acute phase and/or at onset and duration of an acute flare) and for a limited amount of time so as to maximixe short term relief, minimize long term progression of the disease, and minimize long term toxicological and other adverse effects.

In an aspect, there is provided the use of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (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; or a pharmaceutically acceptable salt of any of the foregoing compounds in the manufacture of a medicament for treating thrombotic thrombocytopenic purpura, polyarteritis nodosa, cutaneous lupus, cutaneous form of systemic sclerosis (CREST), systemic sclerosis, mixed connective tissue disease, cryoglobulinemia, primary biliary sclerosis, sclerosing cholangitis, AI urticaria, IgA nephropathy, lupus nephritis, autoimmune hemolytic anemia, granulomatosis with polyangiitis, or pemphigus vulgaris in a mammal.

In another aspect, there is provided the use of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (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; or a pharmaceutically acceptable salt of any of the foregoing compounds in the manufacture of a medicament for treating an acute inflammatory and/or autoimmune disease in a mammal in need thereof where corticosteroid therapy is used as the first or second line therapy in place of or in combination with said corticosteroid therapy; wherein said (E) isomer, (Z) isomer, or a mixture of (E) and (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; or a pharmaceutically acceptable salt of any of the foregoing compounds is to be optionally administered in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.

In another aspect, there is provided the use of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (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; or a pharmaceutically acceptable salt of any of the foregoing compounds in the manufacture of a medicament for treating an inflammatory and/or autoimmune disease in a mammal in need thereof where corticosteroid therapy is used

as the first or second line maintenance therapy in place of or in combination with said corticosteroid therapy; wherein said (E) isomer, (Z) isomer, or a mixture of (E) and (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; or a pharmaceutically acceptable salt of any of the foregoing compounds is to be optionally administered in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.

In another aspect, there is provided a sulfonic acid or carboxylic acid salt of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (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.

In another aspect, there is provided an amorphous form of a pharmaceutically acceptable salt of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (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.

In a further aspect, there is provided a pharmaceutical composition comprising the sulfonic acid or carboxylic acid salt of compound disclosed herein or the amorphous form of a pharmaceutically acceptable salt of compound (I) disclosed herein.

In yet another aspect, there is provided the use of a pharmaceutical composition disclosed herein in the manufacture of a medicament for treating an autoimmune disease, an inflammatory disease, or cancer in a mammal.

Accordingly, in a first aspect disclosed herein is a sulfonic acid or a carboxylic acid salt of compound (I).

Embodiment (1a)

In one embodiment (embodiment (Ia)) of the first aspect, the salt is a sulfonic acid salt of compound (I).

Within embodiment (1a), in one embodiment the sufonic acid salt of compound (I) is mono- or di-methanesulfonic acid, mono or di-benezenesulfonic acid, mono- or di-toluenesulfonic acid, or ethane-1,2-disulfonic acid salt of compound (I). Within embodiment (1a), in another embodiment the sufonic acid salt of compound (I) is mono- or di-methanesulfonic acid salt of compound (I). Within embodiment (1a), in yet another embodiment the sufonic acid salt of compound (I) is di- methanesulfonic acid salt of compound (I). Within embodiment (1a), in another embodiment the sufonic acid salt of compound (I) is mono methanesulfonic acid salt of compound (I).

Embodiment (1b)

In another embodiment (embodiment (1b)) of the first aspect, the salt is a carboxylic acid salt of compound (I).

Within embodiment (1b), in one embodiment the carboxylic acid salt of compound (I) is fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, or malonic acid salt of compound (I).

In a second aspect, disclosed herein is an amorphous form of a pharmaceutically acceptable salt of compound (I).

Embodiment (2a)

In one embodiment (embodiment (2a)) of the second aspect, the amorphous form is of a sulfonic acid salt of compound (I).

Within embodiment (2a), in one embodiment the amorphous form is of mono- or di-methanesulfonic acid, mono or di-benezenesulfonic acid, mono- or di-toluenesulfonic acid, or ethane-1,2-disulfonic acid salt of compound (I). Within embodiment (2a), in another embodiment, the amorphous form is of mono- or di-methanesulfonic acid salt of compound (I). Within embodiment (2a), in another embodiment the sufonic acid salt is the dimethanesulfonic acid salt of compound (I). Within embodiment (2a), in another embodiment the sufonic acid salt is the mono methanesulfonic acid salt of compound (I).

