

MICRONIZED CRYSTALLINE HYDROCHLORIDE SALTS OF ANTIVIRAL HELICASE-PRIMASE INHIBITOR COMPOUNDS

SUMMARY OF THE INVENTION

5 The present invention provides micronized solid crystalline forms of the hydrochloride salt of specific antiviral helicase-primase inhibitor compounds, compositions thereof, methods of producing the same, and methods of using the same in the treatment or prophylaxis of herpes simplex infections and -mediated diseases.

10 BACKGROUND AND PRIOR ART

 The pandemic of viral infections has plagued humanity since ancient times, causing mucocutaneous infection such as herpes labialis and herpes genitalis. Disease symptoms often interfere with everyday activities and occasionally herpes simplex virus 1 and 2 (HSV-1 and HSV-2) infections are the cause of life-threatening (encephalitis) or sight-impairing disease (keratitis),
15 especially in neonates, elderly and the immunocompromised patient population such as transplant or cancer patients or patients with an inherited immunodeficiency syndrome or disease. After infection the alpha herpesviridae persist for life in neurons of the host in a latent form, periodically reactivating and often resulting in significant psychosocial distress for the patient. Currently no cure is available.

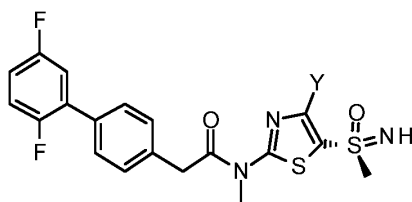
20 So far, vaccines, interleukins, interferones, therapeutic proteins, antibodies, immunomodulators and small-molecule drugs with specific or non-specific modes of action lacked either efficacy or the required safety profile to replace the nucleosidic drugs acyclovir, valacyclovir and famciclovir as the first choice of treatment.

 The known aminothiazoles (e.g. pritelivir, HN0037) are the most potent drugs in
25 development today. These antiviral agents act by inhibiting the herpesviral helicase primase, display low resistance rates *in vitro* and superior efficacy in animal models compared to nucleosidic drugs, however, development is hampered by off-target carbonic anhydrase activity, reduced neuronal tissue and brain penetration and an unusual pharmacokinetic profile.

 Herpes viruses are neurotrophic viruses, which means that after infection they enter and
30 settle in neuronal tissue leading to a persisting presence of herpes viruses for life in neurons of the host in a latent form and a permanent neuronal exposure. Such permanent neuronal exposure with latent forms of herpes viruses is the reason for life-long risk of recurrent and periodically reactivating herpes infections often resulting in significant psychosocial distress for the patient. Such neuronal herpes virus exposure is further the cause of herpesvirus encephalitis (or herpes
35 simplex encephalitis; HSE), which is thought to be caused by the transmission of herpes virus from a peripheral site on the face following HSV-1 reactivation or from neuronal tissue, along a nerve axon to the brain. The virus lies dormant in the ganglion of the trigeminal cranial nerve or in the neuronal tissue and gains access to the brain where it causes HSE. It is therefore important to provide highly active antiviral drugs allowing to treat and eliminate also (dormant) herpes
40 viruses in neuronal tissue and nerves and therewith avoid recurrence and reactivation of herpes

infections or even the severe implications like HSE. Known antiviral drugs as e.g. the known aminothiazoles, having insufficient efficacy to enter neuronal tissue or to cross the blood brain barrier to enter the brain are not able to provide an effective and eradicated cure for treating also latent or dormant forms of herpes viruses or even HSE.

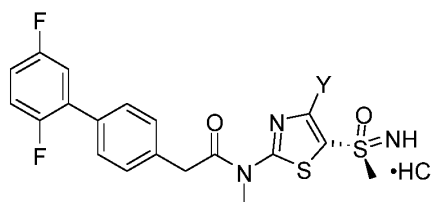
- 5 New solid crystalline salt forms and its deuterated analogues of the antiviral helicase primase inhibitor compound according to the Formula (A), also designated as **IM-250**, have been described in EP patent application EP22151820 (filed 17. Jan. 2022) and in the subsequent international application WO2023/135303A1 (published 20. July 2023):



Formula (A)

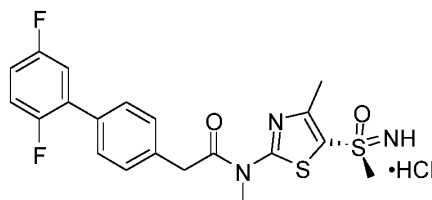
- 10 wherein Y is selected from CH₃ or CD₃.

The present application is directed particularly to hydrochloride salts (HCl salts) of such compounds IM-250 according to the Formula (I):



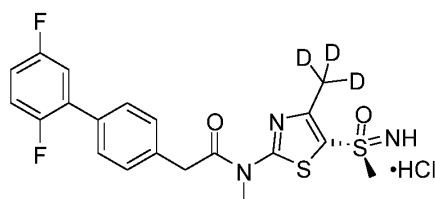
Formula (I)

with Y selected from CH₃ or CD₃, or more specifically having the following formulas:



IM-250 HCl salt

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d₃-IM-250 HCl salt

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WO2017/174640 describes the free base of **IM-250** in its racemic form, WO2019/068817 describes both enantiomers of **IM-250** and pharmaceutically acceptable salts thereof, respectively. WO2022/090409 describes deuterated analogs of **IM-250** and pharmaceutically acceptable salts thereof. Some antiviral results of **IM-250** have been described in *Sci. Transl. Med.* 2021;13:eabf8668 and *Antivir. Res.* 2021;195:105190.

Specific dosage or administration forms of selected salts or crystalline forms of IM-250 have not yet been described.

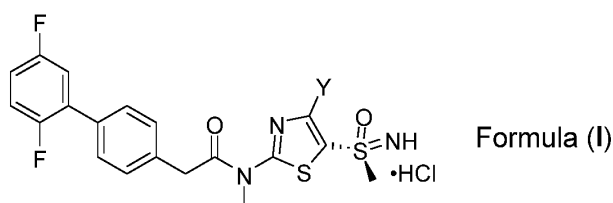
The scientific publication of *Serajuddin A. T. M. "Salt formation to improve drug solubility", Adv. Drug Deliv. Rev. 2007; 59:603-616* discloses the relationship between salt formation of pharmaceutically active species and its influence on solubility, dissolution rate and related factors in the context of drug bioavailability.

Kesisoglu et al. "Understanding the Effect of Apl Properties on Bioavailability Through Absorption Modeling", The AAPS Journal, 2008; 10(4):516-525 describes solid phase and physical properties of active pharmaceutical ingredients and how the particle size of a pharmaceutical ingredient may influence its absorption properties and ultimately the drug bioavailability.

Crystallisation or salt formation may positively influence important drug properties, such as solubility, dissolution rate, bioavailability, hygroscopicity, flavor, developability and physical/chemical stability. There is a need to provide optimized dosage or administration forms of antiviral compounds according Formula (A), which exhibit optimized physicochemical and pharmaceutical properties, without affecting negatively other important parameters, such as hygroscopicity or bioavailability of the active compound with the final goal to obtain an improvement in the production, handling, storage and pharmaceutical properties of said compounds according Formula (A).

SUMMARY

The present invention relates to novel, selected crystalline forms of the hydrochloride salt of the antiviral helicase-primase inhibitor **IM-250** with Formula (I) in micronized form:



wherein Y is selected from CH₃ or CD₃, or a co-crystal, hydrate or solvate thereof.

These novel selected micronized crystalline forms are useful, for example, for treating human patients suffering from a herpes simplex-mediated disorder. The novel micronized solid forms of the present disclosure can be useful for preparing a medicament for treating or preventing herpes simplex virus infections and disease. The novel micronized solid forms of the present disclosure can be used as helicase-primase inhibitors. The inventors of the present invention surprisingly found that providing the selected crystalline hydrochloride salt forms of **IM-250** in micronized form further improves their suitability for providing medicaments with optimized properties, such advantages comprise, for example, allowing administration at a lower dose compared to the non-micronized matched pair due to improved bioavailability. Therewith, the

inventors of the present invention for the first time combined the particular advantages having been shown for the selected **IM-250 HCl salt form** and its deuterated analog with the advantages of providing the drug in micronized form to offer a new and improved **IM-250** dosage or administration form.

