Claims

1. A pharmaceutical formulation comprising the Active Pharmaceutical Ingredient (API) **(**3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, where, in particular, the pharmaceutical formulation is made by a process comprising wet granulation, direct compression or especially roller compaction.

2. The pharmaceutical formulation according to claim 1, wherein the API is (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine in the form of a succinate (1:1) salt in hemihydrate form.

3. The pharmaceutical formulation according to claim 1 or claim 2, obtainable by a process comprising wet granulation.

4. The pharmaceutical formulation according to any one of the preceding claims, obtainable by a process comprising direct compression or roller compaction.

5. The pharmaceutical formulation according to any one of the preceding claims, comprising an inner phase obtained from granulation of the Active Pharmaceutical Ingredient (API) (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine succinate (1:1) salt in hemihydrate form, with one or more pharmaceutically acceptable excipients, where the inner phase is made by a process including wet granulation or roller compaction; and an outer phase comprising a mixture of pharmaceutically acceptable excipients; the manufacture including mixing of inner and outer phase and pressing the resulting material to a tablet which is optionally coated

6. The tablet of claim 5 comprising an inner phase with the Active Pharmaceutical Ingredient (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine succinate (1:1) salt in hemihydrate form, and at least one pharmaceutically acceptable excipient, obtainable by roller compaction and at least one pharmaceutically acceptable ingredient, and an outer phase comprising at least one pharmaceutically acceptable ingredient.

7. The pharmaceutical formulation according to any one of the preceding claims, comprising the Active Pharmaceutical Ingredient (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine succinate (1:1) salt in hemihydrate form, in an amount of 5 to 30 wt.-% = percent by weight, based on the weight of the free base, and at least one pharmaceutically acceptable excipient, one or two fillers, a disintegrant, a glidant and a lubricant, wherein the one or two fillers are selected from the group consisting of mannitol (e.g. in an amount of 10 to 60 wt-%, such as 40 to 50 wt-%) and microcrystalline cellulose (e.g. in an amount of 10 to 50 wt-%, such as 25 to 38 wt-%), the disintegrant is croscarmellose sodium (e.g. in an amount of 1 to 20 wt-%, such as 3 t0 7 wt.-%), the glidant is fumed silica (e.g. in an amount of 1 to 15 wt-%, such as 2 to 5 wt-%) and the lubricant is magnesium stearate (e.g. in an amount of 0.1 to 3 wt.-%, such as 0.2 to 2 wt-%); which tablet has no coating or has a coating, where the percentages refer to the combination of inner and outer phase without coating.

8. The pharmaceutical formulation according to any one of the preceding claims, which is in the form of a capsule, a sachet or especially a tablet which is uncoated or coated.

9. The pharmaceutical formulation according to any one of claims 1 to 8 in the form of a tablet comprising an inner phase obtainable by wet granulation, said inner phase including the Active Pharmaceutical Ingredient (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine succinate (1:1) salt in hemihydrate form in an amount of 5 to 40 wt.-% or 10 to 30 wt-%, and at least one pharmaceutically acceptable excipient, one or two fillers selected from microcrystalline cellulose and mannitol, in a total amount of 5 to 60 wt-%, or 10 to 50 wt-%, a binder selected from hydroxypropyl methylcellulose

and hydroxypropyl cellulose, in an amount from 1 to 15 wt-%, or from 1 to 5 wt-%, the glidant fumed silica, in an amount from 1 to 15 wt.-%, or from 1 to 5 wt.-%, and a disintegrant selected from sodium starch glycolate and croscarmellose sodium, in an amount from 1 to 10 wt-%, or 2 to 5 wt-%; and an outer phase which is a mixture comprising the filler microcrystalline cellulose, in an amount from 5 to 50 wt.-%, or 8 to 25 wt.-%, a disintegrant selected from croscarmellose sodium and sodium starch glycolate, in an amount from 0.5 to 10 wt.-%, or 1 to 3 wt.-%, the glidant fumed silica, in an amount from 1 to 10 wt-%, or 1 to 5 wt.-%, and the lubricant magnesium stearate, in an amount from 0.1 to 3 wt.-%, or 0.2 to 2 wt-%; which tablet has no coating or has a coating, where the percentages refer to the combination of inner and outer phase without coating.

