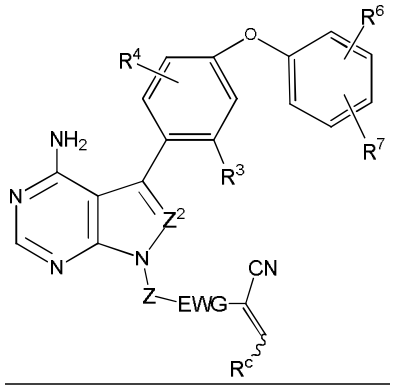
CLAIMS

1. A pharmaceutical composition comprising a Bruton's tyrosine kinase (BTK) inhibitor and a pharmaceutically acceptable carrier or excipient, for use in ~~method of~~ treating a disease chosen from acute respiratory distress syndrome, sepsis, sepsis induced acute lung injury, diffuse alveolar damage, macrophage activation syndrome, secondary hemophagocytic lymphohistiocytosis, cytokine release syndrome, and systemic inflammatory response syndrome in ~~comprising administering to~~ a mammal in need thereof ~~such treatment a pharmaceutical composition comprising a Bruton's tyrosine kinase (BTK) inhibitor and a pharmaceutically acceptable carrier or excipient~~, wherein the BTK inhibitor is a compound of Formula (**I**) or a pharmaceutically acceptable salt thereof:



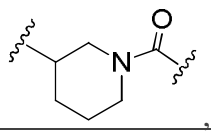
(**I**)

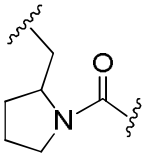
wherein:

Z^2 is –N- or CR^2, wherein R^2 is chosen from hydrogen and alkyl;

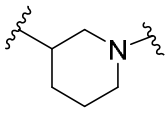
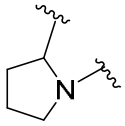
R^3 and R^4 are independently chosen from hydrogen, methyl, chloro, fluoro, cyclopropyl, hydroxy, methoxy, cyano, trifluoromethyl, and trifluoromethoxy;

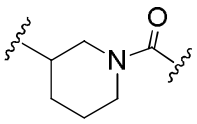
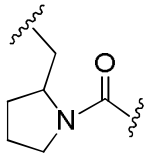
R^6 and R^7 are independently chosen from hydrogen, methyl, methoxy, fluoro, chloro, trifluoromethyl, trifluoromethoxy, and cyano;

-Z-EWG- is chosen from –alkylene-NR'CO-, -alkylene-NR'SO_2-, 

, and 

, wherein:

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

the carbonyl or the sulfonyl group in –alkylene-NR'CO-, -alkylene-NR'SO_2-,  , and  is attached to -C(CN)=CHR^c; and

R' is independently chosen from hydrogen and alkyl;

R^c is chosen from alkyl, haloalkoxy, substituted alkyl, cycloalkyl, cycloalkylene-NR^dR^e, and cycloalkylene-alkylene-NR^dR^e; and

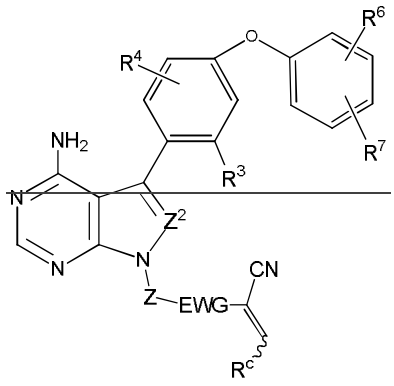
R^d and R^e are independently chosen from hydrogen, alkyl, cycloalkyl, and 3 to 6 membered saturated monocyclic heterocyclyls, wherein:

the heterocyclyls comprise one or two heteroatoms independently chosen from N, O, and S; and

the heterocyclyls are substituted with 0, 1, or 2 substituents independently chosen from hydroxy, alkyl and fluoro.

~~small molecule.~~

~~2. The method according to claim 1, wherein the BTK inhibitor is a compound of Formula (I) or a pharmaceutically acceptable salt thereof:~~



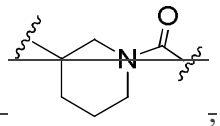
~~(I)~~

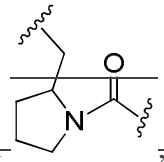
~~wherein:~~

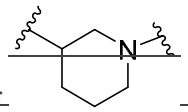
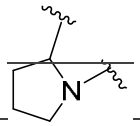
~~Z^2 is N or CR^2; wherein R^2 is chosen from hydrogen and alkyl;~~

