Summary

[0006] Provided herein are stable pharmaceutically acceptable formulations for intravenous injection of tagraxofusp, as exemplified by the following non-limiting list of ~~embodiment~~examples.

[0007] ~~Embodiment~~Example 1 is a stable solution for lyophilization in a pharmaceutically acceptable aqueous carrier comprising:

0.5 to 1.5 mg/mL of tagraxofusp;

2 to 10% w/v of at least one disaccharide sugar;

0.05 to 1.5% w/v of at least one surfactant;

at least one 5 to 25 mM buffering agent; and a pH 6.5-9.0

wherein the surfactant has no more than 3% peroxide.

[0008] ~~Embodiment~~Example 2 is the lyophilization solution of ~~embodiment~~example 1, wherein the lyophilization solution further comprises 2 to 10% w/v of at least one bulking agent.

[0009] ~~Embodiment~~Example 3 is the lyophilization solution of any of the preceding ~~embodiment~~examples, comprising 0.6 to 1.4 mg/mL of tagraxofusp.

[0010] ~~Embodiment~~Example 4 is the lyophilization solution of any of the preceding ~~embodiment~~examples, comprising 0.7 to 1.3 mg/mL of tagraxofusp.

[0011] ~~Embodiment~~Example 5 is the lyophilization solution of any of the preceding ~~embodiment~~examples, comprising 0.8 to 1.2 mg/mL of tagraxofusp.

[0012] ~~Embodiment~~Example 6 is the lyophilization solution of any of the preceding ~~embodiment~~examples, comprising 1 mg/mL of tagraxofusp.

[0013] ~~Embodiment~~Example 7 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the surfactant is present in an amount from 0.07 to 1.5% w/v.

[0014] ~~Embodiment~~Example 8 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the surfactant is present in an amount from 0.1 to 1.3% w/v.

[0015] ~~Embodiment~~Example 9 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the surfactant is present in an amount from 0.15 to 1.2% w/v.

[0016] ~~Embodiment~~Example 10 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the surfactant is present in an amount from 0.25 to 1% w/v.

[0017] ~~Embodiment~~Example 11 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the surfactant is present in an amount from 0.24 to 0.26% w/v.

[0018] ~~Embodiment~~Example 12 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the surfactant is chosen from polysorbates or poloxamers.

[0019] ~~Embodiment~~Example 13 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the surfactant is poloxamer 188, poloxamer 168, poloxamer 144, polysorbate 20, polysorbate 60, or polysorbate 80.

[0020] ~~Embodiment~~Example 14 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the surfactant is polysorbate 80.

[0021] ~~Embodiment~~Example 15 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the disaccharide sugar is present in an amount from 2 to 8% w/v.

[0022] ~~Embodiment~~Example 16 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the disaccharide sugar is present in an amount from 2 to 6% w/v.

[0023] ~~Embodiment~~Example 17 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the disaccharide sugar is present in an amount from 2 to 4% w/v.

[0024] ~~Embodiment~~Example 18 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the disaccharide sugar is present in an amount from 2 to 3% w/v.

[0025] ~~Embodiment~~Example 19 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the disaccharide sugar is present in an amount from 2.45 to 2.55% w/v.

[0026] ~~Embodiment~~Example 20 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the disaccharide sugar is chosen from trehalose, lactose, and sucrose.

[0027] ~~Embodiment~~Example 21 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the disaccharide sugar is sucrose.

[0028] ~~Embodiment~~Example 22 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the bulking agent is present in an amount from 2 to 8% w/v.

[0029] ~~Embodiment~~Example 23 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the bulking agent is present in an amount from 2 to 6% w/v.

[0030] ~~Embodiment~~Example 24 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the bulking agent is present in an amount from 2 to 4% w/v.

[0031] ~~Embodiment~~Example 25 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the bulking agent is present in an amount from 2 to 3% w/v.

[0032] ~~Embodiment~~Example 26 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the bulking agent is present in an amount from 2.45 to 2.55% w/v.

[0033] ~~Embodiment~~Example 27 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the bulking agent is chosen from glycine, maltose, glucose, mannitol, and sorbitol.

[0034] ~~Embodiment~~Example 28 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the bulking agent is mannitol.

[0035] ~~Embodiment~~Example 29 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein at least one buffering agent is at a concentration of from 5 to 15 mM.

[0036] ~~Embodiment~~Example 30 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein at least one buffering agent is at a concentration of from 7 to 12 mM.

[0037] ~~Embodiment~~Example 31 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein at least one buffering agent is at a concentration of 10 mM.

[0038] ~~Embodiment~~Example 32 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the buffering agent is chosen from phosphate, arginine, histidine, and Tris HCl.

[0039] ~~Embodiment~~Example 33 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the buffering agent is Tris HCl.

[0040] ~~Embodiment~~Example 34 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the pH is from 6.5 to 8.

[0041] ~~Embodiment~~Example 35 is the lyophilization solution of any of the preceding ~~embodiment~~examples, wherein the pH is from 7 to 8.

[0042] ~~Embodiment~~Example 36 is a stable pharmaceutically acceptable lyophilization solution in a pharmaceutically acceptable aqueous medium comprising:

0.5 to 1.5 mg/mL of tagraxofusp;
2 to 10% w/v of sucrose;
0.05 to 1.5% w/v of polysorbate 80;
5 to 25 mM Tris HCl; and
having a pH from 6.5 to 9;
wherein the polysorbate 80 has no more than 3% peroxide.

[0043] ~~Embodiment~~Example 37 is the lyophilization solution of ~~embodiment~~example 36, wherein the lyophilization solution further comprises 2 to 10% w/v of mannitol.

[0044] ~~Embodiment~~Example 38 is the lyophilization solution of ~~embodiment~~example 36 comprising:

1 mg/mL of tagraxofusp;

2.45 to 2.55% w/v of sucrose;

2.45 to 2.55% w/v of mannitol;

0.24 to 0.26% w/v of polysorbate 80;

9 to 11 mM Tris HCl; and

having a pH from 6.5 to 9,

wherein the polysorbate 80 has no more than 3% peroxide.

