

PHARMACEUTICAL COMPOSITIONS COMPRISING AZD0780

This application claims priority from U.S. Provisional Patent Application No. 63/549,607, filed February 5, 2024 and U.S. Provisional Patent Application No. 63/726,740, filed December 2,
5 2024, the disclosure of which is incorporated by reference herein in their entirety.

The present disclosure relates to pharmaceutical compositions suitable for oral administration, and more particularly to pharmaceutical tablets comprising the compound known as "AZD0780", and methods of lowering LDL-C levels, reducing cardiovascular risk
10 and/or treating cardiovascular disease in a patient in need thereof.

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
15 metabolism. PCSK9 increases the levels of circulating LDL cholesterol LDL-C via the 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
20 endosomes/lysosomes reduces LDLR recycling and instead targets LDLR for lysosomal 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.

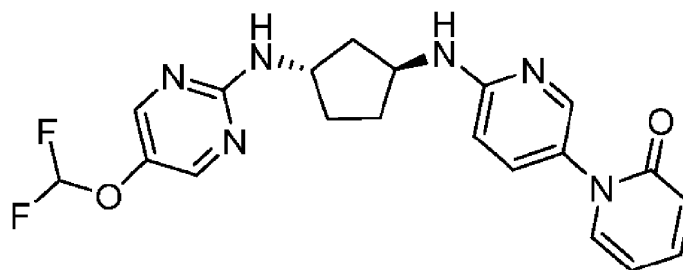
25 For cardiovascular disease, few options exist for inhibiting PCSK9. Statins actually upregulate PCSK9 in HepG2 cells and in human primary hepatocytes through the increased expression of SREBP-2, a transcription factor that upregulates both the LDLR and PCSK9 genes. Since an elevated level of PCSK9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

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%
35 decrease in LDL levels compared to placebo (Elbitor 2016). Patients taking evolocumab showed an about 60-75% decrease in LDL levels. 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 WO2020/0150474, the contents of which are hereby incorporated by reference in their entirety.

To deliver AZD0780 to patients, formulations need to be developed which are stable and have good dissolution properties. In addition, safe and effective dosing regimens need to be developed with the aim of providing a more efficacious treatment compared with current LDL-C lowering approaches for the effective reduction of cardiovascular risk and treatment for cardiovascular disease.

Summary

In some embodiment 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 AZD0780 in a daily dose of from 1 mg to 30 mg, optionally in the form of a pharmaceutically acceptable salt thereof.

In some embodiments, disclosed is AZD0780, or a pharmaceutically acceptable salt thereof, for use in a method of lowering LDL-C levels, reducing cardiovascular risk and/or treatment

of a cardiovascular disease, wherein said AZD0780 is administered in a daily dose of from 1 mg to 30 mg, optionally in the form of a pharmaceutically acceptable salt thereof.

5 In some embodiments, disclosed is the use of AZD0780, or a 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 administration of said medicament comprising AZD0780 in a daily dose of 1 to 30 mg optionally in the form of a pharmaceutically acceptable salt thereof.

10 In some embodiments, disclosed is a pharmaceutical composition comprising:
(a) from about 1 to about 25 wt% 6'-([(1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one structure ("AZD0780"), optionally in the form of a pharmaceutically acceptable salt thereof;
(b) from about 60 to about 95 wt% of two or more pharmaceutical diluents;
15 (c) from about 3 to about 5 wt% of one or more pharmaceutical disintegrants;
(d) from about 0.5 to about 3 wt% of one or more pharmaceutical lubricants;
(e) from 0.0 to about 5 wt% of one or more pharmaceutical glidants (i.e. the pharmaceutical glidant is optional);
(f) from 0.0 to about 5 wt% of one or more pharmaceutical binders (i.e. the pharmaceutical
20 binder is optional).

In some of these embodiments, disclosed is a pharmaceutical composition consisting essentially of:

(a) from about 1 to about 25 wt% AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof;
25 (b) from about 60 to about 95 wt% of two or more pharmaceutical diluents;
(c) from about 3 to about 5 wt% of one or more pharmaceutical disintegrants;
(d) from about 0.5 to about 3 wt% of one or more pharmaceutical lubricants;
(e) from 0.0 to about 5 wt% of one or more pharmaceutical glidants (i.e. the pharmaceutical glidant is optional);
30 (f) from 0.0 to about 5 wt% of one or more pharmaceutical binders (i.e. the pharmaceutical binder is optional).

In some of these embodiments, disclosed is a pharmaceutical composition consisting of:

(a) from about 1 to about 25 wt% AZD0780, optionally in the form of a pharmaceutically
35 acceptable salt thereof;
(b) from about 60 to about 95 wt% of two or more pharmaceutical diluents;
(c) from about 3 to about 5 wt% of one or more pharmaceutical disintegrants;

- (d) from about 0.5 to about 3 wt% of one or more pharmaceutical lubricants;
(e) from 0.0 to about 5 wt% of one or more pharmaceutical glidants (i.e. the pharmaceutical glidant is optional);
(f) from 0.0 to about 5 wt% of one or more pharmaceutical binders (i.e. the pharmaceutical binder is optional).

In some embodiments, disclosed is a pharmaceutical tablet comprising the above pharmaceutical composition. In some of these embodiments, the pharmaceutical tablet comprises a tablet core which comprises the pharmaceutical composition, and the tablet core has a coating. In some of these embodiments, the pharmaceutical tablet consisting essentially of a tablet core which consists essentially of the pharmaceutical composition, and a coating on the tablet core. In some of these embodiments, the pharmaceutical tablet consists of a tablet core which consists of the pharmaceutical composition, and a coating on the tablet core.

In some embodiments, disclosed is a method of treatment of a cardiovascular disease, comprising administering to the subject AZD0780, or a pharmaceutically acceptable salt thereof, in the form of a pharmaceutical composition or pharmaceutical tablet as disclosed herein.

In some embodiments, disclosed is AZD0780, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of a cardiovascular disease, wherein said AZD0780, or a pharmaceutically acceptable salt thereof, is administered in the form of a pharmaceutical composition or pharmaceutical tablet as disclosed herein.

In some embodiments, disclosed is the use of AZD0780, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treatment of a cardiovascular disease, wherein the medicament is a pharmaceutical composition or pharmaceutical tablet as disclosed herein.

Figures

Figure 1 shows coefficient plots and predicted degradation times for tablets comprising AZD0780.

Figure 2 shows measured mixer torque for two compositions comprising AZD0780.

Figure 3 shows the LDL-C change in patients treated with AZD0780 from baseline by time and AZD0780 dose.

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 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.

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).

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

In some embodiment 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 AZD0780 in a daily dose of from 1 mg to 30 mg, optionally in the form of a pharmaceutically acceptable salt thereof.

In some embodiments, disclosed is AZD0780, or a pharmaceutically acceptable salt thereof, for use in a method of lowering LDL-C levels, reducing cardiovascular risk and/or treatment of a cardiovascular disease, wherein said AZD0780 is administered in a daily dose of from 1 mg to 30 mg, optionally in the form of a pharmaceutically acceptable salt thereof.

In some embodiments, disclosed is the use of 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 a method of treatment of a cardiovascular disease, wherein said treatment comprises the administration of said medicament comprising AZD0780 in a daily dose of 1 to 30 mg, optionally in the form of a pharmaceutically acceptable salt thereof.

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, 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 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 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. Particular pharmaceutical compositions and pharmaceutical tablets are disclosed herein.

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

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 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 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 (cardiovascular disease) risk are summarised in Atar 2021. Additional evidence

5 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 than 55 mg/dL or less than 40 mg/dL may be achieved by the treatment disclosed herein.

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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

15 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

20 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).

In some embodiments, the treatment disclosed herein reduces LDL-C, in adults with primary

25 hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH).

Exemplary cardiovascular diseases and conditions include, but are not limited to, 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 conditions include, but are not limited to, hypercholesterolemia, hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia, dyslipidemia, dyslipoproteinemia,

30 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,

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the disease is hyperlipidemia. In certain embodiments, the disease is coronary artery disease.

5 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 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%.

10 In certain embodiments, the disclosed methods of treatment can decrease high levels of circulating serum cholesterol, such as LDL-C and VLDL-Cholesterol. In addition, the disclosed methods are useful for decreasing circulating serum triglycerides, circulating serum lipoprotein A, circulating serum LDL-C and atherogenic lipoproteins. In certain
15 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 mutation through their inhibition of PCSK9.

In some embodiments, AZD0780, or a pharmaceutically acceptable salt thereof, is
20 administered continuously.

The term "continuous" or "continuously" refers to administration of a therapeutic agent, e.g. AZD0780, or a pharmaceutically acceptable salt thereof, at regular intervals without stopping or interruption.

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

30 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.

In some embodiments, AZD0780 is administered in a daily dose of 1 mg, 2 mg, 3 mg, 5 mg,
35 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg.

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.

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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.

10 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. For example, "mg" refers to mass based on AZD0780 free base equivalent mass.

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Expected dose

Following preclinical studies, the expected human daily dose to achieve a LDL-C reduction of 50% was 300 mg/day. This dose was predicted based on LDL-C reduction in a dyslipidemic cynomolgus monkey and allometric scaling of PK from lean rat, dog and
20 cynomolgus monkey.

AZD0780

In certain embodiments, the compositions described herein comprise AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof, in an amount from about 1 wt%, from
25 about 2 wt%, from about 3 wt%, from about 4 wt%, from about 5 wt% , from about 6 wt%, from about 7 wt%, from about 8 wt%, from about 9 wt%, from about 10 wt%, from about 11 wt%, from about 12 wt%, from about 13 wt%, from about 14 wt%, from about 15 wt%, from about 16 wt%, from about 17 wt%, from about 18 wt%, from about 19 wt% , from about 20 wt%, from about 21 wt%, from about 22 wt%, from about 23 wt%, or from about 24 wt%.

30 The amount of AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof, may be up to about 25 wt%, up to 24 wt%, up to 23 wt%, up to 22 wt%, up to 21 wt%, up to 20 wt%, up to 19 wt%, up to 18 wt%, up to 17 wt%, up to 16 wt%, up to 15 wt%, up to 14 wt%, up to 13 wt%, up to 12 wt%, up to 11 wt%, up to 10 wt%, up to 9 wt%, up to 8 wt%, up to 7 wt%, up to 6 wt%, up to 5 wt%, up to 4 wt%, up to 3 wt%, or up to 2 wt%.

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In certain embodiments, the compositions described herein comprise AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof, in an amount of about 1 wt%, 2 wt%,

3 wt%, 4 wt% , 5 wt%, 6 wt%, 7 wt%, 8 wt%, 9 wt%, 10 wt%, 11 wt%, 12 wt%, 13 wt%, 14 wt% , 15 wt%, 16 wt%, 17 wt%, 18 wt%, 19 wt%, 20 wt%, 21 wt%, 22 wt%, 23 wt%, 24 wt%, or 25 wt%.

5 In one embodiment, the pharmaceutical composition comprises 1wt% of AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof.

In one embodiment, the pharmaceutical composition comprises 3wt% of AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof.

10 In one embodiment, the pharmaceutical composition comprises 5wt% of AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof.

In one embodiment, the pharmaceutical composition comprises 10wt% of AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof.

In one embodiment, the pharmaceutical composition comprises 20wt% of AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof.

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In certain embodiments, the AZD0780 used in the compositions is in crystalline form.

In certain embodiments, the AZD0780 used in the compositions is in amorphous form.

Pharmaceutical disintegrants

20 In this specification, the terms “disintegrant” and “disintegrants” are intended to be interpreted in the context of pharmaceutical formulation science. Accordingly, a disintegrant may be, for example: alginic acid, calcium alginate, carboxymethylcellulose calcium, chitosan, croscarmellose sodium, crospovidone, glycine, guar gum, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose (L-HPC), magnesium aluminium silicate,
25 methylcellulose, povidone, sodium alginate, sodium carboxymethylcellulose, sodium starch glycolate, starch, or a combination thereof.

