

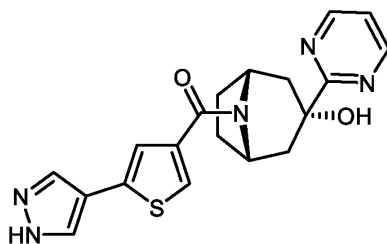
TABLET FORMULATION

Field

The present disclosure generally relates to the formulation of pharmaceutical
5 active agents and excipients, particularly as immediate-release tablet formulations.

Background

Xanamem, also known as UE2343, is an effective inhibitor of 11β -
hydroxysteroid dehydrogenase type 1 (11β -HSD1). Due to its inhibitory action,
Xanamem has been proposed as a treatment of disorders that are ameliorated by the
10 inhibition of 11β -HSD1, such as metabolic syndrome, cardiovascular disorders, and
CNS disorders.



Xanamem.

As with many pharmaceutical active ingredients, such as Xanamem, there is
15 challenges in formulating the active ingredient into a suitable dosage form for
commercial development.

With regards to providing suitable dosage formulations of active ingredients, it is
important that the active ingredient is compatible with the co-formulated excipients,
achieves a desired release profile, has a desired level of shelf stability by not undergoing
20 any problematic degradation, and can be manufactured at scale and in a suitable dosage
per unit formulation.

In particular, further challenges may need to be overcome. Such challenges include those of patient compliance, storage requirements, and manufacturing processes.

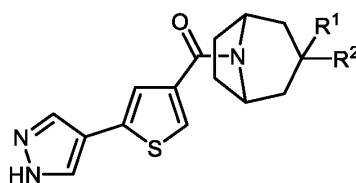
In looking to develop a formulation for oral administration, capsules and tablets may be a preferred option. In particular, with regards to tablets, it is essential to ensure the tablet properties – such as hardness, friability, compressibility, and powder blend flow properties – are suitable for manufacturing processes.

In view that Xanamem is yet to be formulated as a tablet for oral administration, there remains a need for developing a tablet comprising Xanamem that possesses properties to render it suitable for commercial development.

Summary

The present disclosure is predicated in part on the surprising discovery that a mixture of lactose and microcrystalline cellulose can be utilised to provide an immediate-release tablet formulation of Xanamem, and its related analogues, that may demonstrate advantageous properties. Such advantageous properties may include any one or more of compressibility, hardness, and dissolution.

Accordingly, in one aspect, there is provided an immediate-release tablet formulation comprising a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof:

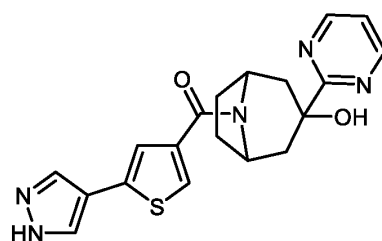


Formula I;

wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, $-O-C_{1-6}$ alkyl, C_{1-6} haloalkyl, $-O-C_{1-6}$ haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-10-membered carbocyclyl, 3-10-membered heterocyclyl, $-CN$, $-CF_3$, $-OR^3$, $-SR^3$, $-NR^3R^4$, $-COR^3$, $-CO_2R^3$, $-CONR^3R^4$, $-NR^3COR^4$, $-SO_2R^3$, $-SO_2NR^3R^4$, and

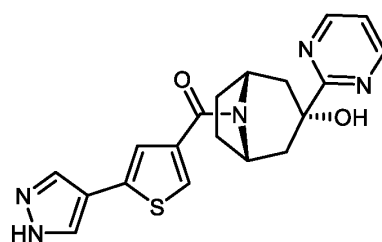
-NR³SO₂R⁴; wherein R³ and R⁴ are each independently selected from the group consisting of hydrogen, C₁₋₆alkyl, 3-7-membered carbocyclyl and 3-7-membered heterocyclyl; wherein each 3-10-membered carbocyclyl, 3-10-membered heterocyclyl, 3-7-membered carbocyclyl, and 3-7-membered heterocyclyl, is unsubstituted or substituted with one or more substituents selected from the group consisting of hydrogen, halogen, C₁₋₆alkyl, -O-C₁₋₆alkyl, C₁₋₆haloalkyl, -O-C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -CN, -CF₃, -OR⁵, -SR⁵, -NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -NR⁵COR⁶, -SO₂R⁵, -SO₂NR⁵R⁶, and -NR⁵SO₂R⁶; and wherein each R⁵ and R⁶ are independently selected from the group consisting of hydrogen and C₁₋₆alkyl; wherein the immediate-release tablet formulation further comprises lactose and microcrystalline cellulose.

In some embodiments, the compound of Formula I is a compound Formula Ia:



Formula Ia.

In some embodiments, the compound of Formula I is a compound Formula Iai:



Formula Iai.

In some embodiments, the ratio (w/w) of lactose to microcrystalline cellulose is between about 80:20 and about 20:80.

In a further aspect, there is provided a process for preparing the immediate-release tablet formulation comprising: preparing granules by blender mixing intragranular components and subsequent granulation using roller compaction and milling; blending the granules with extragranular components to provide a final blend; compressing the final blend using a rotary tablet press to yield a tablet core; and film-coating the tablet cores to provide the immediate-release film-coated tablets.

In a further aspect, there is provided the use of the immediate-release tablet formulation in the manufacture of a medicament for the treatment of a neurological condition.

In a further aspect, there is provided a method of treating a neurological condition in a subject in need thereof, comprising administering the immediate-release tablet formulation.

Any embodiment herein shall be taken to apply *mutatis mutandis* to any other embodiment unless specifically stated otherwise.

The present disclosure is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally-equivalent products, compositions and methods are clearly within the scope of the disclosure, as described herein.

Throughout this specification, unless specifically stated otherwise or the context requires otherwise, reference to a single step, composition of matter, group of steps or group of compositions of matter shall be taken to encompass one and a plurality (i.e. one or more) of those steps, compositions of matter, groups of steps or group of compositions of matter.

Brief Description of the Drawings

Figure 1 shows the dissolution of Xanamem prototype core tablets in 500 mL of 0.1 N HCl, USP type II apparatus (Paddle) at 50 rpm, n=3.

Figure 2 shows the dissolution of Xanamem prototype tablets Lot 22852-7 in 0.1 N HCl, USP type II apparatus.

Figure 3 shows the dissolution of Xanamem prototype tablets in 900 mL of 0.1 N HCl, USP type II apparatus at 50 rpm, n=6.

5 **Figure 4** shows the evaluation of dissolution medium volumes and paddle rotation speed using Xanamem prototype 20 mg tablets in 0.1 N HCl.

Figure 5 shows the particle size distribution of Xanamem (UE2343) drug substance, batch CJ1456 micronized.

10 **Figure 6** shows optical microscope images of Xanamem drug substance, batch CJ1456 under cross-polarised light (top: unmiconized; bottom: micronized).

15 **Figure 7** shows overlay chromatograms for compatibility of Xanamem with excipients (the order from bottom to top: initial, 2 weeks at 25°C, 2 weeks at 50°C, 4 weeks at 25°C, 4 weeks at 50°C). A: pregelatinized starch; B: lactose monohydrate; C: silicified microcrystalline cellulose; D: colloidal silicon dioxide; E: talc; F: croscarmellose sodium; G: sodium starch glycolate; H: magnesium stearate; I: hydrogenated vegetable oil; J: Size 0 hard gelatin capsule; K: Size 0 HMPC capsule; L: polyvinylpyrrolidone; M: HPMC E5; N: excipient mixture.

Figure 8 shows particle size distribution of final blend from compaction study for 10 mg tablet formulation.

20 **Figure 9** shows particle size distribution of final blend for clinical batches.

Figure 10 shows dissolution profiles of Xanamem tablets, 5 mg and 10 mg, in 900 mL of 0.1 N HCl, USP type II apparatus at 50 rpm.

Detailed Description

General Definitions

Unless specifically defined otherwise, all technical and scientific terms used herein shall be taken to have the same meaning as commonly understood by one of
5 ordinary skill in the art (e.g., chemistry, biochemistry, medicinal chemistry, microbiology and the like).

As used herein, the term “and/or”, e.g., “X and/or Y” shall be understood to mean either “X and Y” or “X or Y” and shall be taken to provide explicit support for both meanings or for either meaning, e.g. A and/or B includes the options i) A, ii) B or iii) A
10 and B..

As used herein, the term about, unless stated to the contrary, refers to +/- 20%, typically +/- 10%, typically +/- 5%, of the designated value.

As used herein, the terms “a”, “an” and “the” include both singular and plural aspects, unless the context clearly indicates otherwise.

15 It is to be appreciated that certain features that are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any sub-combination.

Throughout the present specification, various aspects and components of the
20 invention can be presented in a range format. The range format is included for convenience and should not be interpreted as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range, unless specifically indicated. For example, description of a range such
25 as from 1 to 5 should be considered to have specifically disclosed sub-ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 5, from 3 to 5 etc., as well as individual and partial numbers within the recited range, for example, 1, 2, 3, 4, 5, 5.5 and

6, unless where integers are required or implicit from context. This applies regardless of the breadth of the disclosed range. Where specific values are required, these will be indicated in the specification.

Throughout this specification the word "comprise", or variations such as
5 "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of these
10 documents forms part of the common general knowledge in the art, in Australia or in any other country.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those
15 described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the present specification, including definitions, will prevail. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

As used herein, the term "treating" (or "treat", "treatment" etc.) includes a
20 reduction, alleviation and/or elimination of one or more symptoms associated with a specific disorder or condition. Such symptoms may be correlated with a neurological disorder in subjects. For example, as used herein, the phrase "treating a neurological condition" includes improving, reducing, alleviating and/or eliminating symptoms associated with a neurological condition, relative to the symptoms prior to treatment.

25 As used herein, the term "preventing" (or "prevention") includes prophylaxis of the specific disorder or condition. For example, as used herein, the phrase "preventing a neurological condition" refers to preventing the onset or duration of the symptoms associated with a neurological condition in subjects. In some embodiments, the phrase "preventing a neurological condition" refers to slowing or halting the progression of a

neurological condition. In some embodiments, the phrase “preventing a neurological condition” refers to delaying or preventing the onset of the symptoms of neurological condition. Prevention may be absolute (such that no symptoms of the neurological condition are observed), or may be effective only in some individuals, to some extent, or
5 for a limited amount of time.

As used herein, the term “subject” may be used interchangeably with the terms “patient” and “individual”. In some embodiments, the subject is a mammal. In some embodiments, the subject is a human.

As used herein, the term “halogen” means fluorine, chlorine, bromine, or iodine.

10 As used herein, the term “alkyl” encompasses both straight-chain (i.e., linear) and branched-chain hydrocarbon groups. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, i-butyl, sec-butyl, pentyl, and hexyl groups. In one example, the alkyl group is of one to six carbon atoms (i.e. C₁₋₆alkyl).

15 As used herein, the term “alkoxy” refers to the group -O-alkyl, where “alkyl” is as described above. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, and butoxy groups. In one example, the alkoxy group is of one to six carbon atoms (i.e. -O-C₁₋₆alkyl).

20 As used herein, the term “alkenyl” refers to both straight and branched chain unsaturated hydrocarbon groups with at least one carbon-carbon double bond. Examples of alkenyl groups include, but are not limited to, ethenyl, propenyl, butenyl, pentenyl, and hexenyl groups. In one example, the alkenyl group is of two to six carbon atoms (i.e. C₂₋₆alkenyl).

25 As used herein, the term “alkynyl” refers to both straight and branched chain unsaturated hydrocarbon groups with at least one carbon-carbon triple bond. Examples of alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, and hexynyl groups. In one example, the alkynyl group is of two to six carbon atoms (i.e. C₂₋₆alkynyl).

As used herein, the term “haloalkyl” refers to an alkyl group having at least one halogen substituent, where “alkyl” and “halogen” are as described above. Similarly, the term “dihaloalkyl” means an alkyl group having two halogen substituents, and the term “trihaloalkyl” means an alkyl group having three halogen substituents. Examples of haloalkyl groups include fluoromethyl, chloromethyl, bromomethyl, iodomethyl, fluoropropyl, and fluorobutyl groups. Examples of dihaloalkyl groups include difluoromethyl and difluoroethyl groups. Examples of trihaloalkyl groups include trifluoromethyl and trifluoroethyl groups. In one example, the haloalkyl group is of one to six carbon atoms (i.e. C₁₋₆haloalkyl).

As used herein, the term “oxyhaloalkyl” refers to the group -O-haloalkyl, where “haloalkyl” is as described above. Examples of -O-haloalkoxy groups include -O-fluoromethyl, -O-chloromethyl, -O-bromomethyl, -O-iodomethyl, -O-fluoropropyl, and -O-fluorobutyl groups. In one example, the oxyhaloalkyl group is of one to six carbon atoms (i.e. -O-C₁₋₆haloalkyl).

As used herein, the term “carbocyclyl” refers to an aromatic or non-aromatic cyclic group of carbon atoms. A carbocyclyl group may, for example, be monocyclic or polycyclic (i.e. bicyclic, tricyclic). A polycyclic carbocyclyl group may contain fused rings. In one example, the carbocyclyl group is of three to ten carbon atoms (i.e. C₃₋₁₀carbocyclyl). In one example, the carbocyclyl group is of three to seven carbon atoms (i.e. C₃₋₇carbocyclyl). Examples of monocyclic non-aromatic carbocyclyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl groups. Aromatic carbocyclyl groups include phenyl and naphthalenyl.

As used herein, the term “heterocyclyl” refers to an aromatic or non-aromatic cyclic group which is analogous to a carbocyclic group, but in which from one to three of the carbon atoms is/are replaced by one or more heteroatoms independently selected from nitrogen, oxygen, or sulfur. A heterocyclyl group may, for example, be monocyclic or polycyclic (e.g. bicyclic). A polycyclic heterocyclyl may for example contain fused rings. In a bicyclic heterocyclyl group there may be one or more heteroatoms in each ring, or heteroatoms only in one of the rings. A heteroatom may be N, O, or S.

Heterocyclyl groups containing a suitable nitrogen atom include the corresponding N-oxides. In one example, the heterocyclyl group is of three to ten atoms (i.e. 3-10-membered heterocyclyl). In one example, the heterocyclyl group is of three to seven atoms (i.e. 3-7-membered heterocyclyl). Examples of monocyclic non-aromatic heterocyclyl groups include aziridinyl, azetidiny, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl and azepanyl. Examples of bicyclic heterocyclyl groups in which one of the rings is non-aromatic include dihydrobenzofuranyl, indanyl, indolinyl, isoindolinyl, tetrahydroisoquinolinyl, tetrahydroquinolyl, and benzoazepanyl. Examples of monocyclic aromatic heterocyclyl groups (also referred to as monocyclic heteroaryl groups) include furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, isothiazolyl, isoxazolyl, pyrazinyl, pyrazolyl, and pyrimidinyl. Examples of bicyclic aromatic heterocyclyl groups (also referred to as bicyclic heteroaryl groups) include quinoxalinyl, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, naphthyridinyl, quinolinyl, benzofuranyl, indolyl, benzothiazolyl, oxazolyl[4,5-b]pyridyl, pyridopyrimidinyl, isoquinolinyl, and benzohydroxazole.

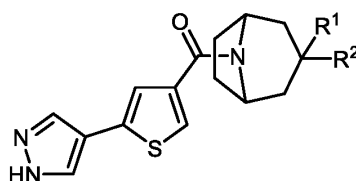
Immediate-Release Tablet Formulation Components

Combination of a Compound of Formula I, Lactose, and Microcrystalline Cellulose

The subject matter of the present disclosure is predicated in part on the surprising discovery that a mixture of lactose and microcrystalline cellulose can be utilised to provide an immediate-release tablet formulation of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, as described herein, that may demonstrate advantageous properties.

Accordingly, there is provided an immediate-release tablet formulation comprising a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof:

11



Formula I;

wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, $-O-C_{1-6}$ alkyl, C_{1-6} haloalkyl, $-O-C_{1-6}$ haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-10-membered carbocyclyl, 3-10-membered heterocyclyl, $-CN$, $-CF_3$, $-OR^3$, $-SR^3$, $-NR^3R^4$, $-COR^3$, $-CO_2R^3$, $-CONR^3R^4$, $-NR^3COR^4$, $-SO_2R^3$, $-SO_2NR^3R^4$, and $-NR^3SO_2R^4$;

wherein R^3 and R^4 are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, 3-7-membered carbocyclyl and 3-7-membered heterocyclyl; wherein each 3-10-membered carbocyclyl, 3-10-membered heterocyclyl, 3-7-membered carbocyclyl, and 3-7-membered heterocyclyl, is unsubstituted or substituted with one or more substituents selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, $-O-C_{1-6}$ alkyl, C_{1-6} haloalkyl, $-O-C_{1-6}$ haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-CN$, $-CF_3$, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^6$, $-NR^5COR^6$, $-SO_2R^5$, $-SO_2NR^5R^6$, and $-NR^5SO_2R^6$; and

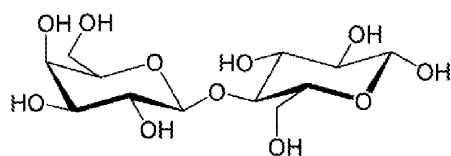
wherein each R^5 and R^6 are independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

and wherein the immediate-release tablet formulation further comprises:

lactose; and

microcrystalline cellulose.

Lactose is a disaccharide sugar having the molecular formula, $D_{12}H_{22}O_{11}$, and the following chemical structure:



Lactose.

Lactose is derived from the condensation reaction of galactose and glucose, and can therefore be hydrolysed into galactose and glucose products. Lactose may be provided
5 in many forms, including as lactose hydrous, lactose anhydrous, lactose monohydrate, or spray-dried lactose. In one example, lactose is lactose hydrous. In one example, lactose is lactose anhydrous. In one example, lactose is lactose monohydrate. In one example, lactose is spray-dried lactose. Spray-dried lactose is available commercially as “Fast Flo 316”, which is a spray-dried mixture of crystalline and amorphous lactose. In one
10 example, lactose is Fast Flo 316. Lactose has long been used as an excipient in pharmaceutical formulations, primarily as a diluent and/or filler, including in compression tableting. It is an ideal excipient in that it is chemically and physically inert to other excipients and active ingredients.

Microcrystalline cellulose (MCC) is a term for refined wood pulp, which is a
15 naturally occurring polymer comprised of glucose units connected by a 1-4 beta glycosidic bond. The linear cellulose chains are bundled together as a microfibril, with each microfibril exhibiting a high degree of three-dimensional internal bonding resulting in a crystalline structure that is physically and chemically inert, and additionally insoluble in water. Due to these properties, microcrystalline cellulose has also been
20 widely employed in the food industry, as an anti-caking agent, emulsifier, extender, and bulking agent. It is also utilised as an excipient in pharmaceutical formulations, primarily as a binder and/or filler.

In the immediate-release tablet formulation described herein, one or both of lactose and microcrystalline cellulose is employed as a diluent. As would be understood
25 by the person skilled in the art, “diluent” refers to a substance used to dilute an active ingredient.

While the use of lactose and microcrystalline cellulose in tablet formulations has been previously reported, the combination of lactose, microcrystalline cellulose, and a compound of Formula I, as described herein, in the preparation of an immediate-release tablet formulation, has been surprisingly discovered to provide one or more advantageous properties to the immediate-release tablet formulation. That is, the particular combination of lactose and microcrystalline cellulose and the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, has been found to impart beneficial tableting properties observed with the immediate-release tablet formulation as described herein. Such beneficial tableting properties may include, for example, one or more of compressibility, tablet hardness, and tablet friability.

In particular, a combination of a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, and microcrystalline cellulose (MCC) may provide some advantageous properties, and such dual combination may experience slow dissolution. The inclusion of lactose unexpectedly increases this rate of dissolution, while maintaining the advantageous properties (e.g., compressibility, tablet hardness, and tablet friability).

Accordingly, in one example, there is provided an immediate-release tablet formulation comprising a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, as described herein; and lactose and microcrystalline cellulose. In one example, there is provided an immediate-release tablet formulation comprising a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, as described herein; and lactose and microcrystalline cellulose in a ratio (w/w) of lactose to microcrystalline cellulose of between about 80:20 and about 20:80. In one example, there is provided an immediate-release tablet formulation comprising a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, as described herein; and lactose and microcrystalline cellulose in a ratio (w/w) of lactose to microcrystalline cellulose of between about 70:30 and about 30:70. In one example, there is provided an immediate-release tablet formulation comprising a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, as described herein; and lactose and microcrystalline cellulose in a ratio (w/w) of lactose to microcrystalline cellulose of between about 60:40

and about 40:60. In one example, there is provided an immediate-release tablet formulation comprising a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, as described herein; and lactose and microcrystalline cellulose in a ratio (w/w) of lactose to microcrystalline cellulose of about 50:50.

5 In some embodiments, the immediate-release tablet formulation comprises lactose and microcrystalline cellulose. In some embodiments, the immediate-release tablet formulation comprises lactose and microcrystalline cellulose in a ratio (w/w) of lactose to microcrystalline cellulose of between about 80:20 and about 20:80. In some
10 embodiments, the immediate-release tablet formulation comprises lactose and microcrystalline cellulose in a ratio (w/w) of lactose to microcrystalline cellulose of between about 80:20 and about 20:80, between about 75:25 and about 25:75, between about 70:30 and about 30:70, between about 65:35 and about 35:65, between about 60:40 and about 40:60, between about 55:45 and about 45:55, or about 50:50. In one example, the immediate-release tablet formulation comprises lactose and microcrystalline
15 cellulose in a ratio (w/w) of lactose to microcrystalline cellulose of between about 80:20 and about 20:80. In one example, the immediate-release tablet formulation comprises lactose and microcrystalline cellulose in a ratio (w/w) of lactose to microcrystalline cellulose of between about 70:30 and about 30:70. In one example, the immediate-release tablet formulation comprises lactose and microcrystalline cellulose in a ratio (w/w) of
20 lactose to microcrystalline cellulose of between about 60:40 and about 40:60. In one example, the immediate-release tablet formulation comprises lactose and microcrystalline cellulose in a ratio (w/w) of lactose to microcrystalline cellulose of about 50:50.

 In some embodiments, the immediate-release tablet formulation comprises a
25 compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, and lactose in a ratio (w/w) of a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, to lactose of between about 10:90 and about 90:10, between about 15:85 and about 80:20, between about 17:83 and about 70:30, between about 20:80 and about 60:40, or between about 30:70 to about 50:50. In one example, the immediate-
30 release tablet formulation comprises a compound of Formula I, or pharmaceutically

acceptable salt or solvate thereof, and lactose in a ratio (w/w) of a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, to lactose is about 17:83. In one example, the immediate-release tablet formulation comprises a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, and lactose in a ratio (w/w) of a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, to lactose is about 32:68.

In some embodiments, the immediate-release tablet formulation comprises a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, and microcrystalline cellulose in a ratio (w/w) of a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, to microcrystalline cellulose of between about 10:90 and about 90:10, between about 15:85 and about 80:20, between about 20:80 and about 70:30, between about 25:75 and about 60:40, between about 30:70 to about 55:45, or between about 40:60 and about 50:50. In one example, the immediate-release tablet formulation comprises a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, and microcrystalline cellulose in a ratio (w/w) of a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, to microcrystalline cellulose is about 24:76. In one example, the immediate-release tablet formulation comprises a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, and microcrystalline cellulose in a ratio (w/w) of a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, to lactose is about 41:59.