[0045] ~~Embodiment~~Example 39 is a lyophile prepared from the lyophilization solution of any of the preceding ~~embodiment~~examples.

[0046] ~~Embodiment~~Example 40 is the lyophile of ~~embodiment~~example 41, wherein the relative percent abundance of an oxidized species of tagraxofusp will increase to no more than 2%, or to no more than 1%, over 12 to 36 months.

[0047] ~~Embodiment~~Example 41 is the lyophile of ~~embodiment~~example 41, wherein the relative percent abundance of an oxidized species of tagraxofusp will increase to no more than 2%, or to no more than 1%, over 18 to 24 months.

[0048] ~~Embodiment~~Example 42 is the lyophile of ~~embodiment~~example 41, wherein the relative percent abundance of an acidic species of tagraxofusp will increase less than the relative percent abundance of the same acidic species of tagraxofusp in a liquid tagraxofusp formulation during storage for 18, 24 or 36 months.

[0049] ~~Embodiment~~Example 43 is the lyophile of ~~embodiment~~example 42, wherein the formulation provides for the required dose of 1 to 1.5 mg on dry weight basis.

[0050] ~~Embodiment~~Example 44 is the lyophile of ~~embodiment~~example 42 or 43, wherein the lyophilized dry product is stable at storage temperatures from 2°C to 8°C for at least 24 months.

[0051] ~~Embodiment~~Example 45 is the lyophile of any one of ~~embodiment~~examples 42 to 44, wherein the lyophilized dry product is stable in storage temperatures from 2°C to 8°C for 24 months to 5 years.

[0052] ~~Embodiment~~Example 46 is the lyophile of any one of ~~embodiment~~examples 42 to 45, wherein an oxidation impurity is at or below 2%, or is at or below 1%, as determined by reversed-phase ultrahigh performance chromatography (RP-UPLC).

[0053] ~~Embodiment~~Example 47 is the lyophile of any one of ~~embodiment~~examples 42 to 46, wherein the oxidation impurity is measurable as a single peak in mass spectral analysis +16 Da from a tagraxofusp peak.

[0054] ~~Embodiment~~Example 48 is the lyophile of any one of ~~embodiment~~examples 42 to 47, wherein in a RP-UPLC analysis the oxidation impurity elutes before tagraxofusp and the oxidation impurity peak on the RP-UPLC chromatogram is the peak closest to the tagraxofusp peak.

[0055] ~~Embodiment~~Example 49 is a stable lyophile comprising:

1 mg of tagraxofusp;

25 mg of at least one disaccharide sugar;

25 mg of at least one surfactant; and

2.4 mg of at least one buffering agent,

wherein, the lyophile has no more than 2% oxidation impurity as determined by reversed-phase ultrahigh performance chromatography (RP-UPLC) for at least 24 months.

[0056] ~~Embodiment~~Example 50 is the stable lyophile of ~~embodiment~~examples 49, further comprising 25 mg of at least one bulking agent.

[0057] ~~Embodiment~~Example 51 is the stable lyophile of ~~embodiment~~example 49 or 50, wherein the relative percent abundance of an oxidized species of tagraxofusp will increase to no more than 2%, or to no more than 1%, over 18 to 24 months.

[0058] ~~Embodiment~~Example 52 is a method of preparing a tagraxofusp lyophile comprising:

a) providing the lyophilization solution of any one of ~~embodiment~~examples 1-41 and

b) lyophilizing the solution to form a lyophile.

[0059] ~~Embodiment~~Example 53 is the method of ~~embodiment~~example 52, wherein the lyophilization occurs at a temperature from -40°C to 25°C over a period of 2 to 7 days.

[0060] ~~Embodiment~~Example 54 is the method of ~~embodiment~~example 52 or 53, wherein the lyophilization comprises a loading step, at least one freezing step, at least one annealing step, and at least one drying step.

[0061] ~~Embodiment~~Example 55 is the method of any one of ~~embodiment~~examples 52 to 54, wherein the lyophilization comprises a loading step, at least two freezing steps, at least two annealing steps, and at least one drying step.

[0062] ~~Embodiment~~Example 56 is the method of any one of ~~embodiment~~examples 52 to 55, wherein the lyophilization comprises a loading step, at least two freezing steps, and at least two annealing steps that occur over a period of no more than one day; and at least one drying step that occurs over a period of one to five days.

[0063] ~~Embodiment~~Example 57 is the method of any one of ~~embodiment~~examples 52 to 56, wherein the lyophilization comprises the following lyophilization cycle:

a) loading a sample comprising the lyophilization solution into a lyophilizer, wherein the sample is pre-chilled by lowering the lyophilizer temperature to 10°C for 10 minutes at ambient lyophilizer pressure;

b) freezing the sample in a first freezing step, wherein the temperature of the lyophilizer is changed from 10°C to -40°C over a period of 180 minutes at ambient lyophilizer pressure;

c) freezing the sample in a second freezing step, wherein the temperature of the lyophilizer is held at -40°C for 60 minutes at ambient lyophilizer pressure;

d) annealing the sample in a first annealing step, wherein the temperature of the lyophilizer is changed from -40°C to -15°C over a period of 60 minutes at ambient lyophilizer pressure;

e) annealing the sample in a second annealing step, wherein the temperature of the lyophilizer is held at -15°C for 60 minutes at ambient lyophilizer pressure;

f) annealing the sample in a third annealing step, wherein the temperature of the lyophilizer changes from -15°C to -40°C over a period of 60 minutes at ambient lyophilizer pressure;

g) annealing the sample in a fourth annealing step by holding the temperature of the lyophilizer at -40°C for about 60 minutes at ambient lyophilizer pressure;