Accordingly, in particular embodiments the one or more pharmaceutical disintegrants comprises one or more pharmaceutical disintegrants selected from alginic acid, calcium
30 alginate, carboxymethylcellulose calcium, chitosan, croscarmellose sodium, crospovidone, glycine, guar gum, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium aluminium silicate, methylcellulose, povidone, sodium alginate, sodium carboxymethylcellulose, sodium starch glycolate and starch.

35 In some embodiments, the one or more pharmaceutical disintegrants comprises one or more pharmaceutical disintegrants selected from alginic acid, calcium alginate, carboxymethylcellulose calcium, chitosan, croscarmellose sodium, crospovidone, glycine,

guar gum, low-substituted hydroxypropyl cellulose, magnesium aluminium silicate, sodium alginate, sodium carboxymethylcellulose and sodium starch glycolate.

5 In one embodiment, the one or more disintegrants is croscarmellose sodium. This is sometimes termed as a superdisintegrant, and acts by water wicking and rapid swelling, which exerts pressure on the surrounding tablet components.

10 In some embodiments, the croscarmellose sodium may have a D_{50} particle size (measured by laser diffraction, e.g. with a Mastersizer 2000) of about 50 μm .

15 In some of these embodiments, the croscarmellose sodium is Ac-Di-Sol™ SD-711. Ac-Di-Sol™ SD-711 has low levels of impurities compared to other commercially available croscarmellose sodium products – for example, it contains no ethanol, between 0 and 1 mg/kg of methanol and less than 10 mg/kg of phosphorus. In addition, the proportion of the croscarmellose sodium which is water soluble, and therefore ineffective, is less than 5 wt%.

20 In certain embodiments, the compositions described herein comprise one or more pharmaceutical disintegrants in an amount from about 3 wt%, from about 3.5 wt%, from about 4 wt%, or from about 4.5 wt%. The amount of the one or more pharmaceutical disintegrants may be up to about 5 wt%, up to 4.5 wt%, up to 4 wt% or up to about 3.5 wt%.

25 In certain embodiments, the compositions described herein comprise one or more pharmaceutical disintegrants in an amount of about 3.0 wt%, 3.5 wt%, 4.0 wt%, 4.5 wt% or 5.0 wt%.

30 In one embodiment, the pharmaceutical composition comprises 4 wt% of one or more disintegrants which is croscarmellose sodium, for example croscarmellose sodium which contains no ethanol, between 0 and 1 mg/kg of methanol and less than 10 mg/kg of phosphorus, and which comprises less than 5 wt% croscarmellose sodium which is water soluble, such as Ac-Di-Sol™ SD-711.

Pharmaceutical lubricants

35 The terms “lubricant” and “lubricants”, as used herein, are intended to be interpreted in the context of pharmaceutical formulation science. Accordingly, a lubricant may be, for example calcium stearate, glyceryl behenate, glyceryl monostearate, glyceryl palmitostearate, a mixture of behenate esters of glycerine (e.g. a mixture of glyceryl bihenate, tribehenin and glyceryl behenate), leucine, magnesium stearate (MgSt), myristic acid, palmitic acid,

poloxamer, polyethylene glycol, potassium benzoate, sodium benzoate, sodium lauryl sulphate, sodium stearate, sodium stearyl fumarate (PRUV), stearic acid, talc, tribehenin and zinc stearate.

- 5 Accordingly, in particular embodiments the one or more pharmaceutical lubricants comprises one or more pharmaceutical lubricants selected from calcium stearate, glyceryl behenate, glyceryl monostearate, glyceryl palmitostearate, a mixture of behenate esters of glycerine (e.g., a mixture of glyceryl behenate, tribehenin and glyceryl behenate), leucine, magnesium stearate, myristic acid, palmitic acid, poloxamer, polyethylene glycol, potassium
10 benzoate, sodium benzoate, sodium lauryl sulphate, sodium stearate, sodium stearyl fumarate, stearic acid, talc, tribehenin and zinc stearate.

- In some embodiments the one or more pharmaceutical lubricants comprises one or more pharmaceutical lubricants selected from calcium stearate, glyceryl behenate, glyceryl
15 monostearate, glyceryl palmitostearate, a mixture of behenate esters of glycerine (e.g., a mixture of glyceryl behenate, tribehenin and glyceryl behenate), leucine, magnesium stearate, myristic acid, palmitic acid, poloxamer, polyethylene glycol, potassium benzoate, sodium benzoate, sodium lauryl sulphate, sodium stearate, sodium stearyl fumarate, stearic acid, tribehenin and zinc stearate.

- 20 According to one embodiment of the disclosure, the one or more pharmaceutical lubricants comprises glyceryl behenate, magnesium stearate, stearic acid, or a combination thereof.

- In one embodiment, the lubricant is glyceryl behenate, magnesium stearate, or a
25 combination thereof.

In one embodiment, the lubricant is magnesium stearate. In some of these embodiments, the magnesium stearate is Ligamed™ MF-2-V.

- 30 Ligamed™ MF-2-V has a specific surface area of 6 to 10 m²/g and a median particle size (D50 particle size - measured by laser diffraction, e.g. with a Mastersizer 2000) of 7 to 11 µm. Its high specific surface area and fine particles offer a high releasing speed during tablet pressing and constant physical performance of the tablets such as hardness and dissolution profiles.

- 35 In certain embodiments, the compositions described herein comprise one or more pharmaceutical lubricants in an amount from about 0.5 wt%, from about 1 wt%, from about

1.5 wt%, from about 2 wt% or from about 2.5 wt%. The amount of the one or more pharmaceutical lubricants may be up to about 3 wt%, up to 2.5 wt%, up to 2 wt%, up to about 1.5 wt% or up to about 1 wt%. In some embodiments, the compositions described herein comprise one or more pharmaceutical lubricants in an amount from 1 wt% up to 2 wt%.

In certain embodiments, the compositions described herein comprise one or more pharmaceutical lubricants in an amount of about 0.5 wt%, 1.0 wt%, 1.5 wt%, 2.0 wt%, 2.5 wt% or 3.0 wt%.

In one embodiment, the pharmaceutical composition comprises 1 wt% of one or more lubricants which is magnesium stearate, for example magnesium stearate with a specific surface area of 6 to 10 m²/g and a median particle size (D50 particle size - measured by laser diffraction, e.g. with a Mastersizer 2000) of 7 to 11 µm, such as Ligamed™ MF-2-V.

In one embodiment, the pharmaceutical composition comprises 2.0wt% of one or more lubricants which is magnesium stearate, for example magnesium stearate with a specific surface area of 6 to 10 m²/g and a median particle size (D50 particle size - measured by laser diffraction, e.g. with a Mastersizer 2000) of 7 to 11 µm, such as Ligamed™ MF-2-V.

Pharmaceutical glidants

The terms “glidants” and “gliding agents” are intended to be interpreted in the context of pharmaceutical formulation science. Accordingly, a glidant may be, for example: silicon dioxide, colloidal silicon dioxide, powdered cellulose, hydrophobic colloidal silica, magnesium oxide, magnesium silicate, magnesium trisilicate, sodium stearate and talc.

Accordingly, in particular embodiments the one or more pharmaceutical glidants comprises one or more pharmaceutical glidants selected from silicon dioxide, colloidal silicon dioxide, powdered cellulose, hydrophobic colloidal silica, magnesium oxide, magnesium silicate, magnesium trisilicate, sodium stearate and talc.

In some embodiments the one or more pharmaceutical glidants comprises one or more pharmaceutical glidants selected from silicon dioxide, colloidal silicon dioxide, powdered cellulose, hydrophobic colloidal silica, magnesium oxide, magnesium silicate and magnesium trisilicate.

In one embodiment, the glidant is silicon dioxide. In some embodiments, the silicon dioxide has a D₅₀ particle size (measured by laser diffraction, e.g. with a Mastersizer 2000) about 3

µm. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling. In some of these embodiments, the silicon dioxide is Syloid™ 244 FP.

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In certain embodiments, the compositions described herein comprise one or more pharmaceutical glidants in an amount from 0.00 wt% (i.e. they are absent from the compositions), from about 1 wt%, from about 2 wt%, from about 3 wt% or from about 4 wt%. The amount of the one or more pharmaceutical glidants may be up to about 5 wt%, up to 4
10 wt%, up to 3 wt%, up to about 2 wt% or up to about 1 wt%. In some embodiments, the compositions described herein comprise one or more pharmaceutical glidants in an amount from 0.0 wt% up to about 1 wt%.

15 In certain embodiments, the compositions described herein do not comprise one or more pharmaceutical glidants.

In certain embodiments, the compositions described herein comprise one or more pharmaceutical glidants in an amount of about 1 wt%. In some of these embodiments, the pharmaceutical glidant is silicon dioxide, for example Syloid™ 244 FP.

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Pharmaceutical binders

In this specification, the terms “binder” and “binders” are intended to be interpreted in the context of pharmaceutical formulation science. Accordingly, a binder may be, for example: arabic gum, gelatin, sodium alginate, pullulan, starch, pregelatinized starch, tragant, dextrin,
25 hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, maltodextrin, methylcellulose, copovidone, povidone, or a combination thereof.

Accordingly, in particular embodiments the one or more pharmaceutical binders comprises one or more pharmaceutical binders selected from arabic gum, gelatin, sodium alginate, pullulan, starch, pregelatinized starch, tragant, dextrin, hydroxyethyl cellulose, hydroxypropyl
30 cellulose, hypromellose, maltodextrin, methylcellulose, copovidone and povidone.

In some embodiments the one or more pharmaceutical binders comprises one or more pharmaceutical binders selected from arabic gum, gelatin, sodium alginate, pullulan, pregelatinized starch, tragant, dextrin, hydroxyethyl cellulose, hydroxypropyl cellulose,
35 hypromellose, maltodextrin, methylcellulose, copovidone and povidone.

In one embodiment, the binder is hydroxypropyl cellulose. In some of these embodiments, the hydroxypropyl cellulose has a D₅₀ particle size (measured by laser diffraction, e.g. with a Mastersizer 2000) of about 45 to 90 µm and/or a molecular weight of about 40 to 80 kDa. Low molecular weight and small particle size enables the hydroxypropyl cellulose to dissolve during granulation using less water. In some embodiments, the hydroxypropyl cellulose is Klucel™ EXF.

In certain embodiments, the compositions described herein comprise one or more pharmaceutical binders in an amount from 0.00 wt% (i.e. they are absent from the compositions), from about 1 wt%, from about 2 wt%, from about 3 wt% or from about 4 wt%. The amount of the one or more pharmaceutical binders may be up to about 5 wt%, up to 4 wt%, up to 3 wt%, up to about 2 wt% or up to about 1 wt%. In some embodiments, the compositions described herein comprise one or more pharmaceutical binders in an amount from 0.0 wt% up to about 1 wt%.

In certain embodiments, the compositions described herein do not comprise one or more pharmaceutical binders.

In certain embodiments, the compositions described herein comprise one or more pharmaceutical binders in an amount of about 3.0 wt%. In some of these embodiments, the pharmaceutical glidant is hydroxypropyl cellulose, for example Klucel™ EXF.

Pharmaceutical diluents

The pharmaceutical compositions of the present disclosure, in one embodiment, comprise one or more pharmaceutical diluents. The term “diluent” is used interchangeably herein with “filler”.

Suitable pharmaceutical diluents are known to those skilled in the art of pharmaceutical formulation science. Suitable pharmaceutical diluents, include, for example, microcrystalline cellulose (MCC), calcium carbonate, calcium phosphate, calcium hydrogen phosphate, calcium sulfate, cellulose acetate, erythritol, ethylcellulose, fructose, inulin, isomalt, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrin, maltose, mannitol, polydextrose, polyethylene glycol, pullulan, simethicone, sodium bicarbonate, sodium carbonate, sodium chloride, sorbitol, starch, sucrose, trehalose and xylitol.