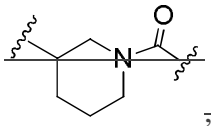
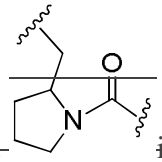
~~R^3 and R^4 are independently chosen from hydrogen, methyl, chloro, fluoro, cyclopropyl, hydroxy, methoxy, cyano, trifluoromethyl, and trifluoromethoxy;~~

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

~~-Z-EWG- is chosen from -alkylene-NR'CO-, -alkylene-NR'SO_2-,~~  ~~,~~

~~and~~  ~~, wherein:~~

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

~~the carbonyl or the sulfonyl group in -alkylene-NR'CO-, -alkylene-NR'SO_2-,~~  ~~,~~  ~~and~~ ~~is attached to -C(CN)=CHR^e; and~~

~~R' is independently chosen from hydrogen and alkyl;~~

~~R^e is chosen from alkyl, haloalkoxy, substituted alkyl, cycloalkyl, cycloalkylene-NR^dR^e, and cycloalkylene-alkylene-NR^dR^e; and~~

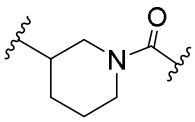
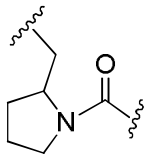
~~R^d and R^e are independently chosen from hydrogen, alkyl, cycloalkyl, and 3 to 6 membered saturated monocyclic heterocyclyls, wherein:~~

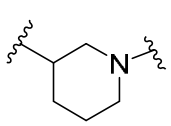
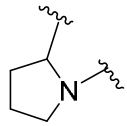
~~the heterocyclyls comprise one or two heteroatoms independently chosen from N, O, and S; and~~

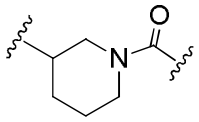
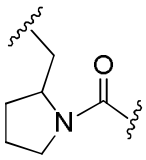
~~the heterocyclyls are substituted with 0, 1, or 2 substituents independently chosen from hydroxy, alkyl and fluoro.~~

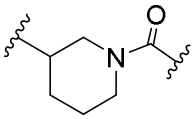
~~3.~~2. The pharmaceutical composition for use ~~method according to any one~~ of claim~~s~~ 1~~-2~~, wherein Z^2 is -N-.

3~~4~~. The pharmaceutical composition for use ~~method~~ according to ~~any one of~~ claim~~s~~ 1~~-~~or 2~~3~~, wherein:

-Z-EWG- is  or , wherein:

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

the carbonyl group in  and  is attached to -C(CN)=CHR^c.

45. The pharmaceutical composition for use ~~method~~ according to any one of claims 1-34, wherein -Z-EWG- is .

56. The pharmaceutical composition for use ~~method~~ according to claim 45, wherein the BTK inhibitor is chosen from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomers of:

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

2-((R)-3-(4-amino-3-(4-(3,4-dichlorophenoxy)-3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

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

(R)-2-(3-(4-amino-3-(4-(3,4-dichlorophenoxy)-3-methoxyphenyl)-1H-pyrazolo-[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile;

(R)-2-(3-(4-amino-3-(4-(2-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(3-(4-amino-3-(4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(3-(4-amino-3-(4-(2,3-difluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(3-(4-amino-3-(4-(2,6-difluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(3-(4-amino-3-(4-(3,5-difluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

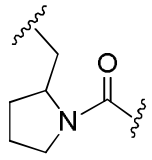
(R)-2-(3-(4-amino-3-(4-(2,5-difluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(3-(4-amino-3-(2-fluoro-4-(phenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(3-(4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)piperidine-1-carbonyl)-3-cyclopropylacrylonitrile; and

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

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

67. The pharmaceutical composition for use ~~method~~ according to any one of claims 1-34, wherein -Z-EWG- is 

.

78. The pharmaceutical composition for use ~~method~~ according to claim 67, wherein the BTK inhibitor is chosen from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomers of:

2-(2-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile;

(R)-2-(2-((4-amino-3-(4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(2-((4-amino-3-(4-(2,6-difluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(2-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(2-((4-amino-3-(4-(2,3-difluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(2-((4-amino-3-(4-(3,5-difluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(2-((4-amino-3-(4-(2-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(S)-2-{2-[4-amino-5-(4-phenoxy-phenyl)-pyrrolo[2,3-d]pyrimidin-7-ylmethyl]-pyrrolidine-1-carbonyl}-3-cyclopropyl-acrylonitrile;

(S)-2-(2-((4-amino-6-methyl-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(S)-2-(2-((4-amino-6-methyl-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl)pyrrolidine-1-carbonyl)-4-(dimethylamino)-4-methylpent-2-enenitrile;

(S)-2-(2-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(R)-2-(2-((4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

