to the subject is from 20 mg to 360 mg per day.
4. The method of any one of the preceding claims, wherein the amount of Compound (I) or a pharmaceutically acceptable salt thereof administered to the subject is from 20 mg to 100 mg per day, optionally 20 mg to 80 mg per day.

5. The method of claim 1 or claim 2, wherein the amount of Compound (I) or a pharmaceutically acceptable salt thereof administered to the subject is about 20 mg per day, about 80 mg per day, or about 360 mg per day.
6. The method of any one of claims 1 to 5, wherein Compound (I) or a pharmaceutically acceptable salt thereof is administered to the subject orally.
7. The method of any one of claims 1 to 6, wherein Compound (I) or a pharmaceutically acceptable salt thereof is administered to the subject once daily.
8. The method of any one of claims 1 to 6, wherein Compound (I) or a pharmaceutically acceptable salt thereof is administered to the subject twice daily.
9. The method of claim 1, wherein the method comprises administering to the subject once daily a pharmaceutical composition comprising a pharmaceutically acceptable excipient and from 5 mg to 360 mg of Compound (I) or a pharmaceutically acceptable salt thereof.
10. The method of claim 9, wherein the pharmaceutical composition comprises from 20 mg to 100 mg of Compound (I) or a pharmaceutically acceptable salt thereof, optionally from 20 mg to 80 mg of Compound (I) or a pharmaceutically acceptable salt thereof.
11. The method of claim 1, wherein the method comprises administering to the subject twice daily a pharmaceutical composition comprising a pharmaceutically acceptable excipient and from 5 mg to 180 mg of Compound (I) or a pharmaceutically acceptable salt thereof.

12. The method of claim 11, wherein the pharmaceutical composition comprises from 10 mg to 50 mg of Compound (I) or a pharmaceutically acceptable salt thereof, optionally from 10 mg to 40 mg of Compound (I) or a pharmaceutically acceptable salt thereof.
13. The method of any one of claims 9 to 12, wherein the pharmaceutical composition is in the form of one or more tablets and is administered to the subject orally.
14. The method of any one of claims 9 to 12, wherein the pharmaceutical composition is in the form of a single tablet and is administered to the subject orally.
15. The method of claim 1, wherein a tablet comprising from 20 mg to 180 mg of Compound (I) is administered orally to the subject once daily.
16. The method of claim 1, wherein a tablet comprising from 10 mg to 100 mg of Compound (I) is administered orally to the subject twice daily.
17. The method of any one of the preceding claims, wherein Compound (I) or a pharmaceutically acceptable salt thereof is administered to the subject for one or more weeks.
18. The method of any one of the preceding claims, wherein Compound (I) or a pharmaceutically acceptable salt thereof is administered to the subject chronically.
19. The method of any one of the preceding claims, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof causes no

significant change in blood pressure of the subject relative to baseline blood pressure of the subject.

20. The method of any one of the preceding claims, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof causes no significant change in resting heart rate of the subject relative to baseline resting heart rate of the subject.

21. The method of any one of the preceding claims, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in end systolic volume (ESV) of the subject as compared to baseline levels.

22. The method of claim 21, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in ESV of at least 10%, as compared to baseline levels.

23. The method of any one of the preceding claims, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in ejection fraction (EF) of the subject as compared to baseline levels.

24. The method of claim 23, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in EF of at least 5%, as compared to baseline levels.

25. The method of any one of the preceding claims, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in stroke volume (SV) of the subject as compared to baseline levels.

26. The method of any one of the preceding claims, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in systemic vascular resistance (SVR) of the subject as compared to baseline levels.

27. The method of claim 26, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in SVR in the subject of at least 5%, as compared to baseline levels.

28. The method of any one of the preceding claims, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in a decrease in serum creatinine of the subject as compared to baseline levels.

29. The method of any one of the preceding claims, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in renin of the subject as compared to baseline levels.

30. The method of claim 29, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in renin of at least 10%, as compared to baseline levels.

31. The method of any one of the preceding claims, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in estimated glomerular filtration rate (eGFR) of the subject as compared to baseline levels.

32. The method of claim 31, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in eGFR of at least 1%, as compared to baseline levels.

33. The method of any one of the preceding claims, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in 6-minute walking distance (6MWD) of the subject as compared to baseline levels.

34. The method of any one of the preceding claims, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in an increase in Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ TSS) of the subject as compared to baseline levels.

35. The method of any one of the preceding claims, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in maintenance or an improvement in New York Heart Association Functional Class (NYHA FC) of the subject as compared to baseline levels.

36. The method of any one of the preceding claims, wherein administration to the subject of Compound (I) or a pharmaceutically acceptable salt thereof results in a

decrease in N-terminal prohormone of brain natriuretic peptide (NT-proBNP) of the subject as compared to baseline levels.

37. The method of any one of claims 21 to 36, wherein the change in ESV, EF, SV, SVR, serum creatinine, renin, eGFR, 6MWD, KCCQ TSS, NYHA FC and/or NT-proBNP is as measured after 1-24 weeks of treatment, optionally after 24 weeks of treatment.

38. The method of any one of the preceding claims, wherein the heart failure is heart failure with preserved ejection fraction (HFpEF), heart failure with ejection fraction $\geq 41\%$ (HF with EF $\geq 41\%$), heart failure with mid-range ejection fraction (HFmrEF), heart failure with reduced ejection fraction (HFrEF) or heart failure with ejection fraction $\leq 35\%$ (HF with EF $\leq 35\%$).

39. Compound (I) or a pharmaceutically acceptable salt thereof for use in the method of any one of the previous claims.

40. A pharmaceutical composition comprising from 5 mg to 360 mg of Compound (I) or a pharmaceutically acceptable salt thereof.

41. The pharmaceutical composition of claim 40, comprising from 20 mg to 180 mg of Compound (I) or a pharmaceutically acceptable salt thereof.

42. The pharmaceutical composition of claim 40 or 41, wherein the pharmaceutical composition is in the form of a tablet suitable for oral administration.

43. The pharmaceutical composition of any one of claims 40 to 42 for use in the method of any one of claims 1 to 38.