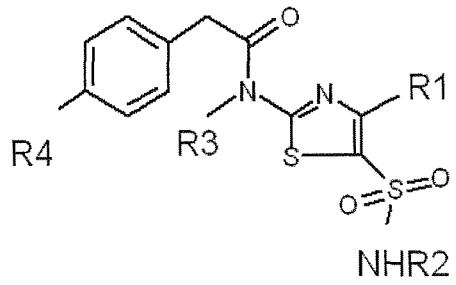
Moreover, the provided HPIs according to general Formula (I) and their pharmaceutically active equivalents exhibit longer half-life as compared to ACV and therefore a lower risk of drug troughs *(see Birkmann et al., Safety and human pharmacokinetics of AIC316, a potent helicase-primase inhibitor of herpes simplex virus (HSV), presented at 24th International Conference on antiviral research, Sofia, Bulgaria – Abstracts/ Antiviral Research 90 (2011) A21-A78).*

The person skilled in the art can derive additional objects and advantages of the present invention from the following more detailed description.

Brief description of the invention

In an aspect, there is provided the use of helicase-primase inhibitor according to Formula (I)



Formula (I),

or pharmaceutically acceptable derivatives thereof, or a stereoisomer thereof, or pharmaceutically acceptable salts, solvates or hydrates thereof in the manufacture of a medicament for treating AD,

whereby

-R1 is selected from hydrogen, C1-C4 alkyl, or cycloalkyl, and / or

-R2 is selected from hydrogen, C1-C4 alkyl, or cycloalkyl, and / or

-R3 is selected from hydrogen, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, hydroxyalkyl, or alkoxyalkyl and / or,

-R4 is selected from substituted or unsubstituted heteroaryl, or aryl;

wherein

a cycloalkyl group denotes a non-aromatic ring system containing three to eight carbon atoms, wherein one or more of the carbon atoms in the ring can be substituted by a group being O, S, SO, SO_2, N or NR';

-R' is independently H, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, or heteroaryl;

an aryl group denotes an aromatic group having five to ten carbon atoms, which can optionally be substituted by one or more substituents R'';

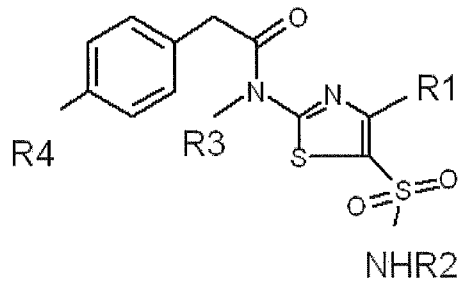
-R'' is independently H, $-CO_2R'$, -CONHR', -CO-alkyl, -CN, alkyl, alkoxy, -OH, -SH, cycloalkyl, heterocycloalkyl, halogen, haloalkyl, haloalkyloxy, hydroxyalkyl, heteroaryl, or aryl

a heteroaryl group denotes a five- or six-membered heterocyclic group which contains at least one heteroatom selected from O, N, and S and may be fused to another aromatic ring.

In another aspect, there is provided a pharmaceutical composition comprising crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide mono methanesulfonic acid monohydrate particles as disclosed herein and at least one pharmaceutically acceptable carrier, excipient, solvent and/or diluent.

In another aspect, there is provided the use of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, characterized by an absolute bioavailability of 70% ± 30% of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide, when said composition containing at least 25 mg as free base equivalent of the crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate is to be administered to said subject.

The present ~~invention~~ disclosure relates to the HPIs according to general Formula (I) or pharmaceutically acceptable derivatives thereof, or a stereoisomer thereof for use in a method of treating AD:



Formula (I),

wherein

-R1 is selected from hydrogen, C1-C4 alkyl, or cycloalkyl,

-R2 is selected from hydrogen, C1-C4 alkyl, or cycloalkyl,

-R3 is selected from hydrogen, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, hydroxyalkyl, or alkoxyalkyl

-R4 is selected from substituted or unsubstituted heteroaryl, or aryl;

whereby

a cycloalkyl group denotes a non-aromatic ring system containing three to eight carbon atoms, wherein one or more of the carbon atoms in the ring can be substituted by a group being O, S, SO, SO_2, N or NR';

-R' is independently H, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, or heteroaryl;

an aryl group denotes an aromatic group having five to ten carbon atoms, which can optionally be substituted by one or more substituents R'';

-R'' is independently H, $-CO_2R'$, -CONHR', -CO-alkyl, -CN, alkyl, alkoxy, -OH, -SH, cycloalkyl, heterocycloalkyl, halogen, haloalkyl, haloalkyloxy, hydroxyalkyl, heteroaryl, or aryl

a heteroaryl group denotes a five- or six-membered heterocyclic group which contains at least one heteroatom selected from O, N, and S and may be fused to another aromatic ring.

Further the present ~~invention~~ disclosure relates to the pharmaceutically acceptable salts, solvates, and hydrates of the HPIs according to general Formula (I) for use in a method of treating AD.

In another embodiment, the present ~~invention~~ disclosure relates to the HPIs according to general Formula (I) or pharmaceutically acceptable derivatives thereof, or a stereoisomer thereof or pharmaceutically acceptable salts, solvates, and hydrates thereof for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

It has been found by the inventors that the HPIs according to the general Formula (I) or pharmaceutically acceptable derivatives thereof, or a stereoisomer thereof as well as pharmaceutically acceptable salts, solvates and hydrates thereof are effective inhibitors of HSV-1 infections, and concomitant, surprisingly and unexpectedly, exhibit superior inhibitory efficacy for the accumulating key AD proteins Aβ and P-tau that occur during HSV-1 infection.