(S)-2-(2-((4-amino-3-(4-(2,3-difluorophenoxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-cyclopropylacrylonitrile;

2-((S)-2-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-4-(ethylamino)-4-methylpent-2-enenitrile;

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

2-((S)-2-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-4-(cyclopropylamino)-4-methylpent-2-enenitrile;

2-((S)-2-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-4-(2-methoxyethylamino)-4-methylpent-2-enenitrile;

(R)-2-(2-((4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidine-1-carbonyl)-3-(1-aminocyclopropyl)acrylonitrile;

2-[(2S)-2-[[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]methyl]pyrrolidine-1-carbonyl]-4-methyl-4-morpholino-pent-2-enenitrile;

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

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

2-[(2S)-2-[[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]methyl]pyrrolidine-1-carbonyl]-4-methyl-4-(1-piperidyl)pent-2-enenitrile; and

2-[(2S)-2-[[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]methyl]- pyrrolidine-1-carbonyl]-3-(3-methyloxetan-3-yl)prop-2-enenitrile;

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

89. The pharmaceutical composition for use ~~method~~ according to any one of claims 1-45, wherein R^c is alkyl.

910. The pharmaceutical composition for use ~~method~~ according to claim 89, wherein R^c is *t*-butyl.

101. The pharmaceutical composition for use ~~method~~ according to claim 910, wherein the BTK inhibitor is chosen from (E) isomer, (Z) isomer, and a mixture of (E) and (Z) isomers of (R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile (Compound (**IA**)), and/or a pharmaceutically acceptable salt any of the foregoing compounds.

112. The pharmaceutical composition for use ~~method~~ according to claim 910, wherein the compound is a substantially pure (E) or (Z) isomer of (R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile (Compound (**IA**)), and/or a pharmaceutically acceptable salt thereof.

123. The pharmaceutical composition for use ~~method~~ according to claim 112, wherein at least about 85% w/w of (R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile or at least about 85% w/w of a pharmaceutically acceptable salt of (R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-4,4-dimethylpent-2-enenitrile is the (E) isomer.

1314. The pharmaceutical composition for use ~~method~~ according to claim 45, wherein R^c is substituted alkyl.

145. The pharmaceutical composition for use ~~method~~ according to claim 134, wherein:

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

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

the piperazinyl ring is additionally optionally and independently substituted with one or two alkyls.

156. The pharmaceutical composition for use ~~method~~ according to claim 145, 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;

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

167. The pharmaceutical composition for use ~~method~~ according to claim 145, wherein R^8 is oxetan-3-yl.

178. The pharmaceutical composition for use ~~method~~ according to claim 167, 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 (Compound (**IB**)); and/or a pharmaceutically acceptable salt of any of the foregoing compounds.

189. The pharmaceutical composition for use ~~method~~ according to claim 167, wherein the BTK inhibitor is a substantially pure (E) or (Z) isomer 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 (Compound (**IB**)), or a pharmaceutically acceptable salt thereof.

1920. The pharmaceutical composition for use ~~method~~ according to claim 189, 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.

201. The pharmaceutical composition for use ~~method~~ according to any one of claims 1-1920, wherein it ~~the pharmaceutical composition~~ is administered in place of a corticosteroid therapy.

212. The pharmaceutical composition for use ~~method~~ according to any one of claims 1-1920, wherein it ~~the pharmaceutical composition~~ is administered in combination with a corticosteroid therapy.

223. The pharmaceutical composition for use ~~method~~ according to any one of claims 1-1920, wherein it ~~the pharmaceutical composition~~ is administered in combination with a noncorticosteroidal immunosuppressive and/or anti-inflammatory agent.

234. The pharmaceutical composition for use ~~method~~ according to any one of claims 1-1920, wherein ~~the pharmaceutical composition~~it is administered in combination with a corticosteroid maintenance therapy.

245. The pharmaceutical composition for use ~~method~~ according to any one of claims 1-234, wherein the mammal is a human.

256. The pharmaceutical composition for use ~~method~~ according to any one of claims 1-245, wherein the pharmaceutical composition is 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.

267. The pharmaceutical composition for use ~~method~~ according to any one of claims 1-256, wherein the pharmaceutical composition is administered in combination with rituximab, ofatumumab, obinutuzumab, or veltuzumab, or a biosimilar version of any of the foregoing.

278. The pharmaceutical composition for use ~~method~~ according to any one of claims 1-256, wherein the pharmaceutical composition is administered in combination with at least one antiviral agent.

289. The pharmaceutical composition for use ~~method~~ according to claim 278, 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.

2930. The pharmaceutical composition for use ~~method~~ according to claim 278 or 289, wherein the antiviral agent comprises remdesivir.