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DESCRIPTION OF FIGURES

- Figure 1 depicts a X-ray powder diffraction (XRPD) pattern of **IM-250 HCl salt**.
 Figure 2 depicts a XRPD pattern of **IM-250 HCl salt** when crystallized from EtOH.
 Figure 3 depicts a XRPD pattern of **deuterated IM-250 HCl salt (d₃-IM-250 HCl salt)**.
 10 Figure 4 microscopy observation of **IM-250 HCl salt** crystals for PSD assessment in transmitted light and cross-polarized light – magnifications x162.
 Figure 5 microscopy observation of **IM-250 HCl salt** crystals (same crystals as in Figure 4) in cross-polarized light – magnifications x162.
 Figure 6 granulometric profile of **IM-250 HCl salt** crystals (cumulated particle size
 15 distribution).
 Figure 7 distribution histogram of **IM-250 HCl salt** PSD assessment.
 Figure 8 particle size distribution by laser diffraction of micronized **IM-250 HCl salt**.
 Figure 9 microscopy observation of micronized **IM-250 HCl salt**.
 Figure 10 overlaid XRPD profiles for the native **IM-250 HCl salt** batch and the same batch
 20 after micronization.
 Figure 11 overlaid DSC profiles for the native **IM-250 HCl salt** batch and the same batch after micronization.
 Figure 12 microscopy observation of **d₃-IM-250 HCl salt** crystals for PSD assessment in transmitted light and cross-polarized light – magnifications x162.
 25 Figure 13 microscopy observation of **d₃-IM-250 HCl salt** crystals (same crystals as in Figure 4) in cross-polarized light – magnifications x162.
 Figure 14 granulometric profile of **d₃-IM-250 HCl salt** crystals (cumulated particle size distribution).
 Figure 15 distribution histogram of **d₃-IM-250 HCl salt** PSD assessment.
 30 Figure 16 particle size distribution by laser diffraction of micronized **d₃-IM-250 HCl salt**.
 Figure 17 microscopy observation of micronized **d₃-IM-250 HCl salt**.
 Figure 18 particle size distribution by laser diffraction and d₉₀ value of **IM-250 HCl salt** (GMP-campaign) before micronization.
 Figure 19 particle size distribution by laser diffraction and d₉₀ value of micronized **IM-250 HCl salt** (GMP-campaign).
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DETAILED DESCRIPTION

In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the disclosure. However, one skilled in the art will understand that the disclosure may be practiced without these details. The description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the claimed subject matter, and is not intended to limit the appended claims to the specific embodiments illustrated. The headings used throughout this disclosure are provided for convenience only and are not to be construed to limit the claims in any way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

DEFINITIONS

Unless the context requires otherwise, throughout the present specification and claims, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is as "including, but not limited to".

Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present disclosure. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment.

Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

Embodiments that reference throughout this specification to "a crystalline form" include the crystalline, salt, co-crystal, hydrate and/or solvate of Formula (I) disclosed herein.

"Deuteration", "deuterium labelled", "deuterium substituted" or "deuterated" in the sense of the present disclosure means that one or more hydrogen atom(s) of the compound of Formula (I) is/are replaced by deuterium (^2H , represented by "D").

In some compounds of Formula (I), residue Y represents CD_3 . It has surprisingly been found, that such deuterated aminothiazole compounds exhibit increased resistance to metabolism and thus be useful for increasing the half-life of a compound of Formula (I), compared to a respective undeuterated compound, when administered to a mammal, e.g. a human. See, for example, Foster in *Trends Pharmacol. Sci.* 1984;5:524. Such deuterated aminothiazole compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogens have been replaced by deuterium (see Experimental Section for details).

Deuterium labelled or substituted therapeutic compounds of the disclosure surprisingly turned out to have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to absorption, distribution, metabolism and excretion (ADME). Substitution with deuterium turned out to afford certain therapeutic advantages resulting from greater metabolic stability, for example

increased in vivo half-life, reduced dosage requirements and/or an improvement in therapeutic index.

The concentration of deuterium may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable or radioactive isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition (about 99.98% hydrogen). Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium with an isotopic purity of at least 50%, preferably an isotopic purity of at least 95%, more preferably an isotopic purity of at least 99%.

The percentage of deuterium incorporation can be obtained by quantitative analysis using a number of conventional methods, such as mass spectroscopy (peak area) or by quantifying the remaining residual ^1H -NMR signals of the specific deuteration site compared to signals from internal standards or other, non-deuterated ^1H signals in the compound.

It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of non-deuterated analogs of compounds of the present invention will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial as compared to the degree of stable isotopic substitution of compounds of this invention. See, for instance, *Comp. Biochem. Physiol.* 1998;119A:725.

The term "isotopic enrichment factor" at a particular position normally occupied by hydrogen refers to the ratio between the abundance of deuterium at the position and the natural abundance of deuterium at that position. By way of example, an isotopic enrichment factor of 3500 means that the amount of deuterium at the particular position is 3500-fold the natural abundance of deuterium, or that 52.5% of the compounds have deuterium at the particular position (i.e., 52.5% deuterium incorporation at the given position). The abundance of deuterium in the oceans of Earth is approximately one atom in 6500 hydrogen atoms (about 154 parts per million (ppm)). Deuterium thus accounts for approximately 0.015 percent (on a weight basis, 0.030 percent) of all naturally occurring hydrogen atoms in the oceans on Earth; the abundance changes slightly from one kind of natural water to another.

The deuterated compounds of this disclosure are preferably characterized by an isotopic enrichment factor of at least 6300, or by a deuteration degree of at least 95%. More preferably by an isotopic enrichment factor of at least 6500, or by a deuteration degree of at least 98%.

Any formula or structure given herein, is also intended to represent compounds comprising in addition further isotopically labeled atoms. Examples of additional isotopes that can be incorporated into compounds of the disclosure include further isotopes of hydrogen, as well as isotopes of carbon, nitrogen, oxygen and fluorine, such as, but not limited to ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F and ^{35}S . The disclosure further comprises various isotopically labeled compounds into which radioactive isotopes such as ^3H , ^{13}C and ^{14}C are incorporated. Such isotopically

labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or radioactive treatment of patients. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

"Pharmaceutically acceptable excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, and/or emulsifier, or a combination of one or more of the above which has been approved by the United States Food and Drug Administration (FDA), European Medicines Agency (EMA) or other national counterparts as being acceptable for use in humans or domestic animals.

A "pharmaceutical composition" refers to a formulation of a compound of the disclosure (e.g. a compound of Formula (I)) and a medium (administration form) generally accepted in the art for the delivery of the biologically active compound to mammals, e.g. humans. Such a medium includes all pharmaceutically acceptable excipients therefor.

The term "effective amount" is meant to include the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, an infection or one or more of the symptoms of a disorder, disease, or condition being treated. The term "effective amount" also refers to the amount of a compound that is sufficient to elicit the biological or medical response of a cell, tissue, system, animal, or human, which is being sought by a researcher, veterinarian, medical doctor, or clinician.

"Prevention" or "preventing" or "prophylaxis" means any treatment of an infection, disease or condition that causes the clinical symptoms of the disease or condition not to develop.

Compounds may, in some embodiments, be administered to a subject (including a human) who is at risk or has a family history of an infection, disease or condition.

"Treating" and "treatment" of a disease include the following:

- (1) preventing or reducing the risk of developing the disease, i.e. causing the clinical symptoms of the disease not to develop in a subject that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,
- (2) inhibiting the disease, i.e. arresting or reducing the development of the disease or its clinical symptoms,
- (3) relieving (healing) the disease, i.e. causing regression of the disease or its clinical symptoms, and
- (4) ameliorating or alleviating the symptoms or impairments caused by the disease.

The terms "subject" or "patient" refer to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation or experiment. The methods described

herein may be useful in human therapy and/or veterinary applications. In some embodiments, the subject is a mammal (or the patient). In some embodiments the subject (or the patient) is human, domestic animals (e.g. dogs and cats), farm animals (e.g. cattle, horses, sheep, goats, and pigs) and/or laboratory animals (e.g. mice, rats, hamsters, guinea pigs, pigs, rabbits, dogs, and monkeys). In some embodiments, the subject (or the patient) is a human. "Human (or patient) in need thereof" refers to a human who may have or is suspect to have an infection or disease or conditions that would benefit from certain treatment; for example, being treated with the compounds disclosed herein according to the present application.

Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter *per se*. For example, description referring to "about x" includes description of "x". Also, the singular forms "a" and "the" include plural references unless the context clearly dictates otherwise. Thus, e.g. reference to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more assays and equivalents thereof known to those skilled in the art.

"Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

The term "substantially as shown in" when referring, for example, to an XRPD pattern, a DSC thermogram or a TGA thermogram includes a pattern, thermogram or spectrum that is not necessarily identical to those depicted herein, but that falls within the limits of experimental error or deviations when considered by one of ordinary skill in the art.

Further the compounds of the present disclosure may be present in the form of solvates, such as those which include as solvate water, or pharmaceutically acceptable solvates, such as alcohols, in particular ethanol. A "solvate" is formed by the interaction of a solvent and a compound. When the solvent is water, the "solvate" is a "hydrate". It is understood, that also a salt of the present disclosure can include a solvate.

Suitable solvents for salt- and solvent formation of the compounds according to Formula (I) as defined herein comprise: acetonitrile, dichloromethane (DCM), alcohols, such as especially methanol, ethanol, 2-propanol (iso-propanol), aldehydes, ketones, especially acetone, ethers, e.g. tetrahydrofuran (THF) or dioxane, esters, e.g. ethyl acetate, or alkanes, such as especially pentane, hexane, heptane or cyclohexane and water, and mixtures thereof.