h) drying the sample in a first primary drying step, wherein the lyophilizer temperature is held at -40°C and the lyophilizer pressure is held at 0.133 mBar for 10 minutes;

i) drying the sample in a second primary drying step, wherein the temperature of the lyophilizer is changed from -40°C to -25°C and the lyophilizer pressure is held at 0.133 mBar over a period of 60 minutes;

j) drying the sample in a third primary drying step, wherein the lyophilizer temperature is held at -25°C and the lyophilizer pressure is held at 0.133 mBar for 2400 minutes;

k) drying the sample in a fourth primary drying step, wherein the temperature of the lyophilizer is changed from -25°C to 25°C and the lyophilizer pressure is held at 0.133 mBar over a period of 840 minutes; and

l) drying the sample in a secondary drying step, wherein the lyophilizer temperature is held at 25°C and the lyophilizer pressure is held at 0.133 mBar for 1390 minutes.

[0064] ~~Embodiment~~Example 58 is a pharmaceutically acceptable formulation reconstituted in an aqueous medium for intravenous injection comprising:

0.5 to 1.5 mg/mL of tagraxofusp;

2 to 10% w/v of at least one disaccharide sugar;

0.05 to 1.5% w/v of at least one surfactant; and

at least one 5 to 25 mM buffering agent.

[0065] ~~Embodiment~~Example 59 is the stable lyophile of ~~embodiment~~example 58, wherein the relative percent abundance of an oxidized species of tagraxofusp will increase to no more than 2%, or to no more than 1%, over 18 to 24 months.

[0066] ~~Embodiment~~Example 60 is the reconstituted formulation for intravenous injection of ~~embodiment~~example 58 or 59, wherein the lyophilization solution further comprises 2 to 10% w/v of at least one bulking agent.

[0067] ~~Embodiment~~Example 61 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 60, comprising 0.5 to 1.5 mg/mL of tagraxofusp, or 0.6 to 1.4 mg/mL of tagraxofusp, or 0.7 to 1.3 mg/mL of tagraxofusp, 0.8 to 1.2 mg/mL of tagraxofusp, or 1 mg/mL of tagraxofusp.

[0068] ~~Embodiment~~Example 62 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 or 61, wherein the surfactant is present in an amount from 0.07 to 1.5% w/v, or from 0.1 to 1.3% w/v, or from 0.15 to 1.2% w/v, or from 0.25 to 1.0% w/v, or from 0.24 to 0.26% w/v.

[0069] ~~Embodiment~~Example 63 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 or 62, wherein the surfactant is chosen from polysorbates or poloxamers.

[0070] ~~Embodiment~~Example 64 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 63, wherein the the surfactant is poloxamer 188, poloxamer 168, poloxamer 144, polysorbate 20, polysorbate 60, or polysorbate 80.

[0071] ~~Embodiment~~Example 65 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 64, wherein the surfactant is polysorbate 80.

[0072] ~~Embodiment~~Example 66 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 65, wherein the disaccharide sugar is present in an amount from 2 to 8% w/v, or from 2 to 6% w/v, or from 2 to 4% w/v, or from 2 to 3% w/v, or from 2.45 to 2.55% w/v.

[0073] ~~Embodiment~~Example 67 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 66, wherein the disaccharide sugar is chosen from trehalose, lactose, and sucrose.

[0074] ~~Embodiment~~Example 68 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 67, wherein the disaccharide sugar is sucrose.

[0075] ~~Embodiment~~Example 69 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 68, wherein the bulking agent is present in an amount from 2 to 8% w/v, or from 2 to 6% w/v, or from 2 to 4% w/v, or from 2 to 3% w/v, or from 2.45 to 2.55% w/v.

[0076] ~~Embodiment~~Example 70 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 69, wherein the bulking agent is chosen from glycine, maltose, glucose, mannitol, and sorbitol.

[0077] ~~Embodiment~~Example 71 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 70, wherein the bulking agent is mannitol.

[0078] ~~Embodiment~~Example 72 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 71, wherein at least one 5 to 15 mM, or 7 to 12 mM, or 9 to 11 mM, or 10 mM, buffering agent is added.

[0079] ~~Embodiment~~Example 73 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 72, wherein the buffering agent is chosen from phosphate, arginine, histidine, and Tris HCl.

[0080] ~~Embodiment~~Example 74 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 73, wherein the buffering agent is Tris HCl.

[0081] ~~Embodiment~~Example 75 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 74, wherein the pH is from 6.5 to 9.

[0082] ~~Embodiment~~Example 76 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 75, wherein the pH is from 7 to 8.

[0083] ~~Embodiment~~Example 77 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 76 comprising:

0.5 to 1.5 mg/mL of tagraxofusp;

2 to 10% w/v of sucrose;

0.05 to 1.5% w/v of polysorbate 80;

5 to 25 mM Tris HCl; and

having a pH from 6.5 to 9.

[0084] ~~Embodiment~~Example 78 is the reconstituted formulation of ~~embodiment~~example 77, wherein the reconstituted formulation further comprises 2 to 10% w/v of mannitol.

[0085] ~~Embodiment~~Example 79 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 78 comprising:

0.9 to 1.1 mg/mL of tagraxofusp;

2.45 to 2.55% w/v of sucrose;

2.45 to 2.55% w/v of mannitol;

0.24 to 0.26% w/v of polysorbate 80;

9 to 11 mM Tris HCl; and

having a pH from 6.5 to 9.

[0086] ~~Embodiment~~Example 80 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 79, wherein the aqueous medium is water for injection (WFI).

[0087] ~~Embodiment~~Example 81 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 80, which upon dilution into an infusion fluid bag provides a fluid in the infusion fluid bag that is substantially free of particulate matter.

[0088] ~~Embodiment~~Example 82 is the reconstituted formulation for intravenous injection of ~~Embodiment~~Example 81, wherein the infusion fluid bag is a 50 cc infusion bag.