Thus, the present ~~invention~~ disclosure provides for a novel antiviral approach for a method of treating the neurodegenerative processes of AD. In particular, the present ~~invention~~ disclosure provides for a novel approach for a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

It is another objective of the present ~~invention~~ disclosure to also provide for a specific form of a salt of the HPI compound N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide which exhibits improved properties in regard to stability and bioavailability, and thus makes this specific form of the salt preferable for the manufacturing of pharmaceutical compositions and to provide pharmaceutical compositions containing such a specific salt so that these pharmaceutical compositions exhibit improved properties in regard to stability and bioavailability of the contained specific form of a salt of the compound N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide. Hereby, it should be noted that specifically in regard of the crystalline mono mesylate monohydrate salt of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]-acetamide, only the free base form of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]–acetamide exhibits bioavailability in a subject since the administered crystalline mono mesylate monohydrate salt of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]-acetamide turns in vivo into the corresponding free base form.

Accordingly, another ~~aspect~~ embodiment of the present ~~invention~~ disclosure is directed to the PK profiles resulting from administration of the crystalline mono mesylate monohydrate salt of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]-acetamide in vivo, when administered in a pharmaceutical composition of the instant ~~invention~~ disclosure to a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD. The PK in vivo profiles of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]-acetamide enable sufficient absolute bioavailability of 70% ± 30% thereof.

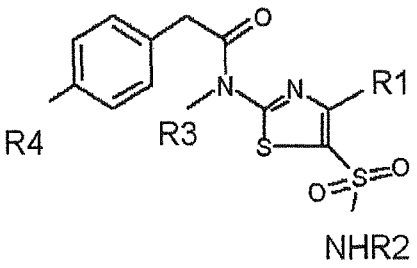
The objectives of the present ~~invention~~ disclosure are solved by the teaching of the independent claims. Further advantageous features, ~~aspects~~embodiments, and details of the ~~invention~~ present disclosure are evident from the dependent claims, the description, the drawings (Figs.), and the examples of the present application.

Detailed Description of the invention

The subject matter of the present invention relates to the novel use of HPIs in a method of treating AD. In particular, the present invention relates to the novel use of HPIs in a method of treating AD in a subject that is having HSV-1 infection and is having AD or said subject is

Claims

1) Helicase-primase inhibitor according to Formula (I)



Formula (I),

or pharmaceutically acceptable derivatives thereof, or a stereoisomer thereof, or pharmaceutically acceptable salts, solvates or hydrates thereof for use in a method of treating AD,

whereby

-R1 is selected from hydrogen, C1-C4 alkyl, or cycloalkyl, and / or

-R2 is selected from hydrogen, C1-C4 alkyl, or cycloalkyl, and / or

-R3 is selected from hydrogen, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, hydroxyalkyl, or alkoxyalkyl and / or,

-R4 is selected from substituted or unsubstituted heteroaryl, or aryl;

wherein

a cycloalkyl group denotes a non-aromatic ring system containing three to eight carbon atoms, wherein one or more of the carbon atoms in the ring can be substituted by a group being O, S, SO, SO_2, N or NR';

-R' is independently H, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, or heteroaryl;

an aryl group denotes an aromatic group having five to ten carbon atoms, which can optionally be substituted by one or more substituents R'';

-R'' is independently H, -CO_2R', -CONHR', -CO-alkyl, -CN, alkyl, alkoxy, -OH, -SH, cycloalkyl, heterocycloalkyl, halogen, haloalkyl, haloalkyloxy, hydroxyalkyl, heteroaryl, or aryl

a heteroaryl group denotes a five- or six-membered heterocyclic group which contains at least one heteroatom selected from O, N, and S and may be fused to another aromatic ring.

2) Helicase-primase inhibitor according to claim 1, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

3) Helicase-primase inhibitor according to claim 2, wherein said subject is having HSV-1 infection and is suspected of having AD, when said subject shows at least the below manifested symptoms of mild cognitive impairment during clinical examination, i.e.

- a change in cognition
- impairment in one or more cognitive domains
- preservation of independence in functional abilities
- not demented,

and wherein said subject is positive for HSV-1 infection when clinically examined by HSV-test.

4) Helicase-primase inhibitor according to any of the claims 2 to 3, characterized in that said subject is positive for HSV-1 infection in an ex vivo HSV-test and possesses a specific genetic factor type 4 allele of the apolipoprotein E gene, i.e. APOE4 when said subject is positive for *APOE4* in an *ex vivo* venous blood sample examined by APOE genotyping test.

5) Helicase-primase inhibitor according to any of the claims 2 to 3, characterized in that said subject is positive for HSV-1 infection in an *ex vivo* HSV-test and said subject is positive for PSEN1 in an *ex vivo* PSEN1 test.

6) Helicase-primase inhibitor according to any of the claims 2 to 3, characterized in that said subject is positive for HSV-1 infection in an *ex vivo* HSV-test and said subject is positive for the presence of Aβ42 and P-tau in an *ex vivo* Tau/Aβ42 test.

