

AZD-0780 IN COMBINATION WITH A STATIN FOR USE IN LOWERING LDL-C LEVELS AND TREATING CARDIOVASCULAR DISEASES

This application claims priority from U.S. Provisional Patent Application No. 63/549,604, filed February 5, 2024, U.S. Provisional Patent Application No. 63/648,276, filed May 16, 2024
5 and U.S. Provisional Patent Application No. 63/733,263, filed December 12, 2024, the disclosure of which is incorporated by reference herein in their entirety.

The present disclosure relates to methods of lowering LDL-C levels, reducing cardiovascular risk and/or treating cardiovascular disease in a patient in need thereof.

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Background

PCSK9, also referred to as “proprotein convertase subtilisin/kexin 9”, is a member of the secretory proprotein convertase family and plays an important role in cholesterol metabolism. PCSK9 increases the levels of circulating LDL cholesterol (LDL-C) via the
15 enhanced degradation of the LDLRs independently of its catalytic activity. Secreted PCSK9 binds to the Epidermal Growth Factor domain A (EGFA) of the LDL receptor (LDLR) at the cell surface and the PCSK9/LDLR complex is internalized into endosomal/lysosomal compartments. The enhanced binding affinity of PCSK9 to the LDLR at the acidic pH of late endosomes/lysosomes reduces LDLR recycling and instead targets LDLR for lysosomal
20 degradation. Genetic association studies have demonstrated that loss-of-function mutations in PCSK9 are associated with low plasma LDL-C levels and a reduction in the incidence of adverse cardiovascular events.

For cardiovascular disease, few options exist for inhibiting PCSK9. Statins actually
25 upregulate PCSK9 in HepG2 cells and in human primary hepatocytes through the increased expression of SREBP-2, a transcription factor that upregulates both the LDLR and PCSK9 genes. Since an elevated level of PCSK9 decreases the abundance of LDLR on the cell surface, increasing doses of statins have failed to achieve proportional LDL-C lowering effects.

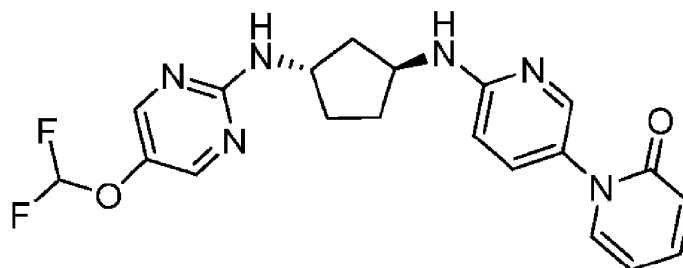
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Two monoclonal antibodies (mAbs) that bind selectively to extracellular PCSK9 and prevent its interaction with the LDLR, alirocumab and evolocumab, have recently received FDA approval for lowering LDL-C levels. In clinical trials, alirocumab showed an about 50% decrease in LDL levels compared to placebo (Elbitor 2016). Patients taking evolocumab
35 showed an about 60-75% decrease in LDL levels. These antibodies lower LDL-C by as much as 60% and lower cardiovascular event rates (Sabatine 2017). The potency of these drugs demonstrates the potential for inhibitors of PCSK9 to be effective treatments for those

with hypercholesterolemia and other cardiovascular diseases. However, both antibody drugs require intravenous administration and can cause allergic reactions or other deleterious immune responses in the body.

- 5 Cardiovascular diseases often require management over a person's lifetime, unlike an infection that could be episodic. Thus, ease of dosing and administration become important factors for patient compliance with maintenance drug treatments.

“AZD0780” refers to a compound with the chemical name 6'-((1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one structure shown below:



AZD0780 is an effective binder to PCSK9, and is currently in early stage clinical trials. The synthesis of AZD0780 is described in WO2020/150473 and WO2020/0150474, the contents of which are hereby incorporated by reference in their entirety.

While much progress has been made in the treatment of cardiovascular disease, many patients treated with statins do not reach LDL-C target levels. Accordingly, it is important to develop new cost-effective LDL-C lowering approaches for the effective reduction of cardiovascular risk and treatment of cardiovascular disease.

Summary

In some embodiments is disclosed a method of lowering LDL-C levels, reducing cardiovascular risk and/or treatment of a cardiovascular disease, comprising administering to a subject in need thereof, a first amount of 6'-((1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one (“AZD0780”) or a pharmaceutically acceptable salt thereof and a second amount of a statin, wherein the first amount and the second amount together comprise a therapeutically effective amount.

In some embodiments is disclosed a method of lowering LDL-C levels, reducing cardiovascular risk and/or treatment of a cardiovascular disease in a subject in need thereof comprising administering to the subject an amount of 6'-([1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one ("AZD0780") or
5 pharmaceutically acceptable salt thereof and an amount of a statin.

In some embodiments is disclosed a method of lowering LDL-C levels, reducing cardiovascular risk and/or treatment of a cardiovascular disease in a subject in need thereof comprising administering to the subject an amount of 6'-([1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one ("AZD0780") or
10 pharmaceutically acceptable salt thereof and an amount of a statin, wherein the amount of AZD0780 or pharmaceutically acceptable salt thereof and the amount of the statin together comprise a therapeutically effective amount.

15 In some embodiments, disclosed is 6'-([1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one ("AZD0780") or a pharmaceutically acceptable salt thereof for use in the lowering of LDL-C levels, reducing cardiovascular risk and/or treatment of a cardiovascular disease in a subject, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said
20 AZD0780 or a pharmaceutically acceptable salt thereof, and ii) a statin to said subject.

In some embodiments, disclosed is a statin for use in the lowering of LDL-C levels, reducing cardiovascular risk and/or treatment of a cardiovascular disease in a subject, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said statin,
25 and ii) 6'-([1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one ("AZD0780") or a pharmaceutically acceptable salt thereof to said subject.

In some embodiments, disclosed is the use of 6'-([1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one ("AZD0780") or a
30 pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the lowering of LDL-C levels, reducing cardiovascular risk and/or treatment of a cardiovascular disease wherein said treatment comprises the separate, sequential or simultaneous administration of i) said medicament comprising AZD0780 or a pharmaceutically acceptable salt thereof and ii) a statin to said subject.

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In some embodiments, disclosed is the use of a statin in the manufacture of a medicament for use in the lowering of LDL-C levels, reducing cardiovascular risk and/or treatment of a

cardiovascular disease wherein said treatment comprises the separate, sequential or simultaneous administration of i) said medicament comprising a statin and ii) 6'-([1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one ("AZD0780") or a pharmaceutically acceptable salt thereof to said subject.

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In some embodiments, disclosed is a kit comprising: a first pharmaceutical composition comprising 6'-([1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one ("AZD0780") or a pharmaceutically acceptable salt thereof; a second pharmaceutical composition comprising a statin; and instructions for using the first and
10 second pharmaceutical compositions in combination. In some embodiments, the instructions are for use of the combination as described herein.

The combination of AZD0780 or a pharmaceutically acceptable salt thereof and a statin may result in fewer side effects or be more effective than current monotherapies or combination
15 therapies. In some embodiments, the combination has a synergistic effect in the lowering of LDL-C levels.

Figures

Figure 1 shows the LDL-C change in patients treated with AZD0780 from baseline by time
20 and AZD0780 dose.

Figure 2 shows the LDL-change in patients treated with either rosuvastatin and placebo or a combination of rosuvastatin and AZD0780 from baseline by time, after a 3-week rosuvastatin run-in period.

Figure 3 shows the LDL-change in patients treated with either rosuvastatin and placebo or a
25 combination of rosuvastatin and AZD0780 1 mg or 30 mg from baseline by time, after a 3-week rosuvastatin run-in period.

Figure 4 shows the overall study design for the Phase IIb study of AZD0780 in combination with a statin.

30 Detailed Description

Numeric ranges are inclusive of the numbers defining the range. Where a range of values is recited, it is to be understood that each intervening integer value, and each fraction thereof, between the recited upper and lower limits of that range is also specifically disclosed, along with each subrange between such values. The upper and lower limits of any range can
35 independently be included in or excluded from the range, and each range where either, neither or both limits are included is also encompassed within the disclosure. Thus, ranges recited herein are understood to be shorthand for all of the values within the range, inclusive

of the recited endpoints. For example, a range of 1 to 10 is understood to include any number, combination of numbers, or sub-range from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

- 5 The term “about” is used herein to mean approximately, roughly, around, or in the regions of. When the term “about” is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term “about” is used herein to modify a numerical value above and below the stated value by a variance of 10 percent, up or down (higher or lower).

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The term “LDL-C level” is used herein to mean the amount of LDL-C in the circulating serum of a patient.

Statins

- 15 Statins include atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, velostatin, compactin, dihydrocompactin, dalvastatin, fluindostatin, rosuvastatin, and simvastatin.

- US4231938 discloses certain compounds isolated after cultivation of a microorganism
20 belonging to the genus *Aspergillus*, such as lovastatin. Also, US4444784 discloses synthetic derivatives of the aforementioned compounds, such as simvastatin. Also, US4739073 discloses certain substituted indoles, such as fluvastatin. Also, US4346227 discloses ML-236B derivatives, such as pravastatin. Also, EP0491226A and US5502199 disclose certain pyridyldihydroxyheptenoic acids, such as cerivastatin. In addition, US5273995 discloses
25 certain 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones such as atorvastatin and any pharmaceutically acceptable form thereof (i.e. LIPITOR®). Atorvastatin calcium (i.e., atorvastatin hemicalcium), disclosed in US5273995 is currently sold as Lipitor®. US RE37,314 E discloses rosuvastatin and rosuvastatin calcium. EP0304063 and US5011930 disclose pitivastatin. US3983140 discloses mevastatin. US4448784 and US4450171
30 disclose velostatin. US4804770 discloses compactin. EP0738510A2 discloses dalvastatin. EP0363934A1 discloses fluindostatin. US4450171 discloses dihydrocompactin.

- In some embodiments, the statin is selected from atorvastatin, rosuvastatin, lovastatin, pravastatin, simvastatin and fluvastatin.

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In some embodiments, the statin is rosuvastatin or a pharmaceutically acceptable salt thereof. In some of these embodiments, the statin is rosuvastatin or rosuvastatin calcium.

Dosing levels

In some embodiments, the statin dosing regimen is a moderate-intensity dosing according to the ACC (American College of Cardiology)/AHA (American Heart Association) (Grundy
5 2018).

This moderate-intensity dosing may be:

	<i>Dosing regimen</i>
Atorvastatin	10 to 20 mg once daily
Fluvastatin	40 mg twice daily; or 80 mg once daily
Lovastatin	40 to 80 mg once daily
Pitavastatin	1 to 4 mg once daily
Pravastatin	40 to 80 mg once daily
Rosuvastatin	5 to 10 mg once daily
Simvastatin	20 to 40 mg once daily

The rosuvastatin may be dosed as rosuvastatin calcium, where the dose given is calculated
10 as rosuvastatin in its free form.

The atorvastatin may be dosed as atorvastatin calcium or atorvastatin calcium trihydrate,
where the dose given is calculated as atorvastatin in its free form.

15 The pravastatin may be dosed as pravastatin calcium, where the dose given is calculated as pravastatin in its free form.

The pitavastatin may be dosed as pitavastatin calcium, where the dose given is calculated
as pitavastatin in its free form.

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In some embodiments, the statin dosing regimen is a high-intensity dosing according to the ACC (American College of Cardiology)/AHA (American Heart Association) (Grundy 2018).

This high-intensity dosing may be:

	<i>Dosing regimen</i>
Atorvastatin	40 to 80 mg once daily
Rosuvastatin	20 to 40 mg once daily

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As above, the rosuvastatin may be dosed as rosuvastatin calcium, where the dose given is calculated as rosuvastatin in its free form.

- 5 As above, the atorvastatin may be dosed as atorvastatin calcium or atorvastatin calcium trihydrate, where the dose given is calculated as atorvastatin in its free form.

In some embodiments, the statin dosing regimen is one appropriate to patients from, for example, Japan:

	<i>Dosing regimen</i>
Atorvastatin	10 to 40 mg once daily
Fluvastatin	60 mg once daily
Pitavastatin	1 to 4 mg once daily
Rosuvastatin	2.5 to 20 mg once daily
Simvastatin	10 to 20 mg once daily

- 10 As above, the rosuvastatin may be dosed as rosuvastatin calcium, where the dose given is calculated as rosuvastatin in its free form.

As above, the atorvastatin may be dosed as atorvastatin calcium or atorvastatin calcium trihydrate, where the dose given is calculated as atorvastatin in its free form.

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As above, the pitavastatin may be dosed as pitavastatin calcium, where the dose given is calculated as pitavastatin in its free form.

- 20 In some embodiments, the patient to be treated will have already been treated with one or more statins previously. In some of these embodiments, the patient to be treated will have already been treated with one or more statins for a period of at least two, three, four, five or six months prior to being treated with a combination of a statin and AZD0780.

- 25 In some embodiments, the patient to be treated will have already been treated with one or more statin previously at a moderate or high intensity (as defined above). In some of these embodiments, the patient to be treated will have already been treated with one or more statins at a moderate or high intensity (as defined above) for a period of at least two, three, four, five or six months prior to being treated with a combination of a statin and AZD0780.

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AZD0780

In some embodiments, AZD0780 is administered in a dose of 1 to 30 mg per day. The daily dose may be up to 3 mg, 5 mg, 10mg, 15 mg, 20 mg, 25 mg or 30 mg. The daily dose may be at least 1 mg, 2 mg, 3 mg, 5mg, 10 mg, 15 mg, 20 mg, or 25 mg.

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In some embodiments, AZD0780 is administered in a daily dose of 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg.

10 In some embodiments, AZD0780 is administered once a day (QD). In some embodiments, AZD0780 is administered in a dose of 1 to 30 mg QD. The once daily dose may be up to 3 mg, 5 mg, 10mg, 15 mg, 20 mg, 25 mg or 30 mg. The once daily dose may be at least 1 mg, 2 mg, 3 mg, 5mg, 10 mg, 15 mg, 20 mg, or 25 mg.

15 In some embodiments, AZD0780 is administered in a once daily dose (QD) of 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg.

In some embodiments, AZD0780 is administered as a free base, i.e. not in salt form.

