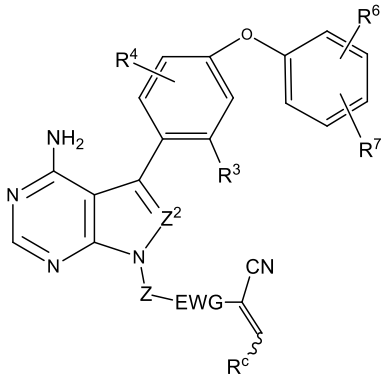
CLAIMS

1. Use of a pharmaceutical composition comprising a Bruton's tyrosine kinase (BTK) inhibitor and a pharmaceutically acceptable carrier or excipient, in the manufacture of a medicament for treating a disease chosen from sepsis, secondary hemophagocytic lymphohistiocytosis, cytokine release syndrome, and systemic inflammatory response syndrome in a mammal in need thereof, wherein the BTK inhibitor is a compound of Formula (**I**) or a pharmaceutically acceptable salt thereof:



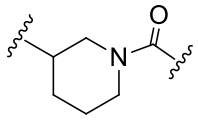
(**I**)

wherein:

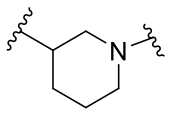
Z^2 is –N-;

R^3 and R^4 are independently chosen from hydrogen, methyl, chloro, fluoro, cyclopropyl, hydroxy, methoxy, cyano, trifluoromethyl, and trifluoromethoxy;

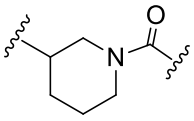
R^6 and R^7 are independently chosen from hydrogen, methyl, methoxy, fluoro, chloro, trifluoromethyl, trifluoromethoxy, and cyano;

-Z-EWG- is 

, wherein:



is substituted with 0, 1, or 2 substituents independently chosen from alkyl, hydroxy, and halo;

the carbonyl group in 

is attached to -C(CN)=CHR^c; and

R^c is –C(CH_3)$_2$-(4-R^8-piperazin-1-yl), wherein

R^8 is chosen from hydrogen, alkyl, alkoxyalkyl, haloalkyl, alkylsulfonyl, alkoxycarbonyl, acyl, and oxetan-3-yl; and

the piperazinyl ring is additionally substituted with zero, one, or two alkyls.

2. The use according to claim 1, wherein the BTK inhibitor is chosen from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomers of:

2-[[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]-pyrimidin-1-yl]-piperidin-1-yl]carbonyl]-4-methyl-4-(4-methylpiperazin-1-yl)pent-2-enenitrile;

2-((R)-3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(piperazin-1-yl)pent-2-enenitrile;

2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]-pyrimidin-1-yl]piperidine-1-carbonyl]-4-(4-ethylpiperazin-1-yl)-4-methyl-pent-2-enenitrile;

(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-(4-isopropylpiperazin-1-yl)-4-methylpent-2-enenitrile;

(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-(4-(tert-butyl)piperazin-1-yl)-4-methylpent-2-enenitrile;

(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-(4-(2-methoxyethyl)piperazin-1-yl)-4-methylpent-2-enenitrile;

(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(methylsulfonyl)piperazin-1-yl)pent-2-enenitrile;

(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)pent-2-enenitrile;

2-((R)-3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)pent-2-enenitrile;

2-((R)-3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-((3S,5R)-3,5-dimethylpiperazin-1-yl)-4-methylpent-2-enenitrile;

(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile;

(R)-4-(4-acetylpiperazin-1-yl)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4-methylpent-2-enenitrile; and

(R)-methyl-4-(5-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-cyano-2-methyl-5-oxopent-3-en-2-yl)piperazine-1-carboxylate;

and a pharmaceutically acceptable salt of any of the foregoing compounds.

3. The use according to claim 1, wherein R^8 is oxetan-3-yl.

4. The use according to claim 1, wherein the BTK inhibitor is chosen from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomers of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile; and a pharmaceutically acceptable salt of any of the foregoing compounds.

5. The use according to claim 1, wherein more than 70% by weight of the BTK inhibitor is a (E) isomeric form of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or a pharmaceutically acceptable salt thereof; or wherein more than 70% by weight or moles of the BTK inhibitor is a (Z) isomeric form of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or a pharmaceutically acceptable salt thereof

6. The use according to claim 5, wherein at least about 85% w/w of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile or at least about 85% w/w of a pharmaceutically acceptable salt of 2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile is the (E) isomer.

7. The use according to any one of claims 1-6, wherein the pharmaceutical composition is to be administered in place of a corticosteroid therapy.

8. The use according to any one of claims 1-6, wherein the pharmaceutical composition is to be administered in combination with a corticosteroid therapy.

9. The use according to any one of claims 1-6, wherein the pharmaceutical composition is to be administered in combination with a noncorticosteroidal immunosuppressive and/or anti-inflammatory agent.

10. The use according to any one of claims 1-6, wherein the pharmaceutical composition is to be administered in combination with a corticosteroid maintenance therapy.

11. The use according to any one of claims 1-10, wherein the mammal is a human.

12. The use according to any one of claims 1-11, wherein the pharmaceutical composition is to be administered in combination with an active pharmaceutical ingredient chosen from interferon alpha, interferon gamma, cyclophosphamide, tacrolimus, mycophenolate mofetil, methotrexate, dapsone, sulfasalazine, azathioprine, an anti-CD20 agent, an anti-TN alpha agent, an anti-IL6 agent toward ligand or its receptors, an anti-IL17 agent to ligand or its receptors, an anti-IL1 agent to ligand or its receptors, an anti-IL2 agent to ligand or its receptors, an anti-CD2 agent, an anti-CD3 agent, an anti-CD80/86 agent, an anti-sphingosine-1-phosphate receptor agent, an anti-C5 agent, an anti-mTOR agent, an anti-calcineurin agent, an anti-BAFF/BlyS agent, leflunomide, and teriflunomide.

13. The use according to any one of claims 1-12, wherein the pharmaceutical composition is to be administered in combination with rituximab, ofatumumab, obinutuzumab, or veltuzumab.

14. The use according to any one of claims 1-12, wherein the pharmaceutical composition is to be administered in combination with at least one antiviral agent.

15. The use according to claim 14, wherein the antiviral agent comprises at least one agent chosen from entry inhibitors, uncoating inhibitors, reverse transcriptase inhibitors, integrase inhibitors, transcription inhibitors, and protease inhibitors.

16. The use according to claim 14 or 15, wherein the antiviral agent comprises remdesivir.

17. The use according to any one of claims 1-16, wherein the pharmaceutical composition is formulated as a tablet for oral administration.

18. The use according to claim 17, wherein the tablet comprises 1 to 1000 mg of the BTK inhibitor.