Accordingly, in particular embodiments the one or more pharmaceutical diluents comprises one or more pharmaceutical diluents selected from microcrystalline cellulose, calcium

carbonate, calcium phosphate, calcium hydrogen phosphate, calcium sulfate, cellulose acetate, erythritol, ethylcellulose, fructose, inulin, isomalt, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrin, maltose, mannitol, polydextrose, polyethylene glycol, pullulan, simethicone, sodium bicarbonate, sodium carbonate, sodium chloride, sorbitol, starch, sucrose, trehalose and xylitol.

In some embodiments the one or more pharmaceutical diluents comprises one or more pharmaceutical diluents selected from microcrystalline cellulose, calcium carbonate, calcium phosphate, calcium hydrogen phosphate, calcium sulfate, cellulose acetate, erythritol, ethylcellulose, fructose, inulin, isomalt, lactitol, lactose, magnesium carbonate, maltitol, maltodextrin, maltose, mannitol, polydextrose, polyethylene glycol, pullulan, simethicone, sodium bicarbonate, sodium carbonate, sodium chloride, sorbitol, starch, sucrose, trehalose and xylitol.

In one embodiment, the one or more pharmaceutical diluents is microcrystalline cellulose. Microcrystalline cellulose is a binder/diluent in oral tablet and capsule formulations and can be used in dry-granulation, wet-granulation, and direct-compression processes.

In some embodiments, the pharmaceutical compositions of the present disclosure comprise two or more pharmaceutical diluents. In one of these embodiments, the two pharmaceutical diluents are microcrystalline cellulose and mannitol.

In some embodiments, the microcrystalline cellulose has a D_{50} particle size (measured by laser diffraction, e.g. with a Mastersizer 2000) about 100 μm . Such a grade may avoid smaller particle sizes and thus result in better flow properties in a powder blend. In some embodiments, the microcrystalline cellulose is Avicel™ PH-102.

In some embodiments, the mannitol is a crystalline grade. Spray-dried mannitol may recrystallize as needle shaped particles after wet granulation.

In some embodiments, the mannitol has an D_{50} particle size (measured by laser diffraction, e.g. with a Mastersizer 2000) of less than 200 μm , less than 170 μm , 160 μm or less, or between 100 and 160 μm .

In some embodiments the mannitol is Pearlitol™ 160C. In other embodiments, the mannitol is Pearlitol™ SD100, also known as Pearlitol™ 100 SD.

In certain embodiments, the compositions described herein comprise one or more pharmaceutical diluents in an amount from about 60 wt%, from about 65 wt%, from about 70 wt%, from about 75 wt%, from about 80 wt%, from about 85 wt%, or from about 90 wt%.

The amount of the one or more pharmaceutical diluents may be up to about 95 wt%, up to 90 wt%, up to 85 wt%, up to 80 wt%, up to 75 wt%, or up to 70 wt%.

In certain embodiments, the compositions described herein comprise one or more pharmaceutical diluents in an amount of about 71 wt%, 84 wt%, 86 wt%, 89 wt%, 90 wt%, 91 wt% or 93 wt%.

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In embodiment where there are two pharmaceutical diluents, they may be in a ratio of 1:1, 2:3, 3:7, 1:2, 1:3 or 1:4. In some embodiments, they are in a ratio 3:7. In certain embodiments, the two pharmaceutical diluents are mannitol and microcrystalline cellulose, in a ratio of 7:3.

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Pharmaceutical composition

The wt% of all the components of the pharmaceutical composition add up to 100 wt%. In some embodiments, the pharmaceutical composition only comprises the listed components, such that the wt% of the listed components totals 100 wt%.

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Thus, in some embodiments there is provided a pharmaceutical composition comprising:

- (a) from about 1 to about 25 wt% AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof;
 - (b) from about 60 to about 95 wt% of two or more pharmaceutical diluents;
 - 25 (c) from about 3 to about 5 wt% of one or more pharmaceutical disintegrants;
 - (d) from about 0.5 to about 3 wt% of one or more pharmaceutical lubricants;
 - (e) from 0.0 to about 5 wt% of one or more pharmaceutical glidants; and
 - (f) from 0.0 to about 5 wt% of one or more pharmaceutical binders;
- wherein the wt% of all the components of the pharmaceutical composition add up to 100 wt%.

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In some embodiments there is provided a pharmaceutical composition consists essentially of:

- 35 (a) from about 1 to about 25 wt% AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof;
- (b) from about 60 to about 95 wt% of two or more pharmaceutical diluents;
- (c) from about 3 to about 5 wt% of one or more pharmaceutical disintegrants;

- (d) from about 0.5 to about 3 wt% of one or more pharmaceutical lubricants;
 - (e) from 0.0 to about 5 wt% of one or more pharmaceutical glidants; and
 - (f) from 0.0 to about 5 wt% of one or more pharmaceutical binders;
- wherein the wt% of all the components of the pharmaceutical composition add up to 100 wt%.

In some embodiments there is provided a pharmaceutical composition which consists of:

- (a) from about 1 to about 25 wt% AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof;
 - (b) from about 60 to about 95 wt% of two or more pharmaceutical diluents;
 - (c) from about 3 to about 5 wt% of one or more pharmaceutical disintegrants;
 - (d) from about 0.5 to about 3 wt% of one or more pharmaceutical lubricants;
 - (e) from 0.0 to about 5 wt% of one or more pharmaceutical glidants; and
 - (f) from 0.0 to about 5 wt% of one or more pharmaceutical binders;
- wherein the wt% of all the components of the pharmaceutical composition add up to 100 wt%.

In some embodiments, the pharmaceutical composition comprises:

- (a) from about 1 to about 20 wt% AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof;
 - (b) from about 71 to about 94 wt% (combined) of two pharmaceutical diluents, which are mannitol and microcrystalline cellulose;
 - (c) from about 3 to about 5 wt% of a pharmaceutical disintegrant, which is croscarmellose sodium;
 - (d) from about 1 to about 2 wt% of a pharmaceutical lubricant, which is magnesium stearate;
 - (e) from 0.0 to about 1 wt% of a pharmaceutical glidant, which is silicon dioxide (i.e. the pharmaceutical glidant is optional);
 - (f) from 0.0 to about 3 wt% of a pharmaceutical binder, which is hydroxypropyl cellulose (i.e. the pharmaceutical binder is optional);
- wherein the component weights add up to 100.

In some embodiments, the pharmaceutical composition consists essentially of:

- (a) from about 1 to about 20 wt% AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof;
- (b) from about 71 to about 94 wt% (combined) of two pharmaceutical diluents, which are mannitol and microcrystalline cellulose;

- (c) from about 3 to about 5 wt% of a pharmaceutical disintegrant, which is croscarmellose sodium;
- (d) from about 1 to about 2 wt% of a pharmaceutical lubricant, which is magnesium stearate;
- (e) from 0.0 to about 1 wt% of a pharmaceutical glidant, which is silicon dioxide (i.e. the pharmaceutical glidant is optional);
- 5 (f) from 0.0 to about 3 wt% of a pharmaceutical binder, which is hydroxypropyl cellulose (i.e. the pharmaceutical binder is optional);
- wherein the component weights add up to 100.
- 10 In some embodiments, the pharmaceutical composition consists of:
- (a) from about 1 to about 20 wt% AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof;
- (b) from about 71 to about 94 wt% (combined) of two pharmaceutical diluents, which are mannitol and microcrystalline cellulose;
- 15 (c) from about 3 to about 5 wt% of a pharmaceutical disintegrant, which is croscarmellose sodium;
- (d) from about 1 to about 2 wt% of a pharmaceutical lubricant, which is magnesium stearate;
- (e) from 0.0 to about 1 wt% of a pharmaceutical glidant, which is silicon dioxide (i.e. the pharmaceutical glidant is optional);
- 20 (f) from 0.0 to about 3 wt% of a pharmaceutical binder, which is hydroxypropyl cellulose (i.e. the pharmaceutical binder is optional);
- wherein the component weights add up to 100.

Coating

- 25 In one embodiment, the composition provided herein is a tablet and has a film coating. The film coating may be applied using conventional methods known to those skilled in the art. A functional coating can be used to provide protection against, for example, moisture ingress or degradation by light, to colour the formulation. Additionally, a functional coating may be used to modify or control the release of AZD0780 from the composition.
- 30 Modified- and controlled-release coatings are known to those skilled in the art and include, for example, enteric coating (e.g., cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, pH-sensitive methacrylic acid/methylmethacrylate 30 copolymers, shellac, and mixtures thereof),
- 35 reverse enteric coating (e.g., maltrin, aminoalkyl methacrylate copolymers available under the trade name of Eudragit® (type EI 00 or EPO), polyvinylacetal diethylaminoacetate e.g., AEA ® available from Sankyo Company Limited, Tokyo (Japan), and the like; and mixtures

thereof) and water insoluble polymer coating (e.g., ethylcellulose, cellulose acetate, cellulose triacetate, cellulose acetate butyrate, polyvinyl acetate, neutral methacrylic acid-methylmethacrylate copolymers (e.g., Eudragit RL, RS, and NE30D, etc.), and mixtures thereof).

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Suitable coatings, such as film coatings, that may be applied to the composition according to the disclosure comprise a film-forming agent, for example a sugar or more particularly a film-forming polymer. Suitable sugar coatings are well known to those skilled in the art and may comprise, for example, sucrose or lactose.

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In one embodiment, the film coating comprises a mixture of polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, iron oxide red, iron oxide yellow and iron oxide black, for example, the mixture sold under the trade name Opadry™ II Beige (85F270011) (Colorcon) – in this mixture the polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, and talc are in amounts of 40, 23.8, 20.2 and 14.8 (all % w/w), respectively with the remainder being yellow, red and black iron oxide.

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Other suitable film coatings are commercially available as concentrates that may be diluted with water and optionally a cellulose ether such as HPMC and a plasticizer such as polyethylene glycol prior to application to the composition. Such concentrates include Opaspray™ coatings from Colorcon, for example Opaspray™ Brown M- 1-25092 and Opaspray Yellow M- 1-22842.

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Suitable film-forming agents include, for example film-forming polymers, such as cellulose ethers, esters and mixed ethers and esters, including esters of water-soluble cellulose ethers, for example hydroxypropyl methylcellulose, hydroxypropyl ethylcellulose, hydroxypropyl cellulose, methylcellulose, hydroxypropyl methylcellulose acetate succinate or hydroxypropyl methylcellulose phthalate; film-forming acrylic polymers, for example methacrylate-methylmethacrylate copolymers; and film-forming vinyl polymers, for example polyvinyl alcohols or polyvinyl acetate phthalate. In some embodiments, the film-forming polymer is a water-soluble film-forming polymer, particularly a water-soluble cellulose ether for example hydroxypropyl methylcellulose (particularly hydroxypropyl methylcellulose with a dynamic viscosity of from 2 to 18cP (measured in a 2%w/v solution at 20°C) and selected from, for example grades 1828, 2208, 2906 and especially 2910 as defined hereinbefore).

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The amount of film-forming agent used will depend upon the desired properties of the film coating and the particular amount needed to achieve a desired property may be selected by those skilled in the art. Generally, the film forming agent will be present in an amount of from

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40 to 90% by weight of the film coating, for example from 50 to 80% of the film coating. In certain embodiments, the film-forming agent is typically present at from about 0.5 to 5% by weight of the formulation. In other embodiments, said film-forming agent is present at from about 2.5 to 5% by weight of the formulation.