What is Claimed:

1. A method of treating thrombotic thrombocytopenic purpura, polyarteritis nodosa, cutaneous lupus, cutaneous form of systemic sclerosis (CREST), systemic sclerosis, mixed connective tissue disease, cryoglobulinemia, primary biliary sclerosis, sclerosing cholangitis, AI urticaria, IgA nephropathy, Lupus Nephritis, autoimmune hemolytic anemia, Granulomatosis with Polyangiitis, or pemphigus vulgaris in a mammal, comprising administering to said mammal a pharmaceutical composition comprising

a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (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; or

a pharmaceutically acceptable salt of any of the foregoing compounds.

2. A method of treating an acute inflammatory and/or autoimmune disease in a mammal in need thereof where corticosteroid therapy is used as the first or second line therapy comprising administering to said mammal in need of said treatment a therapeutically effective amount of

a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (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; or

a pharmaceutically acceptable salt of any of the foregoing compounds in place of or in combination with said corticosteroid therapy; and

optionally administering

said (E) isomer, (Z) isomer, or a mixture of (E) and (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; or

a pharmaceutically acceptable salt of any of the foregoing compounds

in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.

3. A method of treating an inflammatory and/or autoimmune disease in a mammal in need thereof where corticosteroid therapy is used as the first or second line maintenance therapy comprising administering to said mammal in need of said treatment a therapeutically effective amount of

a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (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; or

~~a pharmaceutically acceptable salt of any of the foregoing compounds in place of or in combination with said corticosteroid therapy; and~~

~~optionally administering~~

~~said (E) isomer, (Z) isomer, or a mixture of (E) and (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; or~~

~~a pharmaceutically acceptable salt of any of the foregoing compounds~~

~~in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.~~

~~4. The method of any of Claims 1-3 wherein the pharmaceutical composition comprises~~

~~a compound which 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, or~~

~~a pharmaceutically acceptable salt of said compound,~~

~~and wherein the mammal is a human.~~

~~5. The method of Claim 4 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.~~

~~6. The method of Claim 4 wherein at least about 90% 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 90 % 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 method of any of Claims 1-6 wherein the the compound is 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 is administered to human; and the disease is pemphigus vulgaris.~~

1~~8~~. The use of a~~A~~ compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (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; or a

pharmaceutically acceptable salt of any of the foregoing compounds in the manufacture of a medicament for ~~use in~~ treating thrombotic thrombocytopenic purpura, polyarteritis nodosa, cutaneous lupus, cutaneous form of systemic sclerosis (CREST), systemic sclerosis, mixed connective tissue disease, cryoglobulinemia, primary biliary sclerosis, sclerosing cholangitis, AI urticaria, IgA nephropathy, lupus nephritis, autoimmune hemolytic anemia, granulomatosis with polyangiitis, or pemphigus vulgaris in a mammal.

29. The use of a~~A~~ compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (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; or a pharmaceutically acceptable salt of any of the foregoing compounds in the manufacture of a medicament for ~~use in~~ treating an acute inflammatory and/or autoimmune disease in a mammal in need thereof where corticosteroid therapy is used as the first or second line therapy in place of or in combination with said corticosteroid therapy; ~~and~~ wherein ~~optionally administering~~

said (E) isomer, (Z) isomer, or a mixture of (E) and (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; or

a pharmaceutically acceptable salt of any of the foregoing compounds is to be optionally administered in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.

310. The use of a~~A~~ compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (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; or

a pharmaceutically acceptable salt of any of the foregoing compounds in the manufacture of a medicament

for ~~use in~~ treating an ~~an~~ inflammatory and/or autoimmune disease in a mammal in need thereof where corticosteroid therapy is used as the first or second line maintenance therapy in place of or in combination with said corticosteroid therapy; ~~and~~ wherein ~~optionally administering~~

said (E) isomer, (Z) isomer, or a mixture of (E) and (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; or

a pharmaceutically acceptable salt of any of the foregoing compounds is to be optionally administered in combination with a noncorticosteroidal immunosupressive and/or antiinflammatory agent.

411. The use~~compound~~ of any of Claims 1-3~~8-10~~ wherein the compound 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; or a pharmaceutically acceptable salt of the compound, and wherein the mammal is a human.

512. The use~~compound~~ of Claim 4~~11~~ wherein at least 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.

613. The use~~compound~~ of Claim 4~~11~~ wherein at least 90% 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 90% 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.

714. The use~~compound~~ of any of Claims 3-6~~10-13~~ wherein the compound is 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 the disease to be treated is ~~used in treating~~ pemphigus vulgaris.