20 In some embodiments, AZD0780 is administered as a pharmaceutically acceptable salt thereof, where the dosage is that of AZD0780 not in a salt form. Unless otherwise stated, any reference in this disclosure to an amount of AZD0780, or pharmaceutically acceptable salt thereof, is based on the AZD0780 free base equivalent weight. For example, "wt%" refers to weight % based on AZD0780 free base equivalent weight.

25 The language "pharmaceutical composition" includes compositions comprising an active ingredient and a pharmaceutically acceptable excipient, carrier or diluent, wherein the active ingredient is AZD0780 or a pharmaceutically acceptable salt thereof. The language "pharmaceutically acceptable excipient, carrier or diluent" includes compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment,
30 suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, as ascertained by one of skill in the art. In some embodiments, the pharmaceutical compositions are in solid dosage forms, such as capsules, tablets, granules, powders or sachets. In some embodiments, the pharmaceutical compositions are in the form of a sterile injectable solution
35 in one or more aqueous or non-aqueous non-toxic parenterally acceptable buffer systems, diluents, solubilizing agents, co-solvents, or carriers. A sterile injectable preparation may also be a sterile injectable aqueous or oily suspension or suspension in a non-aqueous

diluent, carrier or co-solvent, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents. The pharmaceutical compositions could be a solution for iv bolus/infusion injection or a lyophilized system (either alone or with excipients) for reconstitution with a buffer system
5 with or without other excipients. The lyophilized freeze-dried material may be prepared from non-aqueous solvents or aqueous solvents. The dosage form could also be a concentrate for further dilution for subsequent infusion.

In some embodiments, AZD0780 or a pharmaceutically acceptable salt thereof is
10 administered orally. In some embodiments, AZD0780 or a pharmaceutically acceptable salt thereof is in tablet dosage form.

The term "treatment" is used synonymously with "therapy". Similarly, the term "treat" can be regarded as "applying therapy" where "therapy" is as defined herein.

15 The term "subject" to which administration is contemplated includes, but is not limited to, humans (i.e., a male or female of any age group, e.g., a paediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle-aged adult or senior adult)) and/or other primates (e.g., cynomolgus monkeys, rhesus monkeys); mammals, including
20 commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs; and/or birds, including commercially relevant birds such as chickens, ducks, geese, quail, and/or turkeys. Preferred subjects are humans.

The reduction of cardiovascular events through the lowering of LDL-C by inhibition of PCSK9
25 has been described, e.g., in Robinson 2015.

Lowering LDL-C levels leads to significant reduction in major vascular events including myocardial infarction, coronary deaths, stroke, and coronary revascularizations (Collins 2016). Current clinical guidelines for LDL-C reduction and the consequent reduction of CVD
30 (cardiovascular disease) risk are summarised in Atar 2021. Additional evidence demonstrates that aggressively lowering LDL-C levels to < 40 mg/dL lowers CVD risk in a wider range of patients (Marston 2021).

In some embodiments, reduction of LDL-C to less than 100 mg/dL, less than 70 mg/dL, less
35 than 55 mg/dL or less than 40 mg/dL may be achieved by the treatment disclosed herein.

In some embodiments, in patients with elevated LDL-C (such as greater than 100 mg/dL), reduction of the untreated level of LDL-C by greater than or equal to 30%, 40%, 50%, 60%, 65%, 70% or 75% may be achieved by the treatment disclosed herein. The term untreated as used herein refers to the level as measured before any LDL-C lowering treatment has
5 been administered, i.e. the LDL-C baseline level.

In some embodiments, the treatment disclosed herein reduces cardiovascular risk (i.e., the incidence of myocardial infarction, ischemic stroke and urgent coronary revascularization, cardiovascular death) in adults with atherosclerotic cardiovascular disease (ASCVD) or at
10 high or intermediate risk for a first ASCVD event (such as myocardial infarction, resuscitated cardiac arrest, fatal coronary heart disease (CHD), fatal and non-fatal stroke, and other atherosclerotic or cardiovascular death). The risk for a first ASCVD event for a patient within 10 years can be categorized into those at low (<5%), borderline (5 to <7.5%), intermediate (7.5 to <20%), and high ($\geq 20\%$) risk (Wong 2022).

15 In some embodiments, the treatment disclosed herein reduces LDL-C, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH).

Exemplary cardiovascular diseases and conditions include, but are not limited to,
20 dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hypoalphalipoproteinemia, metabolic syndrome, diabetic complications, atherosclerosis, stroke, vascular dementia, chronic kidney disease, coronary heart disease, coronary artery disease, retinopathy, inflammation, thrombosis, peripheral vascular disease, heart failure or congestive heart failure. In certain embodiments, exemplary cardiovascular diseases and
25 conditions include, but are not limited to, hypercholesterolemia, hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia, dyslipidemia, dyslipoproteinemia, atherosclerosis, hepatic steatosis, metabolic syndrome, and coronary artery disease. In certain embodiments, the disease is hypercholesterolemia, such as familial hypercholesterolemia or autosomal dominant hypercholesterolemia. In certain embodiments,
30 the disease is hyperlipidemia. In certain embodiments, the disease is coronary artery disease.

In some embodiments, the treatment of a cardiovascular disease includes reducing the LDL-C level to less than 100 mg/dL, less than 70 mg/dL, less than 55 mg/dL or less than 40
35 mg/dL. In some embodiments, the treatment of a cardiovascular disease in patients with elevated LDL-C (such as greater than 100 mg/dL), includes reduction of the untreated level of LDL-C by greater than or equal to 30%, 40%, 50%, 60%, 65%, 70% or 75%.

In certain embodiments, the disclosed methods of treatment can decrease high levels of circulating serum cholesterol, such as LDL-C and VLDL-Cholesterol (very low-density lipoprotein-cholesterol). In addition, the disclosed methods are useful for decreasing
5 circulating serum triglycerides, circulating serum lipoprotein A, circulating serum LDL-C and atherogenic lipoproteins. In certain embodiments, the diseases or conditions treated with the disclosed compounds and compositions include atherosclerosis and atherosclerotic plaque formation. Subjects having a gain-of-function mutation in the PCSK9 gene also benefit with treatment with the disclosed compounds and compositions counteracting the
10 mutation through their inhibition of PCSK9.

In some embodiments the:

- (i) AZD0780 or a pharmaceutically acceptable salt thereof; and
 - (ii) a statin;
- 15 are administered separately, sequentially or simultaneously.

In some embodiments, AZD0780 or a pharmaceutically acceptable salt thereof is given simultaneously with a statin. In some of these embodiments, these are taken without food (e.g. no food at least 2 hours before dosing and at least 1 hour after dosing). In other of
20 these embodiments, these are taken with food.

In the clinical trial NCT05384262 (Part A2), it was found that the pharmacokinetics of AZD0780 were not affected by dosing after intake of a high-calorie, high-fat breakfast.

25 *Patients*

In some embodiments, the patient to be treated has a LDL-C $\leq$ 190 mg/dL before starting treatment.

In some embodiments, the patient to be treated has a LDL-C $\geq$ 100 mg/dL before starting treatment.

- 30 In some embodiments, the patient to be treated has a BMI between 18 and 35 kg/m² inclusive and weighs at least 50 kg and no more than 120 kg inclusive prior to the start of treatment.

In some embodiments, the patient to be treated meets at least one of the inclusion criteria set out in example 1.
35

In some embodiments, the patient to be treated does not meet at least one of the exclusion criteria set out in example 1.

Examples

The combinations of the application will now be further explained by reference to the following non-limiting examples.

5

Example 1

This study (D7960C00001/ NCT05384262) was carried out in healthy male and/or female subjects of non-childbearing potential with elevated LDL-C levels.

- 10 There were 3 types of cohorts, global MAD cohorts (comparative), Japanese single and multiple ascending dose (JSMAD) cohorts (comparative) and rosuvastatin global MAD cohorts.

- 15 In the global MAD cohorts, 3 dose cohorts were investigated (10mg, 30mg, 60 mg once daily). In each cohort, 20 subjects participated and receive either AZD0780 or placebo, randomized 3:1, for 28 days dosing.

- 20 In the JSMAD cohorts, 2 cohorts were investigated (30mg, 60mg once daily). Each cohort of 8 Japanese subjects, randomized 3:1, were given a single dose, a 7-day washout, and then 8 days of daily dosing.

- 25 In the rosuvastatin global MAD cohorts, two dose cohorts were investigated. 35 subjects participated in the first cohort and were be randomized 1:1 to 1 of 2 treatment arms to receive either AZD0780 in combination with rosuvastatin (18 subjects) or placebo (17 subjects) in combination with rosuvastatin. Up to 25 subjects will participate in the second cohort and will be randomized 4:1 to 1 of 2 treatment arms to receive either AZD0780 in combination with rosuvastatin (20 subjects) or placebo in combination with rosuvastatin (5 subjects). Subjects who are eligible for these cohorts began with a minimum of 21 days run-in (which could be up to 28 days), with rosuvastatin 20 mg at home before entering the treatment period, where they received AZD0780 30 mg + rosuvastatin 20 mg or placebo + rosuvastatin 20 mg for 28 days for the first cohort, and AZD0780 1 mg + rosuvastatin 20 mg or placebo + rosuvastatin 20 mg for 28 days for the second cohort.

The study comprised:

- 35 1. An optional Pre-Screening visit may have been completed to collect LDL-C blood samples to assess if subjects meet inclusion criterion ($\text{LDL-C} \geq 70 \text{ mg/dL}$ but $\leq 190 \text{ mg/dL}$ and $\geq 100 \text{ mg/dL}$ but $\leq 190 \text{ mg/dL}$ for the rosuvastatin global MAD cohorts).

2. A Screening Period of maximum 28 days (56 days for rosuvastatin global MAD cohorts).
3. A minimum of 21 days run-in period (maximum of up to 28 days) for rosuvastatin administration (rosuvastatin global MAD cohorts only). During the run-in period, the subjects' LDL-C levels was measured between Day -28 (± 1 day) and Day -22 (± 1 day), and Day -8 (± 1 day) after at least 14 days of rosuvastatin administration). If a subject had less than 30% reduction of LDL-C during the run-in period, they were not eligible to continue with the study.
4. Admission to study centre (Day -1).
5. A Treatment Period during which subjects received:
 - 10 a. Either AZD0780 or placebo on Day 1 followed by 7 days (Day 2 to 7) without dosing. Dosing will resume on Day 8 and continue until Day 15 (8 days). Subjects were discharged from the unit on Day 17 (JSMAD cohorts)
 - b. Either AZD0780 or placebo once daily for 28 days (Day 1 to 28). Subjects were discharged on Day 29 (global MAD cohorts)
 - 15 c. Either AZD0780 + rosuvastatin or placebo + rosuvastatin for 28 days (Days 1 to 28). Subjects will be discharged on Day 29 (rosuvastatin global MAD cohorts).
6. Follow-up Visit(s):
 - a. One Follow-up Visit within 7 to 10 days after the last drug dose for the JSMAD cohorts.
 - b. Two Follow-up Visits, 1 and 2 weeks after the last drug dose for the global MAD cohorts.
 - 20 c. Two Follow-up Visits, 1 and 2 weeks after the last IMP dose for the rosuvastatin global MAD cohorts.

Duration of the Study

The expected duration of study participation for each subject was:

- 25 a. JSMAD cohorts - up to 56 days;
- b. Global MAD cohorts - up to 73 days; and
- c. Rosuvastatin global MAD cohorts up to 99 days.

Inclusion Criteria

- 30 For inclusion in the study, the subject had to fulfil the following criteria:
 1. Provision of signed and dated, written informed consent prior to any study specific procedures (including the Pre-Screening Visit).
 2. Healthy male and female subjects (of non-childbearing potential), aged 18 to 55 years inclusive, with suitable veins for cannulation or repeated venipuncture.
 - 35 3. Females must have a negative pregnancy test at the Screening Visit and on admission to the study centre, must not be lactating and must be of non-childbearing potential, confirmed at the Screening Visit by fulfilling one of the following criteria:

(a) Postmenopausal defined as amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and FSH levels in the postmenopausal range.

5 (b) Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.

4. Have a BMI between 18 and 35 kg/m² inclusive and weigh at least 50 kg and no more than 120 kg inclusive at the Screening Visit and on admission to the study centre.

5. For Japanese subjects, a subject will be considered Japanese if both parents and all grandparents are Japanese, the subject was born in Japan, and the subject has not lived
10 outside Japan for more than 10 years.

6. At the Screening Visit subjects must have LDL-C $\geq$ 70 mg/dL but $\leq$ 190 mg/dL, and triglycerides < 400 mg/dL.

7. For rosuvastatin global MAD cohorts, at the Screening Visit subjects must have LDL-C $\geq$ 100 mg/dL but < 190 mg/dL.

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Exclusion Criteria

Subjects were not randomized in the study if any of the following exclusion criteria were fulfilled:

1. History of any clinically important disease or disorder which, in the opinion of the
20 investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study.
2. History or presence of gastrointestinal, hepatic or renal disease or any other condition known to interfere with absorption, distribution, metabolism or excretion of drugs.
3. Any clinically important illness, medical/surgical procedure or trauma within 4 weeks of the
25 first administration of the drug.
4. SARS-CoV-2 first vaccination within 30 days prior to randomization.
5. SARS-CoV-2 second vaccination within 10 days of screening.
6. Confirmed COVID-19 infection during screening and admission, by PCR test.
7. A LDL-C reduction that is < 30% post rosuvastatin run-in period (Day -8), for the
30 rosuvastatin global MAD cohorts.
8. Any laboratory values with the following deviations at the Screening Visit and on admission to the study centre. Abnormal values may be repeated once at the discretion of the investigator:

- (a) ALT (Alanine aminotransferase) > ULN (upper limit of normal)
- 35 (b) AST (Aspartate aminotransferase) > ULN
- (c) eGFR (calculated using the CKD-EPI formula) < 60 mL/min/1.73 m²
- (d) Potassium < LLN (lower limit of normal)

- (e) Total bilirubin > ULN.
 - (f) Haemoglobin < LLN.
9. Any clinically important abnormalities in clinical chemistry, coagulation, haematology, or urinalysis results other than those described under exclusion criterion number 7, as judged
- 5 by the investigator.
10. Any positive result on Screening for serum hepatitis B surface antigen, hepatitis C antibody and HIV.
11. Abnormal vital signs, after 10 minutes supine rest, at the Screening Visit and on admission to the study centre, defined as any of the following. Abnormal values may be
- 10 repeated once at the discretion of the investigator:
- (a) Systolic BP < 90 mmHg or > 135 mmHg.
 - (b) Diastolic BP < 50 mmHg or > 90 mmHg.
 - (c) Pulse < 50 or > 85 bpm.
12. Any clinically important abnormalities in rhythm, conduction or morphology of the resting
- 15 ECG and any clinically important abnormalities in the 12-lead ECG as considered by the investigator that may interfere with the interpretation of QTc (QT interval corrected for heart rate) interval changes, including abnormal ST-T-wave morphology, particularly in the protocol defined primary lead or left ventricular hypertrophy, at the Screening Visit and/or on admission to the study centre. ECG recording may be repeated once for each visit at the
- 20 discretion of the investigator.
- (a) Prolonged QTcF (QT interval corrected for heart rate) > 450 ms.
 - (b) Shortened QTcF < 340 ms.
 - (c) Family history of long QT syndrome.
 - (d) PR (PQ) interval shortening < 120 ms (PR > 110 ms but < 120 ms is acceptable if

25 there is no evidence of ventricular pre-excitation) – PR(PQ) is ECG interval measured from the onset of the P wave to the onset of the QRS complex

 - (e) PR (PQ) interval prolongation (> 220 ms) intermittent second (Wenckebach block while asleep is not exclusive) or third-degree AV block, or AV dissociation.
 - (f) Persistent or intermittent complete BBB (Bundle branch block), IBBB (Incomplete bundle branch block), or IVCD (Intraventricular conduction delay) with QRS > 110

30 ms. Subjects with QRS (ECG interval measured from the onset of the QRS complex to the J point) > 110 ms but < 115 ms are acceptable if there is no evidence of e.g., ventricular hypertrophy or pre-excitation.
- 35 13. Known or suspected history of drug abuse as judged by the investigator.
14. Current smokers or those who have smoked or used nicotine products (including e-cigarettes) within the previous 3 months.