[0089] ~~Embodiment~~Example 83 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 82, which upon dilution into an infusion fluid bag provides a fluid in the infusion fluid bag that is substantially free of particulate matter and further wherein the fluid in the infusion fluid bag comprises normal saline or Dextrose 5% (w/v).

[0090] ~~Embodiment~~Example 84 is a method for treating a myeloproliferative neoplasm (MPN) with monocytosis, comprising administering to a subject in need thereof an effective amount of the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 83.

[0091] ~~Embodiment~~Example 85 is a method for treating a myeloproliferative neoplasm (MPN), wherein the MPN is polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis

(MF), chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia, chronic eosinophilic leukemia, systemic mastocytosis (SM), symptomatic hypereosinophilic disorder, or other bone marrow disorder that causes the production of excess red blood cells, white blood cells, and/or platelets, or a primary eosinophilic disorder (PED), comprising administering to a subject in need thereof an effective amount of the reconstituted formulation for intravenous injection of any one of ~~embodiment~~example 58 to 83.

[0092] ~~Embodiment~~Example 86 is a method for treating acute myeloid leukemia (AML), comprising administering to a subject in need thereof an effective amount of the reconstituted formulation for intravenous injection of any one of ~~embodiment~~example 58 to 83.

[0093] ~~Embodiment~~Example 87 is a method for treating chronic myelomonocytic leukemia (CMML) comprising administering to a subject in need thereof an effective amount of the reconstituted formulation for intravenous injection of any one of ~~embodiment~~example 58 to 78.

[0094] ~~Embodiment~~Example 88 is a method for treating myelodysplastic syndrome (MDS) comprising administering to a subject in need thereof an effective amount of the reconstituted formulation for intravenous injection of any one of ~~embodiment~~example 58 to 83.

[0095] ~~Embodiment~~Example 89 is a method for treating multiple myeloma in a subject in need thereof, comprising administering to the subject in need thereof an effective amount of the reconstituted formulation for intravenous injection of any one of ~~embodiment~~example 58 to 83.

[0096] ~~Embodiment~~Example 90 is a method for treating blastic plasmacytoid dendritic cell neoplasm (BPDCN) comprising administering to a subject in need thereof an effective amount of the reconstituted formulation for intravenous injection of any one of ~~embodiment~~example 58 to 83.

[0097] ~~Embodiment~~Example 91 is a method of treating an autoimmune disease comprising administering to a subject in need thereof an effective amount of the reconstituted formulation for intravenous injection of any one of ~~embodiment~~example 58 to 83.

[0098] ~~Embodiment~~Example 92 is the method ~~embodiment~~example 91, wherein the autoimmune disease is chosen from lupus (*e.g.*, systemic lupus erythematosus, cutaneous lupus, discoid lupus), Sjogren's syndrome, inflammatory arthritis, systemic sclerosis (SSc), morphea, psoriasis, lichen planus, dermatomyositis, lichen sclerosus, and cutaneous graft-versus-host disease (GVHD), adrenergic drug resistance, alopecia areata, ankylosing spondylitis, antiphospholipid syndrome, autoimmune Addison's disease, autoimmune diseases of the adrenal gland, allergic encephalomyelitis, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune

inflammatory eye disease, autoimmune neonatal thrombocytopenia, autoimmune neutropenia, autoimmune oophoritis and orchitis, autoimmune thrombocytopenia, autoimmune thyroiditis, Behcet's disease, bullous pemphigoid, cardiomyopathy, cardiotomy syndrome, celiac sprue-dermatitis, chronic active hepatitis, chronic fatigue immune dysfunction syndrome (CFIDS), chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, cicatricial pemphigoid, CREST syndrome, cold agglutinin disease, Crohn's disease, dense deposit disease, essential mixed cryoglobulinemia, fibromyalgia-fibromyositis, glomerulonephritis (e.g., IgA nephropathy), gluten-sensitive enteropathy, Goodpasture's syndrome, Graves' disease, Guillain-Barre, hyperthyroidism (i.e., Hashimoto's thyroiditis), idiopathic pulmonary fibrosis, idiopathic Addison's disease, idiopathic thrombocytopenia purpura (ITP), IgA neuropathy, juvenile arthritis, Ménière's disease, mixed connective tissue disease, multiple sclerosis, Myasthenia Gravis, myocarditis, type 1 or immune-mediated diabetes mellitus, neuritis, other endocrine gland failure, pemphigus vulgaris, pernicious anemia, polyarteritis nodosa, polychondritis, polyendocrinopathies, polyglandular syndromes, polymyalgia rheumatica, polymyositis, post-MI, primary agammaglobulinemia, primary biliary cirrhosis, psoriatic arthritis, Raynaud's phenomenon, relapsing polychondritis, Reiter's syndrome, rheumatic heart disease, rheumatoid arthritis, sarcoidosis, stiff-man syndrome, takayasu arteritis, temporal arteritis/giant cell arteritis, ulcerative colitis, urticaria, uveitis, Uveitis Ophthalmia, vasculitides such as dermatitis herpetiformis vasculitis, vitiligo, and Wegener's granulomatosis.

[0099] ~~Embodiment~~Example 93 is a method for treating or inhibiting solid tumors comprising administering to a subject in need thereof an effective amount of the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 58 to 83.

[0100] ~~Embodiment~~Example 94 is the method of ~~embodiment~~example 93, wherein the solid tumor is chosen from sarcomas, carcinomas, and lymphomas.

[0101] ~~Embodiment~~Example 95 is the method of any of ~~embodiment~~examples 84 to 94, wherein tagraxofusp is administered at a dose of 4 µg/kg to 20 µg/kg.

[0102] ~~Embodiment~~Example 96 is the method of any of ~~embodiment~~examples 84 to 94, wherein tagraxofusp is administered at a dose of 6 µg/kg to 16 µg/kg.