In some embodiments, the immediate-release tablet formulation comprises a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, and microcrystalline cellulose, and lactose in a ratio (w/w/w) of a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, to microcrystalline cellulose, to lactose of about 10:50:40, about 11:53:36, about 20:50:30, or about 22:47:31. In one example, the immediate-release tablet formulation comprises a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, and microcrystalline cellulose, and lactose in a ratio (w/w/w) of a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, to microcrystalline cellulose, to lactose of about 11:53:36. In one example, the immediate-release tablet formulation comprises a compound of Formula I,

or pharmaceutically acceptable salt or solvate thereof, and microcrystalline cellulose, and lactose in a ratio (w/w/w) of a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, to microcrystalline cellulose, to lactose of about 22:47:31.

In some embodiments, the immediate-release tablet formulation comprises a
5 compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, and lactose in a ratio (w/w) of a compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, to lactose of between about 10:90 and about 90:10, between about 15:85 and about 80:20, between about 17:83 and about 70:30, between about 20:80 and about 60:40, or between about 30:70 to about 50:50. In one example, the immediate-
10 release tablet formulation comprises a compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, and lactose in a ratio (w/w) of a compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, to lactose is about 17:83. In one example, the immediate-release tablet formulation comprises a compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, and lactose in a ratio
15 (w/w) of a compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, to lactose is about 32:68.

In some embodiments, the immediate-release tablet formulation comprises a compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, and microcrystalline cellulose in a ratio (w/w) of a compound of Formula Iai, or
20 pharmaceutically acceptable salt or solvate thereof, to microcrystalline cellulose of between about 10:90 and about 90:10, between about 15:85 and about 80:20, between about 20:80 and about 70:30, between about 25:75 and about 60:40, between about 30:70 to about 55:45, or between about 40:60 and about 50:50. In one example, the immediate-release tablet formulation comprises a compound of Formula Iai, or pharmaceutically
25 acceptable salt or solvate thereof, and microcrystalline cellulose in a ratio (w/w) of a compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, to microcrystalline cellulose is about 24:76. In one example, the immediate-release tablet formulation comprises a compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, and microcrystalline cellulose in a ratio (w/w) of a compound of

Formula Iai, or pharmaceutically acceptable salt or solvate thereof, to lactose is about 41:59.

In some embodiments, the immediate-release tablet formulation comprises a compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, and microcrystalline cellulose, and lactose in a ratio (w/w/w) of a compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, to microcrystalline cellulose, to lactose of about 10:50:40, about 11:53:36, about 20:50:30, or about 22:47:31. In one example, the immediate-release tablet formulation comprises a compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, and microcrystalline cellulose, and lactose in a ratio (w/w/w) of a compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, to microcrystalline cellulose, to lactose of about 11:53:36. In one example, the immediate-release tablet formulation comprises a compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, and microcrystalline cellulose, and lactose in a ratio (w/w/w) of a compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, to microcrystalline cellulose, to lactose of about 22:47:31.

The immediate-release tablet formulation may comprise any other suitable excipient that is useful in formulating the immediate-release tablet. This includes both intragranular and extragranular components. As used herein, the term “intragranular component” will be understood to be a component added to the formulation prior to the granulation process. Similarly, as used herein, the term “extragranular component” will be understood to be a component added to the formulation after the granulation process and prior to the compaction process. In one example, the immediate-release tablet formulation comprises an intragranular component. In one example, the immediate-release tablet formulation comprises an extragranular component. In one example, the immediate-release tablet formulation comprises both intragranular and extragranular components. In one example, the immediate-release tablet formulation comprises between about 50% and about 99%, between about 60% and about 99%, between about 70% and about 99%, or between about 75% and about 99% of intragranular components. In one example, the immediate-release tablet formulation comprises between about 1%

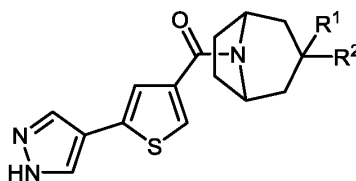
and about 50%, between about 10% and about 40%, between about 15% and about 35%, or between about 20% and about 30% of extragranular components.

Examples of intragranular components include, but are not limited to, an active ingredient, diluent, disintegrant, glidant, and lubricant. Examples of extragranular components include, but are not limited to, a diluent, and lubricant.

Compound of Formula I

As used herein, a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, is considered the active ingredient in the immediate-release tablet formulation. That is, the compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, is the drug substance.

A compound of Formula I has the following chemical structure:



Formula I;

wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, $-O-C_{1-6}$ alkyl, C_{1-6} haloalkyl, $-O-C_{1-6}$ haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-10-membered carbocyclyl, 3-10-membered heterocyclyl, $-CN$, $-CF_3$, $-OR^3$, $-SR^3$, $-NR^3R^4$, $-COR^3$, $-CO_2R^3$, $-CONR^3R^4$, $-NR^3COR^4$, $-SO_2R^3$, $-SO_2NR^3R^4$, and $-NR^3SO_2R^4$.

In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is halogen. In some embodiments, R^1 is chlorine. In some embodiments, R^1 is fluorine. In some embodiments, R^1 is bromine. In some embodiments, R^1 is iodine. In some embodiments, R^1 is C_{1-6} alkyl. In some embodiments, R^1 is $-O-C_{1-6}$ alkyl. In some embodiments, R^1 is C_{1-6} haloalkyl. In some embodiments, R^1 is $-O-C_{1-6}$ haloalkyl. In some embodiments, R^1 is C_{2-6} alkenyl. In some embodiments, R^1 is C_{2-6} alkynyl. In some embodiments, R^1 is 3-

- 10-membered carbocyclyl. In some embodiments, R^1 is a 6-membered carbocyclyl. In some embodiments, R^1 is a 5-membered carbocyclyl. In some embodiments, R^1 is 3-10-membered heterocyclyl. In some embodiments, R^1 is a 6-membered heterocyclyl. In some embodiments, R^1 is a 5-membered heterocyclyl. In some embodiments, R^1 is -CN.
- 5 In some embodiments, R^1 is -CF₃. In some embodiments, R^1 is -OR³. In some embodiments, R^1 is -SR³. In some embodiments, R^1 is -NR³R⁴. In some embodiments, R^1 is -COR³. In some embodiments, R^1 is -CO₂R³. In some embodiments, R^1 is -CONR³R⁴. In some embodiments, R^1 is -NR³COR⁴. In some embodiments, R^1 is -SO₂R³. In some embodiments, R^1 is -SO₂NR³R⁴. In some embodiments, R^1 is -NR³SO₂R⁴.
- 10 In some embodiments, R^2 is hydrogen. In some embodiments, R^2 is halogen. In some embodiments, R^2 is chlorine. In some embodiments, R^2 is fluorine. In some embodiments, R^2 is bromine. In some embodiments, R^2 is iodine. In some embodiments, R^2 is C₁₋₆alkyl. In some embodiments, R^2 is -O-C₁₋₆alkyl. In some embodiments, R^2 is C₁₋₆haloalkyl. In some embodiments, R^2 is -O-C₁₋₆haloalkyl. In some embodiments, R^2
- 15 is C₂₋₆alkenyl. In some embodiments, R^2 is C₂₋₆alkynyl. In some embodiments, R^2 is 3-10-membered carbocyclyl. In some embodiments, R^2 is a 6-membered carbocyclyl. In some embodiments, R^2 is a 5-membered carbocyclyl. In some embodiments, R^2 is 3-10-membered heterocyclyl. In some embodiments, R^2 is a 6-membered heterocyclyl. In some embodiments, R^2 is a 5-membered heterocyclyl. In some embodiments, R^2 is -CN.
- 20 In some embodiments, R^2 is -CF₃. In some embodiments, R^2 is -OR³. In some embodiments, R^2 is -SR³. In some embodiments, R^2 is -NR³R⁴. In some embodiments, R^2 is -COR³. In some embodiments, R^2 is -CO₂R³. In some embodiments, R^2 is -CONR³R⁴. In some embodiments, R^2 is -NR³COR⁴. In some embodiments, R^2 is -SO₂R³. In some embodiments, R^2 is -SO₂NR³R⁴. In some embodiments, R^2 is -NR³SO₂R⁴.
- 25 If present, each 3-10-membered carbocyclyl and 3-10-membered heterocyclyl may be further substituted with one or more substituents selected from the group consisting of hydrogen, halogen, C₁₋₆alkyl, -O-C₁₋₆alkyl, C₁₋₆haloalkyl, -O-C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -CN, -CF₃, -OR⁵, -SR⁵, -NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -NR⁵COR⁶, -SO₂R⁵, -SO₂NR⁵R⁶, and -NR⁵SO₂R⁶.

In some embodiments, the 3-10-membered carbocyclyl is substituted with one or more halogen substituents. In some embodiments, the 3-10-membered carbocyclyl is substituted with one or more C₁₋₆alkyl substituents. In some embodiments, the 3-10-membered carbocyclyl is substituted with one or more -O-C₁₋₆alkyl substituents. In some
 5 embodiments, the 3-10-membered carbocyclyl is substituted with one or more C₁₋₆haloalkyl substituents. In some embodiments, the 3-10-membered carbocyclyl is substituted with one or more -O-C₁₋₆haloalkyl substituents. In some embodiments, the 3-10-membered carbocyclyl is substituted with one or more C₂₋₆alkenyl substituents. In some embodiments, the 3-10-membered carbocyclyl is substituted with one or more C₂₋₆alkynyl substituents. In some embodiments, the 3-10-membered carbocyclyl is substituted with one or more -CN substituents. In some embodiments, the 3-10-membered carbocyclyl is substituted with one or more -CF₃ substituents. In some
 10 embodiments, the 3-10-membered carbocyclyl is substituted with one or more -OR⁵ substituents. In some embodiments, the 3-10-membered carbocyclyl is substituted with one or more -SR⁵ substituents. In some embodiments, the 3-10-membered carbocyclyl is substituted with one or more -COR⁵ substituents. In some embodiments, the 3-10-membered carbocyclyl is substituted with one or more halogen substituents. In some
 15 embodiments, the 3-10-membered carbocyclyl is substituted with one or more -CO₂R⁵ substituents. In some embodiments, the 3-10-membered carbocyclyl is substituted with one or more -CONR⁵R⁶ substituents. In some embodiments, the 3-10-membered carbocyclyl is substituted with one or more -NR⁵COR⁶ substituents. In some
 20 embodiments, the 3-10-membered carbocyclyl is substituted with one or more -SO₂R⁵ substituents. In some embodiments, the 3-10-membered carbocyclyl is substituted with one or more -SO₂NR⁵R⁶ substituents. In some embodiments, the 3-10-membered
 25 carbocyclyl is substituted with one or more -NR⁵SO₂R⁶ substituents.

In some embodiments, R¹ is a 6-membered carbocyclyl and is substituted with one or more substituents selected from the group consisting of hydrogen, halogen, C₁₋₆alkyl, -O-C₁₋₆alkyl, C₁₋₆haloalkyl, -O-C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -CN, -CF₃, -OR⁵, -SR⁵, -NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -NR⁵COR⁶, -SO₂R⁵, -SO₂NR⁵R⁶, and
 30 -NR⁵SO₂R⁶. In some embodiments, R¹ is a 5-membered carbocyclyl and is substituted with one or more substituents selected from the group consisting of hydrogen, halogen,

C₁₋₆alkyl, -O-C₁₋₆alkyl, C₁₋₆haloalkyl, -O-C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -CN, -CF₃, -OR⁵, -SR⁵, -NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -NR⁵COR⁶, -SO₂R⁵, -SO₂NR⁵R⁶, and -NR⁵SO₂R⁶.

In some embodiments, the 3-10-membered heterocyclyl is substituted with one or
5 more halogen substituents. In some embodiments, the 3-10-membered heterocyclyl is substituted with one or more C₁₋₆alkyl substituents. In some embodiments, the 3-10-membered heterocyclyl is substituted with one or more -O-C₁₋₆alkyl substituents. In some embodiments, the 3-10-membered heterocyclyl is substituted with one or more C₁₋₆haloalkyl substituents. In some embodiments, the 3-10-membered heterocyclyl is substituted with one or more -O-C₁₋₆haloalkyl substituents. In some embodiments, the 3-10-membered heterocyclyl is substituted with one or more C₂₋₆alkenyl substituents. In some embodiments, the 3-10-membered heterocyclyl is substituted with one or more C₂₋₆alkynyl substituents. In some embodiments, the 3-10-membered heterocyclyl is substituted with one or more -CN substituents. In some embodiments, the 3-10-membered heterocyclyl is substituted with one or more -CF₃ substituents. In some
15 embodiments, the 3-10-membered heterocyclyl is substituted with one or more -OR⁵ substituents. In some embodiments, the 3-10-membered heterocyclyl is substituted with one or more -SR⁵ substituents. In some embodiments, the 3-10-membered heterocyclyl is substituted with one or more -COR⁵ substituents. In some embodiments, the 3-10-membered heterocyclyl is substituted with one or more halogen substituents. In some embodiments, the 3-10-membered heterocyclyl is substituted with one or more -CO₂R⁵ substituents. In some embodiments, the 3-10-membered heterocyclyl is substituted with one or more -CONR⁵R⁶ substituents. In some embodiments, the 3-10-membered heterocyclyl is substituted with one or more -NR⁵COR⁶ substituents. In some
25 embodiments, the 3-10-membered heterocyclyl is substituted with one or more -SO₂R⁵ substituents. In some embodiments, the 3-10-membered heterocyclyl is substituted with one or more -SO₂NR⁵R⁶ substituents. In some embodiments, the 3-10-membered heterocyclyl is substituted with one or more -NR⁵SO₂R⁶ substituents.

In some embodiments, R² is a 6-membered carbocyclyl and is substituted with
30 one or more substituents selected from the group consisting of hydrogen, halogen, C₁₋

alkyl, -O-C₁₋₆alkyl, C₁₋₆haloalkyl, -O-C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -CN, -CF₃, -OR⁵, -SR⁵, -NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -NR⁵COR⁶, -SO₂R⁵, -SO₂NR⁵R⁶, and -NR⁵SO₂R⁶. In some embodiments, R² is a 5-membered carbocyclyl and is substituted with one or more substituents selected from the group consisting of hydrogen, halogen,

5 C₁₋₆alkyl, -O-C₁₋₆alkyl, C₁₋₆haloalkyl, -O-C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -CN, -CF₃, -OR⁵, -SR⁵, -NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -NR⁵COR⁶, -SO₂R⁵, -SO₂NR⁵R⁶, and -NR⁵SO₂R⁶.

If present, each R³ and R⁴ are independently selected from the group consisting of hydrogen, C₁₋₆alkyl, 3-7-membered carbocyclyl and 3-7-membered heterocyclyl.

10 In some embodiments, R³ is hydrogen. In some embodiments, R³ is C₁₋₆alkyl. In some embodiments, R³ is 3-7-membered carbocyclyl. In some embodiments, R³ is 3-7-membered carbocyclyl. In some embodiments, R³ is a 5-membered carbocyclyl. In some embodiments R³ is a 6-membered carbocyclyl.

15 In some embodiments, R⁴ is hydrogen. In some embodiments, R⁴ is C₁₋₆alkyl. In some embodiments, R⁴ is 3-7-membered carbocyclyl. In some embodiments, R⁴ is 3-7-membered carbocyclyl. In some embodiments, R⁴ is a 5-membered carbocyclyl. In some embodiments R⁴ is a 6-membered carbocyclyl.

If present, each R⁵ and R⁶ are independently selected from the group consisting of hydrogen and C₁₋₆alkyl.

20 In some embodiments, R⁵ is hydrogen. In some embodiments, R⁵ is C₁₋₆alkyl.

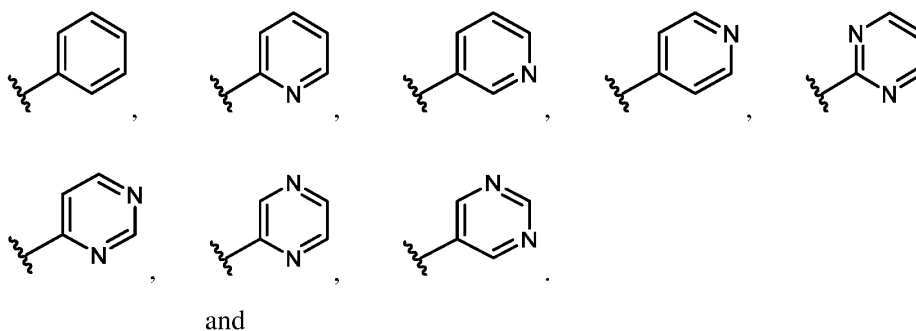
In some embodiments, R⁶ is hydrogen. In some embodiments, R⁶ is C₁₋₆alkyl.

In some embodiments, R¹ and R² are each independently selected from the group consisting of hydrogen, halogen, 3-10-membered carbocyclyl, 3-10-membered heterocyclyl, -OH, -CN, and -NH₂. If present, each 3-10-membered carbocyclyl and 3-

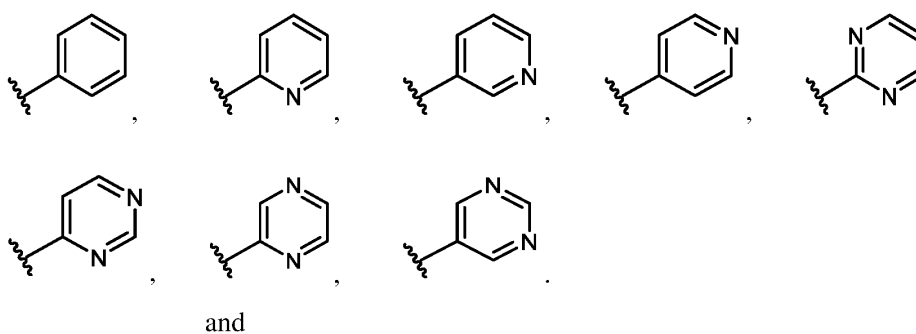
25 10-membered heterocyclyl may be further substituted with one or more substituents selected from the group consisting of hydrogen, halogen, -OH, -CN, -CF₃, -NH₂, and C₁₋₆alkyl.

In some embodiments, R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, 6-membered carbocyclyl, 6-membered heterocyclyl, -OH, -CN, and -NH₂. If present, each 6-membered carbocyclyl and 6-membered heterocyclyl may be further substituted with one or more substituents selected from the
5 group consisting of hydrogen, halogen, -OH, -CN, -CF₃, -NH₂, and C₁₋₆alkyl.

In some embodiments, R^1 is selected from the group consisting of hydrogen, halogen, -OH, -CN, -CF₃, -NH₂, and C₁₋₆alkyl, and R^2 is independently selected from the group consisting of:

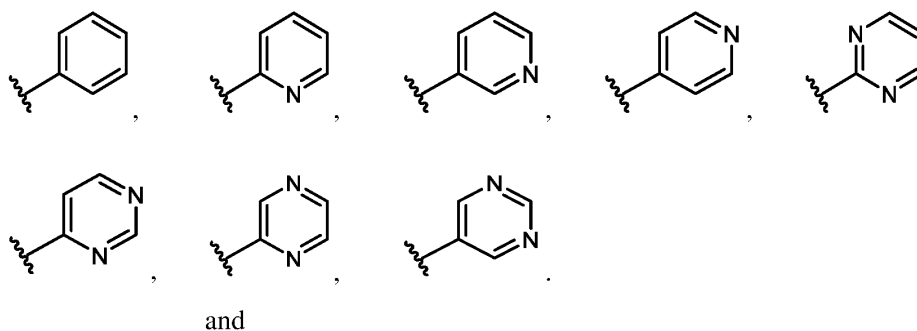


In some embodiments, R^1 is hydrogen and R^2 is independently selected from the
10 group consisting of:

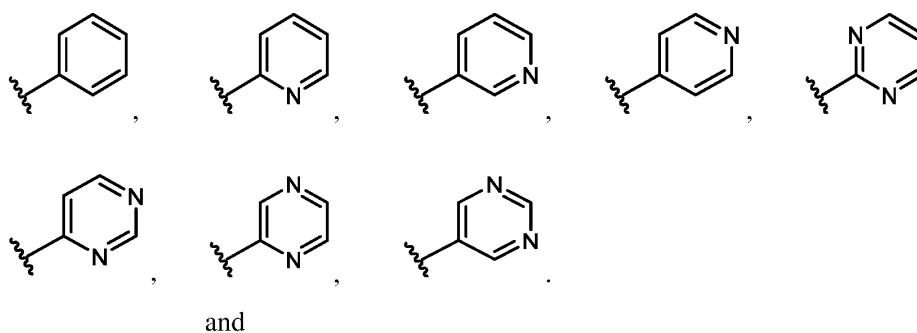


In some embodiments, R^1 is halogen and R^2 is independently selected from the group consisting of:

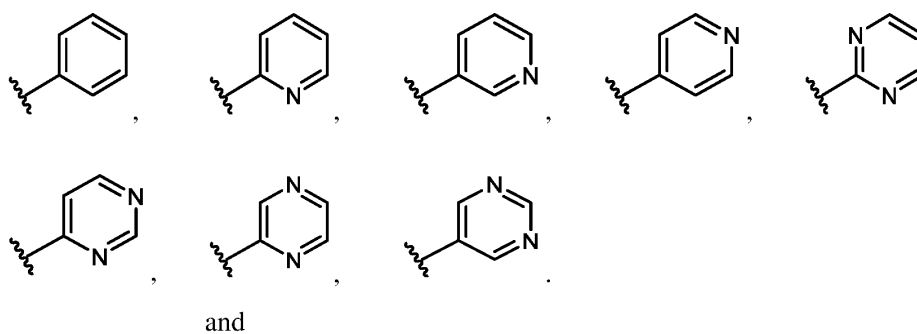
24



In some embodiments, R^1 is -OH and R^2 is independently selected from the group consisting of:

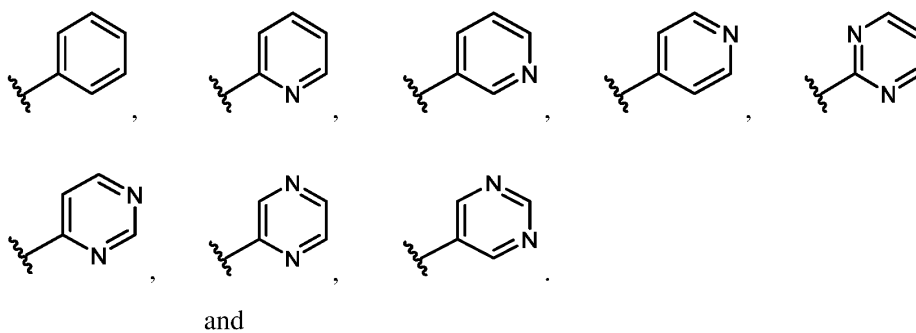


In some embodiments, R^1 is -CN and R^2 is independently selected from the group consisting of:

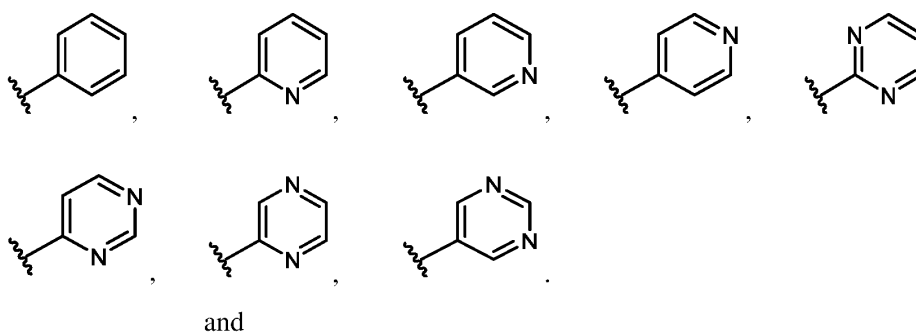


5 In some embodiments, R^1 is -CF₃ and R^2 is independently selected from the group consisting of:

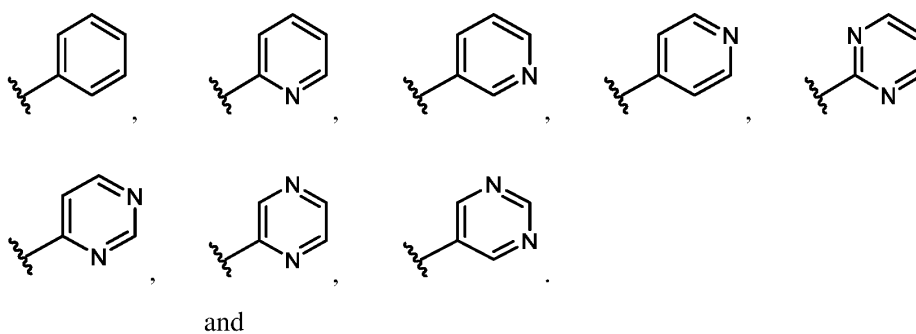
25



In some embodiments, R^1 is $-NH_2$ and R^2 is independently selected from the group consisting of:

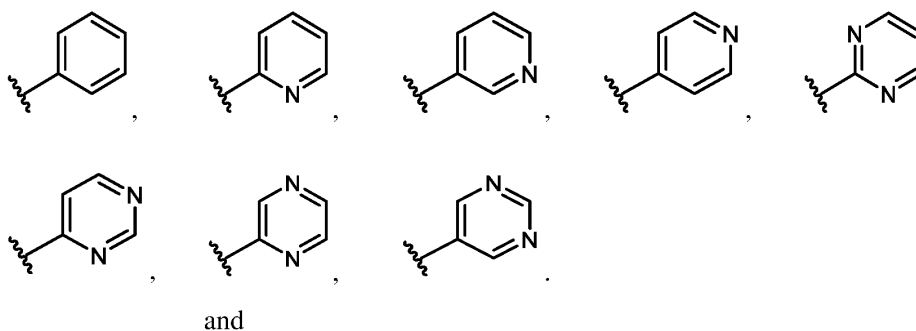


In some embodiments, R^1 is C_{1-6} alkyl and R^2 is independently selected from the group consisting of:

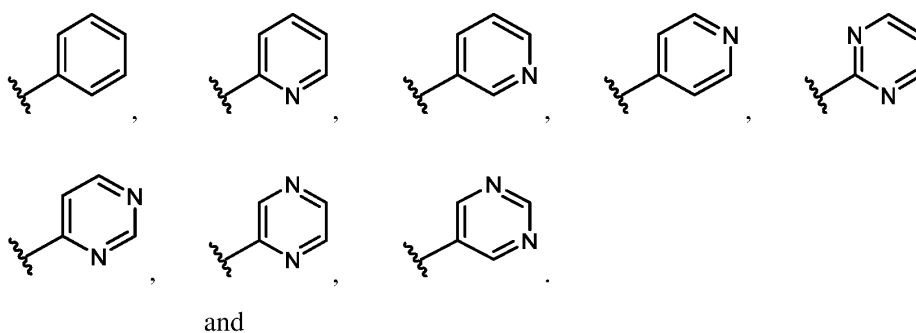


5 In some embodiments, R^1 is chlorine and R^2 is independently selected from the group consisting of:

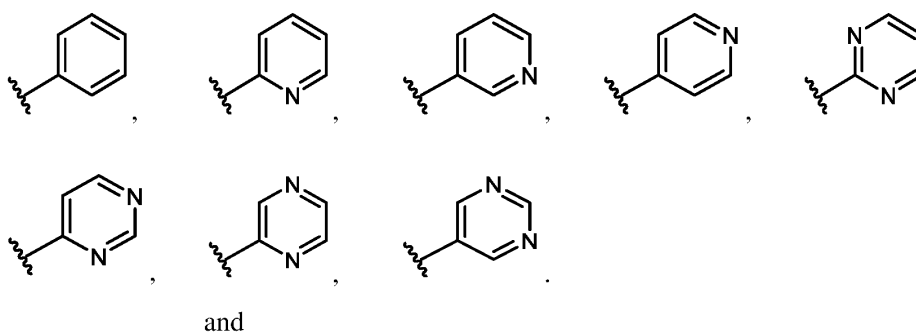
26



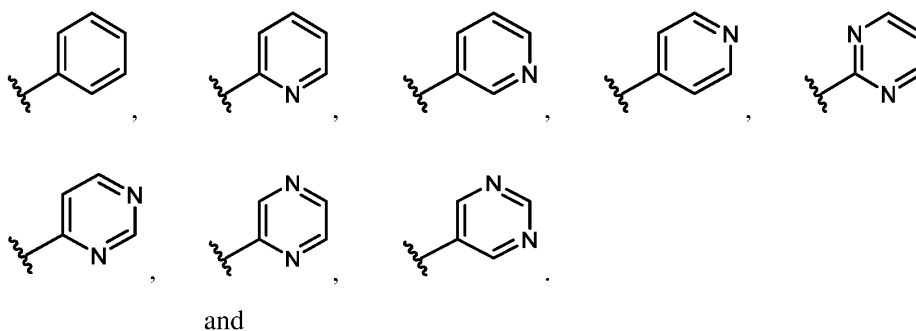
In some embodiments, R^1 is bromine and R^2 is independently selected from the group consisting of:



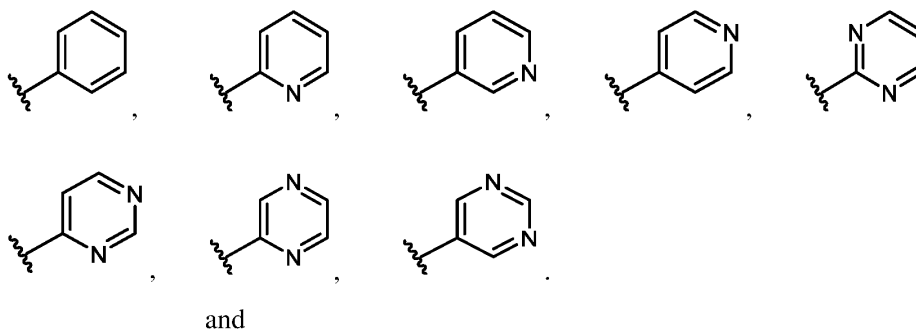
In some embodiments, R^1 is fluorine and R^2 is independently selected from the group consisting of:



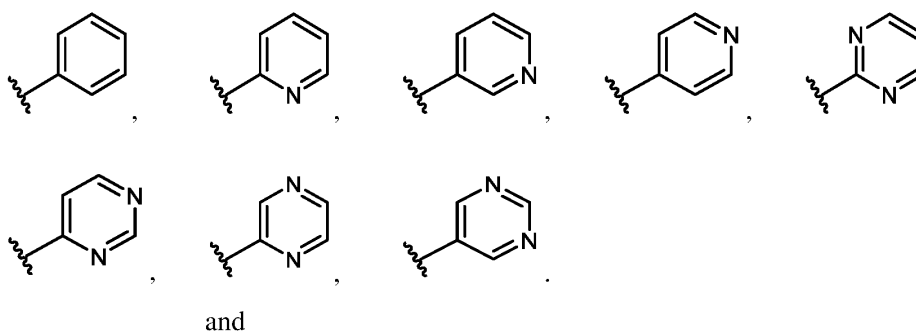
5 In some embodiments, R^1 is iodine and R^2 is independently selected from the group consisting of:



In some embodiments, R^2 is selected from the group consisting of hydrogen, halogen, -OH, -CN, -CF₃, -NH₂, and C₁₋₆alkyl, and R^1 is independently selected from the group consisting of:

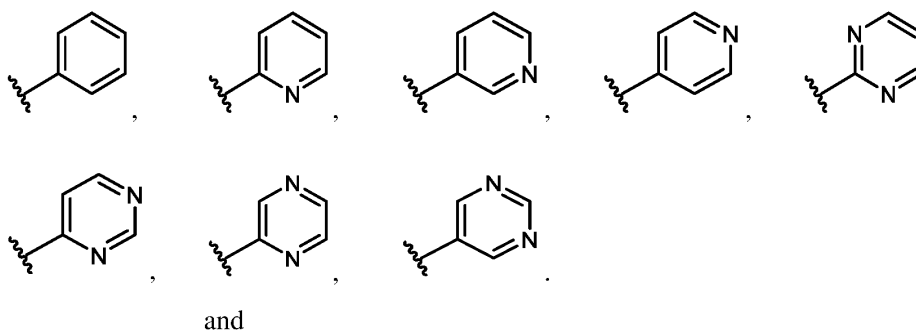


In some embodiments, R^2 is hydrogen and R^1 is independently selected from the group consisting of:

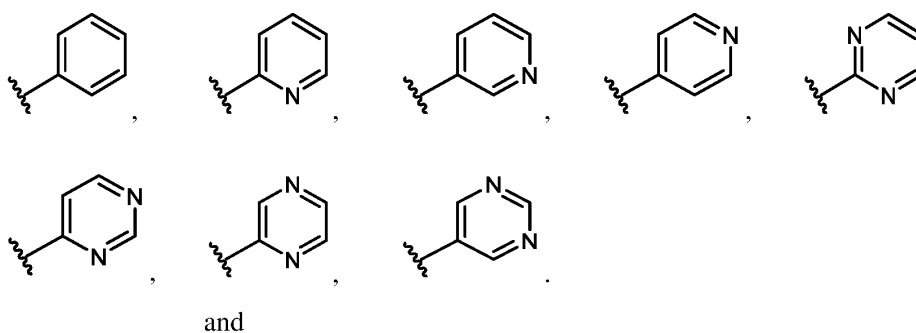


In some embodiments, R^2 is halogen and R^1 is independently selected from the group consisting of:

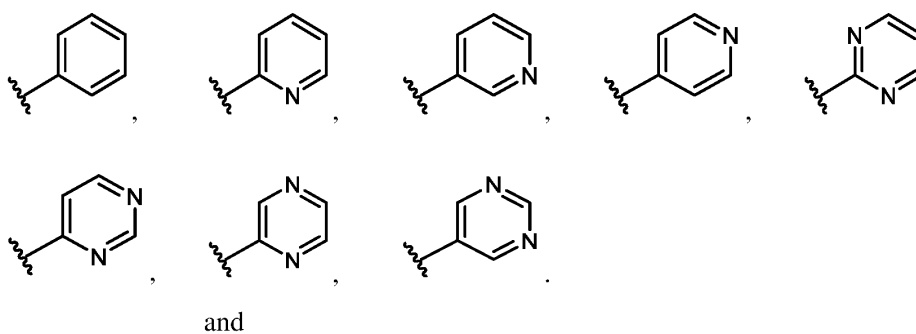
28



In some embodiments, R^2 is -OH and R^1 is independently selected from the group consisting of:

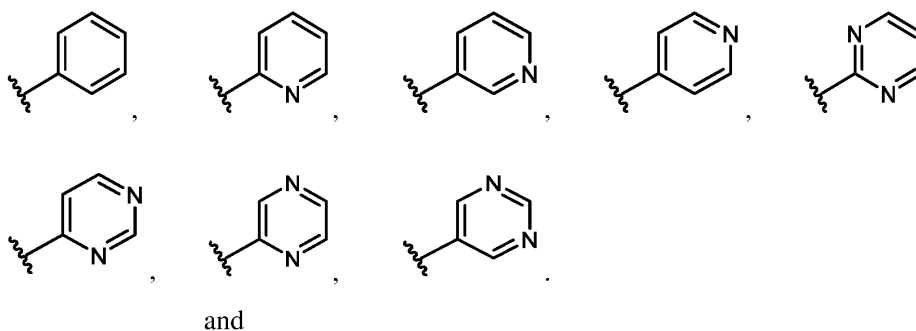


In some embodiments, R^2 is -CN and R^1 is independently selected from the group consisting of:

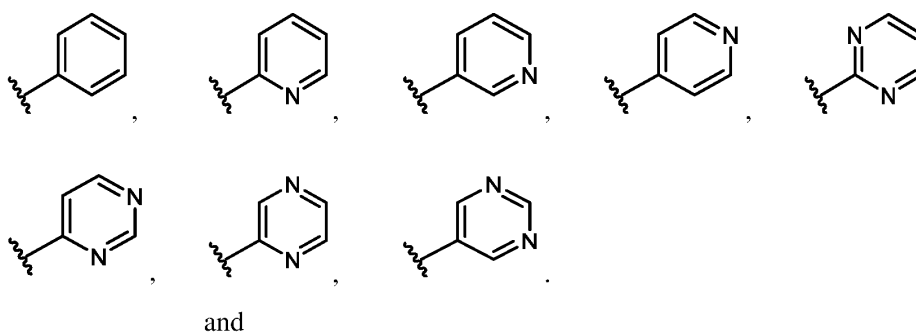


5 In some embodiments, R^2 is -CF₃ and R^1 is independently selected from the group consisting of:

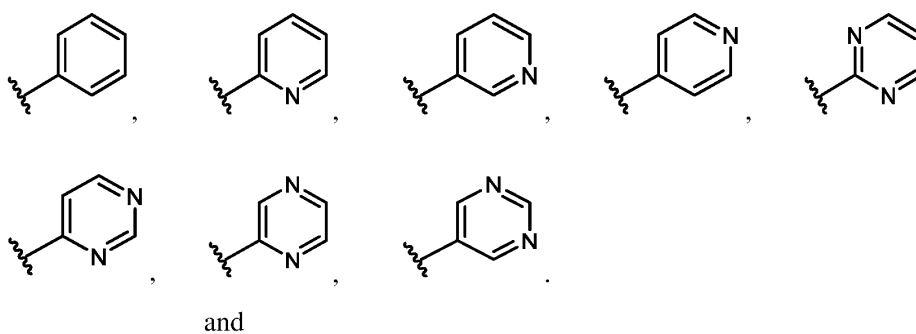
29



In some embodiments, R^2 is $-NH_2$ and R^1 is independently selected from the group consisting of:

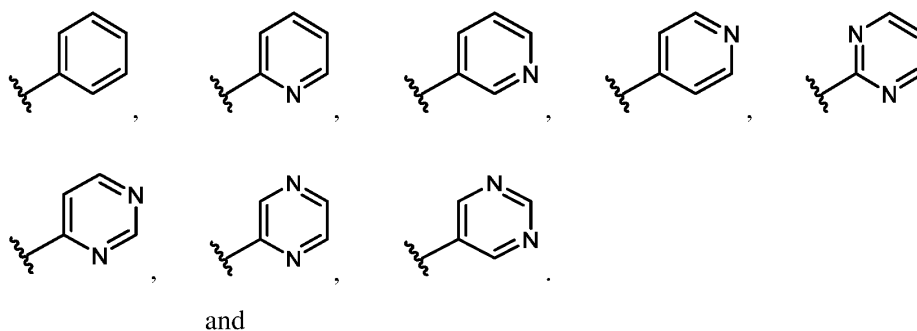


In some embodiments, R^2 is C_{1-6} alkyl and R^1 is independently selected from the group consisting of:

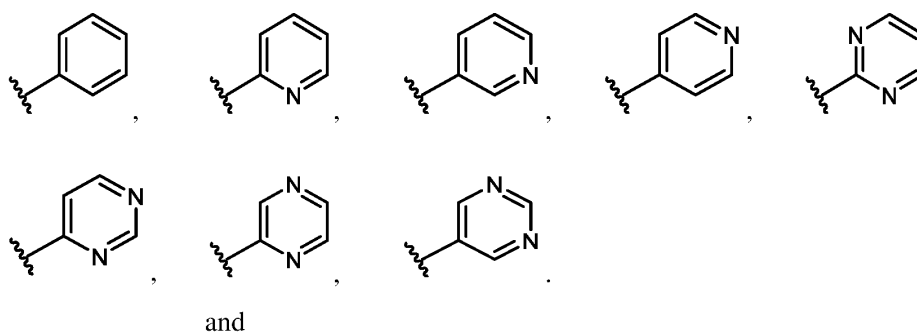


5 In some embodiments, R^2 is chlorine and R^1 is independently selected from the group consisting of:

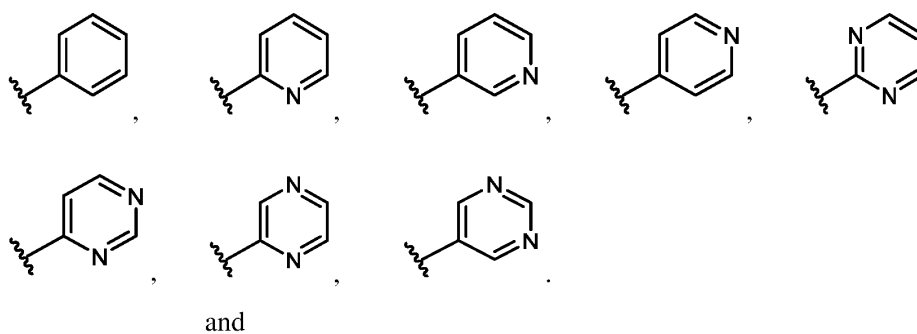
30



In some embodiments, R^2 is bromine and R^1 is independently selected from the group consisting of:

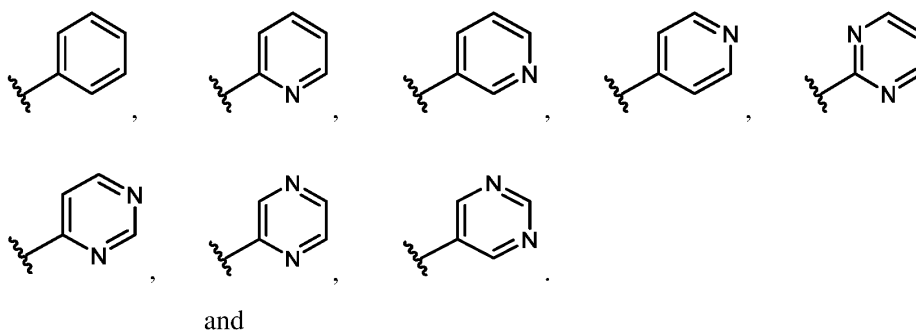


In some embodiments, R^2 is fluorine and R^1 is independently selected from the group consisting of:



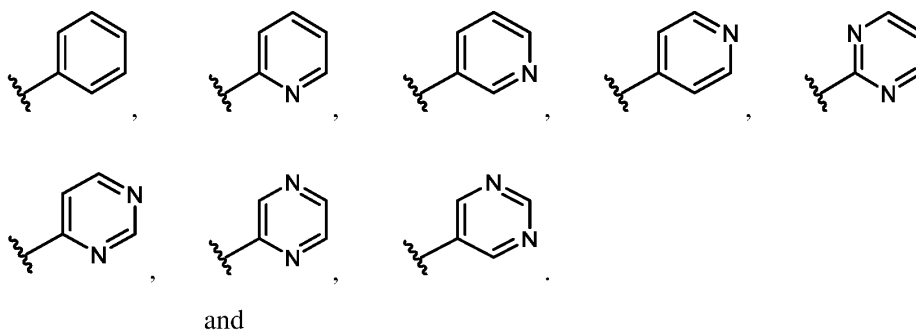
5 In some embodiments, R^2 is iodine and R^1 is independently selected from the group consisting of:

31



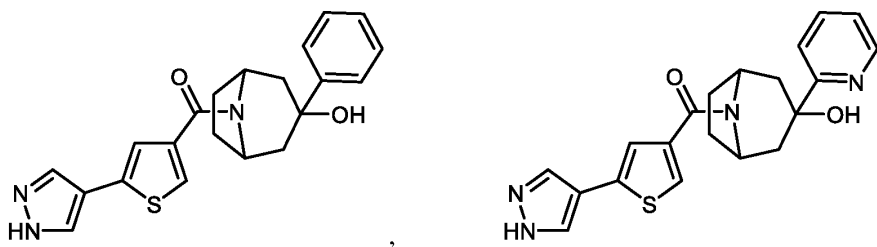
and

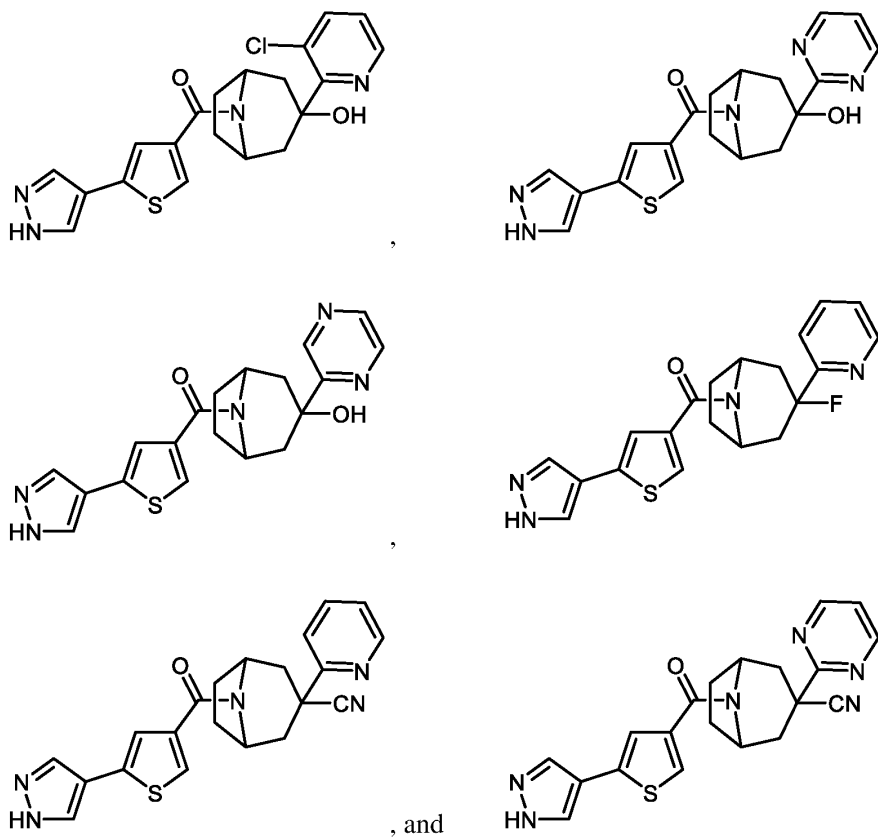
In some embodiments, R^1 and R^2 are each independently selected from the group consisting of:



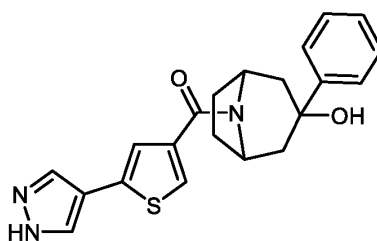
and

In some embodiments, the compound of Formula I is selected from the group consisting of:



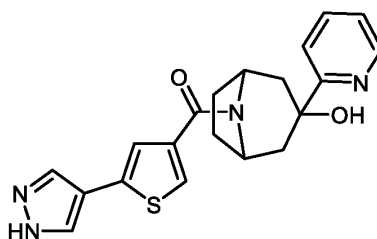


In some embodiments, the compound of Formula I is:

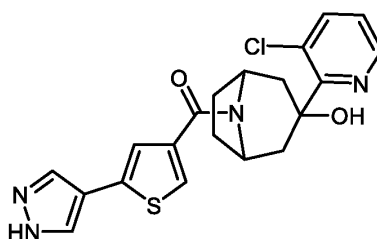


In some embodiments, the compound of Formula I is:

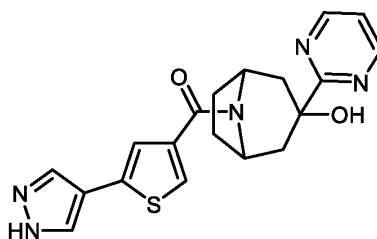
33



In some embodiments, the compound of Formula I is:

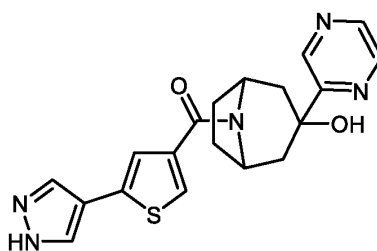


In some embodiments, the compound of Formula I is:



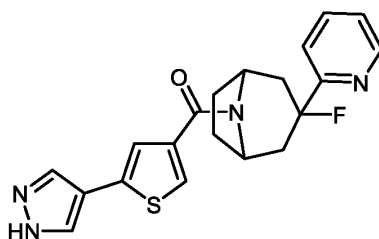
5

In some embodiments, the compound of Formula I is:

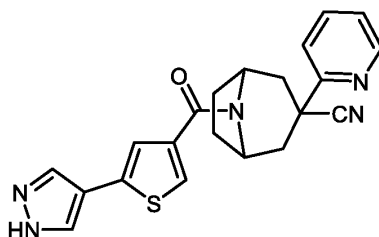


In some embodiments, the compound of Formula I is:

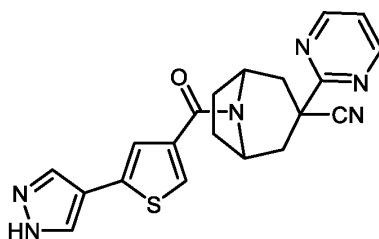
34



In some embodiments, the compound of Formula I is:



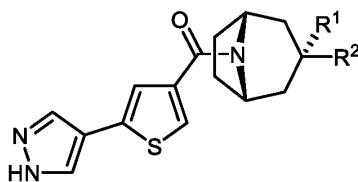
In some embodiments, the compound of Formula I is:



5

As would be understood by the person skilled in the art, the compound of Formula I includes any stereoisomers of the depicted structure. That is, the compound of Formula I includes a racemic mixture.

As used herein, a compound of Formula Ia has the following chemical structure:

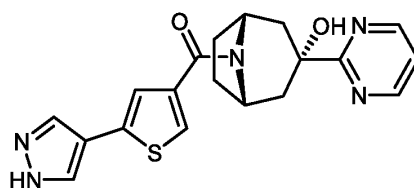


10

Formula Ia.

The definitions of R¹ and R² are the same as those provided for a compound of Formula I. That is, the difference between a compound of Formula I and a compound of Formula Ia is that the stereochemistry in a compound of Formula Ia has been resolved.

In some embodiments, the compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof, has the following chemical structure:



Formula Iai.

The compound of Formula Iai, when having such particular stereochemistry, is also referred to as “UE2343” or “Xanamem”, and has CAS No.: 1346013-80-6. The chemical name (i.e., IUPAC name) of Formula Iai is (5-(1H-Pyrazol-4-yl)thiophen-3-yl)(3-hydroxy-3-(pyrimidin-2-yl)-8-azabicyclo[3.2.1] octan-8-yl)methanone.

The compound of Formula I may be provided in the immediate-release tablet formulation in an suitable form (e.g., amorphous, crystalline). In one example, the compound of Formula I is provided in the immediate-release tablet formulation as an amorphous solid. In one example, the compound of Formula I is provided in the immediate-release tablet formulation as a crystalline solid. In one example, the compound of Formula Ia is provided in the immediate-release tablet formulation as an amorphous solid. In one example, the compound of Formula Ia is provided in the immediate-release tablet formulation as a crystalline solid. In one example, the compound of Formula Iai is provided in the immediate-release tablet formulation as an amorphous solid. In one example, the compound of Formula Iai is provided in the immediate-release tablet formulation as a crystalline solid. The solid may be in the form of a powder. In one example, the compound of Formula I is provided in the immediate-release tablet formulation as a crystalline powder. In one example, the compound of Formula Ia is provided in the immediate-release tablet formulation as a crystalline

powder. In one example, the compound of Formula Iai is provided in the immediate-release tablet formulation as a crystalline powder.

A compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof, may be prepared by any suitable method as would be understood by the person skilled in the art. A compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof, may be prepared in accordance with the procedure described in WO2011135276, which is herein incorporated by reference thereto.

It may be convenient or desirable to prepare, purify and/or handle a corresponding salt of the compound, such as, for example, a pharmaceutically acceptable salt. As used herein, the term "pharmaceutically acceptable salt" refers to pharmaceutically acceptable organic or inorganic salts. Examples of pharmaceutically acceptable salts are discussed in Berge *et al.*, 1977, "Pharmaceutically Acceptable Salts," *J. Pharm. Sci.*, vol. 66, p1-19. For example, if the compound is anionic, or has a functional group that may be anionic (e.g., -COOH may be -COO⁻), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na⁺ and K⁺, alkaline earth cations such as Ca²⁺ and Mg²⁺, and other cations such as Al³⁺. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH₄⁺) and substituted ammonium ions (e.g., NH₃R⁺, NH₂R₂⁺, NHR₃⁺, NR₄⁺). Examples of suitable substituted ammonium ions include, but are not limited to, those derived from ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is N(CH₃)₄⁺. If the compound is cationic, or has a functional group that may be cationic (e.g., -NH₂ may be -NH₃⁺), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the inorganic acids including hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous. Examples of suitable organic anions include, but are not limited to, those derived from the organic acids including 2-acetoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic,

cinna⁵mic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicyclic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to, those derived from polymeric acids including tannic acid and carboxymethyl cellulose.

A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counterion. The counterion may be any
10 organic or inorganic moiety that stabilises the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Instances where multiple charged atoms are part of the pharmaceutically acceptable salt can have multiple counter ions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counterion. It will also be
15 appreciated that non-pharmaceutically acceptable salts also fall within the scope of the present disclosure since these may be useful as intermediates in the preparation of pharmaceutically acceptable salts or may be useful during storage or transport. Unless otherwise specified herein, reference to a particular compound also includes salts thereof.

It may be convenient or desirable to prepare, purify and/or handle a corresponding
20 solvate of the compound. Those skilled in the art of organic chemistry and/or medicinal chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallised. Such complexes are referred to as “solvates”, and as used herein, the term “solvate” refers to such a complex of solute (e.g., a compound, salt of a compound) and solvent.
25 Examples of solvents that may form pharmaceutically acceptable solvates include, but are not limited to, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine. If the solvate is water, the solvate may be conventionally referred to as a “hydrate”. In some embodiments, the pharmaceutically acceptable solvate is a pharmaceutically acceptable hydrate. The hydrate may be, for example, a mono-hydrate,

a di-hydrate, a tri-hydrate, etc. Unless otherwise specified herein, reference to a particular compound also includes solvates thereof.

It may be convenient or desirable to prepare, purify, and/or handle the compound in the form of a prodrug. The term “prodrug”, as used herein, pertains to compound which, when metabolised (e.g., in vivo), yields the desired active compound. Typically, the prodrug is inactive, or less active than the desired active compound, but may provide advantageous handling, administration, or metabolic properties.

Also, as would be understood by a person skilled in the art of organic chemistry and/or medicinal chemistry, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound. For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

In some embodiments, the immediate-release tablet formulation comprises a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of between about 1% and about 50%, between about 5% and about 40%, between about 7.5% and about 30%, or between about 10% and about 20%. In some embodiments, the immediate-release tablet formulation comprises a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of at least about 1%, at least about 5%, at least about 7.5%, at least about 10%, at least about 15%, or at least about 20%. In some embodiments, the immediate-release tablet formulation comprises a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, or less than about 10%. In some embodiments, the immediate-release tablet formulation comprises a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of about 5%, about 7.5%, about 10%, about 12.5%, about 15%, about 17.5%, about 20%, about 25%, or about 30%. In one example, the immediate-release tablet formulation comprises a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of between about 10% and about 20%. In one example, the immediate-release tablet formulation comprises a compound

of Formula I, or a pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of about 10%. In one example, the immediate-release tablet formulation comprises a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of about 20%.

5 *Diluent*

The immediate-release tablet formulation may comprise a diluent. As used herein, and as described above, a “diluent” refers to a substance used to dilute an active ingredient. In one example, the immediate-release tablet formulation comprises a diluent. The diluent may be provided as either of an intragranular component or an extragranular component. In one example, the diluent is an intragranular component. In one example, the diluent is an extragranular component.

Examples of diluents include, but are not limited to, anhydrous lactose, lactose monohydrate, spray-dried lactose, dibasic calcium phosphate dehydrate, dibasic calcium phosphate anhydrous, starch (e.g., maize, potato, wheat, pea), pregelatinised starch, dextrose, dextrin, kaolin, calcium carbonate, calcium lactate, cellulose acetate, erythritol, ethylcellulose, fructose, isomalt, lactitol, polydextrose, semimethicone, trehalose, and sugar alcohols such as sorbitol, xylitol, and mannitol. In one example, the diluent is lactose. In one example, the diluent is lactose monohydrate. In one example, the diluent is microcrystalline cellulose (MCC).

As described herein, lactose may act as a diluent in the immediate-release tablet formulation. Accordingly, in one example, the immediate-release tablet formulation comprises lactose as a diluent. Also as described herein, microcrystalline cellulose (MCC) may act as a diluent in the immediate-release tablet formulation. Accordingly, in one example, the immediate-release tablet formulation comprises microcrystalline cellulose (MCC) as a diluent. In one example, lactose is an intragranular component. In one example, lactose is an extragranular component. In one example, microcrystalline cellulose (MCC) is an intragranular component. In one example, microcrystalline cellulose (MCC) is an extragranular component.

In some embodiments, the immediate-release tablet formulation comprises total lactose in an amount (w/w) of between about 20% and about 70%, between about 30% and about 60%, between about 40% and about 50%, or between about 41% and about 49%. In some embodiments, the immediate-release tablet formulation comprises total lactose in an amount (w/w) of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 42%, at least about 45%, or at least about 47%. In some embodiments, the immediate-release tablet formulation comprises total lactose in an amount (w/w) of less than about 90%, less than about 80%, less than about 70%, less than about 60%, or less than about 50%. In some embodiments, the immediate-release tablet formulation comprises total lactose in an amount (w/w) of about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, or about 50%. In one example, the immediate-release tablet formulation comprises total lactose in an amount (w/w) of between about 40% and about 50%. In one example, the immediate-release tablet formulation comprises total lactose in an amount (w/w) of about 48%. In one example, the immediate-release tablet formulation comprises total lactose in an amount (w/w) of about 42%. In one example, the immediate-release tablet formulation comprises total lactose in an amount (w/w) of about 48.5%. In one example, the immediate-release tablet formulation comprises total lactose in an amount (w/w) of about 42.5%.

In some embodiments, the immediate-release tablet formulation comprises total microcrystalline cellulose in an amount (w/w) of between about 20% and about 50%, between about 25% and about 40%, between about 27.5% and about 35%, or between about 30% and about 32.5%. In some embodiments, the immediate-release tablet formulation comprises total microcrystalline cellulose in an amount (w/w) of at least about 10%, at least about 20%, at least about 25%, at least about 27.5%, at least about 30%, or at least about 32.5%. In some embodiments, the immediate-release tablet formulation comprises total microcrystalline cellulose in an amount (w/w) of less than about 70%, less than about 60%, less than about 50%, less than about 40%, or less than about 35%. In some embodiments, the immediate-release tablet formulation comprises total microcrystalline cellulose in an amount (w/w) of about 25%, about 27.5%, about 28%, about 28.5%, about 29%, about 30%, about 30.5%, about 31%, about 31.5%, about

32%, about 32.5%, or about 33%. In one example, the immediate-release tablet formulation comprises total microcrystalline cellulose in an amount (w/w) of between about 27% and about 33%. In one example, the immediate-release tablet formulation comprises total microcrystalline cellulose in an amount (w/w) of about 32%. In one
5 example, the immediate-release tablet formulation comprises total microcrystalline cellulose in an amount (w/w) of about 28%. In one example, the immediate-release tablet formulation comprises total microcrystalline cellulose in an amount (w/w) of about 32.5%. In one example, the immediate-release tablet formulation comprises total microcrystalline cellulose in an amount (w/w) of about 28.5%.

10 In some embodiments, the immediate-release tablet formulation comprises total diluent in an amount (w/w) of between about 5% and about 90%, between about 10% and about 80%, between about 20% and about 80%, between about 30% and about 80%, or between about 40% and about 80%. In some embodiments, the immediate-release tablet formulation comprises total diluent in an amount (w/w) of at least about 10%, at
15 least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, or at least about 80%. In some embodiments, the immediate-release tablet formulation comprises total diluent in an amount (w/w) of less than about 95%, less than about 90%, less than about 85%, less than about 80%, or less than about 75%. In some embodiments, the immediate-release tablet formulation comprises total
20 diluent in an amount (w/w) of about 40%, about 50%, about 60%, about 70%, about 75%, about 80%, about 85%, or about 90%. In one example, the immediate-release tablet formulation comprises total diluent in an amount (w/w) of about 80%. In one example, the immediate-release tablet formulation comprises total diluent in an amount (w/w) of about 81%. In one example, the immediate-release tablet formulation comprises total
25 diluent in an amount (w/w) of about 70%. In one example, the immediate-release tablet formulation comprises total diluent in an amount (w/w) of about 71%.

Disintegrant

The immediate-release tablet formulation may comprise a disintegrant. As used herein, the term “disintegrant” refers to a substance added to a tablet to facilitate its
30 disintegration into smaller units/fragments to allow for dissolution. The disintegrant may

be provided as either of an intragranular component or an extragranular component. In one example, the disintegrant is an intragranular component. In one example, the disintegrant is an extragranular component.

Examples of disintegrants include, but are not limited to, croscopovidone, 5 croscarmellose sodium (e.g., Ac-Di-Sol SD-711), sodium starch glycolate (e.g., Explotab), low-substituted hydroxypropyl cellulose, chitosan hydrochloride, corn starch, pregelatinised starch, calcium alginate, calcium sodium alginate, docusate sodium, microcrystalline cellulose, hydroxypropyl starch, magnesium aluminate silicate, methylcellulose, sodium alginate, starch, calcium carboxymethylcellulose, calcium 10 cellulose glycolate, carmellose calcium, and powdered cellulose. In one example, the disintegrant is sodium starch glycolate (e.g., Explotab). In one example, the disintegrant is croscarmellose sodium (e.g., Ac-Di-Sol SD-711).

In some embodiments, the immediate-release tablet formulation comprises total sodium starch glycolate in an amount (w/w) of between about 0.1% and about 10%, 15 between about 0.5% and about 5%, or between about 1% and about 3%. In some embodiments, the immediate-release tablet formulation comprises total sodium starch glycolate in an amount (w/w) of at least about 0.1%, at least about 0.5%, at least about 1%, at least about 1.5%, or at least about 2%. In some embodiments, the immediate-release tablet formulation comprises total sodium starch glycolate in an amount (w/w) of 20 less than about 10%, less than about 5%, less than about 4%, less than about 3%, or less than about 2%. In some embodiments, the immediate-release tablet formulation comprises total sodium starch glycolate in an amount (w/w) of about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, or about 3%. In one example, the immediate-release tablet formulation comprises total sodium starch glycolate in an amount (w/w) of about 25 2%.

In some embodiments, the immediate-release tablet formulation comprises total croscarmellose sodium in an amount (w/w) of between about 0.1% and about 10%, between about 0.5% and about 5%, or between about 1% and about 3%. In some 30 embodiments, the immediate-release tablet formulation comprises total croscarmellose sodium in an amount (w/w) of at least about 0.1%, at least about 0.5%, at least about 1%,

at least about 1.5%, or at least about 2%. In some embodiments, the immediate-release tablet formulation comprises total croscarmellose sodium in an amount (w/w) of less than about 10%, less than about 5%, less than about 4%, less than about 3%, or less than about 2%. In some embodiments, the immediate-release tablet formulation comprises total croscarmellose sodium in an amount (w/w) of about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, or about 3%. In one example, the immediate-release tablet formulation comprises total croscarmellose sodium in an amount (w/w) of about 2%.

In some embodiments, the immediate-release tablet formulation comprises total disintegrant in an amount (w/w) of between about 0.5% and about 10%, between about 1% and about 5%, between about 1.5% and about 3%, or between about 2% and about 3%. In some embodiments, the immediate-release tablet formulation comprises total diluent in an amount (w/w) of at least about 0.1%, at least about 0.5%, at least about 1%, at least about 1.5%, or at least about 2%. In some embodiments, the immediate-release tablet formulation comprises total diluent in an amount (w/w) of less than about 5%, less than about 4%, less than about 3%, less than about 2.5%, or less than about 2%. In some embodiments, the immediate-release tablet formulation comprises total diluent in an amount (w/w) of about 0.1%, about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, or about 3%. In one example, the immediate-release tablet formulation comprises total disintegrant in an amount (w/w) of about 4%.

20 *Glidant*

The immediate-release tablet formulation may comprise a glidant. As used herein, the term “glidant” refers to a substance added to a powder to improve its flowability, for example, to enhance the flow of a granular mixture. The glidant is typically provided as an intragranular component. In one example, the glidant is an intragranular component.

Examples of glidants include, but are not limited to, colloidal silicon dioxide, talc, tribasic calcium phosphate, calcium silicate, cellulose (powdered), magnesium oxide, sodium stearate, magnesium silicate, silica, magnesium trisilicate, and hydrophobic colloidal silica. In one example, the glidant is colloidal silicon dioxide (Cab-O-Sil M5P).

In some embodiments, the immediate-release tablet formulation comprises total colloidal silicon dioxide in an amount (w/w) of between about 0.1% and about 10%, between about 0.5% and about 5%, between about 1% and about 3%, or between about 1% and about 2%. In some embodiments, the immediate-release tablet formulation
5 comprises total colloidal silicon dioxide in an amount (w/w) of at least about 0.1%, at least about 0.5%, at least about 1%, at least about 1.5%, at least about 2%, or at least about 2.5%. In some embodiments, the immediate-release tablet formulation comprises total colloidal silicon dioxide in an amount (w/w) of less than about 10%, less than about 7%, less than about 5%, less than about 4%, less than about 3%, less than about 2%, or
10 less than about 1%. In some embodiments, the immediate-release tablet formulation comprises total colloidal silicon dioxide in an amount (w/w) of about 0.1%, about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, or about 3%. In one example, the immediate-release tablet formulation comprises total colloidal silicon dioxide in an amount (w/w) of between about 1% and about 2%. In one example, the immediate-
15 release tablet formulation comprises total colloidal silicon dioxide in an amount (w/w) of about 1%. In one example, the immediate-release tablet formulation comprises total colloidal silicon dioxide in an amount (w/w) of about 2%.

In some embodiments, the immediate-release tablet formulation comprises total glidant in an amount (w/w) of between about 0.1% and about 10%, between about 0.5%
20 and about 5%, between about 1% and about 3%, or between about 1% and about 2%. In some embodiments, the immediate-release tablet formulation comprises total glidant in an amount (w/w) of at least about 0.1%, at least about 0.5%, at least about 1%, at least about 1.5%, at least about 2%, or at least about 2.5%. In some embodiments, the immediate-release tablet formulation comprises total glidant in an amount (w/w) of less
25 than about 10%, less than about 7%, less than about 5%, less than about 4%, less than about 3%, less than about 2%, or less than about 1%. In some embodiments, the immediate-release tablet formulation comprises total glidant in an amount (w/w) of about 0.1%, about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, or about 3%. In one example, the immediate-release tablet formulation comprises total glidant in an amount
30 (w/w) of between about 1% and about 2%. In one example, the immediate-release tablet formulation comprises total glidant in an amount (w/w) of about 1%. In one example, the

immediate-release tablet formulation comprises total glidant in an amount (w/w) of about 2%.

Lubricant

The immediate-release tablet formulation may comprise a lubricant. As used
5 herein, the term “lubricant” refers to a substance added to the formulation to prevent adhesion of the formulation to the surfaces of the dies and/or punches utilised in the tablet manufacturing process. A lubricant may also improve the flow properties of the powder blend and granules.

Examples of lubricants include, but are not limited to, magnesium stearate,
10 magnesium silicate, calcium stearate, sodium lauryl sulfate, sodium stearyl fumarate, magnesium lauryl sulfate, stearic acid, calcium stearate, glyceryl behenate, lauric acid, glyceryl monostearate, glyceryl tristearate, myristic acid, palmitic acid, poloxamer, polyethylene glycol, polysorbate 20, polysorbate 40, potassium benzoate, sodium benzoate, sorbitan monolaurate, sorbitan monooleate, sodium stearate, zinc stearate,
15 sorbitan trioleate, and talc. In one example, the lubricant is magnesium stearate (Hyqual 2257).

In some embodiments, the immediate-release tablet formulation comprises total magnesium stearate in an amount (w/w) of between about 0.1% and about 10%, between about 0.5% and about 5%, between about 1% and about 4%, or between about 1.5% and
20 about 3%. In some embodiments, the immediate-release tablet formulation comprises total magnesium stearate in an amount (w/w) of at least about 0.1%, at least about 0.5%, at least about 1%, at least about 1.5%, at least about 2%, at least about 2.5%, or at least about 3%. In some embodiments, the immediate-release tablet formulation comprises total magnesium stearate in an amount (w/w) of less than about 10%, less than about 5%,
25 less than about 4%, less than about 3%, or less than about 2%. In some embodiments, the immediate-release tablet formulation comprises total magnesium stearate in an amount (w/w) of about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, or about 3%. In one example, the immediate-release tablet formulation comprises magnesium stearate in an amount (w/w) of between about 1.5% and about 3%. In one example, the

immediate-release tablet formulation comprises total magnesium stearate in an amount (w/w) of about 1.5%. In one example, the immediate-release tablet formulation comprises total magnesium stearate in an amount (w/w) of about 3%.