15. History of alcohol abuse or excessive intake of alcohol as judged by the investigator.
16. Positive screen for drugs of abuse, cotinine (nicotine), or alcohol at Screening and/or admission to the study centre.
17. History of severe allergy/hypersensitivity or ongoing clinically important
- 5 allergy/hypersensitivity, as judged by the investigator or history of hypersensitivity to drugs with a similar chemical structure or class to AZD0780.
18. Excessive intake of caffeine-containing drinks or food (e.g., coffee, tea, chocolate) as judged by the investigator.
19. Use of drugs with enzyme inducing properties such as St John's Wort within 3 weeks
- 10 prior to the first administration of drug.
20. 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 prior to the first administration of the drug to be tested or longer if the medication has a long half-life.
- 15 Hormone replacement therapy HRT is not allowed.
21. Plasma donation within one month of the Screening Visit or any blood donation/blood loss > 500 mL during the 3 months prior to the Screening Visit.
22. 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 longest) of the first
- 20 administration of drug in this study. The period of exclusion begins 1 month after the final dose.
23. Subjects who have previously received AZD0780 within 60 days of the first administration of the drug to be tested in this study.
24. Involvement of any Astra Zeneca or study centre employee or their close relatives.
- 25 25. Judgment by the investigator that the subject should not participate in the study if they have any ongoing or recent (i.e., during the Screening Period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions and requirements.
26. Subjects who are vegans or have medical dietary restrictions.
- 30 27. Subjects who cannot communicate reliably with the investigator.
28. Vulnerable subjects, e.g., kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.

Restrictions During the Study

- 35 The following restrictions apply for the specified times during the study period.
1. Subjects took the study drug on an empty stomach (after an overnight fast, with no food at least 2 hours prior to dosing) and wait at least 1 hour after dosing before having a light

breakfast or meal. No fluids were allowed apart from water which can be given until 1 hour prior to dosing and then from 1 hour after dosing (excluding water used in conjunction with drug administration; see Section 5.4.3).

2. Subjects were not allowed to lie fully supine (unless specified for certain assessments) for
5 4 hours after dosing.

3. Subjects were advised not to engage in any strenuous activity from 72 hours prior to check-in until after their final Follow-up Visit.

4. Prior to each treatment period subjects were advised to abstain from alcohol for 72 hours prior to check-in until after their last PK sampling visit. Subjects were also advised to abstain
10 from alcohol for 72 hours before their final Follow-up Visit.

5. Prior to each treatment period subjects were advised to abstain from caffeine-containing foods and beverages for 24 hours prior to check-in until discharge from the study centre.

6. Subjects were advised to abstain from grapefruit or grapefruit juice, Seville oranges, and quinine (e.g., tonic water) from 7 days prior to check-in until after their final Follow-up Visit.

15 7. During residential periods, subjects received a standard diet, which excludes all alcohol and grapefruit-containing products. No additional food or beverages must be consumed while in the study centre.

8. During the subjects' outpatient periods, subjects were advised to abstain from consuming high energy drinks, and food containing poppy seeds and any OTC medication or herbal
20 preparations until after their final Follow-up Visit has been completed. Subjects were advised to limit their caffeine intake to equivalent of 3 servings of coffee per day (1 serving = 12 oz soda, 6 oz coffee, or 8 oz tea). Subjects were advised to consume no more than 2 units of alcohol per day and completely abstain from alcohol from 72 hours prior to their next check-in.

25 9. Prior to any Follow-up Visits subjects fasted overnight; a light breakfast or meal was given after blood samples for PK and PD assessments have been taken.

10. Subjects were required to abstain from blood or plasma donation until 3 months after the medical examination at their final Follow-up Visit.

30 *Drug to be tested*

AZD0780 was used in a 10mg tablet.

Rosuvastatin was used in 5 mg, 10 mg or 20mg tablets.

Dosing

35 JSMAD Cohorts

Subjects received a single dose of AZD0780 or placebo on Day 1, followed by once daily dosing on Days 8 to 15 (there is no dose on Days 2 to 7). The dose was administered on an

empty stomach (after an overnight fast, with no food at least 2 hours prior to dosing) with approximately 240 mL of water. Subjects were allowed to drink water to prevent dehydration until 1 hour before dosing. Water was allowed ad libitum from 1 hour after dosing and a light breakfast or meal was given 1 hour at the earliest after dosing, except on the extensive PK-sampling days where subjects fasted until 4 hours after dosing.

Global MAD Cohorts

Each subject received once daily oral doses of AZD0780 or placebo for 28 days. Daily dosing commenced on Day 1. The dose was administered on an empty stomach (after an overnight fast, with no food at least 2 hours prior to dosing) with approximately 240 mL of water. Subjects were allowed to drink water to prevent dehydration until 1 hour before dosing. Water was allowed ad libitum from 1 hour after dosing and a light breakfast or meal was given 1 hour at the earliest after dosing, except on the extensive PK-sampling days where subjects fasted until 4 hours after dosing.

15

Rosuvastatin Global MAD Cohorts

Each participant participated in a minimum of 21 days run-in period (maximum of up to 28 days). During the run-in period each subject received once daily doses of rosuvastatin 20 mg.

20

The treatment period began with daily dosing commencing on Day 1. Each participant received once daily oral doses of rosuvastatin along with either AZD0780 or placebo. The dose was administered on an empty stomach (after an overnight fast, with no food at least 2 hours prior to dosing) with approximately 240 mL of water. Subjects were allowed to drink water to prevent dehydration until 1 hour before dosing. Water was allowed ad libitum from 1 hour after dosing and a light breakfast or meal was given 1 hour at the earliest after dosing, except on the extensive PK-sampling days where subjects were fasted until 4 hours after dosing.

30 Discontinuation of Study Intervention

Subjects may have been discontinued from study intervention in the following situations:

- Subject decision/withdrawal of consent. The subject is at any time free to discontinue treatment, without prejudice to further treatment.
- Lost to follow-up.
- Any Serious Adverse Event (SAE – see below) that is considered related to study intervention by the investigator.

35

- Any other Adverse Event (AE – see below) that, in the opinion of the investigator or the sponsor, warrants discontinuation of further dosing of the drug being tested.
- Severe non-compliance to study protocol.
- Any significant and clinically relevant changes in the safety parameters (e.g., ECG, BP, pulse, laboratory assessments and AE) making the continuation of drug administration unjustified.
- Subjects who test positive for SARS-CoV-2 infection by PCR (nasal, sputum, and/or throat swab specimen), during the course of the study, will be discontinued from the study and followed up until the outcome of the AE is established.

Adverse Events

Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

Definitions of Serious Adverse Event

A SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Pharmacokinetics**Collection of Pharmacokinetic Samples**

Blood samples for the determination of plasma concentrations of AZD0780 and urine samples for the determination of urine concentrations of AZD0780 were collected for each

5 treatment period as follows:

JSMAD Cohorts

	Treatment Period (Residential)			Follow-up (7 to 10 days dose)/ET
	Days 1 to 9	Day 10	Days 11 to 17	
Plasma for AZD0780 pharmacokinetics	Day 1: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 h post-dose Day 2: 24 and 36 h post-dose Day 3: 48 hours post-dose Day 5: 96 hours post-dose Day 8: pre-dose	Pre-dose	Day 13: pre-dose Day 15: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 h post-dose Day 16: 24 h post-dose	X
Urine for AZD0780 pharmacokinetics	Day 1: pre-dose Day 2: 24 h post-dose (Day 1 dose)		Day 15: pre-dose Day 16: 24 h post-dose Day 17: 48 h post-dose	

Global MAD Cohorts

	Treatment Period (Residential)				Follow-up (7 to 10 days dose)/ET
	Days 1 to 4	Day 5	Days 6 to 10	Days 11 to 29	
Plasma for AZD0780 pharmacokinetics	Day 1: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 h post-dose Day 2: pre-dose (24 h post Day 1 dose) Day 3: pre-dose	Pre-dose	Day 8: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 h post-dose Day 9: pre-dose (24 h post Day 8 dose)	Days 12,15, 18, 22, 25: pre-dose Day 29: 24 h post-dose	X
Urine for AZD0780 pharmacokinetics	Day 1: 0-6, 6-12, 12-24 h post-dose		Day 8: 0-6, 6-12, 12-24 h post-dose		

Rosuvastatin Global MAD Cohorts

	Treatment Period (Residential)				Follow-up (7 to 10 days dose)/ET
	Days 1 to 4	Day 5	Days 6 to 10	Days 11 to 29	
Plasma for AZD0780 pharmacokinetics	Day 1: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 h post-dose Day 2: pre-dose (24 h post Day 1 dose) Day 3: pre-dose	Pre-dose	Day 8: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 h post-dose Day 9: pre-dose (24 h post Day 8 dose)	Days 12,15, 18, 22, 25: pre-dose Day 29: 24 h post-dose	X
Urine for AZD0780 pharmacokinetics	Day 1: 0-6, 6-12, 12-24 h post-dose		Day 8: 0-6, 6-12, 12-24 h post-dose		

Pharmacokinetic Drug Assays

- Samples for determination of AZD0780 concentrations in plasma and urine were
- 5 analysed using validated assays. Additional analyses may have been conducted on the biological samples to further investigate the presence and/or identity of drug metabolites.

Pharmacodynamics**Collection of Pharmacodynamic Samples**

- 10 Blood/plasma/serum samples were collected for measurement of LDL-C and PCSK9 levels and lipid/lipoprotein profiles as follows:

JSMAD Cohorts

	Pre-Screening	Screening ≤ 28 days	Treatment Period (Residential)			Follow-up (7-10 post-dose)/ET
			Days 1 to 9	Day 10	Days 11 to 17	
Serum for LDL-C and lipid profile (total cholesterol, non-HDL-C, HDL-C, triglycerides)	X	X	Day 1: pre-dose Day 2: 24 h post-dose (Day 1 dose) Day 3: 48 h post-dose	Pre-dose	Day 15: pre-dose Day 16: 24 h post-dose Day 17: 48 h post-dose	X
Plasma for total PCSK9 (standard assay)			Day 1: pre-dose			
Plasma for total PCSK9 (modified assay)			Day 1: pre-dose Day 2: 24 h post-dose (Day 1 dose) Day 3: 48 h post-dose	Pre-dose	Day 15: pre-dose Day 16: 24 h post-dose Day 17: 48 h post-dose	
Serum for ApoB			Day 1: pre-dose Day 2: 24 h post-dose (Day 1 dose) Day 3: 48 h post-dose	Pre-dose	Day 15: pre-dose Day 16: 24 h post-dose Day 17: 48 h post-dose	
Serum for Lp(a)			Day 1: pre-dose		Day 16: 24 h post-dose	

ApoB, apolipoprotein B

Lp(a), Lipoprotein(a)

Global MAD Cohorts

	Pre-Screening	Screening ≤ 28 days	Treatment Period (Residential)				Follow-up (7-10 post-dose)/ET
			Days 1 to 4	Day 5	Days 6 to 10	Days 11 to 29	
Serum for LDL-C and lipid profile (total cholesterol, non-HDL-C, HDL-C, triglycerides)	X	X	Days 1 to 3: pre-dose	Pre-dose	Day 8: pre-dose	Days 12, 15, 18, 22, 25: pre-dose Day 29: 24 post-dose	X
Plasma for total PCSK9 (standard assay)			Day 1: pre-dose				
Plasma for total PCSK9 (modified assay)			Day 1: pre-dose		Day 8: pre-dose	Days 15 and 22: pre-dose Day 29: 24 h post-dose	X
Serum for ApoB			Days 1 to 3: pre-dose	Pre-dose	Day 8: pre-dose	Days 12, 15, 18, 22, 25: pre-dose Day 29: 24 h post-dose	X
Serum for Lp(a)			Day 1: pre-dose			Day 15: pre-dose Day 29: 24 h post-dose	X

Rosuvastatin Global MAD Cohorts

	Pre-Screening	Screening ≤ 56 days	Run-in – Day -28 to Day -2	Treatment Period (Residential)				Follow-up (7-10 post-dose)/ET
				Days 1 to 4	Day 5	Days 6 to 10	Days 11 to 29	
Serum for LDL-C and lipid profile (total cholesterol, non-HDL-C, HDL-C, triglycerides)	X	X	Day -28g (± 1 day) Day -8 (± 1 day)h	Days 1 to 3: pre-dose	Pre-dose	Day 8: pre-dose	Days 12, 15, 18, 22, 25: pre-dose Day 29: 24 post-dose	X
Plasma for total PCSK9 (standard assay)				Day 1: pre-dose				
Plasma for total PCSK9 (modified assay)				Day 1: pre-dose		Day 8: pre-dose	Days 15 and 22: pre-dose Day 29: 24 h post-dose	X
Serum for ApoB				Days 1 to 3: pre-dose	Pre-dose	Day 8: pre-dose	Days 12, 15, 18, 22, 25: pre-dose Day 29: 24 h post-dose	X
Serum for Lp(a)				Day 1: pre-dose			Day 15: pre-dose Day 29: 24 h post-dose	X