[0103] ~~Embodiment~~Example 97 is the method of any of ~~embodiment~~examples 84 to 94, wherein tagraxofusp is administered at a dose of 7 µg/kg.

[0104] ~~Embodiment~~Example 98 is the method of any of ~~embodiment~~examples 84 to 94, wherein tagraxofusp is administered at a dose of 9 µg/kg.

[0105] ~~Embodiment~~Example 99 is the method of any of ~~embodiment~~examples 84 to 94, wherein tagraxofusp is administered at a dose of 12 µg/kg.

[0106] ~~Embodiment~~Example 100 is the method of any one of ~~embodiment~~examples 84 to 94, wherein tagraxofusp is administered at a dose of 12 µg/kg over 15 minutes.

[0107] ~~Embodiment~~Example 101 is the method of any of ~~embodiment~~examples 84 to 100, wherein tagraxofusp is administered at a dose that is the maximum tolerated dose.

[0108] ~~Embodiment~~Example 102 is the method of any of ~~embodiment~~examples 84 to 101, wherein tagraxofusp is administered once every day for five days.

[0109] ~~Embodiment~~Example 103 is the method of any of ~~embodiment~~examples 84 to 101, wherein tagraxofusp is administered once every day for three days.

[0110] ~~Embodiment~~Example 104 is the method of any of ~~embodiment~~examples 84 to 103, wherein tagraxofusp is administered for multiple cycles.

[0111] ~~Embodiment~~Example 105 is the method of any one of ~~embodiment~~examples 84 to 102, wherein tagraxofusp is administered on days 1 to 5 of a 21-day cycle.

[0112] ~~Embodiment~~Example 106 is the method of any one of ~~embodiment~~examples 84 to 102, wherein tagraxofusp is administered on days 1 to 5 of a 28-day cycle.

[0113] ~~Embodiment~~Example 107 is the method of any one of ~~embodiment~~examples 84 to 101, and 103, wherein tagraxofusp is administered on days 1 to 3 of a 21-day cycle.

[0114] ~~Embodiment~~Example 108 is the method of any one of ~~embodiment~~examples 84 to 101, wherein tagraxofusp is administered for 5 days during any one of the first 10 days of a 21-day cycle.

[0115] ~~Embodiment~~Example 109 is the stable pharmaceutically acceptable lyophilization solution of any one of ~~embodiment~~examples 1-41 in a vial.

[0116] ~~Embodiment~~Example 110 is the stable pharmaceutically acceptable lyophilization solution of ~~embodiment~~example 38 or 40 in a vial.

[0117] ~~Embodiment~~Example 111 is the lyophile of any one of ~~embodiment~~examples 42 to 51 in a vial.

[0118] ~~Embodiment~~Example 112 is the lyophile of ~~embodiment~~example 49 or 50 in a vial.

[0119] ~~Embodiment~~Example 113 is the lyophile of ~~embodiment~~example 111 or 112 containing water.

[0120] ~~Embodiment~~Example 114 is a vial containing a reconstituted solution of any one of ~~embodiment~~examples 58 to 80.

[0121] ~~Embodiment~~Example 115 is a vial containing a reconstituted solution of any one of ~~embodiment~~examples 58, 60, 77, or 79.

[0122] ~~Embodiment~~Example 116 is the solution, lyophile or vial of any one of ~~embodiment~~examples 109-115 wherein the vial is a 2 mL or a 3 mL vial.

[0123] ~~Embodiment~~Example 117 is a stable solution for lyophilization in a pharmaceutically acceptable aqueous carrier comprising:

0.5 to 1.5 mg/mL of tagraxofusp;

2 to 10% w/v of at least one disaccharide sugar;

0.05 to 1.5% w/v of at least one surfactant;

at least one 5 to 25 mM buffering agent; and a pH 6.5-9.0

wherein the surfactant has no more than 3% peroxide.

[0124] ~~Embodiment~~Example 118 is the lyophilization solution of ~~embodiment~~example 117, wherein the lyophilization solution further comprises 2 to 10% w/v of at least one bulking agent.

[0125] ~~Embodiment~~Example 119 is the lyophilization solution of ~~embodiment~~example 117 or 118, comprising 0.6 to 1.4 mg/mL of tagraxofusp, or, 0.7 to 1.3 mg/mL of tagraxofusp, or 0.8 to 1.2 mg/mL of tagraxofusp, or 1 mg/mL of tagraxofusp.

[0126] ~~Embodiment~~Example 120 is the lyophilization solution of any one of ~~embodiment~~examples 117 to 119, wherein the surfactant is present in an amount from 0.07 to 1.5% w/v, or from 0.1 to 1.3% w/v, or from 0.15 to 1.2% w/v, or from 0.25 to 1% w/v, or from 0.24 to 0.26% w/v.

[0127] ~~Embodiment~~Example 121 is the lyophilization solution of any one of ~~embodiment~~examples 117 to 120, wherein the surfactant is chosen from polysorbates or poloxamers, or wherein the surfactant is poloxamer 188, poloxamer 168, poloxamer 144, polysorbate 20, polysorbate 60, or polysorbate 80, or wherein the surfactant is polysorbate 80.

[0128] ~~Embodiment~~Example 122 is the lyophilization solution of any one of ~~embodiment~~examples 117 to 121, wherein the disaccharide sugar is present in an amount from 2 to 8% w/v, or 2 to 6% w/v, or 2 to 4% w/v, or 2 to 3% w/v, or 2.45 to 2.55% w/v.

[0129] ~~Embodiment~~Example 123 is the lyophilization solution of any one of ~~embodiment~~examples 117 to 122, wherein the disaccharide sugar is chosen from trehalose, lactose, and sucrose, or wherein the disaccharide sugar is sucrose.

[0130] ~~Embodiment~~Example 124 is the lyophilization solution of any one of ~~embodiment~~examples 117 to 123, wherein the bulking agent is present in an amount from 2 to 8% w/v, or from 2 to 6% w/v, or 2 to 4% w/v, or 2 to 3% w/v, or 2.45 to 2.55% w/v.