7) Helicase-primase inhibitor according to any of the claims 2 to 6, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD,

whereby

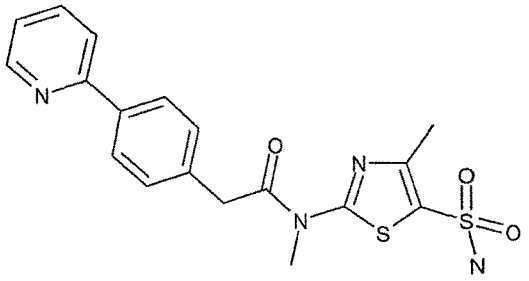
-R1 is selected from hydrogen, or C1-C4 alkyl,
-R2 is selected from hydrogen, or C1-C4 alkyl,
-R3 is selected from hydrogen, alkyl, cycloalkyl, or heterocycloalkyl,
-R4 is selected from substituted or unsubstituted heteroaryl, or aryl.

8) Helicase-primase inhibitor according to any of the claims 2 to 7, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD,

whereby

-R1 is selected from hydrogen,
-R2 is selected from hydrogen,
-R3 is selected from hydrogen, alkyl, or cycloalkyl,
-R4 is selected from substituted or unsubstituted heteroaryl.

9) Helicase-primase inhibitor N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamid

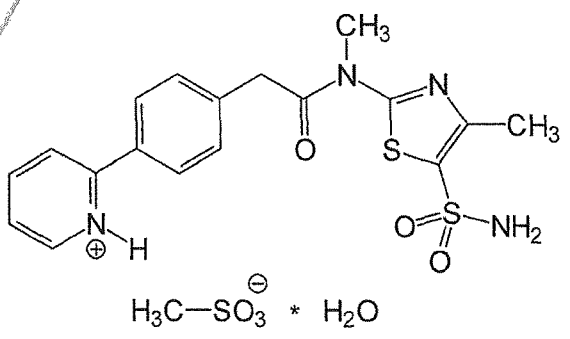


according to any of the claims 2 to 8, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

10) A pharmaceutical composition comprising at least one helicase-primase inhibitor according to any of the claims 2 to 9 and at least one pharmaceutically acceptable carrier, excipient, solvent and/or diluent for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

11) Helicase-primase inhibitor according to any of the claims 1 to 9, or a composition according to claim 10 for oral administration.

12) Helicase-primase inhibitor according to any of the claims 2 to 8, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, whereby said helicase-primase inhibitor is selected from crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate particles of the following formula



wherein said particles have a particle size range from 1 to 500 μm, a particle size distribution which is defined by d(0.1) from 2 to 100 μm, d(0.5) from 30 to 210 μm and d(0.9) from 70 to 400 μm and a specific surface area of less than 1.0 m^2/g.

13) Helicase-primase inhibitor according to any of the claims 2 to 8 and 12, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, wherein the N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate particles of claim 12 have a particle size range from 2 μm to 400 μm.

14) Helicase-primase inhibitor according to any of the claims 2 to 8 and 12 to 13, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, wherein the particles of any of the claims 12 to 13 have a particle size distribution which is defined by d(0.1) from 10 to 75 μm, d(0.5) from 100 to 175 μm, d(0.9) from 200 to 350 μm.

15) Helicase-primase inhibitor according to any of the claims 2 to 8 and 12 to 14, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, wherein the particles of any of the claims 12 to 14 have a specific surface area of less than 0.3 m^2/g.

16) A pharmaceutical composition comprising crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide mono methanesulfonic acid monohydrate particles as defined in any of the claims 12 to 15 and at least one pharmaceutically acceptable carrier, excipient, solvent and/or diluent.

17) The pharmaceutical composition according to claim 16, wherein the crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate particles have a particle size range as defined in claim 13.

18) The pharmaceutical composition according to claim 16 or 17, wherein the crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-

phenyl]acetamide mono methanesulfonic acid monohydrate particles have a particle size distribution as defined in claim 14.

19) The pharmaceutical composition according to any one of the claims 16 to 18, wherein the crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate particles have a specific surface area as defined in claim 15.

20) The pharmaceutical composition according to any of the claims 16 to 19, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, characterized by an absolute bioavailability of 70% ± 30% of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide, when administered in said composition containing at least 25 mg as free base equivalent of the crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate to said subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

21) The pharmaceutical composition according to any of the claims 16 to 20, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, characterized by a mean maximum blood plasma concentration (mean C_{max}) of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide in said subject of at least one of

h) 608 ± 184 ng/ml for a 40 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose administered;

i) 1306 ± 125 ng/ml for a 80 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-

phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose administered;

j) 2613 ± 1341 ng/ml for a 160 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose administered;

k) 3600 ± 752 ng/ml for a 240 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose administered;

l) 4648 ± 1813 ng/ml for a 320 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose administered;

m) 6926 ± 1656 ng/ml for a 400 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose administered;

n) 6921 ± 2190 ng/ml for a 480 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose administered,

in said composition to said subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