Results

Preliminary AE data from some completed cohorts are shown below:

Adverse events (Global MAD cohorts)		Number of adverse events					
		10 mg MAD		30 mg MAD		60 mg MAD	
System organ class	Preferred term	N = 15	%	N = 15	%	N = 15	%
Any adverse event		8	53.4	6	40	6	40
Cardiac disorders	Palpitations	1	6.7	0	0	0	0
	Tachycardia	0	0	1	6.7	0	0
Gastrointestinal disorders	Abdominal pain	0	0	1	6.7	0	0
	Constipation	0	0	1	6.7	3	20.0
	Diarrhoea	0	0	2	13.4	1	6.7
	Nausea	1	6.7	0	0	0	0
	Vomiting	1	6.7	0	0	0	0
General disorders and administration site conditions	Asthenia	1	0	0	0	1	6.7
	Catheter site pain	1	6.7	0	0	0	0
	Infusion site pain	1	6.7	0	0	0	0
	Medical device site reaction	2	13.3	0	0	0	0
	Skin abrasion	0	0	0	0	1	6.7
	Pyrexia	0	0	0	0	0	0
Hepatobiliary disorders	Hypertransaminasaemia	0	0	0	0	0	0
Infections and infestations	Cellulitis	0	0	0	0	0	0
	Otitis media	1	6.7	0	0	0	0
Investigations	Blood pressure increased	0	0	0	0	0	0
	Electrocardiogram QT prolonged	0	0	1	6.7	0	0
Metabolism and nutrition disorders	Decreased appetite	1	6.7	0	0	1	6.7
Musculoskeletal and connective tissue disorders	Musculoskeletal chest pain	0	0	0	0	0	0
	Pain in extremity	0	0	0	0	1	6.7
	Burning sensation	0	0	0	0	1	6.7

Adverse events (Global MAD cohorts)		Number of adverse events					
		10 mg MAD		30 mg MAD		60 mg MAD	
System organ class	Preferred term	N = 15	%	N = 15	%	N = 15	%
Nervous system disorders	Dizziness	2	13.3	0	0	1	6.7
	Headache	1	6.7	0	0	2	13.3
	Somnolence	0	0	0	0	2	13.3
Psychiatric disorders	Anxiety	0	0	1	6.7	0	0
Respiratory, thoracic and mediastinal disorders	Epistaxis	0	0	0	0	1	6.7
Skin and subcutaneous tissue disorders	Dermatitis contact	0	0	2	13.3	0	0
	Rash	0	0	0	0	1	6.7
	Skin irritation	1	6.7	0	0	0	0
	Acne	0	0	0	0	1	6.7

Adverse events (Global MAD cohorts)		Number of adverse events			
		All doses		Pooled placebo	
System organ class	Preferred term	N = 45	%	N = 15	%
Any adverse event		20	44.5	5	33.4
Cardiac disorders	Palpitations	1	2.2	1	6.7
	Tachycardia	1	2.2	0	0
Gastrointestinal disorders	Abdominal pain	1	2.2	1	6.7
	Constipation	4	8.9	2	13.3
	Diarrhoea	3	6.6	0	0
	Nausea	1	2.2	1	6.7
	Vomiting	1	2.2	0	0
General disorders and administration site conditions	Asthenia	2	4.4	0	0
	Catheter site pain	1	2.2	0	0
	Infusion site pain	1	2.2	0	0
	Medical device site reaction	2	4.4	0	0

Adverse events (Global MAD cohorts)		Number of adverse events			
		All doses		Pooled placebo	
System organ class	Preferred term	N = 45	%	N = 15	%
	Skin abrasion	1	2.2	0	0
	Pyrexia	0	0	1	6.7
Hepatobiliary disorders	Hypertransaminasaemia	0	0	1	6.7
Infections and infestations	Cellulitis	0	0	1	6.7
	Otitis media	1	2.2	0	0
Investigations	Blood pressure increased	0	0	1	6.7
	Electrocardiogram QT prolonged	1	2.2	0	0
Metabolism and nutrition disorders	Decreased appetite	2	4.4	0	0
Musculoskeletal and connective tissue disorders	Musculoskeletal chest pain	0	0	1	6.7
	Pain in extremity	1	2.2	1	6.7
Nervous system disorders	Burning sensation	1	2.2	0	0
	Dizziness	3	6.6	1	6.7
	Headache	3	6.6	1	6.7
	Somnolence	2	4.4	0	0
Psychiatric disorders	Anxiety	1	2.2	0	0
Respiratory, thoracic and mediastinal disorders	Epistaxis	1	2.2	0	0
Skin and subcutaneous tissue disorders	Dermatitis contact	2	4.4	1	6.7
	Rash	1	2.2	1	6.7
	Skin irritation	1	2.2	0	0
	Acne	1	2.2	1	6.7

Adverse event (JSMAD cohorts)		Number of adverse events							
		30 mg		60 mg		All doses		Pooled placebo	
System organ class	Preferred term	N = 6	%	N = 2	%	N = 8	%	N = 2	%
Any adverse event		1	16.7	1	50.0	2	25.0	1	50.0
Injury, poisoning and procedural complications	Scratch	1	16.7	0	0	1	12.5	0	0
Skin and subcutaneous tissue disorders	Dermatitis contact	0	0	0	0	0	0	1	50.0
	Skin irritation	0	0	1	50.0	1	12.5	0	0

In the above cohorts, there were no SAEs. All but 2 AEs were reported by the investigator as mild or moderate in intensity. The 2 AEs of severe intensity (tachycardia and ECG QT-prolongation) were reported for the same participant in the 30 mg MAD cohort, for whom treatment with AZD0780 was discontinued due to tachycardia on treatment Day 8 pre-dose. The maximum change in QTcF prolongation for this participant was 31.7 ms, likely explained by the increased mean heart rate, with a mean heart rate of 131 beats per minute, persisting for more than 10 minutes. There was no associated trend of repolarization abnormality or cardiac arrhythmia.

In total, in the above cohorts, treatment with AZD0780 was discontinued for 2 participants, one of whom received placebo.

In the 30mg Rosuvastatin Global MAD Cohort, no SAEs have been reported with dosing complete.

Figures 1 and 2 show preliminary data available from the MAD and combination cohorts.

Figure 1 shows that doses of 10, 30 and 60 mg once daily of AZD0780 alone significantly reduce LDL-C by approximately 30-40%.

Dose	Symbol
Placebo	◇
10mg	□
30mg	○
60mg	△

The effect of AZD0780 alone on LDL-C levels reached steady state around week 2. Patients in the 10 mg cohort were only on treatment for 11 days.

5

Figure 2 shows that administering AZD0780 30 mg for 4 weeks on top of rosuvastatin 20 mg, the percent change from baseline (i.e. the LDL-C level after pre-treatment with 20 mg rosuvastatin) to week 4 in LDL-C was -52%. Thus the cumulative reduction in LDL-C was at least 65%.

10

Dose	Symbol
rosuvastatin 20 mg	○
AZD0780 30 mg + rosuvastatin 20 mg	□

The synergy score for the combination of AZD0780 and rosuvastatin was calculated using the Bliss independence model (Roell 2017). This model is based on the idea of noninteraction, that each drug is acting independently of one another. There are two ways to calculate Bliss independence, either by using the product of the unaffected fractions (Greco 1995) or the sum of the affected fractions minus their product (Bliss 1939), which both give identical results.

15

The log-transformed unaffected fractions were used to enable the use of an ANOVA model to account for variability in the data and provide an assessment of statistical significance according to Demidenko & Miller 2019. The synergy score was defined as the expected unaffected fraction for the combination using the Bliss model divided by the observed unaffected fraction for the combination. If the synergy score is 1, the two drugs are predicted to act additively, while a significant deviation from additivity is classified as synergy if the synergy score >1 or antagonism if the synergy score <1.

20

25

The synergy score calculation is based on the data above, in which the mean LDL-C change from baseline was 30% (SD=0.2, N=26, week 4) based on AZD0780 pooled 30 + 60 mg,

53% (SD=0.13, N=35, week 3) for rosuvastatin 20 mg and 78% (SD=0.07, N=17, week 4 + 3-4 week run-in) for AZD0780 30 mg + rosuvastatin 20 mg. Baseline was defined as LDL-C levels prior to any treatment.

- 5 The statistically significant synergy score for the unaffected fractions is 1.5 ($p < 0.01$), indicating a synergistic effect on LDL-C when combining AZD0780 and rosuvastatin.

The LDL-C difference in change from baseline between the calculated additive effect and the observed effect for AZD0780 30 mg + rosuvastatin 20 mg was 10 percentage points. LDL-C

- 10 values were derived using Friedewald's equation.

Final Results

Final AE data are shown below (as of 23 August 2024):

Adverse events (Global MAD cohorts)		Number of adverse events					
		10 mg MAD		30 mg MAD		60 mg MAD	
System organ class	Preferred term	N = 15	%	N = 15	%	N = 15	%
Any adverse event		5	33.3	6	40	8	53.3
Cardiac disorders	Palpitations	1	6.7	0	0	0	0
	Tachycardia	0	0	1	6.7	0	0
Gastrointestinal disorders	Abdominal pain	1	6.7	1	6.7	0	0
	Constipation	0	0	1	6.7	3	20.0
	Diarrhoea	0	0	2	13.4	1	6.7
	Nausea	2	13.3	0	0	0	0
	Vomiting	1	6.7	0	0	0	0
General disorders and administration site conditions	Asthenia	1	0	0	0	1	6.7
	Catheter site pain	1	6.7	0	0	0	0
	Infusion site pain	0	0	0	0	0	0
	Medical device site reaction	1	6.7	0	0	0	0
	Application site rash	0	0	0	0	0	0
	Pyrexia	0	0	0	0	0	0
	Skin abrasion	0	0	0	0	1	6.7
Hepatobiliary disorders	Hypertransaminasaemia	0	0	0	0	0	0

Adverse events (Global MAD cohorts)		Number of adverse events					
		10 mg MAD		30 mg MAD		60 mg MAD	
System organ class	Preferred term	N = 15	%	N = 15	%	N = 15	%
Infections and infestations	Cellulitis	0	0	0	0	0	0
	Otitis media	1	6.7	0	0	0	0
Investigations	Blood pressure increased	1	6.7	0	0	0	0
	Electrocardiogram QT prolonged	0	0	1	6.7	0	0
Metabolism and nutrition disorders	Decreased appetite	0	0	0	0	1	6.7
Musculoskeletal and connective tissue disorders	Musculoskeletal chest pain	1	6.7	0	0	0	0
	Pain in extremity	1	6.7	0	0	1	6.7
Nervous system disorders	Burning sensation	0	0	0	0	1	6.7
	Dizziness	2	13.3	0	0	1	6.7
	Headache	1	6.7	0	0	2	13.3
	Somnolence	0	0	0	0	2	13.3
Psychiatric disorders	Anxiety	0	0	1	6.7	0	0
Respiratory, thoracic and mediastinal disorders	Epistaxis	0	0	0	0	1	6.7
Skin and subcutaneous tissue disorders	Dermatitis contact	0	0	2	13.3	0	0
	Rash	0	0	0	0	2	13.3
	Skin irritation	0	0	0	0	0	0
	Acne	0	0	0	0	0	0

Adverse events (Global MAD cohorts)		Number of adverse events			
		All doses		Pooled placebo	
System organ class	Preferred term	N = 45	%	N = 15	%
Any adverse event		19	42.2	7	46.7

Adverse events (Global MAD cohorts)		Number of adverse events			
		All doses		Pooled placebo	
System organ class	Preferred term	N = 45	%	N = 15	%
Cardiac disorders	Palpitations	1	2.2	1	6.7
	Tachycardia	0	0	0	0
Gastrointestinal disorders	Abdominal pain	2	4.4	0	0
	Constipation	4	8.9	2	13.3
	Diarrhoea	3	6.6	0	0
	Nausea	2	4.4	1	6.7
	Vomiting	1	2.2	0	0
General disorders and administration site conditions	Asthenia	2	4.4	0	0
	Catheter site pain	1	2.2	0	0
	Infusion site pain	0	0	1	6.7
	Medical device site reaction	1	2.2	0	0
	Application site rash	0	0	1	6.7
	Pyrexia	0	0	1	6.7
	Skin abrasion	1	2.2	0	0
Hepatobiliary disorders	Hypertransaminasaemia	0	0	1	6.7
Infections and infestations	Cellulitis	0	0	1	6.7
	Otitis media	0	0	1	6.7
Investigations	Blood pressure increased	1	2.2	0	0
	Electrocardiogram QT prolonged	1	2.2	0	0
Metabolism and nutrition disorders	Decreased appetite	1	2.2	1	2.2
Musculoskeletal and connective tissue disorders	Musculoskeletal chest pain	1	2.2	0	0
	Pain in extremity	2	4.4	0	0
Nervous system disorders	Burning sensation	1	2.2	0	0
	Dizziness	3	6.6	0	0
	Headache	3	6.6	1	6.7
	Somnolence	2	4.4	0	0
Psychiatric disorders	Anxiety	1	2.2	0	0

Adverse events (Global MAD cohorts)		Number of adverse events			
		All doses		Pooled placebo	
System organ class	Preferred term	N = 45	%	N = 15	%
Respiratory, thoracic and mediastinal disorders	Epistaxis	1	2.2	0	0
Skin and subcutaneous tissue disorders	Dermatitis contact	2	4.4	1	6.7
	Rash	2	4.4	1	6.7
	Skin irritation	0	0	1	6.7
	Acne	0	0	1	6.7

In the above Global MAD cohorts, there were no SAEs. All but 1 AEs were reported by the investigator as mild or moderate in intensity. The AE of severe intensity (tachycardia) was reported for a participant in the 30 mg MAD cohort, for whom treatment with AZD0780 was discontinued due to tachycardia on treatment Day 8 pre-dose.

In total, in the above cohorts, treatment with AZD0780 was discontinued for 2 participants, one of whom received placebo.