[0131] ~~Embodiment~~Example 125 is the lyophilization solution of any one of ~~embodiment~~examples 117 to 124, wherein the bulking agent is chosen from glycine, maltose, glucose, mannitol, and sorbitol, or wherein the bulking agent is mannitol.

[0132] ~~Embodiment~~Example 126 is the lyophilization solution of any one of ~~embodiment~~examples 117 to 125, wherein at least one buffering agent is at a concentration of from 5 to 15 mM, or from 7 to 12 mM, or 10 mM.

[0133] ~~Embodiment~~Example 127 is the lyophilization solution of any one of ~~embodiment~~examples 117 to 126, wherein the buffering agent is chosen from phosphate, arginine, histidine, and Tris HCl, or wherein the buffering agent is Tris HCl.

[0134] ~~Embodiment~~Example 128 is the lyophilization solution of any one of ~~embodiment~~examples 117 to 127, wherein the pH is from 6.5 to 8, or wherein the pH is from 7 to 8.

[0135] ~~Embodiment~~Example 129 is a stable pharmaceutically acceptable lyophilization solution in a pharmaceutically acceptable aqueous medium comprising:

0.5 to 1.5 mg/mL of tagraxofusp;

2 to 10% w/v of sucrose;

0.05 to 1.5% w/v of polysorbate 80;

5 to 25 mM Tris HCl; and

having a pH from 6.5 to 9;

wherein the polysorbate 80 has no more than 3% peroxide.

[0136] ~~Embodiment~~Example 130 is the lyophilization solution of ~~embodiment~~example 129, wherein the lyophilization solution further comprises 2 to 10% w/v of mannitol.

[0137] ~~Embodiment~~Example 131 is the lyophilization solution of ~~embodiment~~example 130 comprising:

1 mg/mL of tagraxofusp;
2.45 to 2.55% w/v of sucrose;
2.45 to 2.55% w/v of mannitol;
0.24 to 0.26% w/v of polysorbate 80;
9 to 11 mM Tris HCl; and
having a pH from 6.5 to 9,

wherein the polysorbate 80 has no more than 3% peroxide.

[0138] ~~Embodiment~~Example 132 is a lyophile prepared from the lyophilization solution of any one of ~~embodiment~~examples 117 to 131.

[0139] ~~Embodiment~~Example 133 is the lyophile of ~~embodiment~~example 132, wherein:

(a) the relative percent abundance of an oxidized species of tagraxofusp will increase to no more than 2%, or to no more than 1%, over 12 to 36 months, or wherein the relative percent abundance of an oxidized species of tagraxofusp will increase to no more than 2%, or to no more than 1%, over 18 to 24 months;.

(b) the relative percent abundance of an acidic species of tagraxofusp will increase less than the relative percent abundance of the same acidic species of tagraxofusp in a liquid tagraxofusp formulation during storage for 18, 24 or 36 months;

(c) the formulation provides for the required dose of 1 to 1.5 mg on dry weight basis;

(d) the lyophilized dry product is stable at storage temperatures from 2°C to 8°C for at least 24 months, or wherein the lyophilized dry product is stable in storage temperatures from 2°C to 8°C for 24 months to 5 years; and/or

(e) an oxidation impurity is at or below 2%, or is at or below 1%, as determined by reversed-phase ultrahigh performance chromatography (RP-UPLC), and/or wherein the oxidation impurity is measurable as a single peak in mass spectral analysis +16 Da from a tagraxofusp peak, and/or wherein in a RP-UPLC analysis the oxidation impurity elutes before tagraxofusp and the oxidation impurity peak on the RP-UPLC chromatogram is the peak closest to the tagraxofusp peak.

[0140] ~~Embodiment~~Example 134 is a stable lyophile comprising:

1 mg of tagraxofusp;

25 mg of at least one disaccharide sugar;

25 mg of at least one surfactant; and

2.4 mg of at least one buffering agent,

wherein, the lyophile has no more than 2% oxidation impurity as determined by reversed-phase ultrahigh performance chromatography (RP-UPLC) for at least 24 months.

[0141] ~~Embodiment~~Example 135 is the stable lyophile of ~~embodiment~~example 134,

(a) further comprising 25 mg of at least one bulking agent;

(b) wherein the relative percent abundance of an oxidized species of tagraxofusp will increase to no more than 2%, or to no more than 1%, over 18 to 24 months

[0142] ~~Embodiment~~Example 136 is a method of preparing a tagraxofusp lyophile comprising:

a) providing the lyophilization solution of any one of ~~embodiment~~examples 117 to 131 and

b) lyophilizing the solution to form a lyophile.

[0143] ~~Embodiment~~Example 137 is the method of ~~embodiment~~example 136, wherein the lyophilization occurs at a temperature from 40°C to 25°C over a period of 2 to 7 days, and/or

wherein the lyophilization comprises a loading step, at least one freezing step, at least one annealing step, and at least one drying step, and/or

wherein the lyophilization comprises a loading step, at least two freezing steps, at least two annealing steps, and at least one drying step, and/or

wherein the lyophilization comprises a loading step, at least two freezing steps, and at least two annealing steps that occur over a period of no more than one day; and at least one drying step that occurs over a period of one to five days.