22) The pharmaceutical composition according to any of the claims 16 to 21, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, characterized by a mean

maximum blood plasma concentration (mean C_{max}) of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide in a subject of at least one of

h) 608 ± 184 ng/ml for a 40 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 10090 ± 3114 ng-h/ml in a subject for a 40 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 72 ± 3 h on average; said dosage being a single oral dose administered;

i) 1306 ± 125 ng/ml for a 80 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 21940 ± 2057 ng-h/ml in a subject for a 80 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 74 ± 5 h on average; said dosage being a single oral dose administered;

j) 2613 ± 1341 ng/ml for a 160 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 40470 ± 16700 ng-h/ml in a subject for a 160 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 63 ± 6 h on average; said dosage being a single oral dose administered;

k) 3600 ± 752 ng/ml for a 240 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized

by an AUC_{0-24h} of 59610 ± 12770 ng-h/ml in a subject for a 240 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 64 ± 5 h on average; said dosage being a single oral dose administered;

l) 4648 ± 1813 ng/ml for a 320 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 76250 ± 27630 ng-h/ml in a subject for a 320 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 57 ± 3 h on average; said dosage being a single oral dose administered;

m) 6926 ± 1656 ng/ml for a 400 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 104800 ± 25740 ng-h/ml in a subject for a 400 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 57 ± 4 h on average; said dosage being a single oral dose administered;

n) 6921 ± 2190 ng/ml for a 480 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 112800 ± 34260 ng-h/ml in a subject for a 480 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 53 ± 4 h on average; said dosage being a single oral dose administered,

in said composition to said subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

25) The pharmaceutical composition according to any of the claims 16 to 20, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, characterized by a mean maximum blood plasma concentration at steady state (mean Cmax,ss) of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide in a subject of at least one of

d) 1358 ± 167 ng/ml for a 25 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a steady state dose after once daily single doses administered for 21 days;

e) 6358 ± 1701 ng/ml for a 100 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a steady state dose after once daily single doses administered for 21 days;

f) 9987 ± 2608 ng/ml for a 200 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a steady state dose after once daily single doses administered for 21 days,

in said composition to said subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

26) The pharmaceutical composition according to any of the claims 16 to 20 and 23, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, characterized by a mean maximum blood plasma concentration at steady state (mean $C_{max,ss}$) of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide in a subject of at least one of

c) 1358 ± 167 ng/ml for a 25 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an $AUC_{\tau,ss}$ of 23430 ± 3020 ng-h/ml in a subject for a 25 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 69 ± 6 h on average, said dosage being a steady state dose after once daily single doses administered for 21 days;

d) 6358 ± 1701 ng/ml for a 100 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an $AUC_{\tau,ss}$ of 108800 ± 28610 ng-h/ml in a subject for a 100 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 60 ± 4 h on average, said dosage being a steady state dose after once daily single doses administered for 21 days,

in said composition to said subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

25) The pharmaceutical composition of claim 20, wherein said absolute bioavailability is achieved in a human.

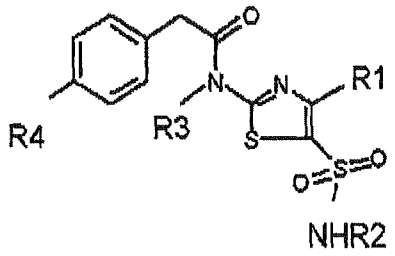
26) The pharmaceutical composition of the claims 16 to 24, wherein said mean C_{max} and $C_{max,ss}$ is achieved in a human.

27) The pharmaceutical composition of the claims 22 and 24, wherein said $AUC_{0\text{-}24h}$ and $t_{1/2z}$ is achieved in a human.

28) The pharmaceutical composition of the claim 24, wherein said $AUC_{\tau,ss}$ and $t_{1/2z}$ is achieved in a human.

AMENDED CLAIMS
received by the International Bureau on 30 October 2014 (30.10.2014)

1) Helicase-primase inhibitor according to Formula (I)



Formula (I),

or pharmaceutically acceptable derivatives thereof, or a stereoisomer thereof, or pharmaceutically acceptable salts, solvates or hydrates thereof for use in a method of treating AD,

whereby

-R1 is selected from hydrogen, C1-C4 alkyl, or cycloalkyl, and / or

-R2 is selected from hydrogen, C1-C4 alkyl, or cycloalkyl, and / or

-R3 is selected from hydrogen, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, hydroxyalkyl, or alkoxyalkyl and / or,

-R4 is selected from substituted or unsubstituted heteroaryl, or aryl;

wherein

a cycloalkyl group denotes a non-aromatic ring system containing three to eight carbon atoms, wherein one or more of the carbon atoms in the ring can be substituted by a group being O, S, SO, SO_2, N or NR';

-R' is independently H, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, or heteroaryl;

an aryl group denotes an aromatic group having five to ten carbon atoms, which can optionally be substituted by one or more substituents R'';

-R'' is independently H, $-CO_2R'$, -CONHR', -CO-alkyl, -CN, alkyl, alkoxy, -OH, -SH, cycloalkyl, heterocycloalkyl, halogen, haloalkyl, haloalkyloxy, hydroxyalkyl, heteroaryl, or aryl

a heteroaryl group denotes a five- or six-membered heterocyclic group which contains at least one heteroatom selected from O, N, and S and may be fused to another aromatic ring.

2) Helicase-primase inhibitor according to claim 1, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

3) Helicase-primase inhibitor for use according to claim 2, wherein said subject is having HSV-1 infection and is suspected of having AD, when said subject shows at least the below manifested symptoms of mild cognitive impairment during clinical examination, i.e.

- a change in cognition
- impairment in one or more cognitive domains
- preservation of independence in functional abilities
- not demented,

and wherein said subject is positive for HSV-1 infection when clinically examined by HSV-test.

4) Helicase-primase inhibitor for use according to any of the claims 2 to 3, characterized in that said subject is positive for HSV-1 infection in an ex vivo HSV-test and possesses a specific genetic factor type 4 allele of the apolipoprotein E gene, i.e. APOE4 when said subject is positive for *APOE4* in an *ex vivo* venous blood sample examined by APOE genotyping test.