In some embodiments, the immediate-release tablet formulation comprises total lubricant in an amount (w/w) of between about 0.1% and about 10%, between about 0.5% and about 5%, between about 1% and about 4%, or between about 1.5% and about 3%. In some embodiments, the immediate-release tablet formulation comprises total lubricant in an amount (w/w) of at least about 0.1%, at least about 0.5%, at least about 1%, at least about 1.5%, at least about 2%, at least about 2.5%, or at least about 3%. In some embodiments, the immediate-release tablet formulation comprises total lubricant in an amount (w/w) of less than about 10%, less than about 5%, less than about 4%, less than about 3%, or less than about 2%. In some embodiments, the immediate-release tablet formulation comprises total lubricant in an amount (w/w) of about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, or about 3%. In one example, the immediate-release tablet formulation comprises total lubricant in an amount (w/w) of between about 1.5% and about 3%. In one example, the immediate-release tablet formulation comprises total lubricant in an amount (w/w) of about 1.5%. In one example, the immediate-release tablet formulation comprises total lubricant in an amount (w/w) of about 3%.

Film Coating

The immediate-release tablet formulation may comprise a film coating. As used herein, the term “film coating” refers to a substance used to coat the tablet.

Examples of film coatings include, but are not limited to, solvents, plasticisers, colourants/pigments, and opaquant-extenders. In one example, the film coating comprises a polymer, plasticiser, and colourant/pigment. In one example, the film coating is Opdary TF (Opadry TF, Titanium-free, 276U180005, white).

In some embodiments, the immediate-release tablet formulation comprises total Opadry TF in an amount (w/w) of between about 0.1% and about 10%, between about 0.5% and about 5%, between about 1% and about 4%, or between about 1.5% and about 3%. In some embodiments, the immediate-release tablet formulation comprises total

Opadry TF in an amount (w/w) of at least about 0.1%, at least about 0.5%, at least about 1%, at least about 1.5%, at least about 2%, at least about 2.5%, or at least about 3%. In some embodiments, the immediate-release tablet formulation comprises total Opadry TF in an amount (w/w) of less than about 10%, less than about 5%, less than about 4%, less than about 3%, or less than about 2%. In some embodiments, the immediate-release tablet formulation comprises total Opadry TF in an amount (w/w) of about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, or about 3%. In one example, the immediate-release tablet formulation comprises total Opadry TF in an amount (w/w) of between about 1.5% and about 3%. In one example, the immediate-release tablet formulation comprises total Opadry TF in an amount (w/w) of about 1.5%. In one example, the immediate-release tablet formulation comprises total Opadry TF in an amount (w/w) of about 3%.

Immediate-Release Tablet

The immediate-release tablet formulation will comprise a net weight. The net weight will be understood to mean the total weight of the intragranular and extragranular components of the tablet. In some embodiments, the net weight of the immediate-release tablet is about 5 mg, about 10 mg, about 25 mg, about 40 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 300 mg, about 500 mg, about 750 mg, or about 1000 mg. In some embodiments, the net weight of the immediate-release tablet is greater than about 5 mg, about 10 mg, about 25 mg, about 40 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 300 mg, about 500 mg, about 750 mg, or about 1000 mg. In some embodiments, the net weight of the immediate-release tablet is between about 5 mg and about 1000 mg, between about 10 mg and about 500 mg, between about 25 mg and about 200 mg, or between about 50 mg and about 100 mg. In one example, the net weight of the immediate-release tablet is about 50 mg. In one example, the net weight of the immediate-release tablet is about 100 mg.

The immediate-release tablet formulation will have a film coating applied. In some embodiments, the weight of the film-coating is about 0.2 mg, about 0.5 mg, about 1.0 mg, about 1.5 mg, about 2.0 mg, about 2.5 mg, about 3.0 mg, about 3.5 mg, about 4.0 mg, about 4.5 mg, or about 5.0 mg. Once the film coating is applied to the immediate-release tablet formulation, the immediate-release tablet formulation will have a total

weight (net weight plus film-coating weight). In one example, the net weight of the immediate-release tablet formulation is about 50 mg, and the total weight of the immediate-release tablet is about 51.5 mg. In one example, the net weight of the immediate-release tablet formulation is about 100 mg, and the total weight of the immediate-release formulation is about 103 mg.

As is common in practice, the amount of the active ingredient may also be used to define the immediate-release tablet formulation. For example, a “10 mg dose tablet” will refer to the immediate-release tablet formulation comprising about 10 mg of active ingredient (i.e., a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof). That is, about a 10 mg dose of the active ingredient is provided in each “10 mg dose tablet”. Similarly, for example, a “5 mg dose tablet” will refer to the immediate-release tablet formulation comprising about 5 mg of active ingredient (i.e., a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof). That is, about a 5 mg dose of the active ingredient is provided in each “5 mg dose tablet”. In one example, the immediate-release tablet formulation is a “10 mg dose tablet”. In one example, the immediate-release tablet formulation is a “5 mg dose tablet”.

In one example, there is provided an immediate-release tablet formulation comprising the compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of about 10% to about 20%; lactose monohydrate in an amount (w/w) of about 40% to about 50%; microcrystalline cellulose in an amount (w/w) of about 25% to 35%; and one or more pharmaceutically acceptable excipients in an amount (w/w) up to 100%.

In one example, there is provided an immediate-release tablet formulation consisting of the compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of about 10% to about 20%; lactose monohydrate in an amount (w/w) of about 40% to about 50%; microcrystalline cellulose in an amount (w/w) of about 25% to 35%; and optionally one or more pharmaceutically acceptable excipients in an amount (w/w) up to 100%.

In one example, there is provided an immediate-release tablet formulation comprising the compound of Formula I, or pharmaceutically acceptable salt or solvate

thereof, in an amount (w/w) of about 10%; lactose monohydrate in an amount (w/w) of about 48.5%; microcrystalline cellulose in an amount (w/w) of about 32.5%; and one or more pharmaceutically acceptable excipients in an amount (w/w) up to 100%.

5 In one example, there is provided an immediate-release tablet formulation consisting of the compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of about 10%; lactose monohydrate in an amount (w/w) of about 48.5%; microcrystalline cellulose in an amount (w/w) of about 32.5%; and optionally one or more pharmaceutically acceptable excipients in an amount (w/w) up to 100%.

10 In one example, there is provided an immediate-release tablet formulation comprising the compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of about 10%; lactose monohydrate in an amount (w/w) of about 48.5%; microcrystalline cellulose in an amount (w/w) of about 32.5%; sodium starch glycolate in an amount (w/w) of about 2%; croscarmellose sodium in an amount (w/w) of about 2%; colloidal silicon dioxide in an amount (w/w) of about 2%; and magnesium stearate in an amount (w/w) of about 3%.

In one example, there is provided an immediate-release tablet formulation consisting of the compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of about 10%; lactose monohydrate in an amount (w/w) of about 48.5%; microcrystalline cellulose in an amount (w/w) of about 32.5%; sodium starch glycolate in an amount (w/w) of about 2%; croscarmellose sodium in an amount (w/w) of about 2%; colloidal silicon dioxide in an amount (w/w) of about 2%; and magnesium stearate in an amount (w/w) of about 3%.

25 In one example, there is provided an immediate-release tablet formulation comprising the compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of about 20%; lactose monohydrate in an amount (w/w) of about 42.5%; microcrystalline cellulose in an amount (w/w) of about 28.5%; and one or more pharmaceutically acceptable excipients in an amount (w/w) up to 100%.

30 In one example, there is provided an immediate-release tablet formulation consisting of the compound of Formula I, or pharmaceutically acceptable salt or solvate

thereof, in an amount (w/w) of about 20%; lactose monohydrate in an amount (w/w) of about 42.5%; microcrystalline cellulose in an amount (w/w) of about 28.5%; and optionally one or more pharmaceutically acceptable excipients in an amount (w/w) up to 100%.

5 In one example, there is provided an immediate-release tablet formulation comprising the compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of about 20%; lactose monohydrate in an amount (w/w) of about 42.5%; microcrystalline cellulose in an amount (w/w) of about 28.5%; sodium starch glycolate in an amount (w/w) of about 2%; croscarmellose sodium in an amount
10 (w/w) of about 2%; colloidal silicon dioxide in an amount (w/w) of about 2%; and magnesium stearate in an amount (w/w) of about 3%.

 In one example, there is provided an immediate-release tablet formulation consisting of the compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of about 20%; lactose monohydrate in an amount (w/w) of
15 about 42.5%; microcrystalline cellulose in an amount (w/w) of about 28.5%; sodium starch glycolate in an amount (w/w) of about 2%; croscarmellose sodium in an amount (w/w) of about 2%; colloidal silicon dioxide in an amount (w/w) of about 2%; and magnesium stearate in an amount (w/w) of about 3%.

10 mg Dose Tablet

20 In one particular example, the immediate-release tablet formulation is a 10 mg dose tablet (i.e., each tablet comprises about 10 mg of the active ingredient). In one example, a 10 mg dose tablet has a net weight of about 50 mg. That is, in a 10 mg dose tablet, with a net weight of about 50 mg, the immediate-release tablet formulation comprises about 40 mg of excipients. In one example, a 10 mg dose tablet has a total
25 weight of about 51.5 mg.

 In one particular example, the immediate-release tablet formulation is a 10 mg dose tablet (i.e., each tablet comprises about 10 mg of the active ingredient), and further comprises a diluent, disintegrant, glidant, lubricant, and film-coating. In one particular example, the immediate-release tablet formulation is a 10 mg dose tablet (i.e., each tablet

comprises about 10 mg of the active ingredient), and further comprises lactose and microcrystalline cellulose. In one particular example, the immediate-release tablet formulation is a 10 mg dose tablet (i.e., each tablet comprises about 10 mg of the active ingredient), and further comprises lactose and microcrystalline cellulose, and a disintegrant, a glidant, a lubricant, and a film-coating. In one particular example, the immediate-release tablet formulation is a 10 mg dose tablet (i.e., each tablet comprises about 10 mg of the active ingredient), and further comprises between about 20 and about 30 mg lactose, between about 10 mg and about 15 mg microcrystalline cellulose, between about 0.5 mg and about 2 mg sodium starch glycolate, between about 0.5 mg and about 2 mg croscarmellose sodium, between about 0.5 mg and about 2 mg colloidal silicon dioxide, between about 1 mg and about 2 mg magnesium stearate, and between about 1 mg and about 2 mg Opadry TF. In one particular example, the immediate-release tablet formulation is a 10 mg dose tablet (i.e., each tablet comprises about 10 mg of the active ingredient), and further comprises about 21.25 mg lactose, about 14.25 mg microcrystalline cellulose, about 1 mg sodium starch glycolate, about 1 mg croscarmellose sodium, about 1 mg colloidal silicon dioxide, about 1.5 mg magnesium stearate, and about 1.5 mg Opadry TF.

In one particular example, the immediate-release tablet formulation is a 10 mg dose tablet (i.e., each tablet comprises about 10 mg of the active ingredient), and further comprises between about 20 mg and about 30 mg lactose, and between about 10 mg and about 15 mg microcrystalline cellulose. In one particular example, the immediate-release tablet formulation is a 10 mg dose tablet (i.e., each tablet comprises about 10 mg of the active ingredient), and further comprises about 21.25 mg lactose, and about 14.25 mg microcrystalline cellulose.

In one example, the immediate-release tablet formulation is a 10 mg dose tablet (i.e., each tablet comprises about 10 mg of the active ingredient) and has a net weight of about 50 mg. In one example, the immediate-release tablet formulation is a 10 mg dose tablet (i.e., each tablet comprises about 10 mg of the active ingredient) and has a total weight of about 51.5 mg.

5 mg Dose Tablet

In one particular example, the immediate-release tablet formulation is a 5 mg dose tablet (i.e., each tablet comprises about 5 mg of the active ingredient). In one example, a 5 mg dose tablet has a net weight of about 50 mg. That is, in a 5 mg dose tablet, with a net weight of about 50 mg, the immediate-release tablet formulation comprises about 45 mg of excipients. In one example, a 5 mg dose tablet has a total weight of about 51.5 mg.

In one particular example, the immediate-release tablet formulation is a 5 mg dose tablet (i.e., each tablet comprises about 5 mg of the active ingredient), and further comprises a diluent, disintegrant, glidant, lubricant, and film-coating. In one particular example, the immediate-release tablet formulation is a 5 mg dose tablet (i.e., each tablet comprises about 5 mg of the active ingredient), and further comprises lactose and microcrystalline cellulose. In one particular example, the immediate-release tablet formulation is a 5 mg dose tablet (i.e., each tablet comprises about 5 mg of the active ingredient), and further comprises lactose and microcrystalline cellulose, and a disintegrant, a glidant, a lubricant, and a film-coating. In one particular example, the immediate-release tablet formulation is a 5 mg dose tablet (i.e., each tablet comprises about 5 mg of the active ingredient), and further comprises between about 20 and about 30 mg lactose, between about 15 mg and about 20 mg microcrystalline cellulose, between about 0.5 mg and about 2 mg sodium starch glycolate, between about 0.5 mg and about 2 mg croscarmellose sodium, between about 0.5 mg and about 2 mg colloidal silicon dioxide, between about 1 mg and about 2 mg magnesium stearate, and between about 1 mg and about 2 mg Opadry TF. In one particular example, the immediate-release tablet formulation is a 5 mg dose tablet (i.e., each tablet comprises about 5 mg of the active ingredient), and further comprises about 24.25 mg lactose, about 16.25 mg microcrystalline cellulose, about 1 mg sodium starch glycolate, about 1 mg croscarmellose sodium, about 1 mg colloidal silicon dioxide, about 1.5 mg magnesium stearate, and about 1.5 mg Opadry TF.

In one particular example, the immediate-release tablet formulation is a 5 mg dose tablet (i.e., each tablet comprises about 5 mg of the active ingredient), and further comprises between about 20 mg and about 30 mg lactose, and between about 15 mg and about 20 mg microcrystalline cellulose. In one particular example, the immediate-release

tablet formulation is a 5 mg dose tablet (i.e., each tablet comprises about 5 mg of the active ingredient), and further comprises about 24.25 mg lactose, and about 16.25 mg microcrystalline cellulose.

5 In one example, the immediate-release tablet formulation is a 5 mg dose tablet (i.e., each tablet comprises about 5 mg of the active ingredient) and has a net weight of about 50 mg. In one example, the immediate-release tablet formulation is a 5 mg dose tablet (i.e., each tablet comprises about 5 mg of the active ingredient) and has a total weight of about 51.5 mg.

Manufacturing Process

10 The immediate-release tablet formulation may be manufactured according to any suitable process as would be understood by the person skilled in the art. This may entail a dry granulation process or a wet granulation process. As would be understood by the person skilled in the art, while dry granulation typically uses mechanical compression or compaction to facilitate the agglomeration of dry powder particles, wet granulation
15 typically uses granulation liquid (e.g., binder, solvent) to facilitate the agglomeration by formation of wet mass by adhesion. Accordingly, in one example, the immediate-release tablet formulation is manufactured using a dry granulation process. In one other example, the immediate-release tablet formulation is manufactured using a wet granulation process.

20 In the manufacturing process, various intragranular and extragranular components are utilised to manufacture the immediate-release tablet formulation. As used herein, and discussed above, the term “intragranular component” will be understood to be a component added to the formulation prior to the granulation process. Similarly, as used herein, the term “extragranular component” will be understood to be a component
25 added to the formulation after the granulation process and prior to the compression process.

Examples of intragranular components include, but are not limited to, an active ingredient, diluent, disintegrant, glidant, and lubricant. In one example, the compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, is an intragranular

component. In one example, lactose is an intragranular component. In one example, microcrystalline cellulose is an intragranular component. Examples of extragranular components include, but are not limited to, a diluent, and lubricant. In one example, microcrystalline cellulose is an extragranular component.

5 Accordingly, in some embodiments, granules may be prepared by blender mixing of intragranular components, and then granulation using roller compaction and milling to produce the granules. Accordingly, in some embodiments, a blend is prepared by blender mixing of the compound of Formula (I), or pharmaceutically acceptable salt or solvate thereof, lactose, and microcrystalline cellulose. In some embodiments, the
10 process comprises blender mixing of further intragranular components, including, but not limited to, any one or more of a diluent, disintegrant, glidant, and lubricant. In one example, a blend is prepared by blender mixing of the compound of Formula (I), or pharmaceutically acceptable salt or solvate thereof, lactose, microcrystalline cellulose, a disintegrant, a glidant, and a lubricant. In one example, a blend is prepared by blender
15 mixing of the compound of Formula (I), or pharmaceutically acceptable salt or solvate thereof, lactose, microcrystalline cellulose, sodium starch glycolate, Croscarmellose sodium, Colloidal silicon dioxide, and magnesium stearate. Subsequent granulation using roller compaction and milling results in the granules.

 In some embodiments, the granules are then blended with extragranular
20 components to yield the final blend. Accordingly, in some embodiments, the granules are blended with extragranular components, including, but not limited to, any one or more of a diluent and lubricant. In one example, the granules are blended with microcrystalline cellulose. In one example, the granules are blended with microcrystalline cellulose and a lubricant. In one example, the granules are blended with
25 microcrystalline cellulose and magnesium stearate.

 In some embodiments, the final blend is then compressed into tablet cores using a rotary tablet press. From here, in some embodiments, the tablet cores are film-coated to provide the immediate-release film-coated tablets. Accordingly, in some
30 embodiments, the tablet cores are film-coated with film-coating components, including, but not limited to, any one or more of a film-coating agent. In one example, the tablet

cores are film-coated with a film-coating agent. In one example, the tablet cores are film-coated with Opadry FT, Titanium Free (276U180005). The film-coating agent may be provided as a suspension, or otherwise as a solid for dissolution in a suitable solvent.

In one example, the immediate-release tablet formulation is manufactured by:

5 blender mixing of the compound of Formula (I), or pharmaceutically acceptable salt or solvate thereof, lactose, microcrystalline cellulose, and any further intragranular components, and then using roller compaction and milling to provide the granules;

 blending the granules with the microcrystalline cellulose and any further extragranular components to yield the final blend;

10 compression of final blend to produce tablet cores; and

 film-coating the tablet cores with a film-coating solvent and/or film-coating material.

In one example, the immediate-release tablet formulation is manufactured by:

 blender mixing of the compound of Formula (I), or pharmaceutically acceptable
15 salt or solvate thereof, lactose, microcrystalline cellulose, sodium starch glycolate, Croscarmellose sodium, Colloidal silicon dioxide, and magnesium stearate and then granulation using roller compaction and milling to provide the granules;

 blending the granules with the microcrystalline cellulose and magnesium stearate to yield the final blend;

20 compression of final blend to produce tablet cores; and

 film-coating the tablet cores with Opadry FT, Titanium Free (276U180005).

Pre-blending

 In some embodiments, the compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, lactose, and microcrystalline cellulose (MCC) are
25 individually screened into a container. If present, other intragranular components are

similarly individually screened into a container. In some embodiments, the components are transferred to a blender. In some embodiments, the intragranular components are blended at about 10 rpm, about 20 rpm, about 30 rpm, about 40 rpm, or about 50 rpm. In one example, the intragranular components are blended at about 30 rpm. The
5 intragranular components may be blended for any suitable time so as to provide the suitable pre-blend. In some embodiments, the intragranular components are blended for at least about 5 minutes, about 10 minutes, about 11 minutes, about 12 minutes, about 13 minutes, about 14 minutes, about 15 minutes, or about 20 minutes. In one example, the intragranular components are blended for about 13 minutes. In one example, the
10 intragranular components are blended at about 30 rpm for 13 minutes.

In some embodiments, if present, a lubricant (e.g., magnesium stearate) may be individually screened and added to the blender. In some embodiments, the lubricant may then be added to the blender and blended at a suitable speed (e.g., blended at about 10, about 20, about 30, about 40, or about 50 rpm) for a suitable time (at least about 1 minute,
15 about 2 minutes, about 3 minutes, about 4 minutes, or about 5 minutes).

Roller Compaction and Milling

In some embodiments, the pre-blend, as described herein, is transferred to a hopper and roller compacted.

In some embodiments, the roll gap is between about 0.1 mm and about 5 mm,
20 between about 0.5 mm and about 4 mm, between about 1.0 mm and about 3 mm, or between about 1.5 mm and about 2.5 mm. In one example, the roll gap is between about 1.5 mm and about 2.5 mm.

In some embodiments, the roll force is between about 1 kN/cm and about 30 kN/cm, between about 5kN/cm and about 20 kN/cm, or between about 6 kN/cm and
25 about 12 kN/cm. In one example, the roll force is between about 6 kN/cm and about 12 kN/cm.

In some embodiments, the roll speed is between about 0.5 rpm and about 20 rpm, between about 1 rpm and about 10 rpm, between about 1 rpm and about 5 rpm, or

between about 1 rpm and about 3 rpm. In one example, the roll speed is between about 1 rpm and about 3 rpm.

In some embodiments, the mill screen size is between about 0.1 mm and about 5 mm, between about 0.2 mm and about 3 mm, between about 0.3 mm and about 1 mm, or
5 between about 0.5 mm and about 0.8 mm. In one example, the mill screen size is about 0.8 mm.

Final Blending

In some embodiments, the extragranular components are individually screened. If present in the extragranular components, microcrystalline cellulose (MCC) may also
10 be individually screened. The extragranular components may be transferred to a blender. The milled granules may be added to the blender. In some embodiments, the extragranular components and the milled granules are blended at about 10, about 20, about 30, about 40, or about 50 rpm. In one example, the extragranular components and milled granules are blended at about 30 rpm. The extragranular components and milled
15 granules may be blended for any suitable time so as to provide the suitable final blend. In some embodiments, the extragranular components and milled granules are blended for at least about 5 minutes, about 10 minutes, about 11 minutes, about 12 minutes, about 13 minutes, about 14 minutes, about 15 minutes, or about 20 minutes. In one example, the extragranular components and milled granules are blended for about 13 minutes. In one
20 example, the extragranular components and milled granules are blended at about 30 rpm for 13 minutes. If present, any other extragranular components (e.g., magnesium stearate) may then be added to the blender and blended at a suitable speed (e.g., blended at about 10, about 20, about 30, about 40, or about 50 rpm) for a suitable time (at least about 1 minute, about 2 minutes, about 3 minutes, about 4 minutes, or about 5 minutes).

25 Compression

Powder compression behaviour is understood to be governed by the physical and mechanical properties of the material, as well as aspects of the compression process such as pressure (i.e., stress), degree of deformation (i.e., strain), and rate of deformation (i.e., strain rate). Typically, a tablet is formed by the densification of a loosely packed powder

sample confined within a rigid die using two rigid punches that approach from above and below the vertical plane. Various compression methods have been used to characterise the compression properties of pharmaceutical powders/tablets. The compression profile of a tablet is understood to be a function of compactability, compressability, and
5 tabletability.