Micronization is the process of reducing the average diameter of a solid material's particles, e.g. by friction. Traditional techniques for micronization focus on mechanical means, such as milling and grinding. Modern techniques make use of the properties of supercritical fluids and manipulate the principles of solubility. The term micronization usually refers to the reduction of average particle diameters to the micrometer range and is used to increase the efficacy of the solid material by e.g. improving solubility or bioavailability, however can beneficially influence other material properties like flow and conveying behaviour (for bulk materials), reactivity, abrasiveness, extraction and reaction behaviour, taste, compressibility, and many more.

5 The term "d₉₀ value" is a percentile value, which refers to 90% (by volume) of the particles have a size that is less than or equal to the value. For example, d₉₀ value of 20.0 µm means 90% (by volume) of the particles is less than or equal to 20.0 µm in size; a d₉₀ value of 10.0 µm means 90% (by volume) of the particles is less than or equal to 10.0 µm in size. The "d₉₀ value" can be derived from a particle-size distribution (PSD) assessment by laser diffraction (granulometry analysis).

Similarly, the terms "d₁₀", "d₂₅", "d₅₀" and/or "d₇₅" define the respective percentage (by volume) of the particles having a size that is less than or equal to the value.

10 The term "d₉₀ particle size distribution" means that 90% (per volume) of the particles have a particle size lower than the d₉₀ value expressed in µm.

Similarly, the terms "d₁₀ particle size distribution", "d₂₅ particle size distribution", "d₅₀ particle size distribution" and/or "d₇₅ particle size distribution" mean that 10%, 25%, 50% and/or 75% (per volume) of the particles have a particle size above or below the respectively defined d₁₀, d₂₅, d₅₀ and/or d₇₅ value expressed in µm.

15 These d-values relate in particular to the cumulative particle volume in the particle distribution curve.

20 This patent application discloses new micronized crystalline forms of antiviral aminothiazole compounds with a more suitable pharmacokinetic and stability profile (e.g. due to improved solubility and bioavailability allowing a higher passage of the antiviral drug compound into neuronal tissue and into the brain). Furthermore, the new micronized crystalline forms of antiviral aminothiazole compounds are characterized by improved compound stability and improved bioavailability, making them more suitable for pharmaceutical development and use as a medicament.

25 **Solid Hydrochloride Salt Forms of Compounds of Formula (I)**

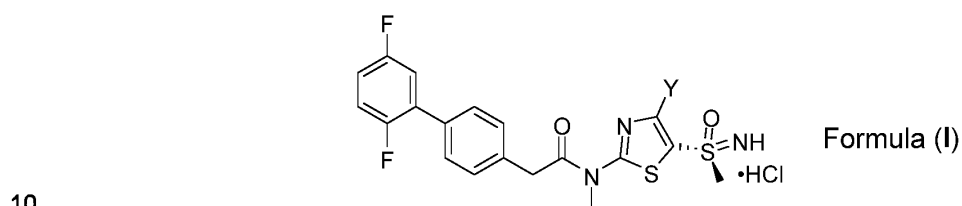
Micronized crystalline HCl salt forms of compounds of Formula (I) may provide the advantage of bioavailability and stability, suitable for use as an active ingredient in a pharmaceutical composition. Surprisingly, the inventors of the present invention have found that **IM-250 HCl salt**, for example, exhibits advantageous physical properties such as good physical and chemical stability, good aqueous solubility and good bioavailability, while being non-hygroscopic. Variations in the crystal structure of a pharmaceutical drug substance or active ingredient may affect the dissolution rate (which may affect bioavailability etc.), manufacturability (e.g. ease of handling, ability to consistently prepare doses of known strength) and stability (e.g. thermal stability, shelf life etc.) of a pharmaceutical drug product or active ingredient. Such variations may affect the preparation or formulation of pharmaceutical compositions in different dosage or delivery forms, such as solutions or solid oral dosage form including tablets and capsules. Compared to other forms such as non-crystalline or amorphous forms, specific crystalline forms may provide desired or suitable hygroscopicity, particle size control, improvement of dissolution rate, solubility, purity, physical and chemical stability, manufacturability, yield and/or process control. Thus, micronized

crystalline hydrochloride salt forms of the compound of Formula (I) may provide additional advantages such as improving: the manufacturing process of the compound, the stability or storability of a drug product form of the compound, the stability or storability of a drug substance of the compound and/or the bioavailability and/or stability of the compound as an active agent.

- 5 In particular embodiments, novel micronized solid forms, such as micronized crystalline forms of compounds of Formula (I) are disclosed.

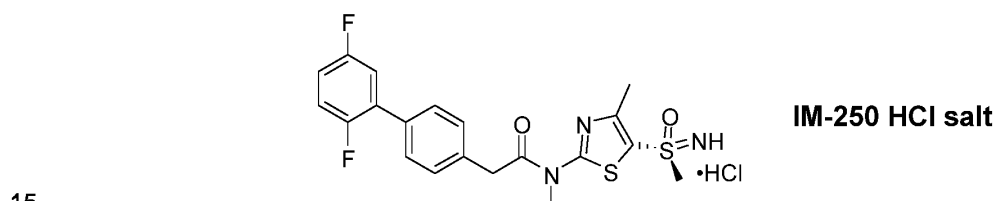
The invention relates in particular to the following embodiments:

In a preferred embodiment in combination with any of the above or below embodiments the micronized, crystalline form is a compound according to Formula (I)



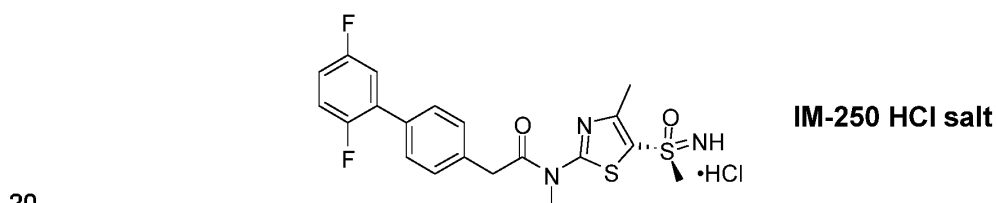
wherein Y is selected from CH₃ and CD₃; or a co-crystal, hydrate or solvate thereof.

In a more preferred embodiment in combination with any of the above or below embodiments the micronized, crystalline form is a compound with the following structure:

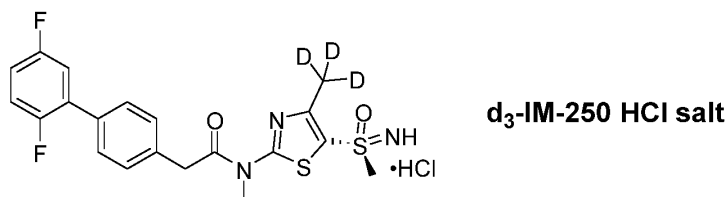


or a co-crystal, hydrate or solvate thereof.

In a more preferred embodiment in combination with any of the above or below embodiments the micronized, crystalline form is of the following structure:

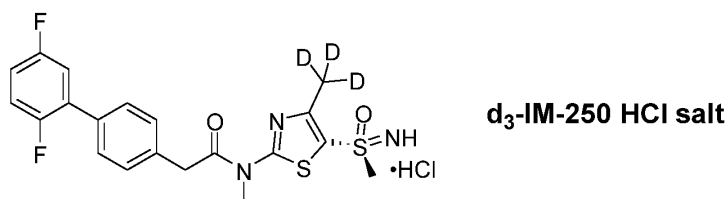


In a more preferred embodiment in combination with any of the above or below embodiments the micronized, crystalline form is a compound with the following structure:



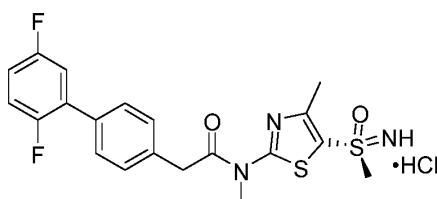
or a co-crystal, hydrate or solvate thereof.

- 5 In a more preferred embodiment in combination with any of the above or below embodiments the micronized, crystalline form is of the following structure:



IM-250 HCl salt

- 10 A further embodiment of the invention relates to a micronized HCl salt of compound IM-250, which is **IM-250 HCl salt** with the structure



- In one embodiment of the invention, such micronized **IM-250 HCl salt** is characterized by an XRPD pattern comprising (characteristic peaks) degree 2θ-reflections (±0.3 degrees 2θ) at 13.7, 17.7 and 22.8 degrees.
- 15 In some embodiments, micronized **IM-250 HCl salt** is characterized by an XRPD pattern comprising degree 2θ-reflections (±0.3 degrees 2θ) at 13.7, 17.7 and 22.8 degrees and one, two or three of the degree 2θ-reflections (±0.3 degrees 2θ) at 17.0, 19.8 and 21.8 degrees.
- In some embodiments, micronized **IM-250 HCl salt** is characterized by an XRPD pattern comprising degree 2θ-reflections (±0.3 degrees 2θ) at 13.7, 17.0, 17.7, 19.8, 21.8 and 22.8 degrees.
- 20 In some embodiments, micronized **IM-250 HCl salt** is characterized by an XRPD pattern comprising at least 4 of the following peaks: 13.7, 17.0, 17.7, 19.8, 21.8 and 22.8 degrees 2θ (±0.3 degrees 2θ).