5) Helicase-primase inhibitor for use according to any of the claims 2 to 3, characterized in that said subject is positive for HSV-1 infection in an *ex vivo* HSV-test and said subject is positive for PSEN1 in an *ex vivo* PSEN1 test.

6) Helicase-primase inhibitor for use according to any of the claims 2 to 3, characterized in that said subject is positive for HSV-1 infection in an *ex vivo* HSV-test and said subject is positive for the presence of Aβ42 and P-tau in an *ex vivo* Tau/Aβ42 test.

7) Helicase-primase inhibitor according to any of the claims 2 to 6, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD,

whereby

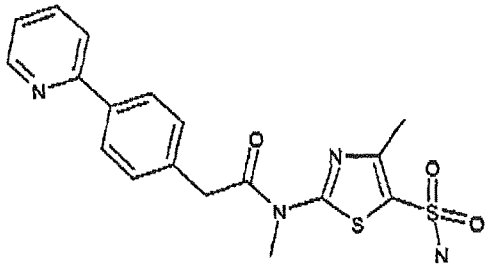
-R1 is selected from hydrogen, or C1-C4 alkyl,
-R2 is selected from hydrogen, or C1-C4 alkyl,
-R3 is selected from hydrogen, alkyl, cycloalkyl, or heterocycloalkyl,
-R4 is selected from substituted or unsubstituted heteroaryl, or aryl.

8) Helicase-primase inhibitor according to any of the claims 2 to 7, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD,

whereby

-R1 is selected from hydrogen,
-R2 is selected from hydrogen,
-R3 is selected from hydrogen, alkyl, or cycloalkyl,
-R4 is selected from substituted or unsubstituted heteroaryl.

9) Helicase-primase inhibitor N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamid

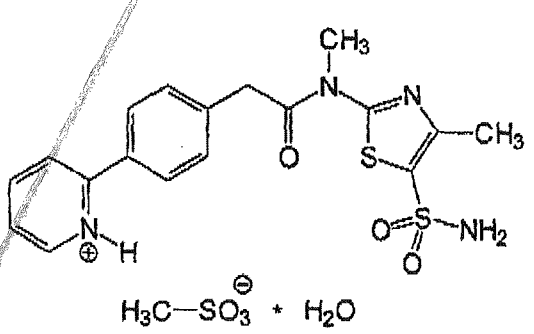


according to any of the claims 2 to 8, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

10) A pharmaceutical composition comprising at least one helicase-primase inhibitor according to any of the claims 2 to 9 and at least one pharmaceutically acceptable carrier, excipient, solvent and/or diluent for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

11) Helicase-primase inhibitor for use according to any of the claims 1 to 9, or a composition according to claim 10 for oral administration.

12) Helicase-primase inhibitor according to any of the claims 2 to 8, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, whereby said helicase-primase inhibitor is selected from crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate particles of the following formula



wherein said particles have a particle size range from 1 to 500 µm, a particle size distribution which is defined by d(0.1) from 2 to 100 µm, d(0.5) from 30 to 210 µm and d(0.9) from 70 to 400 µm and a specific surface area of less than 1.0 m^2/g.

13) Helicase-primase inhibitor according to any of the claims 2 to 8 and 12, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, wherein the N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate particles of claim 12 have a particle size range from 2 µm to 400 µm.

14) Helicase-primase inhibitor according to any of the claims 2 to 8 and 12 to 13, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, wherein the particles of any of the claims 12 to 13 have a particle size distribution which is defined by d(0.1) from 10 to 75 µm, d(0.5) from 100 to 175 µm, d(0.9) from 200 to 350 µm.

15) Helicase-primase inhibitor according to any of the claims 2 to 8 and 12 to 14, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, wherein the particles of any of the claims 12 to 14 have a specific surface area of less than 0.3 m^2/g.

16) A pharmaceutical composition comprising crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide mono methanesulfonic acid monohydrate particles as defined in any of the claims 12 to 15 and at least one pharmaceutically acceptable carrier, excipient, solvent and/or diluent.

17) The pharmaceutical composition according to claim 16, wherein the crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate particles have a particle size range as defined in claim 13.

18) The pharmaceutical composition according to claim 16 or 17, wherein the crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-

phenyl]acetamide mono methanesulfonic acid monohydrate particles have a particle size distribution as defined in claim 14.

19) The pharmaceutical composition according to any one of the claims 16 to 18, wherein the crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate particles have a specific surface area as defined in claim 15.

20) The pharmaceutical composition according to any of the claims 16 to 19, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, characterized by an absolute bioavailability of 70% ± 30% of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide, when administered in said composition containing at least 25 mg as free base equivalent of the crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate to said subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

21) The pharmaceutical composition according to any of the claims 16 to 20, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, characterized by a mean maximum blood plasma concentration (mean C_{max}) of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide in said subject of at least one of

a) 608 ± 184 ng/ml for a 40 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose administered;

b) 1306 ± 125 ng/ml for a 80 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-

phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose administered;

c) 2613 ± 1341 ng/ml for a 160 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose administered;

d) 3600 ± 752 ng/ml for a 240 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose administered;

e) 4648 ± 1813 ng/ml for a 320 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose administered;

f) 6926 ± 1656 ng/ml for a 400 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose administered;

g) 6921 ± 2190 ng/ml for a 480 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose administered,

in said composition to said subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