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Optionally the film coating contains additional components such as plasticizer, colorants, dispersion aids and opacifiers. Plasticizers may be used to improve film flexibility and durability and adhesion properties of the film coating. Suitable plasticizers include, for example glycerin, acetylated monoglycerides, citrate esters (for example triethyl citrate), propylene glycols, polyethylene glycols (for example polyethylene glycols with a molecular weight of from 200 to 500, particularly 300), triacetin (glycerol tri-acetate), triglycerides (for example castor oil), or phthalate esters (for example diethylphthalate). Generally, the plasticizer, when used, is present in an amount of from 1 to 20%, for example 5 to 15% by weight of the film coating.

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Suitable opacifiers and colorants are well known and include for example titanium dioxide, ferric oxides (for example iron oxide).

Suitable dispersion aids include, for example talc.

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The coating may comprise, for example, 2 to 8 wt% of the composition, e.g., from about 3 to 6%, or from about 3.5 to 5 wt%.

Tablets

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In one embodiment, the pharmaceutical tablet comprises 1mg AZD0780.

In one embodiment, the pharmaceutical tablet comprises 3mg AZD0780.

In one embodiment, the pharmaceutical tablet comprises 5mg AZD0780.

In one embodiment, the pharmaceutical tablet comprises 10mg AZD0780.

In one embodiment, the pharmaceutical tablet comprises 20mg AZD0780.

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In one embodiment, the pharmaceutical tablet comprises 30mg AZD0780.

A particular tablet embodiment is set out below:

Component, Grade	10 mg (wt%)
AZD0780	2
Mannitol, Pearlitol 160C	62.4
Microcrystalline cellulose, Avicel PH-102	26.6
Croscarmellose sodium, Ac-Di-Sol SD-711	4
Hydroxypropyl cellulose, Klucel EXF	3
Silicon dioxide, Syloid 244FP	1
Mg stearate, Ligamed MF-2-V	1
Water purified	~0.60 mL/g
Coating Opadry® II 85F270011 Beige	3

Some particular tablet embodiments are set out below:

Component, Grade	1 mg (wt%)	5 mg (wt%)	20 mg (wt%)
AZD0780	1.0	5.0	20.0
Mannitol, Pearlitol 160C	63.0	60.2	49.7
Microcrystalline cellulose, Avicel PH-102	27.0	25.8	21.3
Croscarmellose sodium, Ac-Di-Sol SD-711	4	4	4
Hydroxypropyl cellulose, Klucel EXF	3	3	3
Silicon dioxide, Syloid 244FP	1	1	1
Mg stearate, Ligamed MF-2-V	1	1	1
Water purified	0.465 mL/g	0.465 mL/g	0.465 mL/g
Coating Opadry® II 85F270011 Beige	5	5	5

Further particular tablet embodiments are set out below:

Component, Grade	1 mg (wt%)	3 mg (wt%)	10 mg (wt%)	30 mg (wt%)
AZD0780	1.0	3.0	10.0	10.0
Mannitol, Pearlitol SD100	65.1	63.7	58.8	58.8
Microcrystalline cellulose, Avicel PH-102	27.9	27.3	25.2	25.2
Croscarmellose sodium, Ac-Di-Sol SD-711	4	4	4	4
Mg stearate, Ligamed MF-2-V	2	2	2	2
Coating	1-5	1-5	1-5	1-5

A further tablet embodiment is tablets containing 30 mg AZD0780 with the following composition:

Component, Grade	Amount (mg)	wt%
AZD0780	30.0	10.0
Mannitol, Pearlitol SD100	176.3	58.8
Microcrystalline cellulose, Avicel PH-102	75.7	25.2
Croscarmellose sodium, Ac-Di-Sol SD-711	12.0	4.0
Mg stearate, Ligamed MF-2-V	6.0	2.0
Coating, Opadry II beige	10.3	3.4

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The composition of the coat per unit of tablet is as follows:

Tablet Coating Ingredient	wt%
PVA	40.00
Titanium dioxide	23.82
Macrogol / Polyethylene glycol	20.20
Talc	14.80
Iron oxide yellow	0.90
Iron oxide red	0.22
Black iron oxide / Ferrosoferric oxide	0.06

A further tablet embodiment is tablets containing 30 mg with the following composition:

Component, Grade	Amount (mg)	wt%
AZD0780	30.0	10.0
Mannitol, Pearlitol 100 SD	176.3	58.8
Microcrystalline cellulose, Vivapur 102	75.7	25.2
Croscarmellose sodium, Ac-Di-Sol SD-711	12.0	4.0
Mg stearate, Ligamed MF-2-V	6.0	2.0
Coat, Opadry II beige	10.3	3.4

The composition of the coat per unit of tablet is as follows:

Tablet Coating Ingredient	wt%
PVA	40.00
Titanium dioxide	23.82
Macrogol / Polyethylene glycol	20.20
Talc	14.80
Iron oxide yellow	0.90
Iron oxide red	0.22
Black iron oxide / Ferrosoferric oxide	0.06

5 *Tablet manufacture*

In some embodiments, the tablet is prepared by wet granulation.

In some embodiments, the tablet is prepared by direct compression.

- 10 In some embodiments, the tablet is prepared by first dry blending the AZD0780, one or more disintegrants and the one or more diluents. Following this the one or more lubricants can be added with or without roller compaction, before the tablet is prepared by compression.

Any coating is added following compression.

15 **Examples**

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

Example 1

- The effect of different diluents, disintegrants and lubricants on the stability of AZD0780 in tablets was studied. Six formulations were made according to a Design of Experiments approach where diluents, disintegrants and lubricants were varied in a structured way. The design was a resolution III with four main experiments and two repeats, where the second repeat also contained silica. Each formulation comprises 2wt% AZD0780.

Formulation	Diluent (wt%)	Disintegrant (wt%)	Lubricant (wt%)	Note
1	Mannitol (63) MCC (27)	L-HPC (6)	PRUV (2)	
2	Mannitol (66) MCC (28)	Croscarmellose (3)	MgSt (1)	
3	MCC (65) DCPD (28)	Croscarmellose (3)	PRUV (2)	
4	MCC (64) DCPD (27)	L-HPC (6)	MgSt (1)	
5 (repeat of 1)	Man (63) MCC (27)	L-HPC (6)	PRUV (2)	
6 (repeat* of 4)	MCC (63) DCPD (27)	L-HPC (6)	MgSt (1)	Silica (1wt%)

*not an actual repeat due to the added silica

DCPD = dicalcium phosphate dihydrate

- The formulations (without lubricant) were wet granulated in a lab-scale high shear mixer, dried in an oven, sieved, mixed with a lubricant and compressed into tablets.

- The tablets were then subjected to accelerated stability conditions: 50°C/RH30, 50°C/RH75, 70°C/RH11 and 70°C/RH75 and then their degradation measured by Ultra-high-pressure liquid chromatography (UHPLC) at the following time points:

Conditions/Day	0	3	7	14	28	35
50°C/RH30	X			X		X
50°C/RH75	X		X		X	
70°C/RH11	X		X	X		
70°C/RH75	X	X	X			

Two peaks were detected in all conditions and in all formulations: relative retention time (RRT) 0.304 and RRT 0.675. RRT 0.36 was detected only in formulations 3, 4 and 6.

The results for RRT 0.304 are shown in the table below. This peak shows considerably more predicted degradation than RRT 0.675. Formulations 3 and 4 have borderline 3 years shelf life in open storage at 30°C/RH75 (95th percentile), but more likely have a 5-year shelf life in open storage 30°C/RH75 according to the centre prediction shown in the table below. Formulation 6 has the shortest predicted stability with a 27-month shelf life in open storage at 30°C/RH75 (95th percentile), shown by the highest predicted value after 5 years in the table below. For this formulation it is predicted that the shortest shelf life in open storage at 25°C/RH60 is 46 months.

Modelling results for RRT 0.304

Formulation	R2 (area%)	Ea	n1	n2	Predicted area% after 5 years open storage in 30°C/RH75
1	0.99	49	0.17	0.51	0.060
5 (1)	0.88	50	0.08	0.53	0.066
2	0.92	35	0.08	0.32	0.027
3	0.92	55	0.41	0.67	0.200
4	0.94	68	0.43	0.74	0.195
6 (4 + SiO ₂)	0.97	59	0.25	0.75	0.283

Ea is the activation energy, which describes the temperature sensitivity

n1 describes the moisture sensitivity

n2 describes the degradation rate
(Scrivens et al. 2018; Qiu 2018)

The estimated Accelerated Stability Assessment Program (ASAP) parameters and predicted degradation (centre of the distribution) were entered in Modde 12 (Design of Experiments software) as responses, and all four could be fitted with a significant model:

$$Ea: R^2/Q^2 = 0.91/0.67$$

$$n1: R^2/Q^2 = 0.79/0.54$$

$$n2: R^2/Q^2 = 0.96/0.73$$

$$\text{Degradation after 5 years in 30/75: } R^2/Q^2 = 0.92/0.78$$

Q2 is an estimate of the predictive ability of the model, with a higher Q2 value indicating a better predictive ability.

The models are illustrated in Figure 1 and show the diluent to be the most important factor regards degradation followed by the disintegrant. The least degradation can be expected in the formulation with Mannitol/MCC and croscarmellose (formulation 2), with formulation 1(5) having the next best expected degradation.

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Example 2

The following two compositions were dry blended and then were assessed using Mixer Torque Rheometer (MTR) when mixed with differing levels of purified water.

Component, Grade	(wt%)	
	50:50 diluent	70:30 diluent
AZD0780	40	40
Mannitol, Pearlitol 160C	26	36.4
Microcrystalline cellulose, Avicel PH-102	26	15.6
Croscarmellose sodium, Ac-Di-Sol SD-711	5	4
Hydroxypropyl cellulose, Klucel EXF	2	3
Silicon dioxide, Syloid 244FP	1	1

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Figure 2 shows the measured mixer torque for each composition:

50:50 diluent	
70:30 diluent	

For the 50:50 formulation, the steep increase in torque started at 0.68 g/g and the peak torque was achieved at 0.83 g/g. From this, it was determined that this formulation would require around 0.7 ml/g water in a wet granulation process (Kyttä 2020; Junnila 2022).

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In the 70:30 formulation the Mannitol:MCC ratio is changed from 50:50 to 70:30 and the amount of croscarmellose reduced from 5% to 4%. At the same time the binder concentration is increased from 2% to 3%. For this formulation a steep increase in the torque started around at 0.5 ml/g, which indicates that less water would be required in a wet granulation process than the 50:50 formulation. In addition, in case of a continuous wet granulation process being used, the drying time for granules is limited, and the reduction of water amount in the formulation would be beneficial from that point of view (Dahlgren 2019; Wikström 2023).

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Example 3

A tablet with the following composition:

Component, Grade	10 mg (wt%)
AZD0780	2
Mannitol, Pearlitol 160C	62.4
Microcrystalline cellulose, Avicel PH-102	26.6
Croscarmellose sodium, Ac-Di-Sol SD-711	4
Hydroxypropyl cellulose, Klucel EXF	3
Silicon dioxide, Syloid 244FP	1
Mg stearate, Ligamed MF-2-V	1
Water purified	~0.60 mL/g
Coating Opadry® II 85F270011 Beige	3

5 was manufactured using a wet granulation process. The initial step was dry blending (with an optional dry milling step) of the AZD0780, Pearlitol 160C, Avicel PH-102, Ac-Di-Sol SD-711, Klucel EXF and Syloid 244FP. The purified water was added to carry out a wet granulation (with wet milling if needed), followed by drying and milling. This was followed by dry blending with the addition of the Ligamed MF-2-V and then tablet compression. The tablets were then coated with the film-coat where the coating mixture is first suspended in
10 purified water.

The tablet was tested to confirm AZD0780 strength. A gradient reverse phase LC method was used with mobile phase consisting of ammonium acetate in water and ammonium acetate in acetonitrile, a USP (United States Pharmacopoeia) L1 stationary phase and UV
15 detection. The conditions were selective to AZD0780 in the presence of excipients, synthetic impurities and degradation products. Quantification was performed against an external AZD0780 reference standard, analysed using the same conditions on the same system. AZD0780 was measured to be within 90-110% of the assay target value.