In some embodiments, the final blend is compressed on a rotary tablet press with round punches to provide the tablet cores. In some embodiments, the diameter of the round punches is between about 3 mm and about 10 mm, between about 3.5 mm and about 7 mm, or between about 4 mm and about 5 mm. In one example, the round punches
10 are 4.76 mm diameter round punches.

In some embodiments, the average immediate-release tablet core weight is between about 45 mg and about 55 mg, between about 46 mg and about 54 mg, between about 47 mg and about 53 mg, between about 48 mg and about 52 mg, or between about 48.5 mg and about 51.5 mg. In one example, the average immediate-release tablet core
15 weight is between about 48.5 mg and about 51.5 mg. In one example, the average immediate-release tablet core weight is 50.0 mg ($\pm 3\%$).

In some embodiments, the individual immediate-release tablet core weight is between about 40 mg and about 60 mg, between about 45 mg and about 55 mg, between about 46 mg and about 54 mg, or between about 46.5 mg and about 53.5 mg. In one
20 example, the individual immediate-release tablet core weight is between about 46.5 mg and about 53.5 mg. In one example, the individual immediate-release tablet core weight is about 50.0 mg ($\pm 7\%$).

In some embodiments, the average immediate-release tablet core thickness is between about 1.5 mm and about 3.5 mm, between about 2 mm and about 3 mm, or
25 between about 2.4 mm and about 2.8 mm. In one example, the average immediate-release tablet core thickness is between about 2.4 mm and about 2.8 mm.

In some embodiments, the bulk density (g/mL) of the immediate-release tablet formulation is assessed. As would be understood by the person skilled in the art, “bulk density” is the ratio of the mass of the powder to the volume occupied by the powder.

The total volume includes particle volume, inter-particle void volume, and internal pore volume. Bulk density may be measured by any conventional means as known in the art. In some embodiments, the bulk density (g/mL) of the immediate-release tablet formulation is between about 0.1 g/mL and about 0.9 g/mL, between about 0.2 g/mL and about 0.8 g/mL, between about 0.3 g/mL and about 0.7 g/mL, or between about 0.4 g/mL and about 0.6 g/mL. In one example, the bulk density (g/mL) of the immediate-release tablet formulation is between about 0.4 g/mL and about 0.6 g/mL.

In some embodiments, the tapped density (g/mL) of the immediate-release tablet formulation is assessed. As would be understood by the person skilled in the art, “tapped density” of a powder is the ratio of the mass of the powder to the volume occupied by the powder, after it has been tapped until the volume does not change (intervals of 100 taps). In one example, the powder is tapped for 100 taps. In one example, the powder is tapped for 200 taps. In one example, the powder is tapped for 300 taps. In one example, the powder is tapped for 400 taps. In one example, the powder is tapped for 500 taps. In one example, the powder is tapped for 600 taps. In one example, the powder is tapped for 700 taps. In one example, the powder is tapped for 800 taps. In one example, the powder is tapped for 900 taps. In one example, the powder is tapped for 1000 taps. In some embodiments, the tapped density (g/mL) of the immediate-release tablet formulation is between about 0.3 g/mL and about 1.0 g/mL, between about 0.4 g/mL and about 0.9 g/mL, between about 0.5 g/mL and about 0.85 g/mL, or between about 0.6 g/mL and about 0.8 g/mL. In one example, the tapped density (g/mL) of the immediate-release tablet formulation is between about 0.6 g/mL and about 0.8 g/mL.

In some embodiments, the Carr index, also referred to as Carr’s index or Carr’s compressibility index, of the immediate-release tablet formulation is assessed. The Carr index is calculated as a function of both the bulk density and the tapped density of the powder, and therefore provides an indication as to the flowability and compressibility of the powder. In a free-flowing powder, the bulk density and tapped density would be similar in value, and therefore the Carr index would be small. On the other hand, in a poor-flowing powder, there would be a greater difference between the bulk density and the tapped density, and therefore the Carr index would be large. In some embodiments,

the immediate-release tablet formulation has a Carr's index (%) of less than about 35, about 30, about 25, about 20, or about 15. In one example, the immediate-release tablet formulation has a Carr's index (%) of less than about 25. In one example, the immediate-release tablet formulation has a Carr's index (%) of less than about 20.

5 In some embodiments, the Hausner ratio of the immediate-release tablet formulation is assessed. The Hausner ratio is calculated as a function of both the bulk density and the tapped density of the powder, and provides an indication as to the flowability and compressibility of the powder. In some embodiments, the immediate-release tablet formulation has a Hausner ratio of less than about 2.5, about 2.25, about
10 2.0, about 1.75, about 1.5, about 1.25, or about 1.0. In one example, the immediate-release tablet formulation has a Hausner ratio of less than about 1.5. In one example, the immediate-release tablet formulation has a Hausner ratio of less than about 1.25.

 In some embodiments, the flowability index of the immediate-release tablet formulation is assessed. In one example, the flowability index of the immediate-release
15 tablet formulation is assessed by using a Flodex tool. The Flodex tool takes into account the numerous parameters that affect powder flowability, such as particle size and shape, "fines", unit surface, actual and bulk density, porosity, settling, and electrostatic charge. In some embodiments, the flowability index of the immediate-release tablet formulation is less than about 25 mm, about 20 mm, about 15 mm, about 10 mm, or about 5 mm,
20 when measured using the Flodex tool. In some embodiments, the flowability index of the immediate-release tablet formulation is between about 5 mm and about 20 mm, or between about 10 mm and about 20 mm, when measured using the Flodex tool. In one example, the flowability index of the immediate-release tablet formulation is between about 10 mm and about 20 mm, when measured using the Flodex tool.

25 The hardness of a tablet, which is often referred to as "breaking force", is understood to be the Force (in Newtons, N), required to cause tablet mechanical failure. In some embodiments, the average immediate-release tablet hardness of the cores is between about 0.1 kp and about 20 kp, between about 0.5 kp and about 15 kp, between about 1 kp and about 10 kp, between about 2 kp and about 7 kp, or between about 2.5 kp
30 and about 6.5 kp. In one example, the average immediate-release tablet hardness is

between about 2.5 kp and about 6.5 kp. In some embodiments, the average immediate-release tablet hardness of the cores is at least about 0.5 kp, about 1.0 kp, about 1.5 kp, about 2.0 kp, about 2.5 kp, about 3.0 kp, about 3.5 kp, about 4.0 kp, about 4.5 kp, about 5.0 kp, about 5.5 kp, about 6.0 kp, or about 6.5 kp. As will be understood by the person skilled in the art, tablet hardness is a measure of the breaking point and structural integrity of the tablet. The units, “kp”, refer to Kilopond, which is a unit of force also called a kilogram of force ($1 \text{ kp} = 1 \text{ kgf} = 9.807 \text{ N} = 1.4 \text{ SCU}$). Hardness may be measured by any suitable technique known in the art, including, but not limited to, the Monsanto tester, the Strong-Cobb tester, the Pfizer tester, the Erweka tester, the Dr. Schleuniger Pharmatron tester, and the Kraemer Elektronik’s tablet testing system. Tablet hardness may also be referred to as crushing strength.

In some embodiments, the immediate-release tablet friability of the cores is not more than about 0.1%, about 0.2%, about 0.3%, about 0.4%, or about 0.5%. In one example, the immediate-release tablet friability of the cores is not more than about 0.5%.

In some embodiments, the immediate-release tablet friability of the cores is less than about 1.0%, less than about 0.9%, less than about 0.8%, less than about 0.7%, less than about 0.6%, less than about 0.5%, less than about 0.4%, less than about 0.3%, less than about 0.2%, or less than about 0.1%. As will be understood by the person skilled in the art, tablet friability is a measure of the tendency of the tablet to break into smaller pieces under duress or contact (e.g., rubbing). In particular, tablet friability is defined as the percentage weight loss of powder from the surface of a tablet due to mechanical action. Typically, tablet friability testing involves weighing the sample of tablet cores, and then placing them into a rotating drum. The weight loss is calculated as a percentage.

In some embodiments, the immediate-release tablet (either formulation core or film-coated tablet) disintegration is not more than about 5 minutes, about 8 minutes, about 10 minutes, about 11 minutes, about 12 minutes, about 13 minutes, about 14 minutes, about 15 minutes, or about 20 minutes. In one example, the immediate-release tablet disintegration is not more than about 15 minutes. As would be understood by the person skilled in the art, “disintegration” refers to the mechanical break-up of a compressed tablet into small granules upon ingestion. It is therefore characterised by the

breakdown of the interparticulate bonds that were formed during the compaction of the tablet.

Film-Coating

Following preparation of the tablet cores, the final immediate-release tablet may
5 be prepared by film-coating of the tablet core. In some embodiments, the film-coating suspension is prepared in purified water in a mixing tank. In some embodiments, in a coating pan, the film-coating suspension is sprayed onto the tablet cores that are subjected to hot air flow. In some embodiments, the film-coating process is continued until the target weight gain of about 3% is achieved. In some embodiments, the film-
10 coated tablets are dried and cooled prior to discharging into a storage container.

Release of Active Ingredient

In some embodiments, the immediate-release tablet formulation provides for advantageous release of the active ingredient (i.e., the compound of Formula I, or pharmaceutically acceptable salt or solvate thereof). In some embodiments, at least about
15 50%, about 60%, about 70%, about 80% or about 90% of the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, is released within about 10 minutes to about 60 minutes (as measured in 900 mL dissolution medium, 0.1 N HCl, using USP type II apparatus at 50 rpm paddle rotation speed). In some embodiments, at least about 50%, about 60%, about 70%, about 80% or about 90% of the compound of Formula I, or a
20 pharmaceutically acceptable salt or solvate thereof, is released within about 10 minutes (as measured in 900 mL dissolution medium, 0.1 N HCl, using USP type II apparatus at 50 rpm paddle rotation speed). In some embodiments, at least about 50%, about 60%, about 70%, about 80% or about 90% of the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, is released within about 15 minutes
25 (as measured in 900 mL dissolution medium, 0.1 N HCl, using USP type II apparatus at 50 rpm paddle rotation speed). In some embodiments, at least about 50%, about 60%, about 70%, about 80% or about 90% of the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, is released within about 20 minutes (as measured in 900 mL dissolution medium, 0.1 N HCl, using USP type II apparatus at

50 rpm paddle rotation speed). In some embodiments, at least about 50%, about 60%, about 70%, about 80% or about 90% of the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, is released within about 30 minutes (as measured in 900 mL dissolution medium, 0.1 N HCl, using USP type II apparatus at 50 rpm paddle rotation speed). In some embodiments, at least about 50%, about 60%, about 70%, about 80% or about 90% of the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, is released within about 60 minutes (as measured in 900 mL dissolution medium, 0.1 N HCl, using USP type II apparatus at 50 rpm paddle rotation speed). In some embodiments, at least about 85% of the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, is released within about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 45 minutes, or about 60 minutes (as measured in 900 mL dissolution medium, 0.1 N HCl, using USP type II apparatus at 50 rpm paddle rotation speed). In one example, at least about 85% of the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, is released within about 60 minutes (as measured in 900 mL dissolution medium, 0.1 N HCl, using USP type II apparatus at 50 rpm paddle rotation speed). In one example, at least about 90% of the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, is released within about 60 minutes (as measured in 900 mL dissolution medium, 0.1 N HCl, using USP type II apparatus at 50 rpm paddle rotation speed). In one example, at least about 95% of the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, is released within about 60 minutes (as measured in 900 mL dissolution medium, 0.1 N HCl, using USP type II apparatus at 50 rpm paddle rotation speed).

In some embodiments, the immediate-release tablet formulation provides for complete release of the active ingredient (i.e., the compound of Formula I, or pharmaceutically acceptable salt or solvate thereof). In some embodiments, complete dissolution of the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, is achieved in less than about 60 minutes, about 45 minutes, about 30 minutes, about 20 minutes, or about 15 minutes. In one example, complete dissolution of the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, is achieved in less than about 60 minutes (when measured in 900 mL of 0.1 N HCl using

USP type II apparatus at 50 rpm). In one example, complete dissolution of the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, is achieved in less than about 30 minutes (when measured in 900 mL of 0.1 N HCl using USP type II apparatus at 50 rpm).

5 Methods and Uses

The present disclosure provides for a method of treating or preventing a neurological disease in a subject. The methods can comprise administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof. The methods can comprise administering to
10 the subject a therapeutically effective amount of an immediate-release tablet formulation, as described herein.

The present disclosure provides an immediate-release tablet formulation for preventing or treating a condition associated with 11 β -HSD1 activity. Accordingly, in one example, there is provided an immediate-release tablet formulation for preventing or
15 treating a disorder that is ameliorated through inhibition of 11 β -HSD1.

Numerous conditions have been associated with 11 β -HSD1 activity, including, but not limited to, metabolic syndromes, cardiovascular disorders, and central nervous system (CNS) disorders. Accordingly, in one example, there is provided the immediate-release tablet formulation, as described herein, for use in the treatment of metabolic
20 syndrome. In one example, there is provided the immediate-release tablet formulation, as described herein, for use in the treatment of a cardiovascular disorder. In one example, there is provided the immediate-release tablet formulation, as described herein, for use in the treatment of a central nervous system (CNS) disorder. In one particular example, there is provided the immediate-release tablet formulation, as described herein, for use
25 in the treatment of a neurological disease. In another particular example, there is provided a method of treating or preventing a neurological disease in a subject, comprising administering to the subject the immediate-release tablet formulation, as described herein. In another example, there is provided the use of the immediate-release tablet

formulation, as described herein, in the manufacture of a medicament for the treatment or prevention of a neurological disease.

Examples of neurological diseases include, but are not limited to, Alzheimer's disease and depression. In one example, the neurological disease is Alzheimer's disease.

5 In one example, the neurological disease is depression.

It will be appreciated that the dosage regimens and compositions as described herein may apply to any of the embodiments or examples of the methods as described herein.

Dosage Regimen

10 As used herein, "therapeutically effective amount" refers to a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof, being administered in an amount sufficient to alleviate or prevent to some extent one or more of the symptoms of the disorder or condition being treated, typically without undue adverse side effects or to achieve a desired pharmacological effect or therapeutic
15 improvement with a reduced side effect profile. The results can be the reduction and/or alleviation of the signs, symptoms, or causes of a disease or condition, or any other desired alteration of a biological system. In some embodiments, the term "therapeutically effective amount" refers to a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof, being administered in an amount sufficient to result in a
20 reduction of symptoms associated with a neurological disease. Therapeutically effective amounts may, for example, be determined by routine experimentation, including but not limited to a dose escalation clinical trial. The phrase "therapeutically effective amount" includes, for example, a prophylactically effective amount. In some embodiments, a prophylactically effective amount is an amount sufficient to prevent a neurological
25 disease. It is understood that "an effective amount" or "a therapeutically effective amount" can vary from subject to subject, due to variation in metabolism of the compound and any of age, weight, general condition of the subject, the condition being treated, the severity of the condition being treated, and the judgment of the prescribing physician. An appropriate an effective amount" or "a therapeutically effective amount"

in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

The amount of a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof, that will be effective in the treatment and/or prevention of a particular disorder or condition disclosed herein will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. Such techniques are known to the person skilled in the art.

The precise dose to be administered to the subject will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each subject's circumstances. For example, suitable dosage ranges for oral administration, are generally from about 0.001 milligram to 1000 milligrams of the compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof per kilogram body weight.

In some embodiments, the compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof, is administered in an amount so as to deliver a total daily dosage (in mg) of at least about 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 100, 150, or 200. In some embodiments, the compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof, is administered in an amount so as to deliver a total daily dosage (in mg) of less than about 200, 150, 100, 75, 60, 50, 45, 40, 35, 30, 25, 20, 15, 10, 5, or 1. The total daily dosage may be provided in a range between at any two of these upper and/or lower amounts. For example, a total daily dosage may be provided in an amount of between about 1 and 100 mg, about 5 and 75 mg, about 10 and 50 mg, about 15 and 45 mg, or about 20 and 40 mg.

Accordingly, in some embodiments, the immediate-release tablet formulation described herein is suitable for an active ingredient (i.e., a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof) load of between about 2 mg and about 20 mg, between about 4 mg and about 15 mg, or between about 5 mg and about 10 mg. In one example, the immediate-release tablet formulation described herein is suitable

for an active ingredient (i.e., a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof) load of between about 5 mg and about 10 mg. In one particular example, the immediate-release tablet formulation described herein is suitable for an active ingredient (i.e., a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof) load of about 5 mg. In one particular example, the immediate-release tablet formulation described herein is suitable for an active ingredient (i.e., a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof) load of about 10 mg.

In some embodiments, the immediate-release tablet formulation described herein is suitable for an active ingredient (i.e., a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof) load in an amount (w/w) of between about 1% and about 60%, between about 2% and about 50%, or between about 4% and about 40%, based on the weight of the core tablet (i.e., prior to tablet coating). In one example, the immediate-release tablet formulation described herein is suitable for an active ingredient (i.e., a compound of Formula I, or pharmaceutically acceptable salt or solvate thereof) load in an amount of between about 4% and about 40%.

In some embodiments, a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof, is administered to the subject at a predetermined frequency. In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof, is administered to the subject according to a dosage regimen in which a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof is administered once daily, twice daily, three times daily, or four times daily. In some embodiments, the a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof is administered to the subject according to a dosage regimen in which a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof is administered once daily. In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof is administered to the subject according to a dosage regimen in which a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof is administered twice daily. In some embodiments, a compound of Formula I, or a

pharmaceutically acceptable salt, solvate or prodrug thereof is administered to the subject according to a dosage regimen in which a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof is administered three times daily. In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof is administered to the subject according to a dosage regimen in which a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof is administered four times daily. In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof is administered to the subject according to a dosage regimen in which a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof is administered multiple times daily. In some examples, a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof is administered as a once daily dose of between about 10 mg and 30 mg, for example at about 20 mg. In other examples, a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof is administered as a twice daily dose of between about 5 mg and 20 mg per dose, for example at about 10 mg per dose. In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof is administered as a three-times daily dose of between about 5 mg and 15 mg per dose, for example at about 10 mg per dose.

In some embodiments, a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof, is administered to the subject at a predetermined frequency and/or duration. For example, administration according to any embodiments (e.g. frequency) as described herein may be for a duration of about, or at least about, 1 day, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 12 months, 2 years, or 5 years. Administration of the therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof, may be ongoing so long as a therapeutic effect is received by the subject.

As used herein, the term "administer" and "administering" are used to mean introducing the compound of Formula I, or a pharmaceutically acceptable salt, solvate or

prodrug thereof, into a subject. When administration is for the purpose of treatment, the compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof, is provided at, or after the onset of, a symptom of a neurological disease. The therapeutic administration of this substance serves to attenuate any symptom, or prevent
5 additional symptoms from arising. When administration is for the purposes of preventing or reducing the likelihood of developing a neurological disease, the compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof, is provided in advance of any visible or detectable symptom. The prophylactic administration of the compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug
10 thereof, serves to attenuate subsequently arising symptoms or prevent or reduce the likelihood of the symptoms from arising altogether.

A compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof, may be administered by any suitable route. Examples include, but are not limited to, oral, topical, transdermal, intranasal, vaginal, rectal, intraarterial,
15 intramuscular, intraosseous, intraperitoneal, epidural and intrathecal. In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof, is administered orally. In one example, the immediate-release tablet formulation is administered orally.

A compound of Formula I, or a pharmaceutically acceptable salt, solvate or
20 prodrug thereof, may be administered to the subject with respect to the subject's fasted state, as would be understood by the person skilled in the art. For example, the subject may be administered a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof before, with, or after a meal. In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof
25 is administered to the subject before a meal (i.e., the subject being in a fasted state). In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof is administered to the subject with a meal. In some embodiments, a compound of Formula I, or a pharmaceutically acceptable salt, solvate or prodrug thereof is administered at a certain interval (i.e., 30 mins, 1 hour, 2 hours, 3
30 hours, etc.) following a meal.

Examples

Example 1: Development of Active Ingredient (Xanamem)

To support clinical studies, a tablet formulation was developed. The objective was to develop an immediate-release tablet formulation that is suitable for a drug load
5 between 2 mg and 20 mg.

As both unmicronized and micronized drug substance (Xanamem) batches exhibited poor flow properties (failed to pass through a 34 mm orifice), a dry granulation process was considered for the formulation development. Various excipients and compositions were evaluated in prototype formulations. Excipient selection was based
10 on the following considerations to meet the quality attributes of Xanamem drug product:

- acceptable flow properties of final blend;
- acceptable compressibility;
- suitable tablet hardness to meet friability requirement;
- consistent tablet weight;
- 15 • similar *in vitro* dissolution rate for the low and high tablet strengths to achieve not less than 85% drug release in 30 - 45 minutes; and
- the formulations should be sufficiently robust to accommodate changes in drug load according to clinical requirements.

The core tablet weight was targeted at 50 mg for ease of swallowing in elderly
20 patients. The formulations were designed to have the same tablet weight and different drug load ranging from 4% to 40%.

The granular material was prepared by blender mixing intragranular components using a 4 Qt V-shell blender and then granulated using a Vector roller compactor. The granules were blended with extragranular components to yield the final blend. The final
25 blend was then compressed into tablet cores using a Globe Pharma mini-press with 4.76 mm round punches to obtain a target tablet core weight of 50 mg. The batch sizes were between 100 g and 500 g. Selected tablet core batches were film coated using Opadry TF 276U180005, white. The prototype formulations are presented in the below table.

Table. Composition of Prototype Tablet Formulations.

Tablet strength	2 mg	10 mg	20 mg	2 mg	20 mg	20 mg	20 mg	10 mg	
Batch no.	22852-3	22852-4	22852-5 ^a	22852-6	22852-7	22852-8	22852-9	22852-10	
Component	Formulation percentage (% w/w)								Function
Intragranular components									
Xanamem drug substance	4.0	20.0	40.0	4.0	40.0	40.0	40.0	20.0	Drug substance
Lactose monohydrate (Fast Flo 316)						30.5		42.5	Diluent
Microcrystalline cellulose (Avicel PH102)	66.0	50.0	30.0	66.5	30.5			22.0	Diluent
Mannitol (Pearlitol 100 SD)							30.5		Diluent
Sodium starch glycolate (Explotab), Type A	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	Disintegrant
Croscarmellose sodium (Ac-Di-Sol SD-711)	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	Disintegrant
Colloidal silicon dioxide (Cab-O-Sil MSP)	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	Glidant
Magnesium stearate (Hyqual 2257)	1.0	1.0	1.0	0.5	0.5	0.5	0.5	0.5	Lubricant
Extragranular components									
Lactose monohydrate (Fast Flo 316)						20.5			Diluent
Microcrystalline cellulose (Avicel PH102)	20.0	20.0	20.0	20.5	20.5			6.5	Diluent
Mannitol (Pearlitol 100 SD)							20.5		Diluent
Sodium starch glycolate (Explotab), Type A	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0	Disintegrant
Magnesium stearate (Hyqual 2257)	1.0	1.0	1.0	2.5	2.5	2.5	2.5	2.5	Lubricant
Total core tablet weight (mg)	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	
Film-coating									
Opadry TF, Titanium Free 276U180005, White ^c	-	-	-	3.0 ^a	3.0 ^a	-	-	3.0 ^a	Film-coating material

^a Additional 2% magnesium stearate was added to the final blend to overcome sticking issues during compression

^b Represents 3% weight gain on the tablet core weight
^c Coating solution is prepared at 12% (w/w) total solids in purified water

The results of the physical characterization studies are provided in the below table.