All values determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54 Å.

In some embodiments, micronized **IM-250 HCl salt** has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, or at least nine of the degree 20-reflections with the greatest intensity as the XRPD pattern substantially as shown in FIG. 1.

5 In some embodiments, micronized **IM-250 HCl salt** has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, or at least nine of the degree 20-reflections with the greatest intensity as the XRPD pattern substantially as shown in FIG. 2.

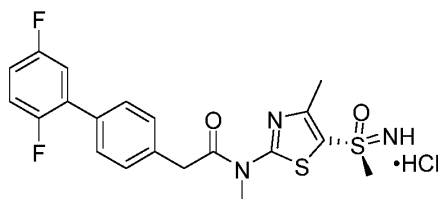
10 In some embodiments, such micronized **IM-250 HCl salt** exhibits an X-ray powder diffraction (XRPD) pattern substantially as shown in FIG. 1.

In some embodiments, such micronized **IM-250 HCl salt** exhibits an X-ray powder diffraction (XRPD) pattern substantially as shown in FIG. 2.

15 In some embodiments, micronized **IM-250 HCl salt** has a thermogravimetric analysis thermogram revealing a mass loss of about 9.8% upon heating with an onset/endset temperature of about 151/170°C.

In some embodiments, micronized **IM-250 HCl salt** has a thermogravimetric analysis thermogram revealing a onset temperature of decomposition of about 221°C.

In some embodiments, provided herein is micronized **IM-250 HCl salt** with the structure



20 wherein hydrochloride and (S)-2-(2',5'-difluoro-[1,1'-biphenyl]-4-yl)-N-methyl-N-(4-methyl-5-(S-methylsulfonimidoyl)thiazol-2-yl)acetamide are in a 1 to 1 ±0.2 molar ratio.

In some embodiments, the **IM-250 HCl salt** is micronized with a d_{90} value of less than or equal to about 20.0 μm , such as ranging from about 1.0 to 20.0 μm , or ranging from about 2.0 to 12.0 μm .

25 In some embodiments, the **IM-250 HCl salt** is micronized with a d_{90} value of less than or equal to 20.0 μm , such as ranging from 1.0 to 20.0 μm , or ranging from 2.0 to 12.0 μm .

In some embodiments, the **IM-250 HCl salt** is micronized to a d_{90} value ranges from about 1.0 to about 2.0 μm , from greater than about 2.0 to about 3.0 μm , from greater than about 3.0 to about 4.0 μm , from greater than about 4.0 to about 6.0 μm , from greater than about 6.0 to about 8.0 μm , from greater than about 8.0 to about 10.0 μm , or from greater than about 10.0 to about 12.0 μm .

30 In some embodiments, the d_{90} value of the **IM-250 HCl salt** ranges from about 2.0 to about 5.0 μm , for example, the d_{90} value is 3.0, 3.5, 3.9 or 4.0 μm .

In some embodiments, the d_{90} value of the **IM-250 HCl salt** ranges from about 9.0 to about 12.0 μm , for example, the d_{90} value is 9.5 or 10.0 μm .

In a preferred embodiment, the d_{90} value of the **IM-250 HCl salt** is less than or equal to about 11.0 μm or is less than or equal to about 10.0 μm .

In a preferred embodiment, the d_{90} value of the **IM-250 HCl salt** is less than or equal to 11.0 μm or is less than or equal to 10.0 μm .

5 In a more preferred embodiment, the d_{90} value of the **IM-250 HCl salt** is less than or equal to about 6.0 μm .

In a more preferred embodiment, the d_{90} value of the **IM-250 HCl salt** is less than or equal to 6.0 μm .

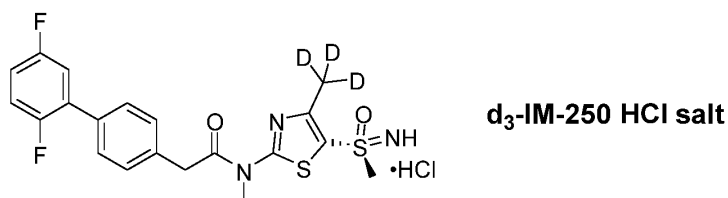
10 In a particular embodiment, the d_{90} value of the **IM-250 HCl salt** is less than or equal to about 4.0 μm .

In a more particular embodiment, the d_{90} value of the **IM-250 HCl salt** is less than or equal to 4.0 μm .

15 The micronized hydrochloride salt, **IM-250 HCl salt**, surprisingly turned out to exhibit several advantages with respect to chemical and physical stability, (lack of) hygroscopicity and improved bioavailability, while other tested salts, as shown in the Examples below, were less advantageous. Accordingly, micronized **IM-250 HCl salt** is a particularly preferred embodiment of the present invention.

Deuterated IM-250 HCl salt – d_3 -IM-250 HCl salt

20 A further embodiment of the invention relates to a micronized deuterated compound of the **IM-250 HCl salt (d_3 -IM-250 HCl salt)** with the structure



25 In one embodiment of the invention, such micronized **d_3 -IM-250 HCl salt** is characterized by an XRPD pattern comprising (characteristic peaks) degree 2θ -reflections (± 0.3 degrees 2θ) at 13.8, 17.8 and 21.8 degrees.

In some embodiments, micronized **d_3 -IM-250 HCl salt** is characterized by an XRPD pattern comprising degree 2θ -reflections (± 0.3 degrees 2θ) at 13.8, 17.8 and 21.8 degrees and one, two, three, four or five of the degree 2θ -reflections (± 0.3 degrees 2θ) at 11.3, 11.9, 19.8, 21.0 and 21.3 degrees.

30 In some embodiments, micronized **d_3 -IM-250 HCl salt** is characterized by an XRPD pattern comprising degree 2θ -reflections (± 0.3 degrees 2θ) at 11.3, 11.9, 13.8, 17.8, 19.8, 21.0, 21.3 and 21.8 degrees.

In some embodiments, micronized **d₃-IM-250 HCl salt** is characterized by an XRPD pattern comprising at least 4 of the following peaks: 11.3, 11.9, 13.8, 17.8, 19.8, 21.0, 21.3 and 21.8 degrees 2 θ (± 0.3 degrees 2 θ).

All values determined on a diffractometer using Cu-K α radiation at a wavelength of 1.54 Å.

5 In some embodiments, micronized **d₃-IM-250 HCl salt** has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, or at least nine of the degree 2 θ -reflections with the greatest intensity as the XRPD pattern substantially as shown in FIG. 3.

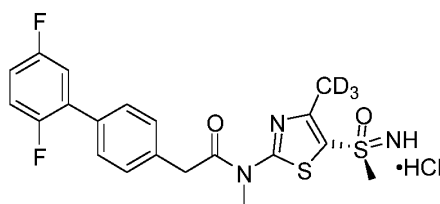
10 In some embodiments, micronized **d₃-IM-250 HCl salt** has a thermogravimetric analysis thermogram revealing a mass loss of about 7.8% upon heating with an onset/endset temperature of about 149/167°C.

In some embodiments, micronized **d₃-IM-250 HCl salt** has a thermogravimetric analysis thermogram revealing a onset temperature of decomposition of about 225°C.

15 In some embodiments, micronized **d₃-IM-250 HCl salt** has a differential scanning calorimetry thermogram comprising an endotherm with an onset at about 188°C.

Accordingly, a micronized **d₃-IM-250 HCl salt** may further be characterized by having a melting point of 188 to 194°C ($\pm 5^\circ\text{C}$).

In some embodiments, provided herein is micronized **d₃-IM-250 HCl salt** with the structure



20 wherein hydrochloride and (S)-2-(2',5'-difluoro-[1,1'-biphenyl]-4-yl)-N-methyl-N-(4-(methyl-d₃)-5-(S-methylsulfonimidoyl)thiazol-2-yl)acetamide are in a 1 to 1 ± 0.2 molar ratio.

In some embodiments, the **d₃-IM-250 HCl salt** is micronized with a d₉₀ value of less than or equal to about 20.0 μm , such as ranging from about 1.0 to 20.0 μm , or ranging from about 2.0 to 12.0 μm .

25 In some embodiments, the **d₃-IM-250 HCl salt** is micronized with a d₉₀ value of less than or equal to 20.0 μm , such as ranging from 1.0 to 20.0 μm , or ranging from 2.0 to 12.0 μm .