20 The dissolution of these tablets was measured in a standard test with greater than 80% dissolution occurring in 1000 ml (for 10 and 20 mg tablets) and in 500 ml (for 1 and 5 mg tablets) in pH 1.2 SGF (simulated gastric fluid) media in a USP apparatus 2 at 50 rpm at 30 minutes.

Example 4

Tablets with the following composition:

Component, Grade	1 mg (wt%)	5 mg (wt%)	20 mg (wt%)
AZD0780	1.0	5.0	20.0
Mannitol, Pearlitol 160C	63.0	60.2	49.7
Microcrystalline cellulose, Avicel PH-102	27.0	25.8	21.3
Croscarmellose sodium, Ac-Di-Sol SD-711	4	4	4
Hydroxypropyl cellulose, Klucel EXF	3	3	3
Silicon dioxide, Syloid 244FP	1	1	1
Mg stearate, Ligamed MF-2-V	1	1	1
Water purified	0.465 mL/g	0.465 mL/g	0.465 mL/g
Coating Opadry® II 85F270011 Beige	5	5	5

were manufactured using a wet granulation process. The initial step was dry blending (with
 5 an optional dry milling step) of the AZD0780, Pearlitol 160C, Avicel PH-102, Ac-Di-Sol SD-711, Klucel EXF and Syloid 244FP. The purified water was added to carry out a wet granulation (with wet milling if needed), followed by drying and milling. This was followed by dry blending with the addition of the Ligamed MF-2-V and then tablet compression. The tablets were then coated with the film-coat where the coating mixture is first suspended in
 10 purified water.

The tablets were tested to confirm AZD0780 strength. A gradient reverse phase LC method was used with mobile phase consisting of ammonium acetate in water and ammonium acetate in acetonitrile, a USP (United States Pharmacopoeia) L1 stationary phase and UV
 15 detection. The conditions were selective to AZD0780 in the presence of excipients, synthetic impurities and degradation products. Quantification was performed against an external AZD0780 reference standard, analysed using the same conditions on the same system. AZD0780 was measured to be within 90-110% of the assay target value.

20 The dissolution of these tablets was measured in a standard test with greater than 80% dissolution occurring in 1000 ml (for 10 and 20 mg tablets) and in 500 ml (for 1 and 5 mg tablets) in pH 1.2 SGF (simulated gastric fluid) media in a USP apparatus 2 at 50 rpm at 30 minutes.

Example 5

Tablets with the following composition:

Component, Grade	1 mg (wt%)	3 mg (wt%)	10 mg (wt%)	30 mg (wt%)
AZD0780	1.0	3.0	10.0	10.0
Mannitol, Pearlitol SD100	65.1	63.7	58.8	58.8
Microcrystalline cellulose, Avicel PH-102	27.9	27.3	25.2	25.2
Croscarmellose sodium, Ac-Di-Sol SD-711	4	4	4	4
Mg stearate, Ligamed MF-2-V	2	2	2	2
Coating	1-5	1-5	1-5	1-5

- were manufactured by sandwiching AZD0780 between mannitol, MCC, and croscarmellose sodium in a suitable blending vessel before batch blending. Magnesium stearate is sieved and added to the blend, followed by another batch blending process to provide the lubricated dry blend. This is then compressed into tablet cores that are then coated using a batch-coater and the coating solution.
- These tablets before coating were tested to confirm AZD0780 strength. A gradient reverse phase LC method was used with mobile phases consisting of ammonium acetate in water and ammonium acetate in acetonitrile/water, a USP L1 stationary phase and UV detection. The conditions were selective to AZD0780 in the presence of excipients, synthetic impurities and degradation products. Quantification was performed against an external AZD0780 reference standard, analysed using the same conditions on the same system. AZD0780 was measured to be within 90 -110 %of the assay target value.

- The dissolution of these tablets before coating was measured in a standard test greater than 80% dissolution occurring in 1000 mL of pH 1.2 media in a USP (United States Pharmacopoeia) apparatus 2 at 50 rpm at 30 minutes.

Example 6

The following blends were made for making tablets by direct compression:

Component	wt%		
<i>Composition</i>	<i>1</i>	<i>2</i>	<i>3</i>
AZD0780	10	10	10
Mannitol, Pearlitol SD100	59.5	58.8	58.1
Microcrystalline cellulose, Avicel PH-102	25.5	25.2	24.9
Croscarmellose sodium, Ac-Di-Sol SD-711	4	4	4
Magnesium stearate, Ligamed MF-2-V	1	2	3

- For each blend, and for AZD0780 alone, the flow function coefficient (FFC) and wall friction angle (WFA) were measured. The FFC was measured using a pre-consolidation force of 2000Pa. The WFA was measured using a 0.4Ra roughness coupon and an ultimate force of 2000Pa.

	WFA average in degrees	standard deviation in degrees	FFC
AZD0780	32		2.5 (Cohesive)
Blend 1	15-19	1.3	8 (Easy flowing)
Blend 2	8 - 12	2.0	11 (Free flowing)
Blend 3	10-12	3.5	9.5 (Easy flowing)

- These results show that the excipients improve the flowability of AZD0780 and reduce its wall friction angle.

- The blends were made into tablets by pressing using a dwell time of 16 ms across a wide range of compression pressures (e.g. 100-600 MPa) to produce 15 point compression curves. Average main compression pressures were around 100-250 mPa and tensile strengths observed for those pressures were in the region of 1-5 mPa.

Example 7

Tablets with the following composition was made using direct compression:

Component, Grade	(wt%)
AZD0780	20.0
Mannitol, Pearlitol SD100	51.1
Microcrystalline cellulose, Avicel PH-102	21.9
Croscarmellose sodium, Ac-Di-Sol SD-711	4
Silicon dioxide, Syloid 244FP	1
Mg stearate, Ligamed MF-2-V	2

- Tablets have been pressed using dwell times of 15, 30, and 50 ms across a wide range of compression forces (eg. 0.5-8 kN) to produce 7 point compression curves. Tablet tensile strengths observed for those pressures were in the region of 1-5 mPa, with hardness increasing proportionately with compression force.

Example 8

- 10 Tablets containing 30 mg AZD0780 with the following composition were prepared:

Component, Grade	Amount (mg)	wt%
AZD0780	30.0	10.0
Mannitol, Pearlitol 100 SD	176.3	58.8
Microcrystalline cellulose, Vivapur 102	75.7	25.2
Croscarmellose sodium, Ac-Di-Sol SD-711	12.0	4.0
Mg stearate, Ligamed MF-2-V	6.0	2.0
Coat, Opadry II beige	10.3	3.4

The composition of the coat per unit of tablet is as follows:

Tablet Coating Ingredient	wt%
PVA	40.00
Titanium dioxide	23.82
Macrogol / Polyethylene glycol	20.20
Talc	14.80
Iron oxide yellow	0.90
Iron oxide red	0.22
Black iron oxide / Ferrosoferric oxide	0.06

The tablets were manufactured using continuous feeding, mixing and tablet compression. A milling step may be added if required.

5 AZD0780, mannitol, microcrystalline cellulose and croscarmellose sodium were continuously fed by individual feeders and subsequently mixed in a continuous blender and moved downstream through the blender where magnesium stearate was added by a separate feeder. The powders were further mixed into a lubricated powder blend followed by transfer to the tablet press where the lubricated powder blend was compressed into tablet cores.

10 This is followed by a coating step which can be carried out using a conventional batch process or semi-continuous process.

The dissolution of these tablets was measured in a standard test (USP29-NF24 c711) with greater than 80% dissolution occurring at 30 minutes in 900 ml pH 1.2 SGF (simulated
15 gastric fluid) media in a USP apparatus 2 at 50 rpm. Additionally, dissolution of these tablets was measured in a second standard test with greater than 80% dissolution occurring at 30 minutes in 900 mL pH 6.8 phosphate buffer media in a USP apparatus 2 at 75 rpm.

Example 9 - Multiple-ascending dose trial

20 This study (D7960C00001/ NCT05384262), which follows a single-ascending dose (SAD) study, was carried out in healthy male and/or female subjects of non-childbearing potential with elevated LDL-C levels.

25 There were 2 types of cohorts, global MAD cohorts and Japanese single and multiple ascending dose (JSMAD) cohorts.

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.

30

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.

35 The study comprised:

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 $\geq 100 \text{ mg/dL}$).
2. A Screening Period of maximum 28 days
- 5 3. Admission to study centre (Day -1).
4. A Treatment Period during which subjects received:
 - 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)
 - 10 b. Either AZD0780 or placebo once daily for 28 days (Day 1 to 28). Subjects were discharged on Day 29 (global MAD cohorts)
4. 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.

15

Duration of the Study

The expected duration of study participation for each subject was:

- a. JSMAD cohorts - up to 56 days;
- b. Global MAD cohorts - up to 73 days.

20

Inclusion Criteria

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).
- 25 2. Healthy male and female subjects (of non-childbearing potential), aged 18 to 55 years inclusive, with suitable veins for cannulation or repeated venipuncture.
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:
 - 30 (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.
 - (b) Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.
- 35 4. Have a BMI between 18 and 35 kg/m^2 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 outside Japan for more than 10 years.
6. At the Screening Visit subjects must have LDL-C ≥ 70 mg/dL but ≤ 190 mg/dL, and triglycerides < 400 mg/dL.

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 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 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. 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) $> \text{ULN}$ (upper limit of normal)
 - (b) AST (Aspartate aminotransferase) $> \text{ULN}$
 - (c) eGFR (calculated using the CKD-EPI formula) $< 60 \text{ mL/min/1.73 m}^2$
 - (d) Potassium $< \text{LLN}$ (lower limit of normal)
 - (e) Total bilirubin $> \text{ULN}$.
 - (f) Haemoglobin $< \text{LLN}$.
8. Any clinically important abnormalities in clinical chemistry, coagulation, haematology, or urinalysis results other than those described under exclusion criterion number 7, as judged by the investigator.
9. Any positive result on Screening for serum hepatitis B surface antigen, hepatitis C antibody and HIV.
10. 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 repeated once at the discretion of the investigator:
 - (a) Systolic BP $< 90 \text{ mmHg}$ or $> 135 \text{ mmHg}$.

(b) Diastolic BP < 50 mmHg or > 90 mmHg.

(c) Pulse < 50 or > 85 bpm.

11. Any clinically important abnormalities in rhythm, conduction or morphology of the resting 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 discretion of the investigator.

10 (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 there is no evidence of ventricular pre-excitation) – PR(PQ) is ECG interval

15 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.

20 (f) Persistent or intermittent complete BBB (Bundle branch block), IBBB (Incomplete bundle branch block), or IVCD (Intraventricular conduction delay) with QRS > 110 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.

12. Known or suspected history of drug abuse as judged by the investigator.

25 13. Current smokers or those who have smoked or used nicotine products (including e-cigarettes) within the previous 3 months.

14. History of alcohol abuse or excessive intake of alcohol as judged by the investigator.

15. Positive screen for drugs of abuse, cotinine (nicotine), or alcohol at Screening and/or admission to the study centre.

30 16. 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 or class to AZD0780.

17. Excessive intake of caffeine-containing drinks or food (e.g., coffee, tea, chocolate) as judged by the investigator.

35 18. Use of drugs with enzyme inducing properties such as St John's Wort within 3 weeks prior to the first administration of drug.

19. 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.
- 5 Hormone replacement therapy HRT is not allowed.
20. 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.
21. 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
- 10 administration of drug in this study. The period of exclusion begins 1 month after the final dose.
22. Subjects who have previously received AZD0780 within 60 days of the first administration of the drug to be tested in this study.
23. Involvement of any Astra Zeneca or study centre employee or their close relatives.
- 15 24. 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.
25. Subjects who are vegans or have medical dietary restrictions.
- 20 26. Subjects who cannot communicate reliably with the investigator.
27. 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

- 25 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
- 30 drug administration; see Section 5.4.3).
2. Subjects were not allowed to lie fully supine (unless specified for certain assessments) for 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.
- 35 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 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.
- 5 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
- 10 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.
- 15 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.