22) The pharmaceutical composition according to any of the claims 16 to 21, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, characterized by a mean

maximum blood plasma concentration (mean C_{max}) of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide in a subject of at least one of

a) 608 ± 184 ng/ml for a 40 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 10090 ± 3114 ng-h/ml in a subject for a 40 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 72 ± 3 h on average; said dosage being a single oral dose administered;

b) 1306 ± 125 ng/ml for a 80 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 21940 ± 2057 ng-h/ml in a subject for a 80 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 74 ± 5 h on average; said dosage being a single oral dose administered;

c) 2613 ± 1341 ng/ml for a 160 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 40470 ± 16700 ng-h/ml in a subject for a 160 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 63 ± 6 h on average; said dosage being a single oral dose administered;

d) 3600 ± 752 ng/ml for a 240 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or

characterized by an AUC_{0-24h} of 59610 ± 12770 ng-h/ml in a subject for a 240 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 64 ± 5 h on average; said dosage being a single oral dose administered;

e) 4648 ± 1813 ng/ml for a 320 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 76250 ± 27630 ng-h/ml in a subject for a 320 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 57 ± 3 h on average; said dosage being a single oral dose administered;

f) 6926 ± 1656 ng/ml for a 400 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 104800 ± 25740 ng-h/ml in a subject for a 400 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 57 ± 4 h on average; said dosage being a single oral dose administered;

g) 6921 ± 2190 ng/ml for a 480 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 112800 ± 34260 ng-h/ml in a subject for a 480 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 53 ± 4 h on average; said dosage being a single oral dose administered,

in said composition to said subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

23) The pharmaceutical composition according to any of the claims 16 to 20, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, characterized by a mean maximum blood plasma concentration at steady state (mean Cmax,ss) of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide in a subject of at least one of

a) 1358 ± 167 ng/ml for a 25 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a steady state dose after once daily single doses administered for 21 days;

b) 6358 ± 1701 ng/ml for a 100 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a steady state dose after once daily single doses administered for 21 days;

c) 9987 ± 2608 ng/ml for a 200 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a steady state dose after once daily single doses administered for 21 days,

in said composition to said subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

24) The pharmaceutical composition according to any of the claims 16 to 20 and 23, for use in a method of treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, characterized by a mean maximum blood plasma concentration at steady state (mean $C_{max,ss}$) of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide in a subject of at least one of

a) 1358 ± 167 ng/ml for a 25 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an $AUC_{\tau,ss}$ of 23430 ± 3020 ng-h/ml in a subject for a 25 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 69 ± 6 h on average, said dosage being a steady state dose after once daily single doses administered for 21 days;

b) 6358 ± 1701 ng/ml for a 100 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an $AUC_{\tau,ss}$ of 108800 ± 28610 ng-h/ml in a subject for a 100 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 60 ± 4 h on average, said dosage being a steady state dose after once daily single doses administered for 21 days,

in said composition to said subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

25) The pharmaceutical composition for use of claim 20, wherein said absolute bioavailability is achieved in a human.

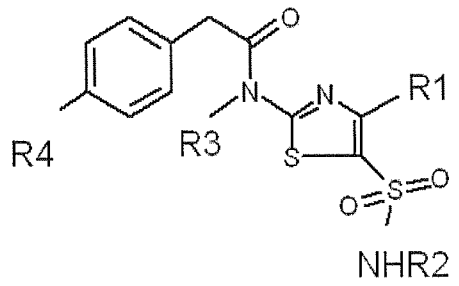
26) The pharmaceutical composition for use of the claims 16 to 24, wherein said mean C_{max} and $C_{max,ss}$ is achieved in a human.

27) The pharmaceutical composition for use of the claims 22 and 24, wherein said AUC_{0-24b} and $t_{1/2z}$ is achieved in a human.

28) The pharmaceutical composition for use of the claim 24, wherein said $AUC_{\tau,ss}$ and $t_{1/2z}$ is achieved in a human.

Claims

1) Use of helicase-primase inhibitor according to Formula (I)



Formula (I),

or pharmaceutically acceptable derivatives thereof, or a stereoisomer thereof, or pharmaceutically acceptable salts, solvates or hydrates thereof in the manufacture of a medicament for treating AD,

whereby

-R1 is selected from hydrogen, C1-C4 alkyl, or cycloalkyl, and / or

-R2 is selected from hydrogen, C1-C4 alkyl, or cycloalkyl, and / or

-R3 is selected from hydrogen, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, hydroxyalkyl, or alkoxyalkyl and / or,

-R4 is selected from substituted or unsubstituted heteroaryl, or aryl;

wherein

a cycloalkyl group denotes a non-aromatic ring system containing three to eight carbon atoms, wherein one or more of the carbon atoms in the ring can be substituted by a group being O, S, SO, SO_2, N or NR';

-R' is independently H, haloalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, or heteroaryl;

an aryl group denotes an aromatic group having five to ten carbon atoms, which can optionally be substituted by one or more substituents R'';

-R'' is independently H, -CO_2R', -CONHR', -CO-alkyl, -CN, alkyl, alkoxy, -OH, -SH, cycloalkyl, heterocycloalkyl, halogen, haloalkyl, haloalkyloxy, hydroxyalkyl, heteroaryl, or aryl

a heteroaryl group denotes a five- or six-membered heterocyclic group which contains at least one heteroatom selected from O, N, and S and may be fused to another aromatic ring.