In some embodiments, the **d₃-IM-250 HCl salt** is micronized to a d₉₀ value ranges from about 1.0 to about 2.0 μm , from greater than about 2.0 to about 3.0 μm , from greater than about 3.0 to about 4.0 μm , from greater than about 4.0 to about 6.0 μm , from greater than about 6.0 to about 8.0 μm ,
30 from greater than about 8.0 to about 10.0 μm , or from greater than about 10.0 to about 12.0 μm .

In some embodiments, the d₉₀ value of the **d₃-IM-250 HCl salt** ranges from about 2.0 to about 5.0 μm , for example, the d₉₀ value is 3.0, 3.5, 3.9 or 4.0 μm .

In some embodiments, the d_{90} value of the **d₃-IM-250 HCl salt** ranges from about 9.0 to about 12.0 μm , for example, the d_{90} value is 9.5 or 10.0 μm .

In a preferred embodiment, the d_{90} value of the **d₃-IM-250 HCl salt** is less than or equal to about 11.0 μm or is less than or equal to about 10.0 μm .

5 In a preferred embodiment, the d_{90} value of the **d₃-IM-250 HCl salt** is less than or equal to 11.0 μm or is less than or equal to 10.0 μm .

In a more preferred embodiment, the d_{90} value of the **d₃-IM-250 HCl salt** is less than or equal to about 6.0 μm .

10 In a more preferred embodiment, the d_{90} value of the **d₃-IM-250 HCl salt** is less than or equal to 6.0 μm .

In a particular embodiment, the d_{90} value of the **d₃-IM-250 HCl salt** is less than or equal to about 4.0 μm .

In a more particular embodiment, the d_{90} value of the **d₃-IM-250 HCl salt** is less than or equal to 4.0 μm .

15 The micronized deuterated HCl salt, **d₃-IM-250 HCl salt**, surprisingly turned out to exhibit several advantages with respect to chemical and physical stability, (lack of) hygroscopicity and improved bioavailability, while other tested salts were less advantageous. Accordingly, micronized crystalline **deuterated IM-250 HCl salt (d₃-IM-250 HCl salt)** is a particularly preferred embodiment of the present invention.

20

Administration forms and Medical Use of the Micronized Solid Forms of Compounds of Formula (I)

A further aspect of the present invention relates to a pharmaceutical formulation, comprising one or more of the compounds of any of the above described embodiments.

25 A further aspect of the present invention relates to the compounds of any of the above described embodiments for the use as a medicament.

Particularly the invention relates to the described compounds for use in the treatment or prophylaxis of a disease or disorder associated with viral infections.

30 More particularly the invention relates to the described compounds for use in the treatment or prophylaxis of a disease or disorder, which is associated with viral infections caused by herpes viruses, such as in particular by Herpes simplex viruses, i.e. for the use in the treatment or prophylaxis of herpes infections, such as herpes simplex infections.

35 In a further aspect the invention relates to the described compounds for use in treating and eliminating latent (dormant) forms of herpes viruses in neuronal tissue and nerves, preferably for avoiding or preventing recurrence and reactivation of herpes infections or even severe implications associated therewith, such as herpes simplex encephalitis (HSE).

In a further aspect the invention relates to the described compounds for use in the treatment or prophylaxis of neurodegenerative diseases caused by viruses, such as in particular Alzheimer's disease caused by viruses, in particular caused by Herpes simplex viruses.

5 In a further aspect the invention relates to the described compounds for the use in the treatment and prophylaxis of herpes infections, in particular Herpes simplex infections, in patients displaying Herpes labialis, Herpes genitalis and Herpes-related keratitis, Alzheimer's disease, encephalitis, pneumonia, hepatitis; in patients with a suppressed immune system, such as AIDS patients, cancer patients, patients having a genetic immunodeficiency, transplant patients; in new-born children and infants; in Herpes-positive patients, in particular Herpes-simplex-positive patients, in
10 patients for suppressing recurrence (suppression therapy); or for use in patients, in particular in Herpes-positive patients, in particular Herpes-simplex-positive patients, who are resistant to nucleosidic antiviral therapy such as acyclovir, penciclovir, famciclovir, ganciclovir, valacyclovir and/or foscarnet or cidofovir.

15 The compounds according to the present invention are considered for the use in the prophylaxis and treatment of the respective disorders and diseases in humans as well as in animals.

Accordingly, the invention relates to the use of the compounds as described herein for the preparation of a medicament.

Further, the invention relates to a method of preventing or treating a disease or disorder associated with viral infections, such as a disease or disorder, which is associated with viral
20 infections caused by herpes viruses, such as in particular by Herpes simplex viruses as well as a method of treating and eliminating latent (dormant) forms of herpes viruses in neuronal tissue and nerves, preferably for avoiding or preventing recurrence and reactivation of herpes infections or even severe implications associated therewith, such as herpes simplex encephalitis (HSE) or a method of preventing or treating neurodegenerative diseases caused by viruses, such as in
25 particular Alzheimer's disease, said methods comprising administering to a human or animal in need thereof an effective amount of a compound or of a composition comprising said compounds as described herein.

In practical use, the compounds used in the present invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional
30 pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing compositions for oral dosage forms, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavouring agents, preservatives, colouring agents and the like in the case of oral liquid preparations, such as, for
35 example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

40 Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If

desired, tablets may be coated by standard aqueous or non-aqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2.0 percent to about 60.0 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray or as eye drops.

The tablets, pills, capsules and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatine; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavouring such as cherry or orange flavour.

The compounds used in the present invention may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral (including intravenous), ocular, pulmonary, nasal and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, gels, ointments, aerosols and the like. Preferably compounds of the present invention are administered orally or topical as eye drops, creams or gels, more preferably the compounds of the present invention are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

The compounds of the present invention may also be present in combination with further active ingredients, in particular with one or more active ingredients exhibiting advantageous effects in the treatment of any of the disorders or diseases as described herein. Very particularly the compounds of the present invention are present in a composition in combination with at least one further active substance being effective in treating a disease or disorder associated with viral infections (antiviral active compounds), preferably a disease or disorder being associated with viral infections caused by herpes viruses, such as in particular by Herpes simplex viruses, thus relating to a so called combination therapy. The at least one further active substance (immune modulators, e.g. glucocorticoids) being effective in treating a disease or disorder associated with viral infections or more preferably antiviral active compounds selected from the group consisting of nucleosidic drugs such as acyclovir, valacyclovir, penciclovir, ganciclovir, famciclovir and trifluridine, as well as compounds such as foscarnet and cidofovir.

Accordingly, the present invention further relates to a pharmaceutical composition comprising one or more of the compounds in micronized form as described herein and at least one pharmaceutically acceptable carrier and/or excipient and/or at least one further active substance being effective in treating a disease or disorder associated with viral infections (antiviral active compounds).

A further aspect of the invention relates to the use of the compounds described herein, which act as helicase primase inhibitors, in a combination therapy with oncolytic viruses for treating tumors, cancer or neoplasia.

A further embodiment of this additional aspect of the invention relates to a pharmaceutical composition for the use as an antidote in a combination therapy with oncolytic viruses for treating cancer, which comprises at least one helicase primase inhibitor as defined in any embodiment described herein, which acts to control, modulate, inhibit or shut off the activity of oncolytic viruses sensitive to said inhibitors used in cancer therapy, and which may further comprise at least one pharmaceutically acceptable carrier and/or excipient and/or at least one further active substance, such as antiviral active or immune modulating compounds, including checkpoint inhibitors, being effective in treating a disease or disorder associated with oncolytic viral infections used in the treatment of cancer.

A further embodiment of this additional aspect of the invention relates to the helicase primase inhibitor compounds or the pharmaceutical compositions of the present invention for the use in a combination therapy with oncolytic viruses as described in detail in WO2020/109389, wherein the cancer to be treated is solid cancer, preferably the cancer disease is selected from liver cancer, lung cancer, colon cancer, pancreas cancer, kidney cancer, brain cancer, melanoma and glioblastoma etc.

A further embodiment of this additional aspect of the invention relates to the helicase primase inhibitor compounds or the pharmaceutical compositions of the present invention for the use in a combination therapy with oncolytic viruses as described in WO2020/109389, wherein the oncolytic viruses are oncolytic herpesviruses.

5 A further embodiment of this additional aspect of the invention relates to the helicase primase inhibitor compounds or the pharmaceutical compositions of the present invention for the use in a combination therapy with oncolytic viruses as described in WO2020/109389, wherein the cancer therapy comprises infusion, injection, intratumoral injection or topical or transdermal application of the oncolytic viruses or oncolytic virus infected cells and/or of the helicase primase inhibitors or the pharmaceutical composition comprising the same.

10 A further embodiment of this additional aspect of the invention relates to the helicase primase inhibitor compounds or the pharmaceutical compositions of the present invention for the use in a combination therapy with oncolytic viruses as described in WO2020/109389, wherein the oncolytic viruses or oncolytic viruses infected cells are selected from an oncolytic wildtype, a clinical isolate or a laboratory herpesvirus strain or a genetically engineered or multi-mutated optionally attenuated or boosted oncolytic herpesvirus.