10. The pharmaceutical formulation according to any one of claims 1 to 8 in the form of a tablet comprising the Active Pharmaceutical Ingredient (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine succinate (1:1) salt in hemihydrate form, in an amount of 5 to 40 wt.-%, one or two fillers, selected from mannitol, lactose, calcium hydrogen phosphate and cellulose, in an amount of 10 to 60 wt-%, or 15 to 50 wt.-%, a disintegrant selected from sodium starch glycolate and croscarmellose sodium, in an amount of 1 to 10 wt-%, or 2 to 5 wt-%, the binder hydroxypropyl methyl cellulose, in an amount from 1 to 15 wt-%, or from 1 to 5 wt-%, the glidant fumed silica, in an amount from 1 to 10 wt-%, or 1 to 5 wt.-%, and the lubricant magnesium stearate, in an amount from 0.1 to 3 wt.-%, or 0.2 to 2 wt-%; which tablet has no coating or has a coating, where the percentages refer to the combination of inner and outer phase without coating.

11. The pharmaceutical formulation according to any one of claims 1 to 8 in the form of a tablet comprising an inner phase obtainable by roller compaction, said inner phase including the Active Pharmaceutical Ingredient (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine succinate (1:1) salt in hemihydrate form, in an amount of 5 to 40 wt.-% or 10 to 30 wt-%, and at least one pharmaceutically acceptable excipient, one or two fillers, selected from microcrystalline cellulose, and mannitol, preferably in a total amount of 5 to 90 wt-%, or 10 to 80 wt-%, optionally a binder selected from hydroxypropyl methylcellulose and hydroxypropyl cellulose, in an amount from 0 to 15 wt-%, or from 1 to 5 wt-%, the glidant fumed silica, in an amount from 1 to 15 wt.-

%, or from 1 to 5 wt.-%, a disintegrant selected from sodium starch glycolate and croscarmellose sodium, in an amount from 1 to 10 wt-%, or 2 to 5 wt-%, and the lubricant magnesium stearate, in an amount from 0.1 to 3 wt.-%, or 0.2 to 2 wt-%; and an outer phase which is a mixture comprising the filler microcrystalline cellulose, in an amount from 2 to 50 wt.-%, or 3 to 25 wt.-%, a disintegrant selected from croscarmellose sodium and sodium starch glycolate, in an amount from 0.5 to 10 wt.-%, or 1 to 4 wt.-%, the glidant, fumed silica, in an amount from 0.5 to 10 wt-%, or 0.5 to 5 wt.-%, and the lubricant magnesium stearate, in an amount from 0.1 to 3 wt.-%, or 0.2 to 2 wt-%; which tablet has no coating or has a coating, where the percentages refer to the combination of inner and outer phase without coating.

12. The pharmaceutical formulation according to any one of the preceding claims, where the API used for the manufacture of the formulation has a particle size, determined by laser diffraction, defined as follows: d10 = 0.2 µm to 1 µm or 0.8 µm; d50 = 1.0 to 2.0 µm or 1.6 µm; and d90 = 2.1 µm to 5 µm, or 3.1 µm.

13. The pharmaceutical formulation according to any one of the preceding claims, showing a dissolution of 95 % in 15 min or less.

14. The pharmaceutical formulation according to any one of claims 1 to 13 for use in the treatment of a proliferative disease.

15. Use of the Active Pharmaceutical Ingredient (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a pharmaceutical formulation as defined in any one of claims 1 to 13 for the treatment of a proliferative disease.

16. Use of a pharmaceutical formulation as defined in any one of claims 1 to 13 comprising a therapeutically effective amount of (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a proliferative,

especially cancer disease in a subject, in which modulation of SHP2 activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, wherein the medicament is to be administered alone or simultaneously or in sequential combination with one, two or three anti-cancer therapeutics.

17. A method of manufacture of a pharmaceutical composition according to any one of claims 1 to 13, comprising combining **(**3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient in a process comprising wet granulation, direct compression or roller compaction.

18. The method according to claim 17 where the pharmaceutical formulation is a tablet,, comprising producing an inner granular phase including **(**3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, by roller compaction, and admixing the granules of the inner granular phase with one or more pharmaceutically acceptable excipients to form an outer phase, thus forming a final blend of the inner and outer phase, and compression of the final blend into tablet cores, and leaving the tablets without a coating or coating the tablet cores with a coating material.