Table. Physical Characterisation of Prototype Tablet Formulations.

Tablet strength		2 mg	10 mg	20 mg	2 mg	20 mg	20 mg	20 mg	10 mg
Batch no.		22852-3	22852-4	22852-5	22852-6	22852-7	22852-8	22852-9	22852-10
Final blend									
Bulk density (g/mL)		0.426	0.481	0.517	NT	0.577	0.714	0.596	0.556
Tapped density (g/mL)		0.582	0.662	0.726		0.750	0.857	0.805	0.811
Carr's index (%)		26.8	27.3	28.8		23.1	16.7	26.0	31.4
Hausner ratio		1.37	1.38	1.40		1.30	1.20	1.35	1.46
Flodex (orifice, mm)		9	10	18		16	7	18	16
Core tablet									
Tablet weight (mg)		48.6-50.9	48.6-50.9	48.2-51.2	47.4-51.1	48.2-51.9	48.7-53.2	43.3-55.8	46.8-52.6
Thickness (mm) (mean)		2.67	2.70-2.71	2.68-2.71	2.65-2.69	2.64-2.70	2.71-2.78	2.49-2.61	2.50-2.64
Hardness (kp) (mean)		3.5-3.6	4.0-4.1	3.8-4.9	2.6-2.9	3.3-3.9	1.6-2.3	2.0-2.2	3.3-4.3
Friability (%)	at target hardness	0.1	0.2	0.1	0.1	0.1	0.2	0.6	0.1
	at low hardness	0.3 (1.8 kp)	0.2 (1.8 kp)	0.1 (1.6 kp)	0.1 (2.3 kp)	0.2 (1.7 kp)	0.4 (1.1 kp)	NT	0.1 (2.8 kp)
	at high hardness	0.1 (5.2 kp)	0.2 (7.4 kp)	NT (7.8 kp)	NT (5.7 kp)	NT (5.7 kp)	0.2 (2.8 kp)	NT	0.0 (4.9 kp)
Disintegration (mm:ss)		00:15	00:18	00:14	00:30	00:07	00:33	00:25	01:53

NT: not tested

5

Formulations 22852-3 to 22852-5 have the same composition, but different drug (Xanamem) load. There was no processing issue for formulation 22852-3 with 4% drug load. However, both formulations 22852-4 and 22852-5 had sticking issues to the lower punch. Additional lubricant was required.

10

To overcome sticking issues, the formulation was adjusted to increase magnesium stearate to 2.5% in extragranular formulation and decrease it to 0.5% in

intragranular formulation. Furthermore, sodium starch glycolate was decreased to 1.0% in both intragranular and extragranular formulation.

Both formulations 22852-6 (2 mg strength) and 22852-7 (20 mg strength) were processed well without issues. Final blend uniformity (BU) and content uniformity (CU) were tested using the HPLC assay method and the results are provided in the below table. Both BU and CU results are acceptable for the prototype formulations.

Table. Blend and Content Uniformity of Prototype Tablet Formulations.

Tablet strength	2 mg	20 mg	20 mg	10 mg
Batch no.	22852-6	22852-7	22852-8	22852-10
Content uniformity (n=10)				
Average % label claim	96.7	94.1	104.2	95.0
Min	89.4	88.5	95.5	91.5
Max	101.2	97.8	124.5	98.1
%RSD	3.8	3.4	8.1	2.3
Acceptance value (AV)	10.6	12.1	22.9	8.8
Blend uniformity (n=5 × 2)				
Average % assay	105.2	97.5	97.0	NT
%RSD	0.6	0.9	5.6	NT

NT: not tested

Dissolution test was performed on selected prototype formulations in 0.1 N HCl with USP type II apparatus. In 500 mL dissolution medium at 50 rpm paddle rotation speed, complete drug release was achieved for the 2 mg tablet strength, while only approximately 60% drug release was achieved in 60 min for the 10 mg and 20 mg tablet strengths as shown in Figure 1. After increasing the rotation speed to 200 rpm for 30 min, the drug release reached over 90%.

Additional dissolution tests were performed at 75 rpm paddle rotation speed and in 900 mL dissolution medium for the 20 mg tablet strength. As shown in Figure 2, complete drug release was only reached in 900 mL dissolution medium at 75 rpm, whereas dissolution was incomplete in 60 min with either 500 mL at 75 rpm or 900 mL at 50 rpm.

Since the tablets with microcrystalline cellulose (MCC) as diluent have slower dissolution rate for the 10 mg and 20 mg tablet strengths compared to the 2 mg tablet strength, soluble excipients including lactose and mannitol were evaluated in the tablet formulation.

5 Formulation 22852-8 with lactose monohydrate had a good flow property, however the individual tablet weight control was poor and the formulation had poor uniformity compared to the formulation 22852-7 with MCC. In addition, the acceptable tablet hardness range is narrow (1.1 – 2.8 kp) compared to formulation 22852-7 (1.7 – 5.7 kp). As expected, complete dissolution was achieved in 30 min in 900 mL of 0.1 N
10 HCl using USP II at 50 rpm, as shown in Figure 3.

Formulation 22852-9 with mannitol was not compressible and could not achieve the tablet hardness higher than 3 kp. It had poor tablet weight control and high friability. Thus, this formulation was not considered.

Based on the physical characterization data and slow dissolution with the MCC
15 formulation, it was recommended to evaluate the formulation with combination of lactose and MCC (60:40) as diluent. In addition, the intra-granulation part was increased from 76% to 90% of the final blend to reduce the potential for segregation.

As the target clinical doses are 5 mg and 10 mg, formulation 22852-10 was prepared with the 10 mg tablet strength. The formulation composition and physical
20 characterization results are provided in the above tables. The final blend showed acceptable flow property and the process went well without any issues. The tablets had acceptable weight control, hardness, friability, and content uniformity. The dissolution profile is presented in Figure 3. The dissolution was comparable to the formulation 22852-8 with lactose and reached completion in 30 min, which was faster than the
25 formulation 22852-7 with MCC alone.

Minor modification was made during the manufacturing process evaluation using GMP equipment by putting all sodium starch glycolate in intra-granulation to further improve the flow properties. The selected clinical formulations for 5 mg and 10 mg tablets are provided in the below Table.

Table. Composition of Xanamem Tablets – 5 mg and 10 mg Dosage Strengths

Component	Weight per Unit (mg)		Formulation Percentage (%w/w)		Function
	5 mg	10 mg	5 mg	10 mg	
Intragranular components					
Xanamem drug substance	5.00	10.00	2.63	20.0	Drug substance
Lactose monohydrate (Fast Flo 316)	24.25	21.25	48.5	42.5	Diluent
Microcrystalline cellulose (Avicel PH102) ^a	13.00	11.00	26.0	22.0	Diluent
Sodium starch glycolate (Explotab), Type A	1.00	1.00	2.0	2.0	Disintegrant
Croscarmellose sodium (Ac-Di-Sol SD-711)	1.00	1.00	2.0	2.0	Disintegrant
Colloidal silicon dioxide (Cab-O-Sil M5P)	1.00	1.00	2.0	2.0	Glidant
Magnesium stearate (Hyqual 2257)	0.25	0.25	0.5	0.5	Lubricant
Extragranular components					
Microcrystalline cellulose (Avicel PH102)	3.25	3.25	6.5	6.5	Diluent
Magnesium stearate (Hyqual 2257)	1.25	1.25	2.5	2.5	Lubricant
Total core tablet weight	50.0	50.0	100.0	100.0	
Film-coating					
Purified water ^b Error! Reference source not found.	-	-	q.s.	q.s.	Film-coating solvent
Opadry TF, Titanium Free 276U180005, White ^d	1.5	1.5	3.0 ^c	3.0 ^c	Film-coating material
Total weight of film-coated tablet	51.5				
^a The microcrystalline cellulose amount is adjusted to compensate for UE2343 drug substance weight based on assay					
^b Water is removed during processing					
^c Represents 3% weight gain on the tablet core weight					
^d Coating solution is prepared at 12% (w/w) total solids					

Development of In Vitro Dissolution Method

The purpose of dissolution method development was to select a suitable *in vitro* dissolution method for Xanamem drug product to ensure batch-to-batch consistency.

Considering the nature of the immediate release dosage formulation, BCS class 1 compound, and physiological relevance, the common dissolution medium of 0.1 N HCl and USP apparatus II (paddles) were selected.

As described herein, the solubility of Xanamem is pH-dependent. It has a solubility of over 2 mg/mL at pH 1 and pKa of 1.5. Thus, the sink condition is easily achieved in 0.1 N HCl dissolution medium.

In early development, the dissolution method with 900 mL of 0.1 N HCl dissolution medium and paddle rotation speed of 100 rpm was used for dissolution test of the capsule formulations (capsule placed in a sinker). The goal was to achieve over 80% drug release in 45 minutes.

5 During the tablet formulation development, 500 mL of 0.1 N HCl dissolution medium and paddle rotation speed of 50 rpm were initially evaluated. Complete drug release was not achieved for 10 mg and 20 mg tablet strengths with microcrystalline cellulose as diluent in the formulation.

10 Subsequently, both 900 mL dissolution medium and 75 rpm rotation speed were evaluated and the results for the 20 mg tablet strength are presented in Figure 2.

As shown in Figure 2, the rank order of dissolution conditions for % drug dissolved of 20 mg tablet with microcrystalline cellulose formulation is: 900 mL with 75 rpm > 500 mL with 75 rpm > 900 mL with 50 rpm > 500 mL with 50 rpm. Only dissolution condition using 900 mL and paddle speed of 75 rpm reached complete
15 dissolution in 30 min and 45 min.

The sink condition was confirmed by dissolving five 20 mg tablets in 500 mL of 0.1 N HCl at 37°C. The resulting concentration was 0.19 mg/mL, which is much higher than the required dissolution sink condition ($> 0.12 \text{ mg/mL}$ calculated using $20 \text{ mg} \times 3 / 500 \text{ mL}$ or $> 0.067 \text{ mg/mL}$ calculated using $20 \text{ mg} \times 3 / 900 \text{ mL}$).

20 To maintain adequate discriminatory power, the dissolution condition with 900 mL of 0.1 N HCl and USP apparatus II at 50 rpm was selected for dissolution test of tablet formulations. The dissolution profiles presented in Figure 3 demonstrated discriminatory power of the method towards formulation changes using different diluents in the tablet formulation.

25 This dissolution method has been validated as a quality control method for release testing and stability studies of Xanamem tablets. The method is acceptable for its intended use.

Example 2: Development of Tablet Components

Properties of Xanamem

Xanamem is a white to off-white crystalline powder. Only one crystalline form has been identified. The drug substance consists of angular plate-like particles with a broad size distribution (range from <10 µm to 250 µm). For tablet formulation, the drug substance was micronized to achieve a Dv90 below 30 µm. Figure 5 shows the particle size distribution of the micronized drug substance batch CJ1465 determined by laser diffraction using heptane with 0.1% Span 80 as dispersant.

The optical microscope images are presented in Figure 6 for unmicronized (with 100X magnification) and micronized (with 200X magnification) drug substance. Both materials are birefringent under cross-polarized light, suggesting high crystallinity.

The solubility of Xanamem is pH dependent. The drug substance has higher solubility in acidic condition (> 2 mg/mL at pH 1) and lower solubility in neutral condition (0.1 mg/mL). Based on the pH solubility data of Xanamem drug substance, the 10 mg dose strength can completely dissolve in 250 mL of aqueous media at intestinal pH. Therefore, the drug substance is considered as having high solubility according to the Biopharmaceutics Classification System (BCS).

The permeability of Xanamem was determined using Caco-2 cell monolayers. The average apparent permeability (Papp A-B) is 20.9×10^{-6} cm/sec at 1 µM in Caco-2 cells with an efflux ratio of 1.3, suggesting that Xanamem is a highly permeable compound.

Based on its high solubility and high permeability, Xanamem is classified as a class 1 compound according to the BCS, published by CDER from Food and Drug Administration in December 2017 (Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System).

Excipients

The conventional approach was used in the solid dosage formulation development. The excipients were selected considering the following requirements:

- compatibility with the drug substance and sufficient stability of the formulation;
- functionality and technical performance in the manufacturing process; and
- 5 • disintegration time and dissolution rate of the drug product.

The drug substance compatibility with selected excipients was evaluated to determine compatible excipients to be used in the drug product formulations to ensure that the quality of the finished product meets the desired expectation. The drug substance (approximately 10 mg) and appropriate amount of each excipient were mixed well in a 4 mL amber glass vial with PTFE lined screw cap and then stored at 25°C and 50°C. Three sample formulations were also prepared using a combination of excipients and 1% drug substance. The samples were pulled after 2 and 4 weeks and analyzed by HPLC for assay and impurities. The assay results are provided in the below Table, and the chromatograms with impurity profiles are shown in Figure 7.

15 Table. Compatibility of Xanamem with Excipients.

Sample No.	Excipient	Function	Drug Substance /Excipient Ratio (w/w)	Duplicate Assay Results (% w/w)				
				Initial	2 weeks		4 weeks	
					25°C	50°C	25°C	50°C
A	Pregelatinized starch (Starcap 1500)	Diluent	1:99	90.5 103.6	98.7 98.2	100.8 96.0	97.4 106.9	98.2 96.6
B	Lactose monohydrate (Granulac 230)	Diluent	1:99	96.7 97.0	99.8 100.9	99.7 99.4	103.4 99.5	97.6 100.0
C	Silicified microcrystalline cellulose (Prosolv HD90)	Diluent	1:99	100.2 100.2	102.8 99.8	98.6 99.2	100.8 101.0	100.1 101.4
D	Colloidal silicon dioxide (Aerosil 200)	Glidant	1:10	100.6 100.1	99.3 101.9	98.7 100.4	99.1 100.5	96.6 100.4
E	Talc (Luzenac Pharma M)	Glidant	1:10	99.1 101.3	100.0 101.7	100.9 101.2	99.9 99.2	102.1 103.7
F	Croscarmellose sodium (Ac-di-sol)	Disintegrant	1:8	101.2 101.1	101.0 98.2	102.0 98.6	101.5 100.6	99.1 99.5
G	Sodium starch glycolate (Explotab)	Disintegrant	1:8	102.0 99.5	99.8 99.5	95.7 101.2	102.4 105.5	98.5 84.0
H	Magnesium stearate	Lubricant	1:2	97.4 94.7	99.8 99.4	98.6 98.5	98.8 98.6	99.5 96.6
I	Hydrogenated vegetable oil (Lubritab)	Lubricant	1:2	101.3 99.6	103.4 103.5	96.5 74.7	99.2 93.1	99.1 101.1
J	Size 0 hard gelatin capsules	Capsule shell	1	95.4 99.4	101.6 98.3	100.2 97.4	99.1 97.7	98.5 96.6
K	Size 0 HPMC capsules	Capsule shell	1	90.1 103.1	108.1 101.1	98.6 102.2	105.1 105.0	102.9 90.3

Sample No.	Excipient	Function	Drug Substance /Excipient Ratio (w/w)	Duplicate Assay Results (% w/w)				
				Initial	2 weeks		4 weeks	
					25°C	50°C	25°C	50°C
L	Polyvinylpyrrolidone (PVP K30) ^a	Binder	1:5	99.9 97.9	104.5 101.4	93.9 99.2	100.3 95.5	106.8 96.4
M	HPMC E5 ^b	Binder	1:5	109.0 93.4	102.0 91.4	97.6 98.5	98.1 99.4	95.9 93.7
N	Excipient mixture ^c		See note c	99.2 100.7	107.9 111.9	99.6 101.2	101.6 101.8	102.7 100.7
a Also contains Starcap 1500 (84), talc (5), Ac-Di-Sol (4), and magnesium stearate (1) in gelatin capsules								
b Also contains Granulac 230 (84), Aerosil (5), Explotab (4), and Lubritab (1) in gelatin capsules								
c Mixture contains UE2343 (1), Prosolv HD90 (94), Explotab (4), and Lubritab (1) in HPMC capsules								

The excipient compatibility studies show no major interactions between Xanamem drug substance and the excipients tested. There is no trend of degradation in any of the binary mixtures or prototype formulations. Variabilities observed in some duplicate assay results are likely due to difficulties in weighing the low amount of drug substance. The overlaid chromatograms show no increase in impurities for any combination of the drug substance and excipients.

Example 3: Development of Manufacturing Process

The dry granulation process by roller compaction was selected for the development of Xanamem tablets.

The Xanamem drug substance has poor flowability. The bulk density is around 0.3 g/mL for unmiconized drug substance and 0.2 g/mL for micronized drug substance. Due to a broad particle size distribution of Xanamem drug substance (range from <10 μm to 250 μm by microscopy), it was decided to reduce the particle size by jet milling to ensure the content uniformity of the tablet formulation with a low drug load. Direct compression process was not considered due to poor flow properties of the drug substance and low dose strength. Therefore, dry granulation by roller compaction was selected as an appropriate granulation method to increase drug substance density and flowability, as well as improve the content uniformity of the tablets. Furthermore, roller compaction process is a continuous process that lends itself to scale-up.

For manufacture of clinical batches, Gerteis Minipactor is used for roller compaction. As the flow property of the final blend is important for tablet weight control,

a roller compaction study with three different roll forces was conducted on 500 g batch sizes for 10 mg tablet strength. The final blends were characterized and compressed to tablet cores using a Korsch XL 100 tablet press with a round 4.76 mm tooling.

The processing parameters and physical characterization data are provided in the below Table. The particle size distribution (PSD) of the final blends is presented in Figure 8.

Table. Manufacturing Process Parameters and Physical Characteristics of Development Batches.

Batch no.	22852-15-T1	22852-15-T2	22852-15-T3
Roller compaction			
Gap width (mm)	2	2	2
Roll force (kN/cm)	2	5	8
Roll speed (rpm)	2	2	2
Tamp/feed ratio (%)	150	150	150
Mill screen size (mm)	0.8	0.8	0.8
Ribbon thickness (mm)	1.2-2.1	1.2-1.4	1.0-1.4
Envelope density (g/mL)	0.8-0.9	1.1-1.4	1.1
Final blend			
Bulk density (g/mL)	0.563	0.625	0.59
Tapped density (g/mL)	0.765	0.811	0.772
Carr's index (%)	26.4	22.9	23.6
Hausner ratio	1.36	1.30	1.31
Flodex (orifice, mm)	26	26	12
Tablet compression			
Feeder speed (rpm)	NA ^a	10	10
Press speed (rpm)	20	30	20
Pre-compression force (kN)	0	0.1	0.8
Main compression force (kN)	12	12.6	11.6
Tablet weight (mg)	46.8-53.0	47.2-53.3	48.1-53.1
Thickness (mm) (mean)	at target hardness	2.59-2.63	2.58-2.63
	at low hardness	2.84 (1.5 kp)	2.78 (1.4 kp)
	at high hardness	2.61 (5.0 kp)	2.58 (4.1 kp)
Hardness (kp) (mean)	3.3-5.1	3.6-4.0	2.6-2.7
Friability (%)	0	0.2	0.1
Disintegration (mm:ss)	00:20	00:21	00:10

a. NA: not applicable. Gravity feeder was used

At higher roll force (5 and 8 kN/cm), the envelope density is higher compared to that at lower roll force (2 kN/cm). The flowability is significantly better at roll force of 8 kN/cm, which is consistent with more larger particles at roll force of 8 kN/cm compared to those at 2 and 5 kN/cm roll forces.

- 5 The tablets produced from these final blends have acceptable tablet weight, hardness, friability, and disintegration time. Therefore, 8 kN/cm roll force was selected for manufacture of clinical batches.

The processing parameters, equipment, and physical characterization data of the manufacturing process for clinical batches are provided in the below Table.

- 10 Table. Manufacturing Process Parameters, Equipment, and Physical Characteristics of Clinical Batches.

Bulk batch no.	M12164	M12165
Strength (mg)	5	10
Batch size (kg)	3.75	3.75
Pre-blend	16 Qt V-Shell Blender	16 Qt V-Shell Blender
Blending speed (rpm)	30	30
Duration (min)	13	13
Duration after adding MgSt (min)	4	4
Roller compaction	Gerteis Minipactor	Gerteis Minipactor
Gap width (mm)	2	2
Roll force (kN/cm)	8	8
Roll speed (rpm)	2	2
Tamp/feed ratio (%)	150	150
Mill screen size (mm)	0.8	0.8
Ribbon thickness (mm)	1.2-2.0	1.2-2.5
Envelope density (g/mL)	1.0-1.1	1.1-1.2
Final blend	16 Qt V-Shell Blender	16 Qt V-Shell Blender
Bulk density (g/mL)	0.608	0.592
Tapped density (g/mL)	0.820	0.797
Carr's index (%)	25.9	25.7
Hausner ratio	1.35	1.35
Flodex (orifice, mm)	18	14
Tablet compression	Korsch XL 100	Korsch XL 100
Feeder type	Gravity	Gravity
Press speed (rpm)	20	20

Pre-compression force (kN)	0.9-1.1	1.0-1.2
Main compression force (kN)	11.3-12.2	11.1-12.0
Tablet weight (mg)	48.2-52.4	48.3-52.2
Thickness (mm) (mean)	2.54-2.61	2.55-2.62
Hardness (kp) (mean)	3.70-4.71	3.89-5.09
Friability (%)	0.1	0.1
Disintegration (mm:ss)	02:40-02:44	02:55-02:59
Film-coating	O'Hara Labcoat MX	O'Hara Labcoat MX
Coating pan (in)	15	15
Spray rate (g/min)	9.5	9.1-10.7
Atomizing air pressure (psi)	15.0-15.1	14.1-15.2
Gun to bed distance (in)	3	5
Pan speed (rpm)	12	8
Inlet air temperature (°C)	51.6-57.0	51.6-60.0
Exhaust air temperature (°C)	42.0-47.5	42.1-45.4

The particle size distribution (PSD) of the final blends is presented in Figure 9. The same equipment train and the same or similar process parameters were applied to 5 mg and 10 mg tablet strengths. The physical characterizations and particle size distributions are comparable for both batches with acceptable tablet weigh, hardness, friability, and uniformity. The disintegration time is slightly longer for these clinical batches compared to the development batches, but is still considered fast. The dissolution results are comparable for the 5 mg and 10 mg tablet strengths as presented in Figure 10.

Acceptable blend uniformity with an RSD of 1.4% was obtained from samples taken at five locations of the final blend for the 5 mg tablet strength as shown in the below Table.

Table. Blend Uniformity for Xanamem 5 mg Tablets.