2) Use of helicase-primase inhibitor according to claim 1, wherein the treatment of AD is in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

3) Use of helicase-primase inhibitor according to claim 2, wherein said subject is having HSV-1 infection and is suspected of having AD, when said subject shows at least the below manifested symptoms of mild cognitive impairment during clinical examination, i.e.

- a change in cognition
- impairment in one or more cognitive domains
- preservation of independence in functional abilities
- not demented,

and wherein said subject is positive for HSV-1 infection when clinically examined by HSV-test.

4) Use of helicase-primase inhibitor according to any of the claims 2 to 3, characterized in that said subject is positive for HSV-1 infection in an ex vivo HSV-test and possesses a specific genetic factor type 4 allele of the apolipoprotein E gene, i.e. APOE4 when said subject is positive for *APOE4* in an *ex vivo* venous blood sample examined by APOE genotyping test.

5) Use of helicase-primase inhibitor according to any of the claims 2 to 3, characterized in that said subject is positive for HSV-1 infection in an *ex vivo* HSV-test and said subject is positive for PSEN1 in an *ex vivo* PSEN1 test.

6) Use of helicase-primase inhibitor according to any of the claims 2 to 3, characterized in that said subject is positive for HSV-1 infection in an *ex vivo* HSV-test and said subject is positive for the presence of Aβ42 and P-tau in an *ex vivo* Tau/Aβ42 test.

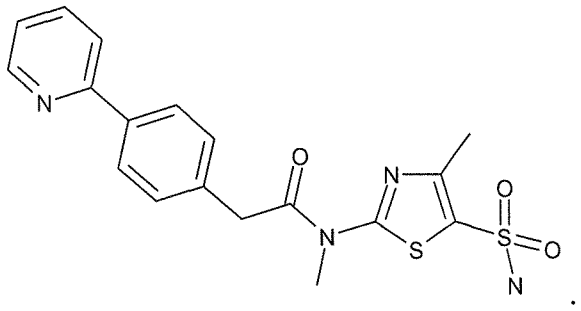
7) Use of helicase-primase inhibitor according to any of the claims 2 to 6, whereby

-R1 is selected from hydrogen, or C1-C4 alkyl,
-R2 is selected from hydrogen, or C1-C4 alkyl,
-R3 is selected from hydrogen, alkyl, cycloalkyl, or heterocycloalkyl,
-R4 is selected from substituted or unsubstituted heteroaryl, or aryl.

8) Use of helicase-primase inhibitor according to any of the claims 2 to 7, whereby

-R1 is selected from hydrogen,
-R2 is selected from hydrogen,
-R3 is selected from hydrogen, alkyl, or cycloalkyl,
-R4 is selected from substituted or unsubstituted heteroaryl.

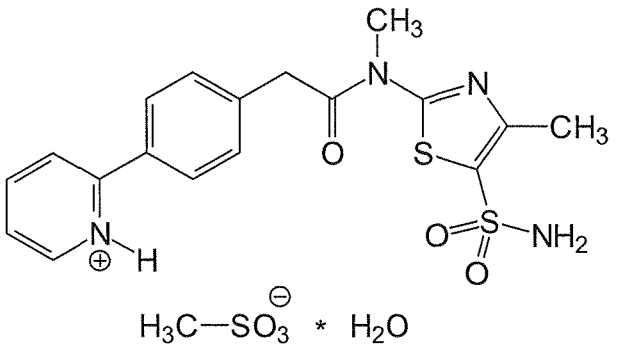
9) Use according to any of the claims 2 to 8, wherein the helicase-primase inhibitor is N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamid



10) Use of a pharmaceutical composition comprising at least one helicase-primase inhibitor according to any of the claims 2 to 9 and at least one pharmaceutically acceptable carrier, excipient, solvent and/or diluent in the manufacture of a medicament for treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD.

11) Use of helicase-primase inhibitor according to any of the claims 1 to 10, wherein the medicament is formulated for oral administration.

12) Use of helicase-primase inhibitor according to any of the claims 2 to 8, whereby said helicase-primase inhibitor is selected from crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate particles of the following formula



wherein said particles have a particle size range from 1 to 500 µm, a particle size distribution which is defined by d(0.1) from 2 to 100 µm, d(0.5) from 30 to 210 µm and d(0.9) from 70 to 400 µm and a specific surface area of less than 1.0 m^2/g.

13) Use of helicase-primase inhibitor according to any of the claims 2 to 8 and 12, wherein the N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate particles of claim 12 have a particle size range from 2 µm to 400 µm.

14) Use of helicase-primase inhibitor according to any of the claims 2 to 8 and 12 to 13, wherein the particles of any of the claims 12 to 13 have a particle size distribution which is defined by d(0.1) from 10 to 75 µm, d(0.5) from 100 to 175 µm, d(0.9) from 200 to 350 µm.

15) Use of helicase-primase inhibitor according to any of the claims 2 to 8 and 12 to 14, wherein the particles of any of the claims 12 to 14 have a specific surface area of less than 0.3 m^2/g.

16) A pharmaceutical composition comprising crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)phenyl]acetamide mono methanesulfonic

acid monohydrate particles as defined in any of the claims 12 to 15 and at least one pharmaceutically acceptable carrier, excipient, solvent and/or diluent.

17) The pharmaceutical composition according to claim 16, wherein the crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate particles have a particle size range as defined in claim 13.