8~~15~~. The use~~method or compound~~ of any of Claims 1-7~~14~~ wherein the compound or a pharmaceutically acceptable salt thereof is to be optionally administered in combination with an immunosuppressive agent selected from interferon alpha, interferon gamma, cyclophosphamide, tacrolimus, mycophenolate mofetil, methotrexate, dapsone, sulfasalazine, azathioprine, an anti-CD20 agent, anti-TNFalpha agent, anti-IL6 agent toward ligand or its receptors, anti-IL17 agent to ligand or its receptors, anti-IL1 agent to ligand or its receptors, anti-IL2 agent to ligand or its receptors, anti-CD2 agent, anti-CD3 agent, anti-CD80/86 agent, anti-sphingosine-1-phosphate receptor agent, anti-C5 agent, anti-mTOR agent, anti-calcineurin agent, anti-BAFF/BlyS agent, leflunomide and teriflunomide.

9~~16~~. The use~~method or compound~~ of any of Claims 1-7~~14~~ wherein the compound or a pharmaceutically acceptable salt thereof is to be optionally administered in combination with rituximab, ofatumumab, obinutuzumab, or veltuzumab, or a biosimilar version thereof.

10~~17~~. A sulfonic acid or carboxylic acid salt of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (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.

1118. The sulfonic acid or carboxylic acid salt of the compound of Claim 1017 wherein the salt is a sulfonic acid salt selected from mono- or di-methanesulfonic acid salt.

~~19. The sulfonic acid salt of the compound of Claim 18 wherein the sulfonic salt is mono- or di-methanesulfonic acid salt.~~

2012. An amorphous form of a pharmaceutically acceptable salt of a compound selected from (E) isomer, (Z) isomer, and a mixture of (E) and (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.

2113. The amorphous form of the pharmaceutically acceptable salt of the compound of Claim 1220 wherein the pharmaceutically acceptable salt is a sulfonic acid or a carboxylic acid salt.

2214. The amorphous form of the pharmaceutically acceptable salt of the compound of Claim 1220 wherein the pharmaceutically acceptable salt is a sulfonic acid salt selected from mono- or di-methanesulfonic acid salt.

~~23. The amorphous form of the pharmaceutically acceptable salt of the compound of Claim 22 wherein the sulfonic salt is mono- or di-methanesulfonic acid salt.~~

2415. The amorphous form of the pharmaceutically acceptable salt of the compound of any of the Claims 12-1420-23 wherein the amorphous form is substantially free of any crystalline form(s) of the pharmaceutically acceptable salt of said compound.

2516. The amorphous form of the pharmaceutically acceptable salt of the compound of any of the Claims 12-1520-24 wherein at least about 90% w/w of the pharmaceutically acceptable salt of said compound is in amorphous form.

2617. The sulfonic acid or carboxylic acid salt of the compound of any of the Claims 10-1117-19 wherein the salt of said compound is a substantially pure E or Z isomer.

2718. The amorphous form of the pharmaceutically acceptable salt of the compound of any of the Claims 12-1620-25 wherein the salt of said compound is a substantially pure E or Z isomer.

2819. The sulfonic acid or carboxylic acid salt of the compound of Claim 1726 wherein at least about 80% w/w of the salt of the compound is the E isomer.

~~29. The sulfonic acid or carboxylic acid salt of the compound of Claim 26 wherein at least about 90% w/w of the salt of the compound is the E isomer.~~

3020. The amorphous form of the pharmaceutically acceptable salt of the compound of Claim 1827 wherein at least about 80% w/w of the pharmaceutically acceptable salt of the compound is the E isomer.

~~31. The amorphous form of the pharmaceutically acceptable salt of the compound of Claim 27 wherein at least about 90% w/w of the pharmaceutically acceptable salt of the compound is the E isomer.~~

~~32~~21. A pharmaceutical composition comprising the sulfonic acid or carboxylic acid salt of compound of any of the Claims 10-11~~17-19~~, 17 and 19~~26, 28 and 29~~ or the amorphous form of a pharmaceutically acceptable salt of compound (I) of any of the Claims 12-16~~20-25~~, 18~~27~~, and 20~~30 and 31~~.

~~33~~22. ~~A method of treating a autoimmune disease, an inflammatory disease, or cancer in a mammal in need of such treatment which method comprises administering to the mammal, the~~The use of a pharmaceutical composition of Claim 21~~32~~ in the manufacture of a medicament for treating an autoimmune disease, an inflammatory disease, or cancer in a mammal.

~~34~~23. The use of Claim 22~~method of Claim 33~~ wherein the mammal is a human.

~~35~~24. The use of Claim 22~~method of Claim 33~~ wherein the autoimmune disease is lupus, pemphigus vulgaris, granulomatosis with polyangiitis, or rheumatoid arthritis.