15 A further embodiment of this additional aspect of the invention relates to a kit comprising at least one of the helicase primase inhibitor compounds or the pharmaceutical composition of the present invention for the use in a combination therapy with oncolytic viruses as described in WO2020/109389, and at least one oncolytic virus selected from a wildtype, a laboratory strain, a clinical isolate and a genetically engineered or multi-mutated oncolytic virus.

A further embodiment of this additional aspect of the invention relates to said kit for the use in the treatment of cancer as defined herein.

20 The helicase primase inhibitor compounds, pharmaceutical compositions or kits for the use in a combination therapy with oncolytic viruses as described herein may be applied to one or more of the following patient groups: infants; herpes-positive patients, in particular oncolytic herpes-simplex-positive patients, for suppressing recurrence or oncolytic viral shedding; patients, in particular herpes-positive patients, in particular oncolytic herpes-simplex-positive patients, who
25 are resistant to nucleosidic antiviral therapy such as acyclovir, penciclovir, famciclovir, ganciclovir, valacyclovir and/or foscarnet or cidofovir.

Preparation of the Micronized HCl salts of the Formula (I)

30 A further aspect of the present invention relates to the preparation of the compounds of the Formula (I) in micronized form, including their co-crystals, hydrates or solvates.

The HCl salt compounds (I) can be prepared as described in in the above mentioned EP patent application EP22151820 and in the subsequent international application PCT/EP2023/050883, followed by a step of micronizing the resulting solid crystal forms until the desired d_{90} value and/or d_{90} particle size distribution is obtained.

35 Suitable measures of micronization comprise milling, grinding, micronization by using supercritical fluids and by manipulating the principles of solubility. The methods may further comprise a step of sieving. In principle, any known technique can be used which is suitable to achieve the intended reduction of average particle diameters to the micrometer range.

In a preferred aspect of the invention, micronization comprises the reduction of the particle size to d_{90} values and/or a d_{90} particle size distribution as defined herein.

Preferably, micronization comprises reducing the particle size (d_{90} value / d_{90} particle size distribution) of the crystalline forms resulting from synthesis and recrystallization by a factor of about 10, preferably by a factor of at least 15, more preferably by a factor of at least 20, even more preferably by a factor of at least 25, in each case compared to the non-micronized form obtainable from the synthesis and (re-)crystallization process.

Particle size distributions might be measured using sieve analysis, or laser diffraction (international standard ISO 13320-1; for further laser diffraction analytical technologies see for example <http://pharmazie-lehrbuch.de/kapitel/3-1.pdf>), or electronic sensing zone, light obstruction, sedimentation or microscopy which are procedures well known by the person skilled in the art. Sieving is one of the oldest methods of classifying powders by particle size distribution. A further method includes the determination of the volume particle size distribution by TEM (see e.g. Clariant Analytical Services TECHNICAL SHEET 106 TEM-Partikelgröße). Such methods are well known and described in the art such as in any analytical chemistry text book or by the United State Pharmacopeia's (USP) publication USP-NF (2004-Chapter 786-(The United States Pharmacopeial Convention, Inc., Rockville, Md.)) which describes the US Food and Drug Administration (FDA) enforceable standards. The used techniques are e.g. described in Pharmaceutical dosage forms: volume 2, 2nd edition, Ed.: H. A. Lieberman, L. Lachman, J. B. Schwartz is a good example. It also mentions (page 187) additional methods: Electronic sensing zone, light obstruction, air permeation, sedimentation in gas or liquid. The values of the particle size distributions used in the present invention are generally obtained by laser diffraction analysis (granulometry analysis).

More specifically the measurement of the particle size distributions are performed by laser diffraction according to Ph.Eur. 2.9.31 and USP <429>. The measurement is performed in suspension in water and Tween 80® using a measurement system from Beckman Coulter. The sample suspension is performed using sonification and calculation of the particle size distribution is performed using Fraunhofer calculation model. These laser diffraction analytical technologies yield volume weighted distributions. Here the contribution of each particle in the distribution relates to the volume of that particle (equivalent to mass if the density is uniform), i.e. the relative contribution will be proportional to size. More specifically the particle size distribution (PSD) in accordance with the present invention is carried out from 5 to 100 g samples up to the 2 kg GMP sample of the evaluated salt form which is analyzed with a laser particle size analyzer. Further details are shown in Examples 3, 5 and 7 below.

The micronized HCl salt compounds of the Formula (I) according to the invention may then be further processed and transferred into suitable pharmaceutical dosage forms, e.g. by filling into capsules, sachets or other comparable dosage forms, or by compressing the micronized particles into an suitable tablet form, including non-coated and coated tablets, retarded release tablet forms, chewable tablets etc.

40

EXPERIMENTAL PART**X-ray powder diffraction (XRPD)**

5 XRPD analysis was performed on a Bruker D2 Phase diffractometer using a copper anti-cathode, a mono-crystalline silicone sample holder and a position sensitive detector (LynxExe). Powder sample was loaded on a flat mono-crystalline silicone sample holder in a way to avoid preferred orientation and to ensure planarity of the specimen surface. Instrument operation conditions were as follows: ambient temperature and atmosphere; X-ray generator voltage 30 kV and intensity 10 mA; X-ray source: target Copper; emission radiation $K\alpha_1 = 0.15406$ nm, $K\alpha_2 = 0.15444$ nm, ratio $K\alpha_2/K\alpha_1 = 0.5$, $K\beta$ filter radiation Nickel; Slit: anti-divergence 1 nM, Sollers slit 2.5° ; Goniometer: angular sector analyzed from 4° to 45° or 4° to 50° for 2θ , step size 0.07° for 2θ ; Sample holder rotation speed: 30 rpm; Detection: exposition time per step size of goniometer 1 s.

Differential scanning calorimeter (DSC)

15 DSC analysis was performed on a Q1000 TA Instruments analyzer. The sample to be analyzed was weighed in an aluminium capsule, which was then crimped and put into the calorimeter oven. Instrument operation conditions were as follows: heater ramp $10^\circ\text{C}/\text{min}$; final temperature 230°C or 240°C ; carrier gas: nitrogen (Messer "qualité Azote 5.0") with flow rate of 50 mL/min.

Thermogravimetric analysis (TGA)

20 TGA analysis was performed on a TA Instruments TGA Hi-Res 2950. The sample was placed in an opened aluminium basket and analysed as follows: mass assay 5 mg; heating ramp $10^\circ\text{C}/\text{min}$; final temperature 500°C ; carrier gas: nitrogen (Messer "qualité Azote 5.0") with flow rate of 95-105 mL/min.

25 Laser diffraction granulometry analysis

Laser diffraction analysis was performed according to Ph.Eur. 2.9.31 and USP <429>.

Optical microscopy and particle-size distribution (PSD) assessment

30 Analysis by optical microscopy is performed on a LEICA DMIRB microscope equipped with a digital camera and a motorized stage. Acquisition of microscopy patterns is performed with a Microvision Instruments image analysis station. A few milligrams of the tested sample are put onto a microscope slide with silicon oil, covered with a coverslip, dispersed by a soft pressure applied onto the coverslip and then analyzed.

35 For the PSD assessment (granulometry analysis), about one milligram of the tested sample is dispersed in soybean oil previously saturated with the crystalline material to analyze. A few microliters are then dropped onto a microscope slide with coverslip and analyzed.

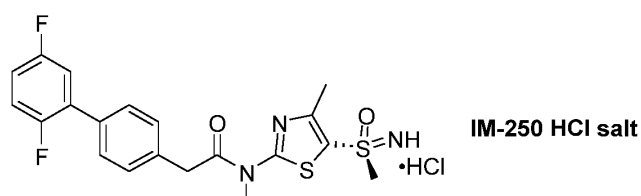
Image analysis (automatic objects detection) is associated to statistical analysis of the detected particles surfaces in order to establish a granulometric profile.

Characteristic diameter values are given as $d_{\min}$, d_{mean} , $d_{\max}$ (expressed as values of the distribution in number of particles), and as $d_x = Y$ which means that x percent of the total measured surface in the observed sample (considered to be the population) is made of particles presenting a diameter below Y μm .

5

Example 1: Synthesis of IM-250 HCl salt

(S)-2-(2',5'-Difluoro-[1,1'-biphenyl]-4-yl)-N-methyl-N-(4-methyl-5-(S-methylsulfonimidoyl)thiazol-2-yl)acetamide hydrochloride



10 IM-250 free base (205 mg, 470 μmol), obtainable as described for example as Example 7(–) in WO2019/068817, or as described in in the international application PCT/EP2023/050883, was solubilized in acetone (5 mL) by stirring on a rotary evaporator at 50°C and atmospheric pressure. A volume of 1N HCl corresponding to a 1:1 stoichiometry was the added. The solvent was then evaporated to dryness at 50°C leading to a film. This film was resuspended and solubilized in EtOH (4 mL) at rt. The solvent was then evaporated to dryness at 50°C leading to a meringue.