18) The pharmaceutical composition according to claim 16 or 17, wherein the crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate particles have a particle size distribution as defined in claim 14.

19) The pharmaceutical composition according to any one of the claims 16 to 18, wherein the crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate particles have a specific surface area as defined in claim 15.

20) Use of the pharmaceutical composition according to any of the claims 16 to 19, in the manufacture of a medicament for treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, characterized by an absolute bioavailability of 70% ± 30% of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide, when said composition containing at least 25 mg as free base equivalent of the crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate is to be administered to said subject.

21) Use of the pharmaceutical composition according to any of the claims 16 to 20, in the manufacture of a medicament for treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, characterized by a mean maximum blood plasma concentration (mean C_{max}) of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide in said subject of at least one of

a) 608 ± 184 ng/ml for a 40 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose to be administered;

b) 1306 ± 125 ng/ml for a 80 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose to be administered;

c) 2613 ± 1341 ng/ml for a 160 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose to be administered;

d) 3600 ± 752 ng/ml for a 240 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose to be administered;

e) 4648 ± 1813 ng/ml for a 320 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose to be administered;

f) 6926 ± 1656 ng/ml for a 400 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose to be administered;

g) 6921 ± 2190 ng/ml for a 480 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a single oral dose to be administered,

in said composition to said subject.

22) Use of the pharmaceutical composition according to any of the claims 16 to 21, in the manufacture of a medicament for treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, characterized by a mean maximum blood plasma concentration (mean C_{max}) of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide in a subject of at least one of

a) 608 ± 184 ng/ml for a 40 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 10090 ± 3114 ng-h/ml in a subject for a 40 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 72 ± 3 h on average; said dosage being a single oral dose to be administered;

b) 1306 ± 125 ng/ml for a 80 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 21940 ± 2057 ng-h/ml in a subject for a 80 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 74 ± 5 h on average; said dosage being a single oral dose to be administered;

c) 2613 ± 1341 ng/ml for a 160 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 40470 ± 16700 ng-h/ml in a subject for a 160 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 63 ± 6 h on average; said dosage being a single oral dose to be administered;

d) 3600 ± 752 ng/ml for a 240 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 59610 ± 12770 ng-h/ml in a subject for a 240 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 64 ± 5 h on average; said dosage being a single oral dose to be administered;

e) 4648 ± 1813 ng/ml for a 320 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 76250 ± 27630 ng-h/ml in a subject for a 320 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 57 ± 3 h on average; said dosage being a single oral dose to be administered;

f) 6926 ± 1656 ng/ml for a 400 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 104800 ± 25740 ng-h/ml in a subject for a 400 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 57 ± 4 h on average; said dosage being a single oral dose to be administered;

g) 6921 ± 2190 ng/ml for a 480 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an AUC_{0-24h} of 112800 ± 34260 ng-h/ml in a subject for a 480 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono

methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 53 ± 4 h on average; said dosage being a single oral dose to be administered,

in said composition to said subject.

23) Use of the pharmaceutical composition according to any of the claims 16 to 20, in the manufacture of a medicament for treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, characterized by a mean maximum blood plasma concentration at steady state (mean Cmax,ss) of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide in a subject of at least one of

a) 1358 ± 167 ng/ml for a 25 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a steady state dose after once daily single doses to be administered for 21 days;

b) 6358 ± 1701 ng/ml for a 100 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a steady state dose after once daily single doses to be administered for 21 days;

c) 9987 ± 2608 ng/ml for a 200 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, said dosage being a steady state dose after once daily single doses to be administered for 21 days,

in said composition to said subject.

24) Use of the pharmaceutical composition according to any of the claims 16 to 20 and 23, in the manufacture of a medicament for treating AD in a subject that is having HSV-1 infection and is having AD or is having HSV-1 infection and is suspected of having AD, characterized by a mean maximum blood plasma concentration at steady state (mean $C_{max,ss}$) of the free base of N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide in a subject of at least one of

a) 1358 ± 167 ng/ml for a 25 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an $AUC_{\tau,ss}$ of 23430 ± 3020 ng-h/ml in a subject for a 25 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 69 ± 6 h on average, said dosage being a steady state dose after once daily single doses to be administered for 21 days;

b) 6358 ± 1701 ng/ml for a 100 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate and/or characterized by an $AUC_{\tau,ss}$ of 108800 ± 28610 ng-h/ml in a subject for a 100 mg dosage as free base equivalent of crystalline N-[5-(aminosulfonyl)-4-methyl-1,3-thiazol-2-yl]-N-methyl-2-[4-(2-pyridinyl)-phenyl]acetamide mono methanesulfonic acid monohydrate, and wherein $t_{1/2z}$ is 60 ± 4 h on average, said dosage being a steady state dose after once daily single doses to be administered for 21 days,

in said composition to said subject.

25) Use of the pharmaceutical composition of claim 20, wherein said absolute bioavailability is achieved in a human.

26) Use of the pharmaceutical composition of the claims 16 to 24, wherein said mean C_{max} and $C_{max,ss}$ is achieved in a human.

27) Use of the pharmaceutical composition of the claims 22 and 24, wherein said $AUC_{0\text{-}24h}$ and $t_{1/2z}$ is achieved in a human.

28) Use of the pharmaceutical composition of the claim 24, wherein said $AUC_{\tau,ss}$ and $t_{1/2z}$ is achieved in a human.