CLAIMS

We claim:

1. A solid oral pharmaceutical formulation which comprises a solid dispersion comprising COMPOUND A.

2. A solid oral pharmaceutical formulation of claim 1, which comprises:
an inner phase which is a solid dispersion comprising COMPOUND A, and
an external phase which comprises additional excipients.

3. A solid oral pharmaceutical formulation of claim 2 wherein the internal phase or the external phase comprises an acidifier.

4. The present invention further relates to a solid oral pharmaceutical formulation of claim 2, which comprises:
an inner phase which is a solid dispersion comprising COMPOUND A, a hydrophilic binder and a surfactant; and
an external phase which comprises additional excipients.

5. A solid oral pharmaceutical formulation of claim 1, which comprises:
an inner phase which is a solid dispersion comprising COMPOUND A, a hydrophilic binder, a surfactant and
an external phase which comprises one or more of an acidifier, a filler, a disintegrant, a flow enhancer and a lubricant.

6. Use of a solid oral pharmaceutical formulation of claim 1 for the preparation of a medicament for the treatment of a proliferative disease.

7. A method of treating a proliferative disease which comprises administering to a patient in need of treatment a therapeutically effective amount of a formulation according to claim 1.

8. Use of the solid oral formulations according to claim 1 for the treatment of a disease which responds to inhibition of B-RAF.

9. Use according to claim 8 wherein the disease is characterzed by a mutation in B-RAF.

10. Use according to claim 9 wherein the disease is melanoma or colorectal cancer.

CLAIMS

1. A solid oral pharmaceutical formulation, which comprises:

an inner phase which is a solid dispersion comprising amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (COMPOUND A); copovidone; and poloxamer 188 or sorbitol; and

an external phase which comprises succinic acid, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, and magnesium stearate.

2. The solid oral pharmaceutical formulation of claim 1, wherein the inner phase comprises from 5% to 40% by weight of amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A), from 50% to 80% by weight of copovidone, and from 5% to 20% by weight of poloxamer 188 or sorbitol.

3. The solid oral pharmaceutical formulation of claim 2, wherein the external phase comprises from 2% to 60% by weight of succinic acid, from 30% to 70% by weight of microcrystalline cellulose, from 5% to 20% by weight of crospovidone, from 0.5% to 5% by weight of colloidal silicon dioxide, and from 0.5% to 5% by weight of magnesium stearate.

4. The solid oral pharmaceutical formulation of claim 1, comprising a blend of the internal and external phases in a ratio of from 80:20 to 40:60.

5. The solid oral pharmaceutical formulation of claim 4, comprising a blend of the internal and external phases in a ratio of from 75:25 to 50:50.

6. The solid oral pharmaceutical formulation of claim 1, comprising 10 mg, 25 mg, 50 mg , or 100 mg of amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-

(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4- yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A).

7. The solid oral pharmaceutical formulation of claim 6, wherein the formulation comprises 15% by weight of amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4- yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A).

8. The solid oral pharmaceutical formulation of claim 1, wherein the formulation is selected from the group consisting of:

A)

Ingredient	**%w/w**
Internal Phase	
amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4- yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A)	15
copovidone	45
Poloxamer 188	5
External Phase	
Succinic acid	13
Microcrystalline cellulose	16
Crosspovidone	5
magnesium Stearate	0.5
Colloidal silicon dioxide	0.5
Total	**100**

and

B)

Ingredient	**%w/w**
Internal	
amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4- yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A)	17
PVP-K30	51
Sorbitol	5
External	
Succinic Acid	9

Microcrystalline cellulose	12
Crosspovidone	5
Mg Stearate	0.5
Colloidal silicon dioxide	0.5
Total	**100**

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9. The solid oral formulation of claim 1, wherein the formulation is selected from the group consisting of:

Ingredient	
Internal Phase (mg)	
amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropy1-1H-pyrazo1-4- yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A)	10.0
Copovidone	29.9
Poloxamer 188	3.3
External Phase (mg)	
Succinic acid	8.7
Cellulose microcrystalline	10.7
Crospovidone	3.3
Colloidal silicon dioxide	0.3
Magnesium Stearate	0.3
Total (mg)	66.6

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Ingredient	
Internal Phase (mg)	
amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropy1-1H-pyrazo1-4- yl)pyrimidin-	25.0