15 This film was resuspended and solubilized in isopropanol (1 mL) at 50°C, kept at rt leading to a partial demixing (after approx. 30 min) and then warmed again to 50°C for resolubilization. Very quickly, a strong crystallization occurred. One additional heating (50°C) and cooling (rt) cycle was performed (each 20 min) and the the sample was kept at rt for 2 days. The supernatant solvent

20 was removed and the powder was finally dried under a dynamic vacuum (70°C for 40 min) to obtain **IM-250 HCl salt** as colorless crystals.

XRPD analysis was conducted. FIG. 1 shows a XRPD pattern of **IM-250 HCl salt**. XRPD peaks were identified and are included in Table 1 below.

25 **Table 1:** XRPD Peak positions ($^{\circ}2\Theta$) and intensities

$^{\circ}2\text{-Theta } (^{\circ}2\Theta)$	Relative intensity (%)
9.1	24
11.2	13
11.8	20
13.7	100
14.1	17
16.4	23
17.0	55
17.3	21
17.7	98

2-Theta (°2θ)	Relative intensity (%)
18.2	34
19.4	26
19.8	42
21.1	23
21.3	33
21.8	33
22.6	15
22.8	62
23.4	11
23.7	11
24.0	15
24.2	16
25.0	30
26.3	35
26.9	12
27.1	19
27.4	11
27.7	22
32.0	11

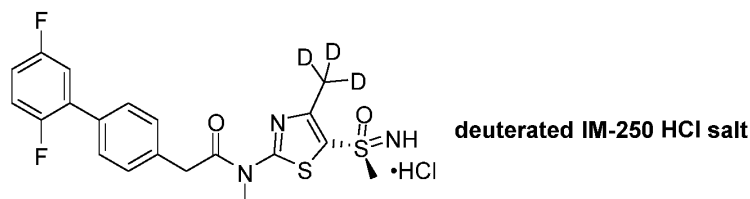
TGA and DSC analysis were performed. The TGA analysis showed a mass loss of 9.8% upon heating with an onset/endset temperature of 151/170°C before the main thermal decomposition can be detected with an onset temperature of 221°C. The 9.8% mass loss can be attributed to the departure of the HCl moiety. The DSC analysis revealed no true melting point. The not resolved double endothermic events observed from 160°C are concomitant to the loss of the HCl moiety observed on the TGA profile.

Alternative synthesis of **IM-250 HCl salt** with EtOH:

IM-250 free base (4.75 g), obtainable as described as Example 7(–) in WO2019/068817, was solubilized in acetone (150 mL) by stirring on a rotary evaporator at rt and atmospheric pressure. A volume of 1N HCl corresponding to a 1:1 stoichiometry was then added. The solvent was partially evaporated (about 100 mL) at 50°C. To better trap the water brought by the HCl solution, EtOH (50 mL) was added to the solution before performing a new evaporation up to a remaining volume of a few milliliters (syrupy liquid). The sample was then brought back at rt, leading to a beginning of crystallization. Additional EtOH (50 mL) was then added to the sample (always in order to help better removing the water brought with the HCl solution) leading to a non-expected increase of the crystallization. XRPD analysis was conducted. FIG. 2 shows a XRPD pattern of **IM-250 HCl salt**. The XRPD peaks identified were similar as shown in FIG. 1, indicating that the same HCl polymorph was produced.

Example 2: Synthesis of deuterated IM-250 HCl salt (d₃-IM-250 HCl salt)

(S)-2-(2',5'-Difluoro-[1,1'-biphenyl]-4-yl)-N-methyl-N-(4-(methyl-d₃)-5-(S-methylsulfonimidoyl)thiazol-2-yl)acetamide hydrochloride



- 5 To a solution of deuterated IM-250 free base (850 mg), obtainable as described as in WO2022/090409 or in the international application PCT/EP2023/050883, in acetone (50 mL) was added a quantity of 1N HCl corresponding to a 1:1 stoichiometry. The solution was homogenized at 40°C before the solvents were removed in vacuo (50°C), triggering the spontaneous crystallization of a white solid when only a few mL remained in the flask. In order to completely
- 10 remove the water brought by the HCl addition, EtOH (2 x 5 mL) was added to the flask and the concentration at 50°C was completed to dryness (only partial resolubilisation was observed during EtOH addition and stirring at 50°C). More EtOH (5 mL) was then added to the flask, which was stirred at 50°C and room temperature to resuspend the crystals. The supernatant was removed from the solid, which was then further dried under vacuum at 50-60°C for about 3 h. White crystals
- 15 of **deuterated IM-250 HCl salt (d₃-IM-250 HCl salt)** were obtained with good yield.

XRPD analysis was conducted. FIG. 3 shows a XRPD pattern of **IM-250 HCl salt (d₃-IM-250 HCl salt)**. XRPD peaks were identified and are included in Table 2 below.

Table 2: XRPD Peak positions (°2Θ) and intensities

°2-Theta (°2Θ)	Relative intensity (%)
9.2	27
11.3	13
11.9	15
13.8	100
14.2	23
16.5	32
16.9	29
17.4	13
17.8	90
18.3	30
19.5	17
19.8	28
21.0	25
21.3	24

°2-Theta (°2θ)	Relative intensity (%)
21.8	29
22.9	54
24.0	18
24.3	14
25.1	33
26.3	37
26.9	10
27.2	18
27.5	11
27.8	36
32.0	10
33.2	12

5 TGA and DSC analysis were performed. The TGA analysis showed a mass loss of 7.8% upon heating with an onset/endset temperature of 149/167°C before the main thermal decomposition can be detected with an onset temperature of 225°C. The 7.8% mass loss can be attributed to the departure of the HCl moiety. The DSC analysis revealed no true melting point, rather a wide endotherm with onset at about 188°C and peak at 194°C (transition enthalphy –15 J/g).

Example 3: Particle size distribution assessment of IM-250 HCl salt

10 Particle size distribution (PSD) assessment of the **IM-250 HCl salt** batch as prepared in Example 1 with EtOH was performed by microscopy and image analysis. Microscopy pictures are reported in Figure 4 and 5. PSD quantitative results, granulometric profile and distribution histogram are reported in Table 3, Figure 6 and Figure 7, respectively. The sample mostly contains large birefringent particles: 90% of particles have a particle size (d₉₀) below or equal to about 203 µm.

15 **Table 3:** Quantitative results of **IM-250 HCl salt** PSD assessment

Number of analyzed particles	Characteristic diameters (µm)							
	d _{min}	d _{mean}	d _{max}	d ₁₀	d ₂₅	d ₅₀	d ₇₅	d ₉₀
4003	1	14	335	11	23	47	106	203

With another batch of crude **IM-250 HCl salt** from another experiment an particle size (d₉₀) below or equal to about 193 µm was measured.

20 **Example 4: Micronization of IM-250 HCl salt**

IM-250 HCl salt was micronized at HOLOPHARM, leading to sample with a mean d₉₀ value of 6.1 µm. Figure 8 shows the particle size distribution of the micronized sample and Figure 9 a microscopy picture. As displayed in Figure 10 and Figure 11, the micronized sample shows the

same diffraction peak positions and the same DSC profile as the non-micronized bulk, indicating both samples comprise the same crystal form. The **IM-250 HCl salt** has shown to be chemically and physically stable as a bulk powder, as no change is observed after at least 3-weeks storage, both at 40°C/75%RH and at 60°C. By repeating this experiment, micronized material with $d_{90} = 3.3 \mu\text{m}$ and $d_{90} = 3.9 \mu\text{m}$, respectively, was obtained.

Example 5: Particle size distribution assessment of deuterated IM-250 HCl salt

Particle size distribution (PSD) assessment of a **d₃-IM-250 HCl salt** batch was performed by microscopy and image analysis. Microscopy pictures are reported in Figure 12 and 13. PSD quantitative results, granulometric profile and distribution histogram are reported in Table 4, Figure 14 and Figure 15, respectively. The sample mostly contains large birefringent particles: 90% of particles have a particle size (d_{90}) below or equal to about 156 μm .

Table 4: Quantitative results of **deuterated IM-250 HCl salt** PSD assessment

Number of analyzed particles	Characteristic diameters (μm)							
	d_{min}	d_{mean}	d_{max}	d_{10}	d_{25}	d_{50}	d_{75}	d_{90}
8750	1	15	540	15	30	59	99	156

Example 6: Micronization of deuterated IM-250 HCl salt

d₃-IM-250 HCl salt was micronized at HOLOPHARM in a similar manner, leading to sample with a mean d_{90} value of 3.0 μm . Figure 16 shows the particle size distribution of the micronized sample and Figure 17 a microscopy picture. XRPD analyses did not evidence any differences in the diffraction peak positions and intensities of **d₃-IM-250 HCl salt** before and after micronization. No change in the crystalline phase was observed.