Adverse event (Rosuvastatin Global MAD; 20 mg)		Number of adverse events							
		AZD0780 1 mg		AZD0780 30 mg		All doses		Pooled placebo	
System organ class	Preferred term	N = 20	%	N = 18	%	N = 38	%	N = 22	%
Any adverse event		10	50.0	3	16.7	13	34.2	8	36.4
Infections and infestations	Oral herpes	0	0	0	0	0	0	1	4.5
Nervous system disorders	Dizziness postural	0	0	1	5.6	1	2.6	0	0
	Headache	1	5.0	0	0	1	2.6	1	4.5
	Somnolence	1	5.0	0	0	1	2.6	0	0
Cardiac disorders	AV block	1	5.0	0	0	1	2.6	0	0
	VT	0	0	1	5.6	1	2.6	1	4.5

Adverse event (Rosuvastatin Global MAD; 20 mg)		Number of adverse events							
		AZD0780 1 mg		AZD0780 30 mg		All doses 38		Pooled placebo 22	
System organ class	Preferred term	N = 20	%	N = 18	%	N = 38	%	N = 22	%
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	0	0	1	5.6	1	2.6	0	0
	Wheezing	0	0	0	0	0	0	1	4.5
Gastrointestina l disorders	Constipation	4	20.0	0	0	4	10.5	0	0
	Diarrhoea	0	0	1	5.6	1	2.6	0	0
	Flatulence	1	5.0	0	0	1	2.6	0	0
	Gingival bleeding	0	0	1	5.6	1	2.6	0	0
Skin and subcutaneous tissue disorders	Dermatitis contact	0	0	0	0	0	0	1	4.5
	Rash erythematous	0	0	1	5.6	1	5.6	0	0
Musculoskelet al and connective tissue disorders	Back pain	1	5.0	0	0	1	2.6	1	4.5
	Myalgia	0	0	1	5.6	1	2.6	0	0
	Pain in extremity	1	5.0	0	0	1	2.6	0	0
General disorders and administration site conditions	Axillary pain	1	5.0	0	0	1	2.6	0	0
	Feeling hot	0	0	0	0	0	0	1	4.5
	Medical device site reaction	0	0	1	5.6	1	2.6	0	0
	Non-cardiac chest pain	0	0	0	0	0	0	1	4.5
	Pyrexia	0	0	1	5.6	1	2.6	0	0
	Vessel puncture site bruise	1	5.0	0	0	1	2.6	0	0
Investigations	Alanine aminotransferase increased	1	5.0	0	0	1	2.6	0	0
Injury, poisoning and	Animal scratch	0	0	0	0	0	0	1	4.5
	Contusion	1	5.0	0	0	1	2.6	1	4.5

Adverse event (Rosuvastatin Global MAD; 20 mg)		Number of adverse events							
		AZD0780 1 mg		AZD0780 30 mg		All doses		Pooled placebo	
System organ class	Preferred term	N = 20	%	N = 18	%	N = 38	%	N = 22	%
procedural complications	Skin abrasion	1	5.0	0	0	1	2.6	0	0

In the above Rosuvastatin Global MAD cohorts, there were no SAEs.

In total, in the above Rosuvastatin Global MAD cohorts, treatment was discontinued for 3
5 participants who received AZD0780, and one participant who received placebo.

Adverse event (JSMAD cohorts)		Number of adverse events							
		30 mg		60 mg		All doses		Pooled placebo	
System organ class	Preferred term	N = 6	%	N = 6	%	N = 12	%	N = 4	%
Any adverse event		1	16.7	1	16.7	2	16.7	1	25.0
Injury, poisoning and procedural complications	Scratch	1	16.7	0	0	1	8.3	0	0
Skin and subcutaneous tissue disorders	Dermatitis contact	0	0	0	0	0	0	1	25.0
General disorders and administratio n site conditions	Medical device site dermatitis	0	0	1	16.7	1	8.3	0	0

In the above JSMAD cohorts, there were no SAEs and no participants were discontinued from the trial.

Figure 3 shows that administering AZD0780 1 mg or AZD0780 30 mg for 4 weeks on top of rosuvastatin 20 mg, the percent change from baseline (i.e. the LDL-C level after pre-treatment with 20 mg rosuvastatin) to week 4 in LDL-C was -27.9% and -52.1%, respectively. Thus the cumulative reduction in LDL-C was approximately 78% from untreated baseline for the AZD0780 30 mg + rosuvastatin 20 mg cohort.

Dose	Symbol
Placebo + rosuvastatin 20 mg	□
AZD0780 1 mg + rosuvastatin 20 mg	○
AZD0780 30 mg + rosuvastatin 20 mg	△

Example 2

This will be a randomized, multicentre, parallel-group, double-blind, placebo-controlled, dose-ranging, Phase IIb study in approximately 375 participants with dyslipidemia.

The study population will consist of male and female participants of non-childbearing potential, 18 to 75 years of age with a fasting LDL-C of ≥ 70 (1.8 mmol/L) and < 190 mg/dL (4.9 mmol/L) at screening. The Participants will also be receiving moderate or high-intensity statin therapy for at least 2 months prior to screening. The Participants will continue their statin therapy throughout the study.

Participants will be randomized to once daily dosing of placebo or one of the AZD0780 doses. Dosing should be supervised and documented by study staff when study intervention is administered in the clinic. Eligible participants will be randomized across 5 different treatment arms in a 1:1:1:1:1 ratio for a 12-week treatment period. The planned treatments arms are AZD0780 1 mg, AZD0780 3 mg, AZD0780 10 mg, AZD0780 30 mg, and placebo, all in addition to the continuing statin therapy.

The study will comprise 3 periods totalling up to 17 weeks:

- A screening period of up to 3 weeks
- A treatment period of 12 weeks
 - Dispensing visits will be at Week 1, Week 4, and Week 8

- The visit frequency will be at Week 1, Week 2, and Week 4; then once monthly up to Week 12
 - A final follow-up visit at Week 14 (safety follow-up period)
- 5 The planned treatments arms are placebo, AZD0780 1 mg once daily, AZD0780 3 mg once daily, AZD0780 10 mg once daily, and AZD0780 30 mg once daily, during the 12 week treatment period.

The overall study design is illustrated in Figure 4.

10

Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male and females of non-childbearing potential 18 to 75 years of age, inclusive, at the time of signing the informed consent.
- 15 2. Participants with a fasting LDL-C ≥ 70 mg/dL (1.8 mmol/L) and < 190 mg/dL (4.9 mmol/L) at screening.
3. Participants with fasting triglycerides < 400 mg/dL (< 4.52 mmol/L) at screening.
4. Should be receiving moderate or high-intensity statin therapy for ≥ 2 months prior to screening, according to ACC/AHA guidelines on blood cholesterol management, or to local
- 20 guidelines, eg, Japanese Atherosclerosis Society guidelines.
5. There should be no planned medication or dose change during study participation. Fibrate therapy and derivatives are prohibited.
6. Body mass index of at least 19.0 kg/m^2 .
7. Male participants:
 - 25 (a) Males must be surgically sterile or using, in conjunction with their female partner, a highly effective method of contraception for the duration of the study (from the time they sign consent) and for 3 months after the final follow up visit to prevent pregnancy in a partner. Acceptable methods of contraception include birth control pills, injections, implants, or patches, IUDs, tubal ligation/occlusion, and vasectomy. A barrier method is not necessary if
 - 30 the female partner is sterilized. Male study participants must not donate or bank sperm during this same time period.
8. Female participants:
 - (a) Female participants must not be pregnant and must have a negative pregnancy test at screening and randomization, must not be lactating, and must not be of childbearing
 - 35 potential. Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been

amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age- specific requirements apply:

(i) Women < 50 years of age would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment

5 and FSH levels in the postmenopausal range.

(ii) Women $\geq$ 50 years of age would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

9. Restrictions for male participants

10 (a) All male participants should avoid fathering a child by either true abstinence or by using (together with their female partner/spouse) a highly effective contraception form of birth control in combination with a barrier method, starting from the time of study intervention administration until 3 months after the Final Follow-Up visit. Acceptable methods of preventing pregnancy include birth control pills, injections, implants, or patches, IUDs, tubal

15 ligation/occlusion, and vasectomy.

(b) Male participants who have been sterilized are required to use 1 barrier method of contraception (condom) from the time of study intervention administration until after the Final Follow-Up Visit. A barrier method is not necessary if the female partner is sterilized.

(c) Male participants should not donate sperm for the duration of the study and for at least 3
20 months post final dose.

10. Capable of giving signed informed consent

11. Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses.

25 **Exclusion Criteria**

Participants are excluded from the study if any of the following criteria apply:

1. Estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73m² using the Chronic Kidney Disease-Epidemiology Collaboration equation at Visit 1.

2. History or presence of gastrointestinal, hepatic or renal disease or any other conditions
30 known to interfere with absorption, distribution, metabolism, or excretion of drugs.

3. Any uncontrolled or serious disease, or any medical (e.g., known major active infection or major haematological, renal, metabolic, gastrointestinal, respiratory, or endocrine dysfunction) or surgical condition that, in the opinion of the investigator, may either interfere with participation in the clinical study and/or put the participant at significant risk.

35 4. Poorly controlled type 2 diabetes mellitus, defined as HbA1c > 10% at Visit 1.

5. Acute ischemic cardiovascular event in the last 12 months prior to randomization however patients can be included if it is > 6 months from CABG surgery and > 3 months after PCI.

6. Heart failure with New York Heart Association (NYHA) Class III-IV.
7. Malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in-situ, or Stage 1 prostate carcinoma) within the last 10 years.
8. Recipient of any major organ transplant, e.g., lung, liver, heart, bone marrow, renal.
- 5 9. LDL or plasma apheresis within 12 months prior to randomization.
- 10 10. Uncontrolled hypertension defined as average sitting SBP > 160 mmHg or DBP > 90 mmHg at Visit 1. It is recommended that antihypertensive treatment should be considered/initiated at the PI's discretion and in accordance with applicable clinical guidelines in order to optimize blood pressure for participants with hypertension during the clinical study.
11. Heart rate after 10 minutes supine rest < 50 bpm or > 100 bpm at Visit 1.
12. Any laboratory values with the following deviations at Screening Visit 1; test may be repeated at the discretion of the investigator if abnormal:
 - (a) Any positive result on screening for hepatitis B, hepatitis C or HIV.
 - 15 (b) ALT > 1.5 x ULN
 - (c) AST > 1.5 x ULN
 - (d) TBL > ULN
 - (e) Haemoglobin < 12 g/dL in men or < 11 g/dL in women
 - (f) Potassium < LLN
- 20 13. Any clinically important abnormalities in rhythm, conduction or morphology of the resting ECG and any clinically important abnormalities in the 12 lead ECG as judged by the investigator including shortened QTcF < 340ms; family history of long QT syndrome; PR interval shortening < 120 ms; PR interval prolongation > 220 ms, intermittent second or third degree AV block or AV dissociation; persistent or intermittent complete bundle branch block,
- 25 incomplete bundle branch, or interventricular conduction delay with QRS > 110 ms
14. QTcF > 450 ms; high degree atrioventricular-block grade II-III and sinus node dysfunction with significant sinus pause untreated with pacemaker; and cardiac tachyarrhythmias.
15. Known or suspected history of drug abuse as judged by the investigator.
- 30 16. History of alcohol abuse or excessive intake of alcohol as judged by the investigator.
17. History of severe allergy/hypersensitivity or ongoing clinically important allergy/hypersensitivity, as judged by the investigator or history of hypersensitivity to drugs with a similar chemical structure.
18. Any clinically important illness, medical/surgical procedure or trauma within 4 weeks of
- 35 the first administration of study intervention. History or evidence of any other clinically significant disorder (e.g., cognitive impairment), condition, or disease other than those outlined above that, in the opinion of the investigator or Sponsor physician, if consulted, may

compromise the ability of the participant to give written informed consent, would pose a risk to participant safety, or interfere with the study evaluation, procedures, or completion.

19. Current/previous administration of inclisiran.
20. Lomitapide within 12 months prior to randomization.
- 5 21. Previous administration of PCSK9 inhibition treatment within 12 months prior to randomization (approved or investigational).
22. Fibrate therapy and derivatives are prohibited.
23. Receiving or has received within 14 days of screening, medication that contains a black box warning for significant QT prolongation.
- 10 24. Participation in another clinical study with a study intervention administered in the last 3 months prior to randomization or 5 half-lives from last dose to first administration of study intervention, whichever is the longest.
25. Received another new chemical entity (defined as a compound which has not been approved for marketing) within 30 days of last follow-up to first administration of the study
- 15 intervention of this study or 5 half-lives from last dose to first administration of study intervention, whichever is the longest.
26. Use of other investigational products or investigational devices during the course of the study.
27. Involvement in the planning and/or conduct of the study (applies to both Sponsor staff
- 20 and/or staff at the study site or their close relatives).
28. Judgement by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements.
29. As judged by the investigator, any evidence of disease conditions that, in the investigator's opinion, makes it undesirable for the participant to participate in the trial.
- 25 30. Previous screening in the present study. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. At the investigator's discretion, participants may be rescreened once during the recruitment period.
31. Participants who cannot communicate reliably with the investigator.
32. Vulnerable participants, e.g., kept in detention, protected adults under guardianship,
- 30 trusteeship, or committed to an institution by governmental or juridical order.
33. Plasma donation within 1 month of the visit at the clinic or any blood donation/blood loss > 500 mL (> 400 mL in Japan only) during the 3 months prior to screening visit.

Lifestyle Considerations

35 *Pregnancy*

Participants will be instructed that if they or their partner becomes pregnant during the study this should be reported to the investigator. The investigator should also be notified of

pregnancy occurring during the study but confirmed after completion of the study. In the event that a participant's partner is subsequently found to be pregnant after the participant is included in the study, then consent will be sought from the partner (via the participant's request that their partner contact the study site) and, if granted, any pregnancy will be followed, and the status of mother and/or child will be reported to the Sponsor after delivery.

Meals and Dietary Restrictions

For all study visits (including screening), participants must be fasted for 8 hours prior to blood sampling for LDL-C and other lipid profile. No fluids will be allowed apart from water, which can be given until 1 hour before blood sampling for LDL-C and other lipid profile.

Caffeine, Alcohol, and Tobacco

Participants who use alcohol may participate in the study unless their consumption is deemed excessive by the investigator.

Activity

Participants should not start any new physical training activities or increase the intensity of their usual physical training from 5 days prior to randomization until the end of the study.