2-yl)amino)propan-2-yl)carbamate (Compound A)	
Copovidone	74.8
Poloxamer 188	8.4
External Phase (mg)	
Succinic acid	21.7
Cellulose microcrystalline	26.7
Crospovidone	8.4
Colloidal silicon dioxide	0.9
Magnesium Stearate	0.9
Total (mg)	166.5

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Ingredient	
Internal Phase (mg)	
amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4- yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A)	50.0
Copovidone	150.0
Poloxamer 188	16.7
External Phase (mg)	
Succinic acid	43.3
Cellulose microcrystalline	53.3
Crospovidone	16.7
Colloidal silicon dioxide	1.7
Magnesium Stearate	1.7
Total (mg)	333.4

, and

Ingredient	
Internal Phase (mg)	
amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4- yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A)	100.0
Copovidone	300.0
Poloxamer 188	33.3
External Phase (mg)	
Succinic acid	86.7
Cellulose microcrystalline	106.7
Crospovidone	33.3
Colloidal silicon dioxide	3.3
Magnesium Stearate	3.3
Total (mg)	666.6

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10. The solid oral pharmaceutical formulation of claim 8, comprising a blend of the internal and external phases in a ratio of from 75:25 to 50:50.

11. The solid oral pharmaceutical formulation of claim 8, formulated as a capsule or a tablet.

12. The solid oral pharmaceutical formulation of claim 8, wherein the formulation is prepared by a process comprising: (i) blending a mixture comprising amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4- yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (COMPOUND A); copovidone; and poloxamer 188 or sorbitol to provide a first blend; (ii) extruding the first blend to provide an extrudate; (iii) milling the extrudate to provide a milled extrudate; (iv)

blending the milled extrudate with at least one of succinic acid, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, and magnesium stearate to provide a second blend; (v) optionally repeating step (iv) as needed to provide a third blend comprising the succinic acid, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, and the milled extrudate; and (vi) optionally tableting or encapsulating the third blend.

13. The solid oral pharmaceutical formulation of claim 8, wherein the formulation is formulation **A)** and reaches a maximum plasma concentration (Cmax) of amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4- yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (compound A) compound A at 4 hours (Tmax) after administration.

14. The solid oral pharmaceutical formulation of claim 8, wherein the formulation is formulation **A)**, and the formulation reaches a mean maximum plasma concentration (Cmax) of 11,833 ng/mL and produces a mean area under the plasma concentration versus time curve (AUC) of 32,686 ng*hr/ml when orally dosed to a monkey, wherein a dose of amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4- yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A) is 200 mg.

15. The solid oral pharmaceutical formulation of claim 8, wherein the formulation provides a mean maximum plasma concentration (Cmax) of amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A) that is about five times greater than the mean maximum plasma concentration of amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A) administered as microemulsion formulation when orally dosed to a monkey, wherein a dose of amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-

pyrazol-4- yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A) as a solid oral pharmaceutical formulation is 200 mg and a dose of amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4- yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A) as a microemulsion formulation is 50 mg/kg.

16. The solid oral pharmaceutical formulation of claim 15, wherein the formulation provides a plasma concentration versus time curve (AUC) of amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A) that is greater than the plasma concentration versus time curve (AUC) produced by amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A) administered as microemulsion formulation when orally dosed to a monkey, wherein a dose of Compound A as a solid oral pharmaceutical formulation is 200 mg and a dose of amorphous (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A) as a microemulsion formulation is 50 mg/kg.

17. The solid oral pharmaceutical formulation of claim 8, wherein the formulation has a physical stability of at least four weeks upon storage under accelerated stability conditions of 40 °C/ 75 % RH.

18. The solid oral pharmaceutical formulation of claim 17, wherein the formulation is formulation **A)**, and wherein:

- in-vitro 2-stage dissolution studies indicate no change in dissolution kinetics of the solid dispersion between initial (0 week) and 4-week time points under accelerated stability conditions; and/or
- the formulation is free of crystalline (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4- yl)pyrimidin-2-

yl)amino)propan-2-yl)carbamate (Compound A) at the 4-week time point upon storage at accelerated stability conditions of 40 °C/ 75 % RH for 4 weeks; and/or

- the formulation is free of degradation products and 100% assay content results for (S)-methyl (1- ((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4- yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (Compound A) upon storage at accelerated stability conditions at 40 ° C/75 % RH.

19. The solid oral pharmaceutical formulation of claim 8, wherein the formulation exhibits a glass transition temperature (Tg) of 97 °C or 109 °C.