20 *Drug to be tested*

The tablet of example 3 was used in this trial.

Dosing

JSMAD Cohorts

- 25 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
- 30 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
- 35 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.

5 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.
- 10 • Any Serious Adverse Event (SAE – see below) that is considered related to study intervention by the investigator.
- 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.
- 15 • 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
- 20 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
25 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.

30

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.

35 *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.
- 5 • 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
- 10 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
- 15 samples for the determination of urine concentrations of AZD0780 were collected for each treatment period as follows:

JSMAD Cohorts

	Treatment Period (Residential)			
	Days 1 to 9	Day 10	Days 11 to 17	Follow-up (7 to 10 days dose)/ET
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	
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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

- 5 Samples for determination of AZD0780 concentrations in plasma and urine were 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**

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

5 *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

Results

Preliminary AE data from the 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
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

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	%
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
	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

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

- 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, treatment with AZD0780 was discontinued for 2 participants, one of whom received placebo.

Figure 3 shows preliminary data available from the MAD cohorts. Doses of 10, 30 and 60 mg once daily significantly reduce LDL-C by approximately 30-40%.

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

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

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

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	%
	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	Hypertransaminaemia	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	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

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	%
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
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
Hepatobiliary disorders	Skin abrasion	1	2.2	0	0
	Hypertransaminasaemia	0	0	1	6.7
	Cellulitis	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	%
Infections and infestations	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
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.

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

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
Collins 2016	Collins et al. Lancet. 2016; 388(10059): 2532-2561	10.1016/S0140-6736(16)31357-5
Dahlgren 2019	Dahlgren et al., J Pharm Sci. 2019; 108(11): 3502-3514	10.1016/j.xphs.2019.06.023
Elbitar 2016	Elbitar et al., Expert Opin Therapeutic Patents 2016 26:1377-1392.	10.1080/13543776.2016.1206080
Junnila 2022	Junnila et al., Eur J Pharm Sci. 2022; 172:106151	10.1016/j.ejps.2022.106151
Kyttä 2020	Kyttä et al., Powder Technol. 2020; 376:187-198	10.1016/j.powtec.2020.08.030
Marston 2021	Marston et al., Circulation. 2021; 144(21): 1732-1734	10.1161/CIRCULATIONAHA.121.056536
Qiu 2018	Qiu 2018. pp. 75-103 In: Accelerated Predictive Stability, Fundamentals and Pharmaceutical Industry Practice, Qiu and Scrivens (Eds.), Academic Press, Elsevier 2018	10.1016/B978-0-12-802786-8.00004-8
Robinson 2015	Robinson et al., Artherosclerosis 2015 243:593-597.	10.1016/j.atherosclerosis.2015.10.023
Sabatine 2017	Sabatine et al., N Engl J Med. 2017; 376(18): 1713-1722	10.1056/NEJMoa1615664

Scrivens 2018	Scrivens et al., pp. 33-73 In: Accelerated Predictive Stability, Fundamentals and Pharmaceutical Industry Practice, Qui and Scrivens (Eds.), Academic Press, Elsevier 2018	10.1016/B978-0-12-802786-8.00003-6
Wikström 2023	Wikström et al., Int J Pharm. 2023; 645, 123368	10.1016/j.ijpharm.2023.123368

Statements

1. A pharmaceutical composition comprising:
 - (a) from about 1 to about 25 wt% 6'-([(1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one ("AZD0780"), optionally in the form of a pharmaceutically acceptable salt thereof;
 - (b) from about 60 to about 95 wt% of two or more pharmaceutical diluents;
 - (c) from about 3 to about 5 wt% of one or more pharmaceutical disintegrants;
 - (d) from about 0.5 to about 3 wt% of one or more pharmaceutical lubricants;
 - (e) from 0.0 to about 5 wt% of one or more pharmaceutical glidants; and
 - (f) from 0.0 to about 5. wt% of one or more pharmaceutical binders.
2. The pharmaceutical composition according to statement 1, comprising AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof, in an amount:
 - (i) from about 1 to about 24 wt%;
 - (ii) from about 1 to about 23 wt%;
 - (iii) from about 1 to about 22 wt%;
 - (iv) from about 1 to about 21 wt%; or
 - (v) from about 1 to about 20 wt%.
3. The pharmaceutical composition according to statement 1, comprising AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof, in an amount:
 - (i) from about 1 to about 17 wt%;
 - (ii) from about 1 to about 14 wt%;
 - (iii) from about 1 to about 12 wt%;
 - (iv) from about 1 to about 11 wt%; or
 - (v) from about 1 to about 10 wt%.
4. The pharmaceutical composition according to statement 1, comprising AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof, in an amount:
 - (i) of about 1 wt%;
 - (ii) of about 3 wt%;
 - (iii) of about 5 wt%;
 - (iv) of about 10 wt%; or
 - (v) of about 20 wt%.
5. The pharmaceutical composition according to any one of statements 1 to 4, wherein the AZD0780 is in crystalline form.

6. The pharmaceutical composition according to any one of statements 1 to 5, wherein the two or more pharmaceutical diluents are selected from microcrystalline cellulose, calcium carbonate, calcium phosphate, calcium hydrogen phosphate, calcium sulfate, cellulose acetate, erythritol, ethylcellulose, fructose, inulin, isomalt, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrin, maltose, mannitol, polydextrose, polyethylene glycol, pullulan, simethicone, sodium bicarbonate, sodium carbonate, sodium chloride, sorbitol, starch, sucrose, trehalose and xylitol.
7. The pharmaceutical composition according to any one of statements 1 to 5, wherein the two or more pharmaceutical diluents comprises one or more pharmaceutical diluents selected from microcrystalline cellulose, calcium carbonate, calcium phosphate, calcium hydrogen phosphate, calcium sulfate, cellulose acetate, erythritol, ethylcellulose, fructose, inulin, isomalt, lactitol, lactose, magnesium carbonate, maltitol, maltodextrin, maltose, mannitol, polydextrose, polyethylene glycol, pullulan, simethicone, sodium bicarbonate, sodium carbonate, sodium chloride, sorbitol, starch, sucrose, trehalose and xylitol.
8. The pharmaceutical composition according to either statement 6 or statement 7, wherein the two or more pharmaceutical diluents comprise at least one selected from microcrystalline cellulose and mannitol.
9. The pharmaceutical composition according to statement 8, wherein the two or more pharmaceutical diluents comprise microcrystalline cellulose and mannitol.
10. The pharmaceutical composition according to either statement 8 or statement 9, wherein the microcrystalline cellulose has a D_{50} particle size of about 100 μm .
11. The pharmaceutical composition according to any one of statements 8 to 10, wherein the mannitol has a D_{50} particle size of less than 200 μm .
12. The pharmaceutical composition according to any one of statements 1 to 11, comprising two or more pharmaceutical diluents in an amount:
- (i) from about 65 to about 95 wt%;
 - (ii) from about 65 to about 90 wt%;
 - (iii) from about 70 to about 90 wt%;
 - (iv) from about 75 to about 85 wt%; or
 - (v) of about 71 wt%, 84 wt%, 86 wt%, 89 wt%, 90 wt%, 91 wt%, or 93 wt%.

13. The pharmaceutical composition according to any one of statements 1 to 12, comprising two pharmaceutical diluents, wherein the two pharmaceutical diluents are in a ratio of 1:1, 2:3, 3:7, 1:2, 1:3 or 1:4, for example 3:7.

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14. The pharmaceutical composition according to statement 12, wherein the two pharmaceutical diluents are microcrystalline cellulose and mannitol in a ratio of 3:7.

15. The pharmaceutical composition according to any one of statements 1 to 14, wherein
10 the one or more pharmaceutical disintegrants is selected from alginic acid, calcium alginate, carboxymethylcellulose calcium, chitosan, croscarmellose sodium, crospovidone, glycine, guar gum, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium aluminium silicate, methylcellulose, povidone, sodium alginate, sodium carboxymethylcellulose, sodium starch glycolate and starch.

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16. The pharmaceutical composition according to any one of statements 1 to 14, wherein
the one or more pharmaceutical disintegrants is selected from alginic acid, calcium alginate,
carboxymethylcellulose calcium, chitosan, croscarmellose sodium, crospovidone, glycine,
guar gum, low-substituted hydroxypropyl cellulose, magnesium aluminium silicate, sodium
20 alginate, sodium carboxymethylcellulose and sodium starch glycolate.

17. The pharmaceutical composition according to either statement 15 or statement 16, wherein the one or more pharmaceutical disintegrants is croscarmellose sodium.

25 18. The pharmaceutical composition according to statement 17, wherein the croscarmellose sodium contains no ethanol, up to 1 mg/kg of methanol and less than 10 mg/kg of phosphorus, and which comprises less than 5.0 wt% croscarmellose sodium which is water soluble.

30 19. The pharmaceutical composition according to either statement 17 or statement 18, wherein the croscarmellose sodium has a D₅₀ particle size of about 50 µm.

20. The pharmaceutical composition according to any one of statements 1 to 19, comprising one or more pharmaceutical disintegrants in an amount:

- 35 (i) from about 3 to about 4.5 wt%;
(ii) from about 3.5 to about 5 wt%;
(iii) from about 3.5 to about 4.5 wt%; or

(iv) of about 3.5 wt%, 4.0 wt% or 4.5 wt%.

21. The pharmaceutical composition according to any one of statements 1 to 20,
comprising one or more pharmaceutical disintegrants in an amount of about 4 wt%, wherein
5 the one or more pharmaceutical disintegrants is croscarmellose sodium.

22. The pharmaceutical composition according to any one of statements 1 to 21, wherein
the one or more pharmaceutical lubricants is selected from calcium stearate, glyceryl
behenate, glyceryl monostearate, glyceryl palmitostearate, a mixture of behenate esters of
10 glycerine, leucine, magnesium stearate, myristic acid, palmitic acid, poloxamer, polyethylene
glycol, potassium benzoate, sodium benzoate, sodium lauryl sulphate, sodium stearate,
sodium stearyl fumarate, stearic acid, talc, tribehenin and zinc stearate.

23. The pharmaceutical composition according to any one of statements 1 to 21, wherein
15 the one or more pharmaceutical lubricants is selected from calcium stearate, glyceryl
behenate, glyceryl monostearate, glyceryl palmitostearate, a mixture of behenate esters of
glycerine (e.g., a mixture of glyceryl behenohate, tribehenin and glyceryl behenate), leucine,
magnesium stearate, myristic acid, palmitic acid, poloxamer, polyethylene glycol, potassium
benzoate, sodium benzoate, sodium lauryl sulphate, sodium stearate, sodium stearyl
20 fumarate, stearic acid, tribehenin and zinc stearate.

24. The pharmaceutical composition according to either statement 22 or statement 23,
wherein the one or more pharmaceutical lubricants comprises glyceryl behenate,
magnesium stearate, stearic acid, or a combination thereof.

25

25. The pharmaceutical composition according to statement 24, wherein the one or more
pharmaceutical lubricants is glyceryl behenate, magnesium stearate, or a combination
thereof.

30 26. The pharmaceutical composition according to statement 25, wherein the one or more
pharmaceutical lubricants is magnesium stearate.

27. The pharmaceutical composition according to statement 26, wherein the magnesium
stearate has a specific surface area of 6 to 10 m²/g.

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28. The pharmaceutical composition according to either statement 26 or statement 27,
wherein the magnesium stearate has a D₅₀ particle size of from about 7 to about 11 µm.