20 Discontinuation of Study Intervention

An individual participant will not receive further IMP if any of the following occur in the participant in question:

- Hy's Law (HL) defined as 'an increase in AST of ALT $\geq 3 \times$ ULN and TBL $\geq 2 \times$ ULN' where no other reason, other than IMP, can be found to explain the combination of increases.
- A severe hypersensitivity reaction.
- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment.
- An SAE that is assessed as possibly related to the study intervention by the Investigator.
- An AE or other safety reasons as judged by the investigator and/or sponsor where continued treatment may put the participant at undue risk.
- Severe noncompliance with the protocol
- Pregnancy; if a participant becomes pregnant during the study the study intervention should be discontinued immediately and a Sponsor representative notified.

- Signs or symptoms of severe hepatic impairment (see Liver Chemistry Stopping Criteria below)
- Cardiovascular findings (see Cardiac Stopping Criteria below)
- Respiratory symptoms (see Respiratory stopping criteria below)

5

Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined below or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, if the investigator

10 believes that it is in best interest of the participant.

- ALT and/or AST are $> 3 \times \text{ULN}$ and TBL $> 2 \times \text{ULN}$
- ALT and/or AST are $\geq 5 \times \text{ULN}$ for ≥ 14 consecutive days, at any time after initial confirmatory results
- ALT and/or AST are $> 8 \times \text{ULN}$
- 15 • ALT or AST $> 3 \times \text{ULN}$ with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$)
- ALT or AST $> 3 \times \text{ULN}$ and INR (international normalized ratio) > 1.5 (applicable for participants with a baseline INR ≤ 1.1)

20 **Cardiac Stopping Criteria**

Discontinuation of study intervention for abnormal cardiac tests is required by the investigator when a participant meets one of the conditions outlined below:

- Average absolute (regardless of baseline value) cardiac QTc interval corrected for heart rate by QTcF > 500 msec, or an increase of QTcF > 60 msec above the
- 25 baseline value, confirmed (persistent for ≥ 5 minutes) on a repeat 12-lead ECG.

Any one of the following:

- Tachycardia, defined as resting supine pulse rate > 125 beats per minute persisting for at least 10 minutes.
- Symptomatic bradycardia, defined as resting supine pulse rate < 40 beats per minute
- 30 while awake, persisting for at least 10 minutes.
- Asymptomatic bradycardia, defined as resting supine pulse rate < 30 beats per minute while awake persisting for at least 10 minutes.
- Hypertension, defined as an increase from baseline in resting supine systolic > 40 mmHg or above 180 mmHg and persisting for at least 10 minutes and/or increase
- 35 from baseline in resting supine diastolic BP > 20 mmHg or above 100 mmHg and persisting for at least 10 minutes.

Respiratory stopping criteria

Discontinuation of study intervention is required by the investigator when a participant with respiratory disease meets the condition below:

- 5 • Exacerbation of known respiratory disease that requires hospital admission.

Adverse Events*Definition of Adverse Events*

10 An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

15

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

20 *Definitions of Serious Adverse Event*

A SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- 25 • Results in death.
- Is immediately life-threatening.
- 25 • Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity or substantial disruption of
- the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the subject or may require medical
- 30 intervention to prevent one of the outcomes listed above.

Endpoints

The primary endpoint of the study is percent change from baseline of LDL-C at Week 12.

35 Secondary endpoints of the study are percent change from baseline to Week 12 in:

- Non-HDL-C

- Very-low-density lipoprotein cholesterol (VLDL-C)
- ApoA1
- ApoB
- Total cholesterol
- 5 • HDL-C
- Triglycerides
- Lp(a)
- Remnant cholesterol (calculated from standard lipid profile)
- High-sensitivity C-reactive protein (hsCRP)

10

Results

This study (D7960C00006/NCT06173570) was carried out. The total number of patients studied who were receiving moderate or high-intensity statin therapy for at least 2 months prior to screening was 307.

15

The moderate or high-intensity statin therapies included treatment with:

Statin	Dose
Atorvastatin	10 mg once daily
Atorvastatin	20 mg every other day
Atorvastatin	20 mg once daily
Atorvastatin	30 mg once daily
Atorvastatin	40 mg three times a week
Atorvastatin	40 mg once daily
Atorvastatin	60 mg once daily
Atorvastatin	80 mg once daily
Atorvastatin	80 mg once a week
Atorvastatin calcium	10 mg once daily
Atorvastatin calcium	20 mg once daily
Atorvastatin calcium	30 mg once daily
Atorvastatin calcium	40 mg once daily
Atorvastatin calcium	60 mg once daily
Atorvastatin calcium	80 mg once daily
Atorvastatin calcium trihydrate	10 mg once daily
Atorvastatin calcium trihydrate	20 mg once daily
Pitavastatin calcium	1 mg once daily

Pitavastatin calcium	2 mg once daily
Pravastatin	40 mg once daily
Pravastatin	80 mg once daily
Rosuvastatin	5 mg once daily
Rosuvastatin	10 mg every other day
Rosuvastatin	10 mg once daily
Rosuvastatin	15 mg once daily
Rosuvastatin	20 mg once daily
Rosuvastatin	40 mg once daily
Rosuvastatin calcium	2.5 mg once daily
Rosuvastatin calcium	5 mg once daily
Rosuvastatin calcium	10 mg once daily
Rosuvastatin calcium	20 mg once daily
Rosuvastatin calcium	30 mg once daily
Rosuvastatin calcium	40 mg once daily
Simvastatin	20 mg once daily
Simvastatin	40 mg once daily

Primary Endpoint

The reduction in LDL-C (placebo adjusted) at Week 12 is shown below for each dose level of AZD0780:

Dose + statin	n	% LDL-C from baseline	p
Placebo	66	0	
AZD0780 1 mg	62	-34.48	<0.001
AZD0780 3 mg	64	-38.43	<0.001
AZD0780 10 mg	55	-45.79	<0.001
AZD0780 30 mg	60	-50.67	<0.001

5

There were statistically significant reductions in LDL-C from baseline to Week 12 for all AZD0780 doses compared with placebo, and the magnitude of LDL-C reduction increased with higher doses of AZD0780. Reductions in LDL-C were evident by Week 1 and reached steady state by approximately Week 2.

10

Secondary Endpoints

The reduction in total cholesterol (placebo adjusted) at Week 12 is shown below for each dose level of AZD0780:

Dose + statin	n	% total cholesterol from baseline
Placebo	63	0
AZD0780 1 mg	68	-20.13
AZD0780 3 mg	63	-21.18
AZD0780 10 mg	64	-26.38
AZD0780 30 mg	55	-26.92

The reduction in Non-HDL-C (placebo adjusted) at Week 12 is shown below for each dose level of AZD0780:

Dose + statin	n	% Non-HDL-C from baseline
Placebo	63	0
AZD0780 1 mg	67	-29.14
AZD0780 3 mg	63	-31.19
AZD0780 10 mg	62	-36.89
AZD0780 30 mg	55	-42.67

- 5 The reduction in Apo-B (placebo adjusted) at Week 12 is shown below for each dose level of AZD0780:

Dose + statin	n	% Apo-B from baseline
Placebo	62	0
AZD0780 1 mg	66	-26.17
AZD0780 3 mg	63	-26.08
AZD0780 10 mg	64	-35.88
AZD0780 30 mg	55	-37.68

Adverse events

AZD0780	1 mg N=75 n (%)	3 mg N=70 n (%)	10 mg N=66 n (%)	30 mg N=62 n (%)	Total N=273 n (%)	Placebo N=69 n (%)
Any AE	28 (37.3)	23 (32.9)	26 (39.4)	25 (40.3)	102 (37.4)	23 (33.3)
Any SAE	2 (2.7)	2 (2.9)	2 (3.0)	1 (1.6)	7 (2.6)	0
Any SAE with outcome death	0	0	0	0	0	0
Any AE leading to discontinuation of IP	1 (1.3)	1 (1.4)	0	3 (4.8)	5 (1.8)	2 (2.9)
Any AE leading to interruption of IP	1 (1.3)	1 (1.4)	3 (4.5)	1 (1.6)	6 (2.2)	2 (2.9)
Any AE leading to withdrawal of the subject from the study	0	0	0	0	0	0
Any possibly related AE	2 (2.7)	5 (7.1)	0	1 (1.6)	8 (2.9)	2 (2.9)

There were few participants reporting SAEs across AZD0780 groups, and no SAEs in the placebo group. There were no SAEs with outcome death, and no SAEs were deemed related to AZD0780.

5

There were no AE leading to withdrawal of the subject from the study. The proportion of participants reporting AE was similar across AZD0780 groups and placebo, and there were no dose-dependent patterns in the AZD0780 groups.

10

AZD0780 was safe and tolerable with no new safety concerns identified in the study.

References

A number of publications are cited above in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below. The entirety of each of these references is incorporated

5 herein.

	Reference	Doi
Atar 2021	Atar et al., Atherosclerosis. 2021; 319: 51-61	10.1016/j.atherosclerosis.2020.12.013
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Statements

1. A method of lowering LDL-C levels, reducing cardiovascular risk and/or treating a cardiovascular disease, comprising administering to a subject in need thereof, a first amount of 6'-((1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-
5 bipyridin]-2-one ("AZD0780") or a pharmaceutically acceptable salt thereof and a second amount of a statin, wherein the first amount and the second amount together comprise a therapeutically effective amount.
2. The method according to statement 1, which is a method of lowering LDL-C levels.
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3. The method according to statement 2, wherein the subject is an adult with primary hyperlipidemia.
4. The method according to any one of statements 1 to 3, wherein the LDL-C level is
15 reduced to:
(a) less than 100 mg/dL;
(b) less than 70 mg/dL;
(c) less than 55 mg/dL; or
(d) less than 40 mg/dL.
20
5. The method according to any one of statements 1 to 4, wherein the reduction of the untreated level of LDL-C is by:
(a) greater than or equal to 30%;
(b) greater than or equal to 40%;
25 (c) greater than or equal to 50%;
(d) greater than or equal to 60%;
(e) greater than or equal to 65%;
(f) greater than or equal to 70%; or
(g) great than or equal to 75%.
30
6. The method according to statement 1, which is a method of reducing cardiovascular risk.
7. The method according to statement 6, wherein the subject is an adult with
35 atherosclerotic cardiovascular disease (ASCVD) or at high or intermediate risk for a first ASCVD event.

8. The method according to statement 1, which is a method of treating a cardiovascular disease.

9. The method according to statement 8, wherein the cardiovascular disease treated is selected from dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hypoalphalipoproteinemia, metabolic syndrome, diabetic complications, atherosclerosis, stroke, vascular dementia, chronic kidney disease, coronary heart disease, coronary artery disease, retinopathy, inflammation, thrombosis, peripheral vascular disease, heart failure and congestive heart failure.

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10. The method according to either statement 8 or statement 9, wherein the cardiovascular disease to be treated is selected from hypercholesterolemia, hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia, dyslipidemia, dyslipoproteinemia, atherosclerosis, hepatic steatosis, metabolic syndrome and coronary artery disease.

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11. The method according to any one of statements 8 to 10, wherein the cardiovascular disease to be treated is:

(a) hypercholesterolemia, such as familial hypercholesterolemia;

(b) hyperlipidemia; or

20 (c) coronary artery disease.

12. The method according to any one of statements 1 to 11, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered once daily.

25 13. The method according to statement 12, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered in a dose of 1 to 30 mg per day of AZD0780.

14. The method according to statement 13, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered in a dose of 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 15 mg, 30 20 mg, 25 mg, or 30 mg per day of AZD0780.

15. The method according to any one of statements 1 to 14, wherein the statin is administered in a moderate-intensity dosing or high-intensity dosing, as defined by the ACC (American College of Cardiology) and the AHA (American Heart Association).

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16. The method according to any one of statements 1 to 15, wherein the statin is administered according to one of the following regimens:

- (a) Atorvastatin, 10 to 20 mg once daily;
(b) Fluvastatin, 40 mg twice daily, or 80 mg once daily;
(c) Lovastatin, 40 to 80 mg once daily;
(d) Pitavastatin, 1 to 4 mg once daily;
- 5 (e) Pravastatin, 40 to 80 mg once daily;
(f) Rosuvastatin, 5 to 10 mg once daily, optionally as rosuvastatin calcium;
(g) Simvastatin, 20 to 40 mg once daily;
(h) Atorvastatin, 40 to 80 mg once daily;
(i) Rosuvastatin, 20 to 40 mg once daily, optionally as rosuvastatin calcium;
- 10 (j) Atorvastatin, 10 to 40 mg once daily;
(k) Fluvastatin, 60 mg once daily;
(l) Rosuvastatin, 2.5 to 20 mg once daily, optionally as rosuvastatin calcium; or
(m) Simvastatin, 10 to 20 mg once daily.
- 15 17. The method according to statement 16, wherein the statin is rosuvastatin which is administered according to one of the following:
(a) 2.5 to 20 mg once daily, optionally as rosuvastatin calcium;
(b) 5 to 10 mg once daily, optionally as rosuvastatin calcium; or
(c) 20 to 40 mg once daily, optionally as rosuvastatin calcium.
- 20 18. The method according to any one of statements 1 to 11, wherein AZD0780 or a pharmaceutically acceptable salt thereof is administered once daily in a dose of 1 mg to 30 mg of AZD0780 and the statin is rosuvastatin which is administered once daily in a dose of 2.5 mg to 40 mg, optionally as rosuvastatin calcium.
- 25 19. The method according to any one of statements 1 to 18, wherein the subject has been treated with one or more statins prior to starting the method of treatment.
20. The method according to statement 19, wherein the subject has been treated with
30 one or more statins for a period of at least two months prior to starting the method of treatment.
21. The method according to statement 20, wherein the subject has been treated with
35 one or more statins for a period of at least six months prior to starting the method of treatment.

22. The method according to any one of statements 19 to 21, wherein the previous statin treatment was at a moderate-intensity dosing or high-intensity dosing, as defined by the ACC (American College of Cardiology) and the AHA (American Heart Association).

5 23. The method according to any one of statements 1 to 22, wherein the subject to be treated has a LDL-C $\leq$ 190 mg/dL before starting treatment.

24. The method according to any one of statements 1 to 23, wherein the subject to be treated has a LDL-C $\geq$ 100 mg/dL before starting treatment.