[0144] ~~Embodiment~~Example 138 is the method of ~~embodiment~~example 136 or 137, wherein the lyophilization comprises the following lyophilization cycle:

a) loading a sample comprising the lyophilization solution into a lyophilizer, wherein the sample is pre-chilled by lowering the lyophilizer temperature to 10°C for 10 minutes at ambient lyophilizer pressure;

b) freezing the sample in a first freezing step, wherein the temperature of the lyophilizer is changed from 10°C to -40°C over a period of 180 minutes at ambient lyophilizer pressure;

c) freezing the sample in a second freezing step, wherein the temperature of the lyophilizer is held at 40°C for 60 minutes at ambient lyophilizer pressure;

d) annealing the sample in a first annealing step, wherein the temperature of the lyophilizer is changed from 40°C to -15°C over a period of 60 minutes at ambient lyophilizer pressure;

e) annealing the sample in a second annealing step, wherein the temperature of the lyophilizer is held at -15°C for 60 minutes at ambient lyophilizer pressure;

f) annealing the sample in a third annealing step, wherein the temperature of the lyophilizer changes from 15°C to -40°C over a period of 60 minutes at ambient lyophilizer pressure;

g) annealing the sample in a fourth annealing step by holding the temperature of the lyophilizer at 40°C for about 60 minutes at ambient lyophilizer pressure;

h) drying the sample in a first primary drying step, wherein the lyophilizer temperature is held at 40°C and the lyophilizer pressure is held at 0.133 mBar for 10 minutes;

i) drying the sample in a second primary drying step, wherein the temperature of the lyophilizer is changed from 40°C to -25°C and the lyophilizer pressure is held at 0.133 mBar over a period of 60 minutes;

j) drying the sample in a third primary drying step, wherein the lyophilizer temperature is held at -25°C and the lyophilizer pressure is held at 0.133 mBar for 2400 minutes;

k) drying the sample in a fourth primary drying step, wherein the temperature of the lyophilizer is changed from 25°C to 25°C and the lyophilizer pressure is held at 0.133 mBar over a period of 840 minutes; and

l) drying the sample in a secondary drying step, wherein the lyophilizer temperature is held at 25°C and the lyophilizer pressure is held at 0.133 mBar for 1390 minutes.

[0145] ~~Embodiment~~Example 139 is a pharmaceutically acceptable formulation reconstituted in an aqueous medium for intravenous injection comprising:

0.5 to 1.5 mg/mL of tagraxofusp;

2 to 10% w/v of at least one disaccharide sugar;

0.05 to 1.5% w/v of at least one surfactant; and

at least one 5 to 25 mM buffering agent.

[0146] ~~Embodiment~~Example 140 is the reconstituted formulation for intravenous injection of ~~embodiment~~example 139,

(a) the relative percent abundance of an oxidized species of tagraxofusp will increase to no more than 2%, or to no more than 1%, over 18 to 24 months;

(b) the lyophilization solution further comprises 2 to 10% w/v of at least one bulking agent;

(c) the formulation comprises 0.5 to 1.5 mg/mL of tagraxofusp, or 0.6 to 1.4 mg/mL of tagraxofusp, or 0.7 to 1.3 mg/mL of tagraxofusp, 0.8 to 1.2 mg/mL of tagraxofusp, or 1 mg/mL of tagraxofusp;

(d) the surfactant is present in an amount from 0.07 to 1.5% w/v, or from 0.1 to 1.3% w/v, or from 0.15 to 1.2% w/v, or from 0.25 to 1.0% w/v, or from 0.24 to 0.26% w/v;

(e) the surfactant is chosen from polysorbates or poloxamers, or wherein the surfactant is poloxamer 188, poloxamer 168, poloxamer 144, polysorbate 20, polysorbate 60, or polysorbate 80, or wherein the surfactant is polysorbate 80;

(f) the disaccharide sugar is present in an amount from 2 to 8% w/v, or from 2 to 6% w/v, or from 2 to 4% w/v, or from 2 to 3% w/v, or from 2.45 to 2.55% w/v;

(g) the disaccharide sugar is chosen from trehalose, lactose, and sucrose, or wherein the disaccharide sugar is sucrose;

(h) . the bulking agent is present in an amount from 2 to 8% w/v, or from 2 to 6% w/v, or from 2 to 4% w/v, or from 2 to 3% w/v, or from 2.45 to 2.55% w/v; (i) the bulking agent is chosen from glycine, maltose, glucose, mannitol, and sorbitol, or wherein the bulking agent is mannitol;

(j) at least one 5 to 15 mM, or 7 to 12 mM, or 9 to 11 mM, or 10 mM, buffering agent is added;

(k) the buffering agent is chosen from phosphate, arginine, histidine, and Tris HCl, or wherein the buffering agent is Tris HCl; and/or

(l) the pH is from 6.5 to 9, or wherein the pH is from 7 to 8.

[0147] ~~Embodiment~~Example 141 is the reconstituted formulation for intravenous injection of ~~embodiment~~example 139 or 140 comprising:

0.5 to 1.5 mg/mL of tagraxofusp;

2 to 10% w/v of sucrose;

0.05 to 1.5% w/v of polysorbate 80;

5 to 25 mM Tris HCl; and

having a pH from 6.5 to 9,

wherein the aqueous medium is water for injection (WFI).

[0148] ~~Embodiment~~Example 142 is the reconstituted formulation of ~~embodiment~~example 141, wherein the reconstituted formulation further comprises 2 to 10% w/v of mannitol.

[0149] ~~Embodiment~~Example 143 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 139 to 142 comprising:

0.9 to 1.1 mg/mL of tagraxofusp;

2.45 to 2.55% w/v of sucrose;

2.45 to 2.55% w/v of mannitol;

0.24 to 0.26% w/v of polysorbate 80;

9 to 11 mM Tris HCl; and

having a pH from 6.5 to 9.

[0150] ~~Embodiment~~Example 144 is the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 139 to 143, which upon dilution into an infusion fluid bag provides a fluid in the infusion fluid bag that is substantially free of particulate matter.