29. The pharmaceutical composition according to any one of statements 1 to 28, comprising one or more pharmaceutical lubricants in an amount:
- (i) from about 0.5 to about 2.5 wt%;
 - 5 (ii) from about 1 to about 2.5 wt%;
 - (iii) from about 1 to about 2 wt%; or
 - (iv) of about 0.5 wt%, 1.0 wt%, 1.5 wt%, 2.0 wt%, 2.5 wt%, or 3.0 wt%.
30. The pharmaceutical composition according to any one of statements 1 to 30, comprising one or more pharmaceutical lubricants in an amount of from about 1 to about 2 wt%, wherein the one or more pharmaceutical lubricants is magnesium stearate, optionally wherein the magnesium stearate has a specific surface area of 6 to 10 m²/g and/or a D₅₀ particle size of from about 7 to about 11 µm.
31. The pharmaceutical composition according to any one of statements 1 to 30, wherein the one or more pharmaceutical glidants is selected from silicon dioxide, colloidal silicon dioxide, powdered cellulose, hydrophobic colloidal silica, magnesium oxide, magnesium silicate, magnesium trisilicate, sodium stearate and talc.
32. The pharmaceutical composition according to any one of statements 1 to 30, wherein the one or more pharmaceutical glidants is selected from silicon dioxide, colloidal silicon dioxide, powdered cellulose, hydrophobic colloidal silica, magnesium oxide, magnesium silicate and magnesium trisilicate.
33. The pharmaceutical composition according to either statement 31 or statement 32, wherein the one or more pharmaceutical glidants is silicon dioxide.
34. The pharmaceutical composition according to statement 33, wherein the silicon dioxide has a D₅₀ particle size of about 3 µm.
35. The pharmaceutical composition according to any one of statements 1 to 34 comprising one or more pharmaceutical glidants in an amount:
- (i) from 0.0 to about 4 wt%;
 - (ii) from 0.0 to about 3 wt%;
 - 35 (iii) from 0.0 to about 2 wt%;
 - (iv) from 0.0 to about 1 wt%; or
 - (v) of 0.00 wt%, about 1.0 wt%, about 2.0 wt%, or about 3.0 wt%.

36. The pharmaceutical composition according to any one of statements 1 to 35 comprising one or more pharmaceutical glidants in an amount of about 1 wt%, wherein the one or more pharmaceutical glidants is silicon dioxide.

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37. The pharmaceutical composition according to any one of statements 1 to 36, wherein the one or more pharmaceutical binders is selected from arabic gum, gelatin, sodium alginate, pullulan, starch, pregelatinized starch, tragant, dextrin, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, maltodextrin, methylcellulose, copovidone and povidone.

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38. The pharmaceutical composition according to any one of statements 1 to 36, wherein the one or more pharmaceutical binders is selected from arabic gum, gelatin, sodium alginate, pullulan, pregelatinized starch, tragant, dextrin, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, maltodextrin, methylcellulose, copovidone and povidone.

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39. The pharmaceutical composition according to either statement 37 or statement 38, wherein the one or more pharmaceutical binders is hydroxypropyl cellulose.

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40. The pharmaceutical composition according to statement 39, wherein the hydroxypropyl cellulose has a D_{50} particle size from about 45 to about 90 μm .

41. The pharmaceutical composition according to either statement 39 or statement 40, wherein the hydroxypropyl cellulose has a molecular weight from about 40 to about 80 kDa.

25

42. The pharmaceutical composition according to any one of statements 1 to 30, which does not comprise a pharmaceutical glidant.

30 43. The pharmaceutical composition according to any one of statements 1 to 42 comprising one or more pharmaceutical binders in an amount:

(i) from 0.0 to about 4 wt%;

(ii) from 0.0 to about 3 wt%;

(iii) from 0.0 to about 2 wt%;

35 (iv) from 0.0 to about 1 wt%; or

(v) of 0.00 wt%, about 1 wt%, about 2 wt%, or about 3 wt%.

44. The pharmaceutical composition according to any one of statements 1 to 42 comprising one or more pharmaceutical binders in an amount of about 3 wt%, wherein the one or more pharmaceutical glidants is hydroxypropyl cellulose.
- 5 45. The pharmaceutical composition according to any one of statements 1 to 36 which does not comprise a pharmaceutical binder.
46. The pharmaceutical composition according to statements 42, which does not comprise a pharmaceutical binder.
- 10 47. The pharmaceutical composition according to statement 1, which comprises:
(a) from about 1 to about 20 wt% AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof;
(b) from about 71 to about 94 wt% (combined) of two pharmaceutical diluents, which are
15 mannitol and microcrystalline cellulose;
(c) from about 3 to about 5 wt% of a pharmaceutical disintegrant, which is croscarmellose sodium;
(d) from about 1 to about 2 wt% of a pharmaceutical lubricant, which is magnesium stearate;
(e) from 0.0 to about 1 wt% of a pharmaceutical glidant, which is silicon dioxide; and
20 (f) from 0.0 to about 3 wt% of a pharmaceutical binder, which is hydroxypropyl cellulose.
48. A pharmaceutical tablet comprising the pharmaceutical composition according to any one of statements 1 to 47.
- 25 49. The pharmaceutical tablet according to statement 48 comprising AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof, in an amount:
(i) from about 1 to about 30 mg;
(ii) from about 1 to about 20 mg;
(iii) from about 1 to about 10 mg;
30 (iv) from about 10 to about 30 mg; or
(v) of about 1 mg, 3 mg, 5 mg, 10 mg, 20 mg, or 30 mg.
50. The pharmaceutical tablet according to either statement 48 or statement 49,
35 comprising a tablet core which comprises the pharmaceutical composition, wherein the tablet core has a coating.

51. The pharmaceutical tablet according to statement 50, wherein the coating is a functional coating selected from enteric coating, reverse enteric coating and water insoluble polymer coating.
- 5 52. The pharmaceutical tablet according to statement 50, wherein the coating is a film coating comprising a film-forming agent selected from a sugar or film-forming polymer.
53. The pharmaceutical tablet according to statement 52, wherein the film coating comprises one or more additional components selected from plasticizer, colorant, dispersion
10 aid and opacifier.
54. The pharmaceutical tablet according to any one of statements 48 to 53, wherein the tablet is prepared by wet granulation or direct compression.
- 15 55. The pharmaceutical tablet according to any one of statements 48 to 54, wherein the tablet is prepared by first dry blending the AZD0780, or pharmaceutically acceptable salt thereof, one or more disintegrants and the one of more diluents.
56. A method of lowering LDL-C levels, reducing cardiovascular risk and/or treating a
20 cardiovascular disease, comprising administering to the subject 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 form of a pharmaceutical composition according to any one of statements 1 to 47 or in the form of a pharmaceutical tablet according to any one of statements 48 to 55.
- 25 57. A method of lowering LDL-C levels, reducing cardiovascular risk and/or treating a cardiovascular disease, comprising administering to a subject in need thereof AZD0780, or a pharmaceutically acceptable salt thereof, in a daily dose of from 1 mg to 30 mg.
- 30 58. The method according to either statement 56 or 57, which is a method of lowering LDL-C levels.
59. The method according to statement 58, wherein the subject is an adult with primary
hyperlipidemia.
- 35 60. The method according to any one of statements 56 to 59, 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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61. The method according to any one of statements 56 to 60, 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%
- 10 (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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62. The method according to either statement 56 or statement 57, which is a method of reducing cardiovascular risk.

63. The method according to statement 62, wherein the subject is an adult with
20 atherosclerotic cardiovascular disease (ASCVD) or at high or intermediate risk for a first ASCVD event.

64. The method according to either statement 56 or statement 57, which is treating a cardiovascular disease.

25

65. The method according to statement 64, wherein the cardiovascular disease treated is selected from the group consisting of dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hypoalphalipoproteinemia, metabolic syndrome, diabetic complications, atherosclerosis, stroke, vascular dementia, chronic kidney disease,
30 coronary heart disease, coronary artery disease, retinopathy, inflammation, thrombosis, peripheral vascular disease, heart failure and congestive heart failure.

66. The method according to statement 65, wherein the cardiovascular disease to be treated is selected from hypercholesterolemia, hyperlipidemia, hyperlipoproteinemia,
35 hypertriglyceridemia, dyslipidemia, dyslipoproteinemia, atherosclerosis, hepatic steatosis, metabolic syndrome and coronary artery disease.

67. The method according to statement 65, wherein the cardiovascular disease to be treated is:

(a) hypercholesterolemia, such as familial hypercholesterolemia;

(b) hyperlipidemia; or

5 (c) coronary artery disease.

68. The method according to any one of statements 56 to 67, wherein the daily dose is up to 3 mg, 5 mg, 10mg, 15 mg, 20 mg, 25 mg or 30 mg.

10 69. The method according to any one of statements 56 to 68, wherein the daily dose is at least 1 mg, 2 mg, 3 mg, 5mg, 10 mg, 15 mg, 20 mg, or 25 mg.

70. The method according to any one of statements 56 to 69, wherein the daily dose is:

(ii) from about 1 to about 20 mg;

15 (iii) from about 1 to about 10 mg;

(iv) from about 10 to about 30 mg; or

(v) of about 1 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg.

71. The method according to any one of statements 56 to 70, wherein AZD0780, or a
20 pharmaceutically acceptable salt thereof, is administered in a once daily dose (QD).

72. The method according to statement 71 wherein the once daily dose (QD) is 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg.

25 73. The method according to any one of statements 56 to 72, wherein AZD0780, or a pharmaceutically acceptable salt thereof, is administered orally.

74. The method according to any one of statements 56 to 73, wherein AZD0780, or a pharmaceutically acceptable salt thereof, is in tablet dosage form.

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75. 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 method of lowering LDL-C levels, reducing cardiovascular risk and/or treating a cardiovascular disease, wherein said AZD0780 is administered in the form of a
35 pharmaceutical composition according to any one of statements 1 to 47 or in the form of a pharmaceutical tablet according to any one of statements 48 to 55.

76. 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 method of lowering LDL-C levels, reducing cardiovascular risk and/or treating a cardiovascular disease, wherein said AZD0780 is administered in a daily dose of from 1 mg to 30 mg, optionally in the form of a pharmaceutically acceptable salt thereof.

77. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to either statement 75 or 76, which is a method of lowering LDL-C levels.

78. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to statement 77, wherein the subject is an adult with primary hyperlipidemia.

79. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to any one of statements 75 to 78, 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.

80. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to any one of statements 75 to 79, 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%.

81. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to either statement 75 or statement 76, which is a method of reducing cardiovascular risk.

82. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to statement 81, wherein the subject is an adult with atherosclerotic cardiovascular disease (ASCVD) or at high or intermediate risk for a first ASCVD event.

83. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to either statement 75 or statement 76, which is treating a cardiovascular disease.

84. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to statement 83, wherein the cardiovascular disease treated is selected from the group comprising 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.

85. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to statement 84, 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.

86. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to statement 84, wherein the cardiovascular disease to be treated is:
(a) hypercholesterolemia, such as familial hypercholesterolemia;
(b) hyperlipidemia; or
(c) coronary artery disease.

87. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to any one of statements 75 to 86, wherein the daily dose of AZD0780 is up to 3 mg, 5 mg, 10mg, 15 mg, 20 mg, 25 mg or 30 mg, optionally in the form of a pharmaceutically acceptable salt thereof.

88. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to any one of statements 75 to 87, wherein the daily dose of AZD0780 is at least 1 mg, 2 mg, 3 mg, 5mg, 10 mg, 15 mg, 20 mg, or 25 mg, optionally in the form of a pharmaceutically acceptable salt thereof.

89. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to any one of statements 75 to 88, wherein the daily dose of AZD0780 is:
(ii) from about 1 to about 20 mg, optionally in the form of a pharmaceutically acceptable salt thereof;

(iii) from about 1 to about 10 mg, optionally in the form of a pharmaceutically acceptable salt thereof;

(iv) from about 10 to about 30 mg, optionally in the form of a pharmaceutically acceptable salt thereof; or

5 (v) of about 1 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg, optionally in the form of a pharmaceutically acceptable salt thereof.

90. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to any one of statements 75 to 89, wherein AZD0780, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose (QD).
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91. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to statement 90, wherein the once daily dose (QD) is 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg, optionally in the form of a pharmaceutically acceptable salt thereof.
15

92. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to any one of statements 75 to 91, wherein AZD0780, or a pharmaceutically acceptable salt thereof, is administered orally.

20 93. AZD0780, or a pharmaceutically acceptable salt thereof, for use according to any one of statements 75 to 92, wherein AZD0780, or a pharmaceutically acceptable salt thereof, is in tablet dosage form.

94. 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 a method of lowering LDL-C levels, reducing cardiovascular risk and/or treating a cardiovascular disease, wherein the medicament is a pharmaceutical composition according to any one of statements 1 to 47 or a pharmaceutical tablet according to any one of statements 48 to 55.
25

30 95. 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 a method of lowering LDL-C levels, reducing cardiovascular risk and/or treatment of a cardiovascular disease, wherein said treatment
35 comprises the administration of said medicament comprising AZD0780 in a daily dose of 1 to 30 mg, optionally in the form of a pharmaceutically acceptable salt thereof.

96. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to either statement 94 or 95, which is a method of lowering LDL-C levels.
97. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to
5 statement 96, wherein the subject is an adult with primary hyperlipidemia.
98. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to any one of statements 94 to 97, wherein the LDL-C level is reduced to:
- (a) less than 100 mg/dL;
- 10 (b) less than 70 mg/dL;
- (c) less than 55 mg/dL; or
- (d) less than 40 mg/dL.
99. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to any one
15 of statements 94 to 98, 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%;
- 20 (e) greater than or equal to 65%;
- (f) greater than or equal to 70%; or
- (g) greater than or equal to 75%.
100. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to either
25 statement 94 or statement 95, which is a method of reducing cardiovascular risk.
101. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to statement 100, wherein the subject is an adult with atherosclerotic cardiovascular disease (ASCVD) or at high or intermediate risk for a first ASCVD event.
- 30 102. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to either statement 94 or statement 95, which is a treatment of a cardiovascular disease.
103. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to
35 statement 102, wherein the cardiovascular disease treated is selected from the group comprising 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.

- 5 104. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to statement 103, 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

105. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to statement 103, wherein the cardiovascular disease to be treated is:

(a) hypercholesterolemia, such as familial hypercholesterolemia;

(b) hyperlipidemia; or

- 15 (c) coronary artery disease.

106. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to any one of statements 94 to 105, wherein the daily dose of AZD0780 is up to 3 mg, 5 mg, 10mg, 15 mg, 20 mg, 25 mg or 30 mg, optionally in the form of a pharmaceutically acceptable salt thereof.

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107. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to any one of statements 94 to 106, wherein the daily dose of AZD0780 is at least 1 mg, 2 mg, 3 mg, 5mg, 10 mg, 15 mg, 20 mg, or 25 mg, optionally in the form of a pharmaceutically acceptable salt thereof.

25

108. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to any one of statements 94 to 107, wherein the daily dose of AZD0780 is:

(ii) from about 1 to about 20 mg, optionally in the form of a pharmaceutically acceptable salt thereof;

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(iii) from about 1 to about 10 mg, optionally in the form of a pharmaceutically acceptable salt thereof;

(iv) from about 10 to about 30 mg, optionally in the form of a pharmaceutically acceptable salt thereof; or

- 35 (v) of about 1 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg, optionally in the form of a pharmaceutically acceptable salt thereof.

109. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to any one of statements 94 to 108, wherein AZD0780, or a pharmaceutically acceptable salt thereof, is administered in a once daily dose (QD).
- 5 110. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to statement 109 wherein the once daily dose (QD) of AZD0780 is 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg, optionally in the form of a pharmaceutically acceptable salt thereof.
- 10 111. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to any one of statements 94 to 110, wherein AZD0780, or a pharmaceutically acceptable salt thereof, is administered orally.
112. Use of AZD0780, or a pharmaceutically acceptable salt thereof, according to any one
15 of statements 94 to 111, wherein AZD0780, or a pharmaceutically acceptable salt thereof, is in tablet dosage form.

Claims

1. A pharmaceutical composition comprising:
 - (a) from about 1 to about 25 wt% 6'-([1S,3S)-3-([5-(difluoromethoxy)-2-pyrimidinyl]amino)cyclopentyl]amino)-2H-[1,3'-bipyridin]-2-one ("AZD0780"), optionally in the form of a pharmaceutically acceptable salt thereof;
 - (b) from about 60 to about 95 wt% of two or more pharmaceutical diluents;
 - (c) from about 3 to about 5 wt% of one or more pharmaceutical disintegrants;
 - (d) from about 0.5 to about 3 wt% of one or more pharmaceutical lubricants;
 - (e) from 0.0 to about 5 wt% of one or more pharmaceutical glidants; and
 - (f) from 0.0 to about 5 wt% of one or more pharmaceutical binders.
2. The pharmaceutical composition according to claim 1, comprising AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof, in an amount:
 - (i) from about 1 to about 24 wt%;
 - (ii) from about 1 to about 23 wt%;
 - (iii) from about 1 to about 22 wt%;
 - (iv) from about 1 to about 21 wt%; or
 - (v) from about 1 to about 20 wt%.
3. The pharmaceutical composition according to either claim 1 or claim 2, wherein the two or more pharmaceutical diluents are selected from microcrystalline cellulose, calcium carbonate, calcium phosphate, calcium hydrogen phosphate, calcium sulfate, cellulose acetate, erythritol, ethylcellulose, fructose, inulin, isomalt, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrin, maltose, mannitol, polydextrose, polyethylene glycol, pullulan, simethicone, sodium bicarbonate, sodium carbonate, sodium chloride, sorbitol, starch, sucrose, trehalose and xylitol.
4. The pharmaceutical composition according to claim 3, wherein the two or more pharmaceutical diluents comprise microcrystalline cellulose and mannitol.
5. The pharmaceutical composition according to any one of claims 1 to 4, comprising two of more pharmaceutical diluents in an amount:
 - (i) from about 65 to about 95 wt%;
 - (ii) from about 65 to about 90 wt%;
 - (iii) from about 70 to about 90 wt%;
 - (iv) from about 75 to about 85 wt%; or
 - (v) of about 71 wt%, 84 wt%, 86 wt%, 89 wt%, 90 wt%, 91 wt%, or 93 wt%.

6. The pharmaceutical composition according to any one of claims 1 to 5, comprising two pharmaceutical diluents, which are microcrystalline cellulose and mannitol in a ratio of 3:7.

5

7. The pharmaceutical composition according to any one of claims 1 to 6, wherein the one or more pharmaceutical disintegrants is selected from alginic acid, calcium alginate, carboxymethylcellulose calcium, chitosan, croscarmellose sodium, crospovidone, glycine, guar gum, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium aluminium silicate, methylcellulose, povidone, sodium alginate, sodium carboxymethylcellulose, sodium starch glycolate and starch.

10

8. The pharmaceutical composition according to claim 7, wherein the one or more pharmaceutical disintegrants is croscarmellose sodium.

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9. The pharmaceutical composition according to any one of claims 1 to 8, comprising one or more pharmaceutical disintegrants in an amount:

(i) from about 3 to about 4.5 wt%;

(ii) from about 3.5 to about 5 wt%;

20 (iii) from about 3.5 to about 4.5 wt%; or

(iv) of about 3.5 wt%, 4.0 wt% or 4.5 wt%.

10. The pharmaceutical composition according to any one of claims 1 to 9, comprising one or more pharmaceutical disintegrants in an amount of about 4 wt%, wherein the one or more pharmaceutical disintegrants is croscarmellose sodium.

25

11. The pharmaceutical composition according to any one of claims 1 to 10, wherein the one or more pharmaceutical lubricants is selected from calcium stearate, glyceryl behenate, glyceryl monostearate, glyceryl palmitostearate, a mixture of behenate esters of glycerine, leucine, magnesium stearate, myristic acid, palmitic acid, poloxamer, polyethylene glycol, potassium benzoate, sodium benzoate, sodium lauryl sulphate, sodium stearate, sodium stearyl fumarate, stearic acid, talc, tribehenin and zinc stearate.

30

12. The pharmaceutical composition according to claim 11, wherein the one or more pharmaceutical lubricants is magnesium stearate.

35

13. The pharmaceutical composition according to any one of claims 1 to 12, comprising one or more pharmaceutical lubricants in an amount:
- (i) from about 0.5 to about 2.5 wt%;
 - (ii) from about 1 to about 2.5 wt%;
 - 5 (iii) from about 1 to about 2 wt%; or
 - (iv) of about 0.5 wt%, 1.0 wt%, 1.5 wt%, 2.0 wt%, 2.5 wt%, or 3.0 wt%.
14. The pharmaceutical composition according to any one of claims 1 to 13, comprising one or more pharmaceutical lubricants in an amount of from about 1 to about 2 wt%, wherein
10 the one or more pharmaceutical lubricants is magnesium stearate.
15. The pharmaceutical composition according to any one of claims 1 to 14, wherein the one or more pharmaceutical glidants is selected from silicon dioxide, colloidal silicon dioxide, powdered cellulose, hydrophobic colloidal silica, magnesium oxide, magnesium silicate,
15 magnesium trisilicate, sodium stearate and talc.
16. The pharmaceutical composition according to claim 15, wherein the one or more pharmaceutical glidants is silicon dioxide.
- 20 17. The pharmaceutical composition according to any one of claims 1 to 14, which does not comprise a pharmaceutical glidant.
18. The pharmaceutical composition according to any one of claims 1 to 17, wherein the one or more pharmaceutical binders is selected from arabic gum, gelatin, sodium alginate,
25 pullulan, starch, pregelatinized starch, tragant, dextrin, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, maltodextrin, methylcellulose, copovidone and povidone.
19. The pharmaceutical composition according to claim 18, wherein the one or more pharmaceutical binders is hydroxypropyl cellulose.
30
20. The pharmaceutical composition according to any one of claims 1 to 17, which does not comprise a pharmaceutical binder.
21. The pharmaceutical composition according to claim 1, which comprises:
- 35 (a) from about 1 to about 20 wt% AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof;

(b) from about 71 to about 94 wt% (combined) of two pharmaceutical diluents, which are mannitol and microcrystalline cellulose;

(c) from about 3 to about 5 wt% of a pharmaceutical disintegrant, which is croscarmellose sodium;

5 (d) from about 1 to about 2 wt% of a pharmaceutical lubricant, which is magnesium stearate;

(e) from 0.0 to about 1 wt% of a pharmaceutical glidant, which is silicon dioxide; and

(f) from 0.0 to about 3 wt% of a pharmaceutical binder, which is hydroxypropyl cellulose.

10 22. A pharmaceutical tablet comprising the pharmaceutical composition according to any one of claims 1 to 21.

23. The pharmaceutical tablet according to claim 22 comprising AZD0780, optionally in the form of a pharmaceutically acceptable salt thereof, in an amount:

(i) from about 1 to about 30 mg;

15 (ii) from about 1 to about 20 mg;

(iii) from about 1 to about 10 mg;

(iv) from about 10 to about 30 mg; or

(v) of about 1 mg, 3 mg, 5 mg, 10 mg, 20 mg, or 30 mg.

20 24. The pharmaceutical tablet according to either claim 22 or claim 23, comprising a tablet core which comprises the pharmaceutical composition, wherein the tablet core has a coating.

25 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 a method of lowering LDL-C levels, reducing cardiovascular risk and/or treating a cardiovascular disease, wherein said AZD0780 is administered in the form of a pharmaceutical composition according to any one of claims 1 to 21 or in the form of a pharmaceutical tablet according to any one of claims 22 to 24.