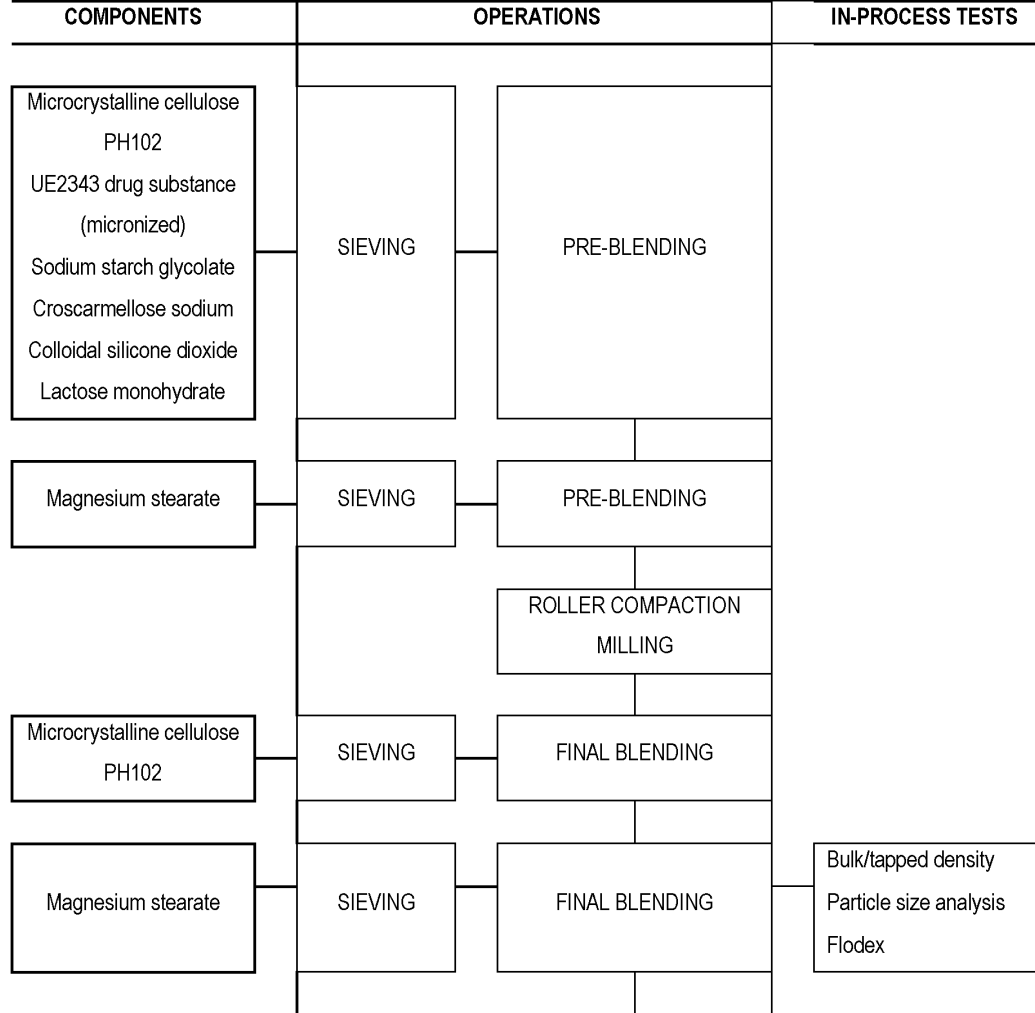
Sample location	% Label claim
Top left front	101.4
Top left back	98.0
Top right front	100.7
Top right back	99.2
Bottom	98.8
Average	99.6
%RSD	1.4

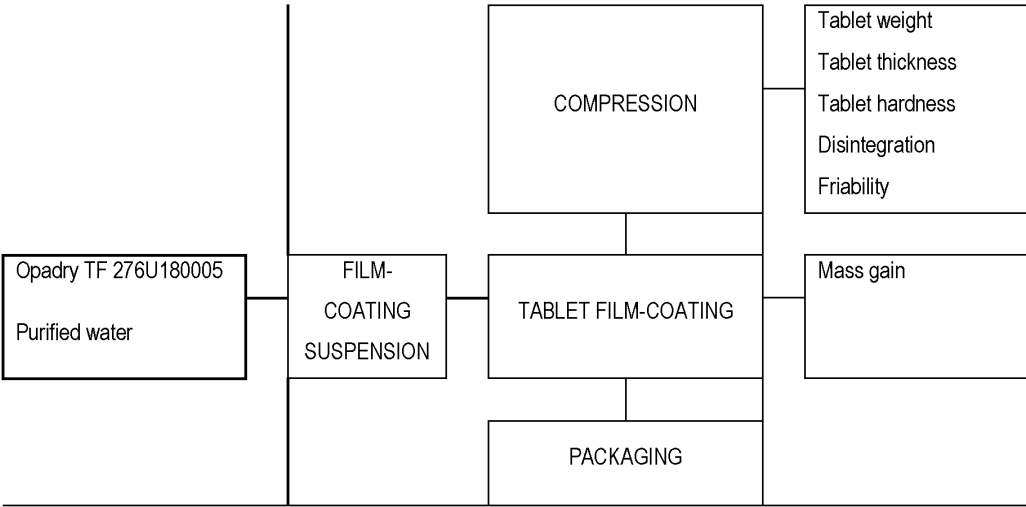
The manufacturing process has been developed for the manufacture of 5 mg and 10 mg tablets. The clinical tablet batches produced meet the predefined acceptance criteria.

5 **Example 4: Tablet Manufacturing**

The Xanamem tablets are manufactured using a dry granulation process, as depicted in the below Figure.

Figure. Flow Diagram for the Manufacturing Process of Xanamem tablets.





A pre-blend of intragranular components is prepared by blender mixing and then granulated using roller compaction and milling to produce granules. The granules are blended with extragranular components to yield the final blend. The final blend is then compressed into tablet cores using a rotary tablet press. The Xanamem tablet cores are film coated using a white ready-to-use coating material to obtain the final tablets.

Pre-blending

Microcrystalline cellulose, Xanamem drug substance, sodium starch glycolate, croscarmellose sodium, colloidal silicon dioxide, and lactose monohydrate are individually screened into a container. The materials are transferred to a blender and blended at 30 rpm for about 13 min or equivalent. Then magnesium stearate is screened and added to the blender and blended for about additional 4 min or equivalent.

Roller Compaction and Milling

The pre-blend is transferred to a hopper and roller compacted using the following recommended settings:

Table. Roller compaction settings.

Process parameters	Recommended range
Roll gap	1.5 – 2.5 mm
Roll force	6 – 12 kN/cm
Roll speed	1 – 3 rpm
Mill screen size	0.8 mm

Final Blending

Extragranular components microcrystalline cellulose and magnesium stearate are screened separately. The microcrystalline cellulose and the compacted milled granules
5 are added to the blender and blended at 30 rpm for about 13 min or equivalent. Then magnesium stearate is added to the blender and blended for about additional 4 min or equivalent.

Compression

The final blend is compressed on a rotary tablet press with 4.76 mm round
10 punches. The compression parameters can be adjusted during the run to achieve the desired tablet weight and hardness. In-process tests are performed as outlined in the below Table.

Table. Core Tablet, in Process Testing.

Parameters	Acceptance criteria
Average tablet weight	50.0 mg (± 3%) 48.5 – 51.5 mg
Individual tablet weight	50.0 mg (± 7%) 46.5 – 53.5 mg
Average thickness	2.4 – 2.8 mm
Average hardness	Recommended 2.5 – 6.5 kp
Friability	NMT 0.5%
Disintegration	NMT 15 min

Film-coating

The film-coating suspension is prepared in purified water in a mixing tank. In a coating pan, the film-coating suspension is sprayed onto the cores subjected to a hot air flow. In-process samples are taken periodically to measure and record the weight gain.

5 The coating process is continued until the target weight gain of 3% is achieved. The film-coated tablets are dried and cooled before discharging into storage container.

The finished product is bulk packaged into HDPE containers that are lined with 2 polyethylene bags.

Packaging

10 The Xanamem tablets are packaged in the primary packaging intended for clinical use.

Example 5: Description and Composition of Immediate-Release Tablet Formulation

Xanamem tablets are supplied as 5 mg and 10 mg immediate release film-coated tablets for oral administration. Both 5 mg and 10 mg tablet strengths are white, round tablets with the same tablet size and weight. The composition of the Xanamem tablets is provided in the below Table, along with the function of each component.

15

Table. Composition of Xanamem Immediate-Release Tablets – 5 mg and 10 mg.

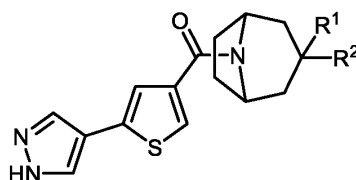
Component	Weight per Unit (mg)		Formulation Percentage (% w/w)		Function	Reference to Standards
	5 mg	10 mg	5 mg	10 mg		
Intragranular components						
UE2343 drug substance	5.00	10.00	10.00	20.0	Drug substance	In-house monograph
Lactose monohydrate (Fast Flo 316)	24.25	21.25	48.5	42.5	Diluent	NF, Ph.Eur., JP
Microcrystalline cellulose (Avicel PH102) ^a	13.00	11.00	26.0	22.0	Diluent	NF, Ph.Eur., JP
Sodium starch glycolate (Explotab), Type A	1.00	1.00	2.0	2.0	Disintegrant	NF, Ph.Eur.
Croscarmellose sodium (Ac-Di-Sol SD-711)	1.00	1.00	2.0	2.0	Disintegrant	NF, Ph.Eur., JP
Colloidal silicon dioxide (Cab-O-Sil M5P)	1.00	1.00	2.0	2.0	Glidant	NF, Ph.Eur., JP

Magnesium stearate (Hyqual 2257)	0.25	0.25	0.5	0.5	Lubricant	NF, Ph.Eur., JP
Extragranular components						
Microcrystalline cellulose (Avicel PH102)	3.25	3.25	6.5	6.5	Diluent	NF, Ph.Eur., JP
Magnesium stearate (Hyqual 2257)	1.25	1.25	2.5	2.5	Lubricant	NF, Ph.Eur., JP
Total core tablet weight	50.0	50.0	100.0	100.0		
Film-coating						
Purified water ^b Error! Reference source not found.	-	-	q.s.	q.s.	Film-coating solvent	USP
Opadry TF, Titanium Free 276U180005, White ^d	1.5	1.5	3.0 ^e	3.0 ^e	Film-coating material	
Total weight of film-coated tablet	51.5					
^d The microcrystalline cellulose amount is adjusted to compensate for UE2343 drug substance weight based on assay ^e Water is removed during processing ^f Represents 3% weight gain on the tablet core weight ^g Coating solution is prepared at 12% (w/w) total solids. Opadry TF 276U180005 contains 35% w/w calcium carbonate, 30% w/w isomalt, 19% w/w HPMC 2910 (6 mPas), 13% w/w HPMC 2910 (15 mPas), and 3% w/w medium chain triglycerides						

The tablets are packaged into 40 cc white HDPE bottles with CRC induction-sealed caps (33 mm finish screw cap).

CLAIMS

1. An immediate-release tablet formulation comprising a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof:



5

Formula I;

wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, $-O-C_{1-6}$ alkyl, C_{1-6} haloalkyl, $-O-C_{1-6}$ haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-10-membered carbocyclyl, 3-10-membered heterocyclyl, $-CN$, $-CF_3$, $-OR^3$, $-SR^3$, $-NR^3R^4$, $-COR^3$, $-CO_2R^3$, $-CONR^3R^4$, $-NR^3COR^4$, $-SO_2R^3$, $-SO_2NR^3R^4$, and $-NR^3SO_2R^4$;

wherein R^3 and R^4 are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, 3-7-membered carbocyclyl and 3-7-membered heterocyclyl; wherein each 3-10-membered carbocyclyl, 3-10-membered heterocyclyl, 3-7-membered carbocyclyl, and 3-7-membered heterocyclyl, is unsubstituted or substituted with one or more substituents selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, $-O-C_{1-6}$ alkyl, C_{1-6} haloalkyl, $-O-C_{1-6}$ haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-CN$, $-CF_3$, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-COR^5$, $-CO_2R^5$, $-CONR^5R^6$, $-NR^5COR^6$, $-SO_2R^5$, $-SO_2NR^5R^6$, and $-NR^5SO_2R^6$; and

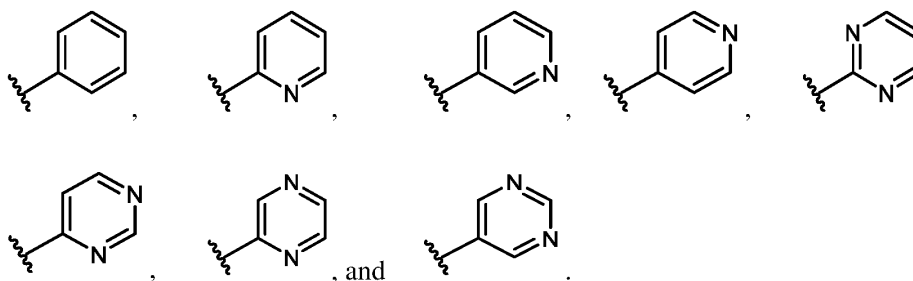
wherein each R^5 and R^6 are independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

wherein the immediate-release tablet formulation further comprises:

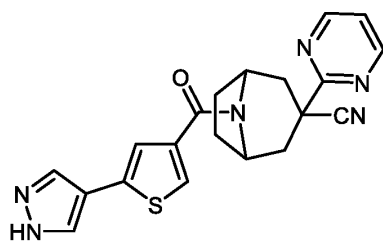
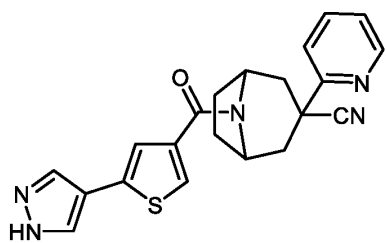
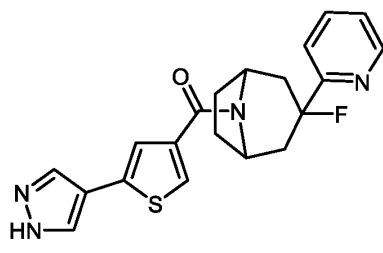
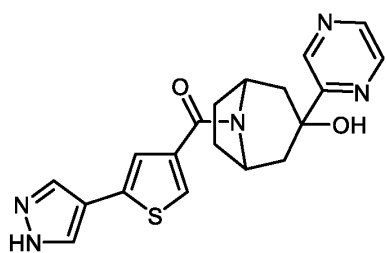
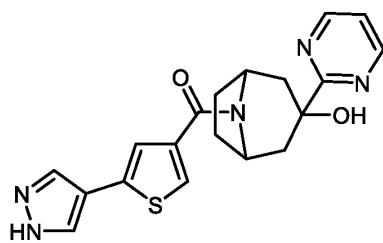
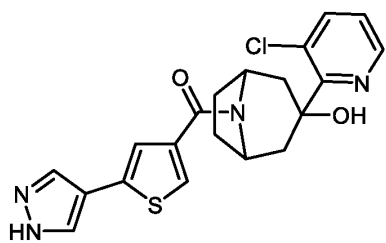
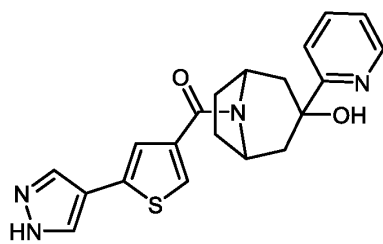
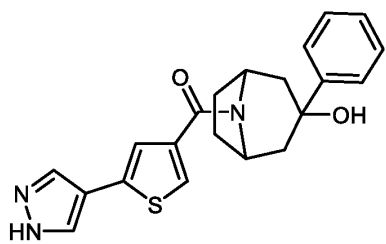
lactose; and

microcrystalline cellulose.

2. The immediate-release tablet formulation of claim 1, wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, 3-10-membered carbocyclyl, 3-10-membered heterocyclyl, -OH, -CN, and -NH₂; and wherein if present, each 3-10-membered carbocyclyl and 3-10-membered heterocyclyl may be further substituted with one or more substituents selected from the group consisting of hydrogen, halogen, -OH, -CN, -CF₃, -NH₂, and C₁₋₆alkyl.
3. The immediate-release tablet formulation of claim 1 or claim 2, wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, 6-membered carbocyclyl, 6-membered heterocyclyl, -OH, -CN, and -NH₂; and wherein if present, each 6-membered carbocyclyl and 6-membered heterocyclyl may be further substituted with one or more substituents selected from the group consisting of hydrogen, halogen, -OH, -CN, -CF₃, -NH₂, and C₁₋₆alkyl.
4. The immediate-release tablet formulation of any one of claims 1 to 3, wherein R^1 is selected from the group consisting of hydrogen, halogen, -OH, -CN, -CF₃, -NH₂, and C₁₋₆alkyl, and R^2 is independently selected from the group consisting of:



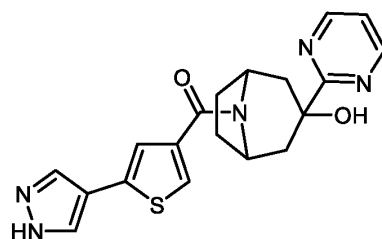
5. The immediate-release tablet formulation of any one of claims 1 to 4, wherein the compound of Formula I is selected from the group consisting of:



, and

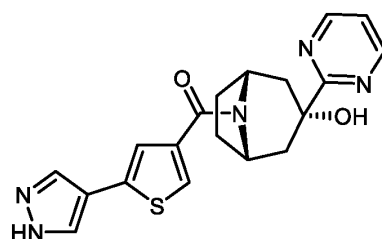
6. The immediate-release tablet formulation of any one of claims 1 to 5, wherein the compound of Formula I is compound Formula Ia:

91



Formula Ia.

7. The immediate-release tablet formulation of any one of claims 1 to 6, wherein the compounds of Formula I is compound Formula Iai:



Formula Iai.

8. The immediate-release tablet formulation of any one of claims 1 to 7, wherein the ratio (w/w) of lactose to microcrystalline cellulose is between about 50:50 and about 70:30.

10 9. The immediate-release tablet formulation of any one of claims 1 to 8, wherein the ratio (w/w) of lactose to microcrystalline cellulose is between about 80:20 and about 20:80.

10. The immediate-release tablet formulation of any one of claims 1 to 9, wherein the ratio (w/w) of lactose to microcrystalline cellulose is about 60:40.

15 11. The immediate-release tablet formulation of any one of claims 1 to 10, wherein the amount (w/w) of the compound of Formula I is about 2%, 4%, 5%, 10%, 20%, 40% or 50%.

12. The immediate-release tablet formulation of any one of claims 1 to 11, wherein the amount (w/w) of the compound of Formula I is between about 4% and about 40%.
13. The immediate-release tablet formulation of any one of claims 1 to 12, wherein the amount (w/w) of Formula I is about 10%.
- 5 14. The immediate-release tablet formulation of any one of claims 1 to 12, wherein the amount (w/w) of Formula I is about 20%.
15. The immediate-release tablet formulation of claim 13, wherein the absolute amount of the compound of Formula I is 5 mg.
16. The immediate-release tablet formulation of claim 14, wherein the absolute
10 amount of the compound of Formula I is 10 mg.
17. The immediate-release tablet formulation of any one of claims 1 to 16, wherein the lactose and microcrystalline cellulose are each a diluent.
18. The immediate-release tablet formulation of any one of claims 1 to 17, further comprising a pharmaceutically acceptable excipient selected from the group consisting
15 of a disintegrant, glidant, and lubricant.
19. The immediate-release tablet formulation of claim 18, wherein the disintegrant is selected from the group consisting of sodium starch glycolate and croscarmellose sodium.
20. The immediate-release tablet formulation of claim 18, wherein the glidant is
20 colloidal silicon dioxide.
21. The immediate-release tablet formulation of claim 18, wherein the lubricant is magnesium stearate.
22. The immediate-release tablet formulation of any one of claims 1 to 21, comprising:

the compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of about 10% to about 20%;

lactose monohydrate in an amount (w/w) of about 40% to about 50%;

microcrystalline cellulose in an amount (w/w) of about 25% to 35%; and

5 one or more pharmaceutically acceptable excipients in an amount (w/w) up to 100%.

23. The immediate-release tablet formulation of claim 22, comprising:

the compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of about 10%;

10 lactose monohydrate in an amount (w/w) of about 48.5%;

microcrystalline cellulose in an amount (w/w) of about 32.5%; and

one or more pharmaceutically acceptable excipients in an amount (w/w) up to 100%.

24. The immediate-release tablet formulation of claim 23, comprising:

15 the compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of about 10%;

lactose monohydrate in an amount (w/w) of about 48.5%;

microcrystalline cellulose in an amount (w/w) of about 32.5%;

sodium starch glycolate in an amount (w/w) of about 2%;

20 croscarmellose sodium in an amount (w/w) of about 2%;

colloidal silicon dioxide in an amount (w/w) of about 2%; and

magnesium stearate in an amount (w/w) of about 3%.

25. The immediate-release tablet formulation of claim 22, comprising:
- the compound of Formula I, or pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of about 20%;
- 5 lactose monohydrate in an amount (w/w) of about 42.5%;
- microcrystalline cellulose in an amount (w/w) of about 28.5%; and
- one or more pharmaceutically acceptable excipients in an amount (w/w) up to 100%.
26. The immediate-release tablet formulation of claim 25, comprising:
- 10 the compound of Formula Iai, or pharmaceutically acceptable salt or solvate thereof, in an amount (w/w) of about 20%;
- lactose monohydrate in an amount (w/w) of about 42.5%;
- microcrystalline cellulose in an amount (w/w) of about 28.5%;
- sodium starch glycolate in an amount (w/w) of about 2%;
- 15 croscarmellose sodium in an amount (w/w) of about 2%;
- colloidal silicon dioxide in an amount (w/w) of about 2%; and
- magnesium stearate in an amount (w/w) of about 3%.
27. The immediate-release tablet formulation of any one of claims 1 to 26, wherein the tablet is a film-coated tablet.
- 20 28. The immediate-release tablet formulation of any one of claims 1 to 27, for use in the treatment of a neurological disease.

29. The immediate-release tablet formulation of claim 28, wherein the neurological disease is Alzheimer's disease.
30. The immediate-release tablet formulation of claim 28, wherein the neurological condition is depression.
- 5 31. The immediate-release tablet formulation of any one of claims 1 to 30, wherein the compound of Formula I is in the form of a crystalline powder.
32. The immediate-release tablet formulation of any one of claims 1 to 31, wherein at least 80% of the compound of Formula I is released within about 10 to about 60 minutes.
- 10 33. The immediate-release tablet formulation of any one of claims 1 to 32, wherein the overall mass of the tablet is about 50 mg.
34. The immediate-release tablet formulation of any one of claims 1 to 33, wherein the tablet comprises between about 75% and about 95% of intragranular components.
35. The immediate-release tablet formulation of any one of claims 1 to 34,
15 manufactured by a dry granulation process.
36. A process for preparing the immediate-release tablet formulation of any one of claims 1 to 35, comprising:
- preparing granules by blender mixing intragranular components and subsequent granulation using roller compaction and milling;
- 20 blending the granules with extragranular components to provide a final blend;
- compressing the final blend using a rotary tablet press to yield a tablet core; and
- film-coating the tablet cores to provide the immediate-release film-coated tablets.
37. Use of the immediate-release tablet formulation according to any one of claims 1 to 35, in the manufacture of a medicament for the treatment of a neurological condition.

38. A method of treating a neurological condition in a subject in need thereof, comprising administering the immediate-release tablet formulation according to any one of claims 1 to 35.