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25. 6'-([[(1S,3S)-3-([5-(Difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one ("AZD0780") or a pharmaceutically acceptable salt thereof for use in lowering LDL-C levels, reducing cardiovascular risk and/or treating a cardiovascular disease in a subject, wherein said treatment comprises the separate, sequential or simultaneous
15 administration of i) said AZD0780 or a pharmaceutically acceptable salt thereof, and ii) a statin to said subject.

26. AZD0780 or a pharmaceutically acceptable salt thereof for use according to statement 25, wherein the use is a method of lowering LDL-C levels.

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27. AZD0780 or a pharmaceutically acceptable salt thereof for use according to statement 26, wherein the subject is an adult with primary hyperlipidemia.

28. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one
25 of statements 25 to 27, wherein the LDL-C level is reduced to:

- (a) less than 100 mg/dL;
- (b) less than 70 mg/dL;
- (c) less than 55 mg/dL; or
- (d) less than 40 mg/dL.

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29. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one of statements 25 to 28, wherein the reduction of the untreated level of LDL-C is by:

- (a) greater than or equal to 30%;
- (b) greater than or equal to 40%;
- 35 (c) greater than or equal to 50%;
- (d) greater than or equal to 60%;
- (e) greater than or equal to 65%;

(f) greater than or equal to 70%; or

(g) great than or equal to 75%.

30. AZD0780 or a pharmaceutically acceptable salt thereof for use according to
5 statement 25, wherein the use is a method of reducing cardiovascular risk.

31. AZD0780 or a pharmaceutically acceptable salt thereof for use according to
statement 30, wherein the subject is an adult with atherosclerotic cardiovascular disease
(ASCVD) or at high or intermediate risk for a first ASCVD event.

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32. AZD0780 or a pharmaceutically acceptable salt thereof for use according to
statement 25, wherein the use is a method of treating a cardiovascular disease.

33. AZD0780 or a pharmaceutically acceptable salt thereof for use according to
15 statement 32, wherein the cardiovascular disease treated is selected from dyslipidemia,
hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hypoalphalipoproteinemia,
metabolic syndrome, diabetic complications, atherosclerosis, stroke, vascular dementia,
chronic kidney disease, coronary heart disease, coronary artery disease, retinopathy,
inflammation, thrombosis, peripheral vascular disease, heart failure and congestive heart
20 failure.

34. AZD0780 or a pharmaceutically acceptable salt thereof for use according to either
statement 32 or statement 33, wherein the cardiovascular disease to be treated is selected
from hypercholesterolemia, hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia,
25 dyslipidemia, dyslipoproteinemia, atherosclerosis, hepatic steatosis, metabolic syndrome
and coronary artery disease.

35. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one
of statements 32 to 34, wherein the cardiovascular disease to be treated is:
30 (a) hypercholesterolemia, such as familial hypercholesterolemia;
(b) hyperlipidemia; or
(c) coronary artery disease.

36. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one
35 of statements 25 to 35, wherein the AZD0780 or a pharmaceutically acceptable salt thereof
is administered once daily.

37. AZD0780 or a pharmaceutically acceptable salt thereof for use according to statement 36, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered in a dose of 1 to 30 mg per day of AZD0780.
- 5 38. AZD0780 or a pharmaceutically acceptable salt thereof for use according to statement 37, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered in a dose of 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg per day of AZD0780.
- 10 39. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one of statements 25 to 38, wherein the statin is administered in a moderate-intensity dosing or high-intensity dosing, as defined by the ACC (American College of Cardiology) and the AHA (American Heart Association).
- 15 40. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one of statements 25 to 39, wherein the statin is administered according to one of the following regimens:
- (a) Atorvastatin, 10 to 20 mg once daily;
 - (b) Fluvastatin, 40 mg twice daily, or 80 mg once daily;
 - 20 (c) Lovastatin, 40 to 80 mg once daily;
 - (d) Pitavastatin, 1 to 4 mg once daily;
 - (e) Pravastatin, 40 to 80 mg once daily;
 - (f) Rosuvastatin, 5 to 10 mg once daily, optionally as rosuvastatin calcium;
 - (g) Simvastatin, 20 to 40 mg once daily;
 - 25 (h) Atorvastatin, 40 to 80 mg once daily;
 - (i) Rosuvastatin, 20 to 40 mg once daily, optionally as rosuvastatin calcium;
 - (j) Atorvastatin, 10 to 40 mg once daily;
 - (k) Fluvastatin, 60 mg once daily;
 - (l) Rosuvastatin, 2.5 to 20 mg once daily, optionally as rosuvastatin calcium; or
 - 30 (m) Simvastatin, 10 to 20 mg once daily.
41. AZD0780 or a pharmaceutically acceptable salt thereof for use according to statement 40, wherein the statin is rosuvastatin which is administered according to one of the following:
- 35 (a) 2.5 to 20 mg once daily, optionally as rosuvastatin calcium;
 - (b) 5 to 10 mg once daily, optionally as rosuvastatin calcium; or
 - (c) 20 to 40 mg once daily, optionally as rosuvastatin calcium.

42. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one of statements 25 to 35, wherein AZD0780 or a pharmaceutically acceptable salt thereof is administered once daily in a dose of 1 mg to 30 mg of AZD0780 and the statin is
5 rosuvastatin which is administered once daily in a dose of 2.5 mg to 40 mg, optionally as rosuvastatin calcium.
43. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one of statements 25 to 42, wherein the subject has been treated with one or more statins prior
10 to starting the method of treatment.
44. AZD0780 or a pharmaceutically acceptable salt thereof for use according to statement 43, wherein the subject has been treated with one or more statins for a period of at least two months prior to starting the method of treatment.
15
45. AZD0780 or a pharmaceutically acceptable salt thereof for use according to statement 44, wherein the subject has been treated with one or more statins for a period of at least six months prior to starting the method of treatment.
- 20 46. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one of statements 43 to 45, wherein the previous statin treatment was at a moderate-intensity dosing or high-intensity dosing, as defined by the ACC (American College of Cardiology) and the AHA (American Heart Association).
- 25 47. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one of statements 25 to 46, wherein the subject to be treated has a LDL-C $\leq$ 190 mg/dL before starting treatment.
- 30 48. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one of statements 25 to 47, wherein the subject to be treated has a LDL-C $\geq$ 100 mg/dL before starting treatment.
49. A statin for use in lowering LDL-C levels, reducing cardiovascular risk and/or treating a cardiovascular disease in a subject, wherein said treatment comprises the separate,
35 sequential or simultaneous administration of i) said statin, and ii) 6'-((1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one ("AZD0780") or a pharmaceutically acceptable salt thereof to said subject.

50. The statin for use according to statement 49, wherein the use is a method of lowering LDL-C levels.
- 5 51. The statin for use according to statement 50, wherein the subject is an adult with primary hyperlipidemia.
52. The statin for use according to any one of statements 49 to 51, wherein the LDL-C level is reduced to:
- 10 (a) less than 100 mg/dL;
(b) less than 70 mg/dL;
(c) less than 55 mg/dL; or
(d) less than 40 mg/dL.
- 15 53. The statin for use according to any one of statements 49 to 52, wherein the reduction of the untreated level of LDL-C is by:
- (a) greater than or equal to 30%;
(b) greater than or equal to 40%;
(c) greater than or equal to 50%;
20 (d) greater than or equal to 60%;
(e) greater than or equal to 65%;
(f) greater than or equal to 70%; or
(g) great than or equal to 75%.
- 25 54. The statin for use according to statement 49, wherein the use is a method of reducing cardiovascular risk.
55. The statin for use according to statement 54, wherein the subject is an adult with atherosclerotic cardiovascular disease (ASCVD) or at high or intermediate risk for a first
30 ASCVD event.
56. The statin for use according to statement 49, wherein the use is a method of treating a cardiovascular disease.
- 35 57. The statin for use according to statement 56, wherein the cardiovascular disease treated is selected from dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hypoalphalipoproteinemia, metabolic syndrome, diabetic complications,

atherosclerosis, stroke, vascular dementia, chronic kidney disease, coronary heart disease, coronary artery disease, retinopathy, inflammation, thrombosis, peripheral vascular disease, heart failure and congestive heart failure.

- 5 58. The statin for use according to either statement 56 or statement 57, wherein the cardiovascular disease to be treated is selected from hypercholesterolemia, hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia, dyslipidemia, dyslipoproteinemia, atherosclerosis, hepatic steatosis, metabolic syndrome and coronary artery disease.
- 10 59. The statin for use according to any one of statements 56 to 58, wherein the cardiovascular disease to be treated is:
- (a) hypercholesterolemia, such as familial hypercholesterolemia;
 - (b) hyperlipidemia; or
 - (c) coronary artery disease.
- 15 60. The statin for use according to any one of statements 49 to 59, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered once daily.
61. The statin for use according to statement 60, wherein the AZD0780 or a
- 20 pharmaceutically acceptable salt thereof is administered in a dose of 1 to 30 mg per day of AZD0780.
62. The statin for use according to statement 61, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered in a dose of 1 mg, 2 mg, 3 mg, 5
- 25 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg per day of AZD0780.
63. The statin for use according to any one of statements 49 to 62, wherein the statin is administered in a moderate-intensity dosing or high-intensity dosing, as defined by the ACC (American College of Cardiology) and the AHA (American Heart Association).
- 30 64. The statin for use according to any one of statements 49 to 63, wherein the statin is administered according to one of the following regimens:
- (a) Atorvastatin, 10 to 20 mg once daily;
 - (b) Fluvastatin, 40 mg twice daily, or 80 mg once daily;
 - 35 (c) Lovastatin, 40 to 80 mg once daily;
 - (d) Pitavastatin, 1 to 4 mg once daily;
 - (e) Pravastatin, 40 to 80 mg once daily;

- (f) Rosuvastatin, 5 to 10 mg once daily, optionally as rosuvastatin calcium;
(g) Simvastatin, 20 to 40 mg once daily;
(h) Atorvastatin, 40 to 80 mg once daily;
(i) Rosuvastatin, 20 to 40 mg once daily, optionally as rosuvastatin calcium;
5 (j) Atorvastatin, 10 to 40 mg once daily;
(k) Fluvastatin, 60 mg once daily;
(l) Rosuvastatin, 2.5 to 20 mg once daily, optionally as rosuvastatin calcium; or
(m) Simvastatin, 10 to 20 mg once daily.
- 10 65. The statin for use according to statement 64, wherein the statin is rosuvastatin which is administered according to one of the following:
(a) 2.5 to 20 mg once daily, optionally as rosuvastatin calcium;
(b) 5 to 10 mg once daily, optionally as rosuvastatin calcium; or
(c) 20 to 40 mg once daily, optionally as rosuvastatin calcium.
- 15 66. The statin for use according to any one of statements 49 to 59, wherein AZD0780 or a pharmaceutically acceptable salt thereof is administered once daily in a dose of 1 mg to 30 mg of AZD0780 and the statin is rosuvastatin which is administered once daily in a dose of 2.5 mg to 40 mg, optionally as rosuvastatin calcium.
- 20 67. The statin for use according to any one of statements 49 to 66, wherein the subject has been treated with one or more statins prior to starting the method of treatment.
68. The statin for use according to statement 67, wherein the subject has been treated
25 with one or more statins for a period of at least two months prior to starting the method of treatment.
69. The statin for use according to statement 68, wherein the subject has been treated
30 with one or more statins for a period of at least six months prior to starting the method of treatment.
70. The statin for use according to any one of statements 67 to 69, wherein the previous statin treatment was at a moderate-intensity dosing or high-intensity dosing, as defined by the ACC (American College of Cardiology) and the AHA (American Heart Association).
- 35 71. The statin for use according to any one of statements 49 to 70, wherein the subject to be treated has a LDL-C $\leq$ 190 mg/dL before starting treatment.

72. The statin for use according to any one of statements 49 to 71, wherein the subject to be treated has a LDL-C $\geq$ 100 mg/dL before starting treatment.

- 5 73. The use of 6'-([1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one ("AZD0780") or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in lowering LDL-C levels, reducing cardiovascular risk and/or treating a cardiovascular disease wherein said treatment comprises the separate, sequential or simultaneous administration of
- 10 i) said medicament comprising AZD0780 or a pharmaceutically acceptable salt thereof and
ii) a statin to said subject.

74. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to statement 73, wherein the medicament is for use in lowering LDL-C levels.

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75. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to statement 74, wherein the subject is an adult with primary hyperlipidemia.

76. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to any one of statements 73 to 75, wherein the LDL-C level is reduced to:

20

- (a) less than 100 mg/dL;
- (b) less than 70 mg/dL;
- (c) less than 55 mg/dL; or
- (d) less than 40 mg/dL.

25

77. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to any one of statements 73 to 76, wherein the reduction of the untreated level of LDL-C is by:

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- (a) greater than or equal to 30%;
- (b) greater than or equal to 40%;
- (c) greater than or equal to 50%;
- (d) greater than or equal to 60%;
- (e) greater than or equal to 65%;
- (f) greater than or equal to 70%; or
- (g) greater than or equal to 75%.

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78. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to statement 73, wherein the medicament is for use in reducing cardiovascular risk.

79. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to statement 78, wherein the subject is an adult with atherosclerotic cardiovascular disease (ASCVD) or at high or intermediate risk for a first ASCVD event.

5

80. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to statement 73, wherein the medicament is for use in treating a cardiovascular disease.

81. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to statement 80, wherein the cardiovascular disease treated is selected from dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hypoalphalipoproteinemia, metabolic syndrome, diabetic complications, atherosclerosis, stroke, vascular dementia, chronic kidney disease, coronary heart disease, coronary artery disease, retinopathy, inflammation, thrombosis, peripheral vascular disease, heart failure and congestive heart failure.

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82. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to either statement 80 or statement 81, wherein the cardiovascular disease to be treated is selected from hypercholesterolemia, hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia, dyslipidemia, dyslipoproteinemia, atherosclerosis, hepatic steatosis, metabolic syndrome and coronary artery disease.

20

83. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to any one of statements 80 to 82, wherein the cardiovascular disease to be treated is:

(a) hypercholesterolemia, such as familial hypercholesterolemia;

(b) hyperlipidemia; or

(c) coronary artery disease.

25

84. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to any one of statements 73 to 83, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered once daily.

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85. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to statement 84, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered in a dose of 1 to 30 mg per day of AZD0780.

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86. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to statement 85, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered in a dose of 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg per day of AZD0780.