Example 7: Micronization and PSD determination of IM-250 HCl salt (GMP-campaign)

The micronization was performed using spiral jet mill 100 from Hosokawa-Alpine. Starting material was 1.9 kg of **IM-250 HCl salt** with a PSD distribution according to Figure 18 with a d_{90} value of 139.8 μm . The micronization was performed using nitrogen as milling as with a pressure of 5 bar. The product is constantly transferred using a double screw feeder into the mill and collected in a fine filter bag after micronization and was isolated in 97% yield. The particle size distribution is performed by laser diffraction according to Ph.Eur. 2.9.31 and USP <429>. The measurement is performed in suspension in water and Tween 80® using a measurement system from Beckman Coulter. The sample suspension is performed using sonification and calculation of the particle size distribution is performed using Fraunhofer calculation model. The micronized material had a mean d_{90} value of 8.7 μm and PSD distribution according to Figure 19. The micronisation reduced the d_{90} value by a factor of 16.

Example 8: Bioavailability of micronized IM-250 HCl salt/d₃-IM-250 HCl salt versus non-micronized matched pairs in male mice

The oral bioavailability of suspended micronized crystalline **IM-250 HCl salt** (and **d₃-IM-250 HCl salt**) versus suspended non-micronized crystalline **IM-250 HCl salt** (and **d₃-IM-250 HCl salt**) after single dose oral administration in male C57bl/6 mice (ca. 8 weeks old) was examined. Animals (3 per group) had food withdrawn approximately 2 h before administration of 10 mg/kg of the test items. The suspensions were prepared directly by adding powder to 0.5% HPMC in PBS, ultrasonicated and orally administered with a gavage volume of 5 mL/kg. Blood samples (20 µL) were taken at 0.5 h, 1 h, 2 h, 5 h, 12 h and 24 h via capillary microsampling, collected from the tail vein into Li-heparin tubes. The samples were frozen on dry ice within 1-2 min of sampling and stored at -20°C until LC-MS/MS analysis measured via non-chiral LC-MS. The peak blood concentration (C_{max}), elimination half-life ($t_{1/2}$) and area-under-curve ($AUC_{0-24 h}$) was determined. The following data (Table 5) was obtained:

Table 5: Effect of micronization for micronized **IM-250 HCl salt**/d₃-**IM-250 HCl salt** in male mice on PK parameters compared to non-micronized matched pair

Sample	non-micronized IM-250 HCl salt	micronized IM-250 HCl salt	non-micronized d ₃ -IM-250 HCl salt	micronized d ₃ -IM-250 HCl salt
particle size d ₉₀ [µM]	193	3.3	156	3.9
C_{max} [ng/mL]	1210	4270	2570	3860
$t_{1/2}$ [h]	5.7	4.7	6.9	6.1
$AUC_{0-24 h}$ [ng/mL*h]	14400	41500	28600	44800

Relative bioavailability in male mice of different salt forms

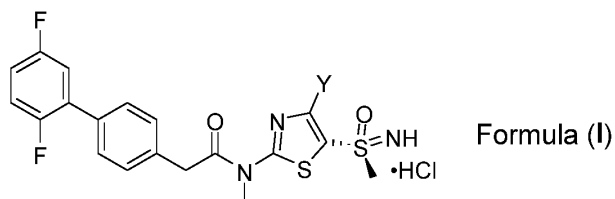
In the international application PCT/EP2023/050883 the relative bioavailability of different crystalline and salt forms versus suspended IM-250 (derived from a DMSO stock solution) after single dose oral administration in male C57bl/6 mice has been evaluated. The area-under-curve ($AUC_{0-24 h}$) and relative bioavailability towards the IM-250 suspension was calculated and compared between **IM-250 free base Form I**, an **IM-250 napadisylate salt** and **IM-250 HCl salt**. In a further test the effect of deuteration of the **IM-250 HCl salt** on PK parameters in male mice has been evaluated. All those IM-250 forms tested therein were non-micronized. In those comparative evaluation the inventors already showed the surprising improvement achievable with the HCl salts (deuterated and undeuterated).

Now, with the additional step of micronization, the pharmacokinetic properties of those selected salt forms can further be improved as shown herein.

Conclusion: With both micronized test items an improved bioavailability was obtained, as evident within this matched-pair comparison for C_{max} and $AUC_{0-24 h}$. This may allow a lower dosing in patients compared to non-micronized material.

CLAIMS:

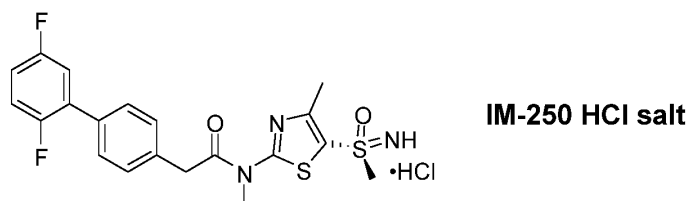
1. A micronized, crystalline form of a compound according to Formula (I)



wherein Y is selected from CH₃ and CD₃;

5 or a co-crystal, hydrate or solvate thereof, wherein the micronized crystalline form is characterized by a particle size (d₉₀ value / d₉₀ particle size distribution), which is reduced by a factor of at least 10 compared to the non-micronized form.

10 2. A micronized, crystalline form of the compound according to claim 1, with the following structure:



or a co-crystal, hydrate or solvate thereof.

15 3. A micronized, crystalline form of a compound according to claim 2, which is characterized by an X-ray powder diffractogram comprising at least 4 of the following peaks (±0.2 degrees 2θ): 13.7, 17.0, 17.7, 19.8, 21.8 and 22.8 degrees, as determined on a diffractometer using Cu-Kα radiation at a wavelength of 1.54 Å.

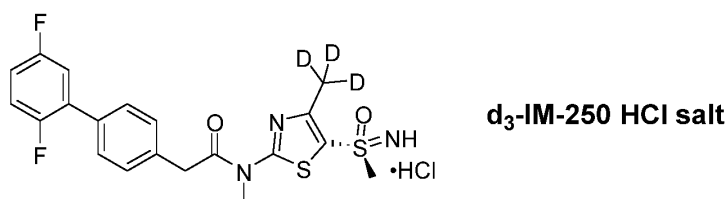
20 4. A micronized, crystalline form according to any one of claims 2 to 3, having an XRPD pattern substantially as shown in Figure 1 or 2.

25 5. A micronized, crystalline form according to any one of claims 2 to 4, wherein hydrochloride and (S)-2-(2',5'-difluoro-[1,1'-biphenyl]-4-yl)-N-methyl-N-(4-methyl-5-(S-methylsulfonimidoyl)thiazol-2-yl)acetamide are present in a 1:1 molar ratio.

6. A micronized, crystalline form according to any one of claims 2 to 5, with a d₉₀ value of less than or equal to about 20.0 μm, determined as defined in the specification.

30 7. A micronized, crystalline form according to any one of claims 2 to 5, with a d₉₀ value of less than or equal to about 6.0 μm, determined as defined in the specification.

8. A micronized, crystalline form of a compound according to claim 1, with the following structure:



or a co-crystal, hydrate or solvate thereof.

9. A micronized, crystalline form of a compound according to claim 8, which is characterized by an X-ray powder diffractogram comprising at least 4 of the following peaks (± 0.2 degrees 2θ): 11.3, 11.9, 13.8, 17.8, 19.8, 21.0, 21.3 and 21.8 degrees, as determined on a diffractometer using Cu-K α radiation at a wavelength of 1.54 Å.

10. A micronized, crystalline form according to any one of claims 8 to 9, having an XRPD pattern substantially as shown in Figure 3.

11. A micronized, crystalline form according to any one of claims 8 to 10, wherein hydrochloride and (S)-2-(2',5'-difluoro-[1,1'-biphenyl]-4-yl)-N-methyl-N-(4-(methyl-d₃)-5-(S-methylsulfonyl)thiazol-2-yl)acetamide are present in a 1:1 molar ratio.

12. A micronized, crystalline form according to any one of claims 8 to 11, with a d₉₀ value of less than or equal to about 20.0 μm , determined as defined in the specification.

13. A micronized, crystalline form according to any one of claims 8 to 12, with a d₉₀ value of less than or equal to about 6.0 μm , determined as defined in the specification.

14. A pharmaceutical composition comprising a therapeutically effective amount of a micronized, crystalline form of Formula (I) according to any one of claims 1 to 13, and at least one pharmaceutically acceptable carrier and/or excipient and/or at least one further active substance being effective in treating a disease or disorder associated with viral infections (antiviral active compounds).

15. The micronized, crystalline forms of any one of claims 1 to 13, or the pharmaceutical composition of claim 14 for the use in the prophylaxis and treatment of a herpes simplex infection or -mediated disorder, including the treatment or elimination of latent forms of herpes viruses in neuronal tissue and nerves, and including prevention and treatment of recurrence and reactivation of herpes infections or severe implications associated therewith, such as herpes simplex encephalitis (HSE).