5

87. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to any one of statements 73 to 86, wherein the statin is administered in a moderate-intensity dosing or high-intensity dosing, as defined by the ACC (American College of Cardiology) and the AHA (American Heart Association).

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88. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to any one of statements 73 to 87, wherein the statin is administered according to one of the following regimens:

- (a) Atorvastatin, 10 to 20 mg once daily;
- 15 (b) Fluvastatin, 40 mg twice daily, or 80 mg once daily;
- (c) Lovastatin, 40 to 80 mg once daily;
- (d) Pitavastatin, 1 to 4 mg once daily;
- (e) Pravastatin, 40 to 80 mg once daily;
- (f) Rosuvastatin, 5 to 10 mg once daily, optionally as rosuvastatin calcium;
- 20 (g) Simvastatin, 20 to 40 mg once daily;
- (h) Atorvastatin, 40 to 80 mg once daily;
- (i) Rosuvastatin, 20 to 40 mg once daily, optionally as rosuvastatin calcium;
- (j) Atorvastatin, 10 to 40 mg once daily;
- (k) Fluvastatin, 60 mg once daily;
- 25 (l) Rosuvastatin, 2.5 to 20 mg once daily, optionally as rosuvastatin calcium; or
- (m) Simvastatin, 10 to 20 mg once daily.

89. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to statement 88, wherein the statin is rosuvastatin which is administered according to one of the following:

- 30 (a) 2.5 to 20 mg once daily, optionally as rosuvastatin calcium;
- (b) 5 to 10 mg once daily, optionally as rosuvastatin calcium; or
- (c) 20 to 40 mg once daily, optionally as rosuvastatin calcium.

35 90. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to any one of statements 73 to 83, wherein AZD0780 or a pharmaceutically acceptable salt thereof is administered once daily in a dose of 1 mg to 30 mg of AZD0780 and the statin is

rosuvastatin which is administered once daily in a dose of 2.5 mg to 40 mg, optionally as rosuvastatin calcium.

91. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to any one of statements 73 to 90, wherein the subject has been treated with one or more statins prior to starting the method of treatment.

92. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to statement 91, wherein the subject has been treated with one or more statins for a period of at least two months prior to starting the method of treatment.

93. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to statement 92, wherein the subject has been treated with one or more statins for a period of at least six months prior to starting the method of treatment.

94. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to any one of statements 91 to 93, wherein the previous statin treatment was at a moderate-intensity dosing or high-intensity dosing, as defined by the ACC (American College of Cardiology) and the AHA (American Heart Association).

95. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to any one of statements 73 to 94, wherein the subject to be treated has a LDL-C $\leq$ 190 mg/dL before starting treatment.

96. The use of AZD0780 or a pharmaceutically acceptable salt thereof according to any one of statements 73 to 95, wherein the subject to be treated has a LDL-C $\geq$ 100 mg/dL before starting treatment.

97. The use of a statin in the manufacture of a medicament for use in the lowering of LDL-C levels, reducing cardiovascular risk and/or treating a cardiovascular disease wherein said treatment comprises the separate, sequential or simultaneous administration of i) said medicament comprising a statin and ii) 6'-([1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one ("AZD0780") or a pharmaceutically acceptable salt thereof to said subject.

98. The use of the statin according to statement 97, wherein the medicament is for use in lowering LDL-C levels.

99. The use of the statin according to statement 98, wherein the subject is an adult with primary hyperlipidemia.

5 100. The use of the statin according to any one of statements 97 to 99, wherein the LDL-C level is reduced to:

- (a) less than 100 mg/dL;
- (b) less than 70 mg/dL;
- (c) less than 55 mg/dL; or
- 10 (d) less than 40 mg/dL.

101. The use of the statin according to any one of statements 97 to 100, wherein the reduction of the untreated level of LDL-C is by:

- (a) greater than or equal to 30%;
- 15 (b) greater than or equal to 40%;
- (c) greater than or equal to 50%;
- (d) greater than or equal to 60%;
- (e) greater than or equal to 65%;
- (f) greater than or equal to 70%; or
- 20 (g) great than or equal to 75%.

102. The use of the statin according to statement 97, wherein the medicament is for use in reducing cardiovascular risk.

25 103. The use of the statin according to statement 102, wherein the subject is an adult with atherosclerotic cardiovascular disease (ASCVD) or at high or intermediate risk for a first ASCVD event.

30 104. The use of the statin according to statement 97, wherein the medicament is for use in treating a cardiovascular disease.

105. The use of the statin according to statement 104, wherein the cardiovascular disease treated is selected from dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hypoalphalipoproteinemia, metabolic syndrome, diabetic complications, atherosclerosis, stroke, vascular dementia, chronic kidney disease, coronary heart disease, coronary artery disease, retinopathy, inflammation, thrombosis, peripheral vascular disease, heart failure and congestive heart failure.

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106. The use of the statin according to either statement 104 or statement 105, wherein the cardiovascular disease to be treated is selected from hypercholesterolemia, hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia, dyslipidemia, dyslipoproteinemia,
5 atherosclerosis, hepatic steatosis, metabolic syndrome and coronary artery disease.

107. The use of the statin according to any one of statements 104 to 106, wherein the cardiovascular disease to be treated is:
(a) hypercholesterolemia, such as familial hypercholesterolemia;
10 (b) hyperlipidemia; or
(c) coronary artery disease.

108. The use of the statin according to any one of statements 97 to 107, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered once daily.
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109. The use of the statin according to statement 108, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered in a dose of 1 to 30 mg per day of AZD0780.

20 110. The use of the statin according to statement 109, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered in a dose of 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg per day of AZD0780.

111. The use of the statin according to any one of statements 97 to 110, wherein the statin
25 is administered in a moderate-intensity dosing or high-intensity dosing, as defined by the ACC (American College of Cardiology) and the AHA (American Heart Association).

112. The use of the statin according to any one of statements 97 to 111, wherein the statin is administered according to one of the following regimens:
30 (a) Atorvastatin, 10 to 20 mg once daily;
(b) Fluvastatin, 40 mg twice daily, or 80 mg once daily;
(c) Lovastatin, 40 to 80 mg once daily;
(d) Pitavastatin, 1 to 4 mg once daily;
(e) Pravastatin, 40 to 80 mg once daily;
35 (f) Rosuvastatin, 5 to 10 mg once daily, optionally as rosuvastatin calcium;
(g) Simvastatin, 20 to 40 mg once daily;
(h) Atorvastatin, 40 to 80 mg once daily;

- (i) Rosuvastatin, 20 to 40 mg once daily, optionally as rosuvastatin calcium;
- (j) Atorvastatin, 10 to 40 mg once daily;
- (k) Fluvastatin, 60 mg once daily;
- (l) Rosuvastatin, 2.5 to 20 mg once daily, optionally as rosuvastatin calcium; or
- 5 (m) Simvastatin, 10 to 20 mg once daily.

113. The use of the statin according to statement 112, wherein the statin is rosuvastatin which is administered according to one of the following:

- (a) 2.5 to 20 mg once daily, optionally as rosuvastatin calcium;
- 10 (b) 5 to 10 mg once daily, optionally as rosuvastatin calcium; or
- (c) 20 to 40 mg once daily, optionally as rosuvastatin calcium.

114. The use of the statin according to any one of statements 97 to 107, wherein AZD0780 or a pharmaceutically acceptable salt thereof is administered once daily in a dose of 1 mg to 30 mg of AZD0780 and the statin is rosuvastatin which is administered once daily in a dose of 2.5 mg to 40 mg, optionally as rosuvastatin calcium.
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115. The use of the statin according to any one of statements 97 to 114, wherein the subject has been treated with one or more statins prior to starting the method of treatment.
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116. The use of the statin according to statement 115, wherein the subject has been treated with one or more statins for a period of at least two months prior to starting the method of treatment.

- 25 117. The use of the statin according to statement 116, wherein the subject has been treated with one or more statins for a period of at least six months prior to starting the method of treatment.

- 30 118. The use of the statin according to any one of statements 115 to 117, wherein the previous statin treatment was at a moderate-intensity dosing or high-intensity dosing, as defined by the ACC (American College of Cardiology) and the AHA (American Heart Association).

- 35 119. The use of the statin according to any one of statements 97 to 118, wherein the subject to be treated has a LDL-C $\leq$ 190 mg/dL before starting treatment.

120. The use of the statin according to any one of statements 97 to 119, wherein the subject to be treated has a LDL-C $\geq$ 100 mg/dL before starting treatment.

121. A kit comprising: a first pharmaceutical composition comprising 6'-([1S,3S)-3-([5-
5 (difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one
("AZD0780") or a pharmaceutically acceptable salt thereof; a second pharmaceutical
composition comprising a statin; and instructions for using the first and second
pharmaceutical compositions in combination.

Claims

1. 6'-([1S,3S)-3-([5-(Difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one ("AZD0780") or a pharmaceutically acceptable salt thereof for use in a treatment which is lowering LDL-C levels, reducing cardiovascular risk and/or treating a cardiovascular disease in a subject, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said AZD0780 or a pharmaceutically acceptable salt thereof, and ii) a statin to said subject.
2. AZD0780 or a pharmaceutically acceptable salt thereof for use according to claim 1, wherein the treatment is a method of lowering LDL-C levels.
3. AZD0780 or a pharmaceutically acceptable salt thereof for use according to either claim 1 or claim 2, wherein the LDL-C level is reduced to:
- (a) less than 100 mg/dL;
 - (b) less than 70 mg/dL;
 - (c) less than 55 mg/dL; or
 - (d) less than 40 mg/dL.
4. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one of claims 1 to 3, wherein the reduction of the untreated level of LDL-C is by:
- (a) greater than or equal to 30%;
 - (b) greater than or equal to 40%;
 - (c) greater than or equal to 50%;
 - (d) greater than or equal to 60%;
 - (e) greater than or equal to 65%;
 - (f) greater than or equal to 70%; or
 - (g) greater than or equal to 75%.
5. AZD0780 or a pharmaceutically acceptable salt thereof for use according to claim 1, wherein the treatment is a method of reducing cardiovascular risk.
6. AZD0780 or a pharmaceutically acceptable salt thereof for use according to claim 1, wherein the treatment is a method of treating a cardiovascular disease.

7. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one of claims 1 to 6, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered once daily.
- 5 8. AZD0780 or a pharmaceutically acceptable salt thereof for use according to claim 7, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered in a dose of 1 to 30 mg per day of AZD0780.
9. AZD0780 or a pharmaceutically acceptable salt thereof for use according to claim 8,
10 wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered in a dose of 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg per day of AZD0780.
10. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one
15 of claims 1 to 9, wherein the statin is administered in a moderate-intensity dosing or high-intensity dosing, as defined by the ACC (American College of Cardiology) and the AHA (American Heart Association).
11. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one
20 of claims 1 to 10, wherein the statin is rosuvastatin which is administered according to one of the following:
(a) 2.5 to 20 mg once daily, optionally as rosuvastatin calcium;
(b) 5 to 10 mg once daily, optionally as rosuvastatin calcium; or
(c) 20 to 40 mg once daily, optionally as rosuvastatin calcium.
- 25 12. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one of claims 1 to 6, wherein AZD0780 or a pharmaceutically acceptable salt thereof is administered once daily in a dose of 1 mg to 30 mg of AZD0780 and the statin is rosuvastatin which is administered once daily in a dose of 2.5 mg to 40 mg, optionally as
30 rosuvastatin calcium.
13. AZD0780 or a pharmaceutically acceptable salt thereof for use according to any one of claims 1 to 12, wherein the subject has been treated with one or more statins prior to starting the method of treatment.
- 35 14. A statin for use in a treatment which is lowering LDL-C levels, reducing cardiovascular risk and/or treating a cardiovascular disease in a subject, wherein said

treatment comprises the separate, sequential or simultaneous administration of i) said statin, and ii) 6'-([1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one ("AZD0780") or a pharmaceutically acceptable salt thereof to said subject.

5 15. The statin for use according to claim 14, wherein the treatment is a method of lowering LDL-C levels.

16. The statin for use according to either claim 14 or claim 15, wherein the LDL-C level is reduced to:

- 10 (a) less than 100 mg/dL;
(b) less than 70 mg/dL;
(c) less than 55 mg/dL; or
(d) less than 40 mg/dL.

15 17. The statin for use according to any one of claims 14 to 16, wherein the reduction of the untreated level of LDL-C is by:

- (a) greater than or equal to 30%;
(b) greater than or equal to 40%;
(c) greater than or equal to 50%;
20 (d) greater than or equal to 60%;
(e) greater than or equal to 65%;
(f) greater than or equal to 70%; or
(g) greater than or equal to 75%.

25 18. The statin for use according to claim 14, wherein the treatment is a method of reducing cardiovascular risk.

19. The statin for use according to claim 14, wherein the treatment is a method of treating a cardiovascular disease.

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20. The statin for use according to any one of claims 14 to 19, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered once daily.

21. The statin for use according to claim 20, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered in a dose of 1 to 30 mg per day of AZD0780.

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22. The statin for use according to claim 21, wherein the AZD0780 or a pharmaceutically acceptable salt thereof is administered in a dose of 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg per day of AZD0780.
- 5 23. The statin for use according to any one of claims 14 to 22, wherein the statin is administered in a moderate-intensity dosing or high-intensity dosing, as defined by the ACC (American College of Cardiology) and the AHA (American Heart Association).
24. The statin for use according to any one of claims 14 to 23, wherein the statin is
10 rosuvastatin which is administered according to one of the following:
(a) 2.5 to 20 mg once daily, optionally as rosuvastatin calcium;
(b) 5 to 10 mg once daily, optionally as rosuvastatin calcium; or
(c) 20 to 40 mg once daily, optionally as rosuvastatin calcium.
- 15 25. The statin for use according to any one of claims 14 to 19, wherein AZD0780 or a pharmaceutically acceptable salt thereof is administered once daily in a dose of 1 mg to 30 mg of AZD0780 and the statin is rosuvastatin which is administered once daily in a dose of 2.5 mg to 40 mg, optionally as rosuvastatin calcium.
- 20 26. The statin for use according to any one of claims 14 to 25, wherein the subject has been treated with one or more statins prior to starting the method of treatment.
27. A kit comprising: a first pharmaceutical composition comprising 6'-((1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one
25 ("AZD0780") or a pharmaceutically acceptable salt thereof; a second pharmaceutical composition comprising a statin; and instructions for using the first and second pharmaceutical compositions in combination.