[0151] ~~Embodiment~~Example 145 is a method for treating a disease comprising administering to a subject in need thereof an effective amount of the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 139 to 144, wherein the disease is

a) a myeloproliferative neoplasm (MPN) with monocytosis,

b) a myeloproliferative neoplasm (MPN), wherein the MPN is polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis (MF), chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia, chronic eosinophilic leukemia, systemic mastocytosis (SM), symptomatic hypereosinophilic disorder, or other bone marrow disorder that causes the production of excess red blood cells, white blood cells, and/or platelets, or a primary eosinophilic disorder (PED)

c) acute myeloid leukemia (AML),

d) chronic myelomonocytic leukemia (CMML),

e) myelodysplastic syndrome (MDS),

f) multiple myeloma,

g) blastic plasmacytoid dendritic cell neoplasm (BPDCN),

h) an autoimmune disease,

i) an autoimmune disease, wherein the autoimmune disease is chosen from lupus (e.g., systemic lupus erythematosus, cutaneous lupus, discoid lupus), Sjogren's syndrome, inflammatory arthritis, systemic sclerosis (SSc), morphea, psoriasis, lichen planus, dermatomyositis, lichen sclerosus, and cutaneous graft-versus-host disease (GVHD),

adrenergic drug resistance, alopecia areata, ankylosing spondylitis, antiphospholipid syndrome, autoimmune Addison's disease, autoimmune diseases of the adrenal gland, allergic encephalomyelitis, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inflammatory eye disease, autoimmune neonatal thrombocytopenia, autoimmune neutropenia, autoimmune oophoritis and orchitis, autoimmune thrombocytopenia, autoimmune thyroiditis, Behcet's disease, bullous pemphigoid, cardiomyopathy, cardiotomy syndrome, celiac sprue-dermatitis, chronic active hepatitis, chronic fatigue immune dysfunction syndrome (CFIDS), chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, cicatricial pemphigoid, CREST syndrome, cold agglutinin disease, Crohn's disease, dense deposit disease, essential mixed cryoglobulinemia, fibromyalgia-fibromyositis, glomerulonephritis (e.g., IgA nephropathy), gluten-sensitive enteropathy, Goodpasture's syndrome, Graves' disease, Guillain-Barre, hyperthyroidism (i.e., Hashimoto's thyroiditis), idiopathic pulmonary fibrosis, idiopathic Addison's disease, idiopathic thrombocytopenia purpura (ITP), IgA neuropathy, juvenile arthritis, Ménière's disease, mixed connective tissue disease, multiple sclerosis, Myasthenia Gravis, myocarditis, type 1 or immune-mediated diabetes mellitus, neuritis, other endocrine gland failure, pemphigus vulgaris, pernicious anemia, polyarteritis nodosa, polychondritis, polyendocrinopathies, polyglandular syndromes, polymyalgia rheumatica, polymyositis, post-MI, primary agammaglobulinemia, primary biliary cirrhosis, psoriatic arthritis, Raynaud's phenomenon, relapsing polychondritis, Reiter's syndrome, rheumatic heart disease, rheumatoid arthritis, sarcoidosis, stiff-man syndrome, takayasu arteritis, temporal arteritis/giant cell arteritis, ulcerative colitis, urticaria, uveitis, Uveitis Ophthalmia, vasculitides such as dermatitis herpetiformis vasculitis, vitiligo, and Wegener's granulomatosis

[0152] ~~Embodiment~~Example 146 is a method for treating or inhibiting solid tumors comprising administering to a subject in need thereof an effective amount of the reconstituted formulation for intravenous injection of any one of ~~embodiment~~examples 139 to 144, optionally wherein the solid tumor is chosen from sarcomas, carcinomas, and lymphomas.

[0153] ~~Embodiment~~Example 147 is the stable pharmaceutically acceptable lyophilization solution of any one of ~~embodiment~~examples 117 to 131 in a vial.

[0154] ~~Embodiment~~Example 148 is the lyophile of any one of ~~embodiment~~examples 132 to 135 in a vial.

[0155] ~~Embodiment~~Example 149 is a vial containing a reconstituted solution of any one of ~~embodiment~~examples 139 to 144.

[0156] ~~Embodiment~~Example 150 is the solution, lyophile or vial of any one of ~~embodiment~~examples 147 to 149 wherein the vial is a 2 mL or a 3 mL vial.

[0156a] In one aspect, the disclosure provides a stable solution in a pharmaceutically acceptable aqueous carrier comprising:

0.5 to 1.5 mg/mL of tagraxofusp;

2 to 10% w/v of at least one disaccharide sugar;

0.05 to 1.5% w/v of at least one surfactant;

at least one 5 to 25 mM buffering agent; and a pH 6.5-9.0

wherein the surfactant has no more than 3% peroxide.

[0156b] In another aspect, the disclosure provides a stable solution in a pharmaceutically acceptable aqueous medium comprising:

0.5 to 1.5 mg/mL of tagraxofusp;

2 to 10% w/v of sucrose;

0.05 to 1.5% w/v of polysorbate 80;

5 to 25 mM Tris HCl; and

having a pH from 6.5 to 9;

wherein the polysorbate 80 has no more than 3% peroxide.

[0156c] In another aspect, the disclosure provides a formulation for intravenous injection comprising the stable solution as disclosed herein.

[0156d] In one aspect, the disclosure provides use of the stable solution as disclosed herein or the formulation for intravenous injection as disclosed herein, in the manufacture of a medicament for treating a disease, wherein the disease is

a) a myeloproliferative neoplasm (MPN) with monocytosis,

b) a myeloproliferative neoplasm (MPN), wherein the MPN is polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis (MF), chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia, chronic eosinophilic leukemia, systemic mastocytosis (SM), symptomatic hypereosinophilic disorder, or other bone marrow disorder that causes the production of excess red blood cells, white blood cells, and/or platelets, or a primary eosinophilic disorder (PED)

c) acute myeloid leukemia (AML),

d) chronic myelomonocytic leukemia (CMML),

e) myelodysplastic syndrome (MDS),

f) multiple myeloma,

g) blastic plasmacytoid dendritic cell neoplasm (BPDCN),

h) an autoimmune disease,

i) an autoimmune disease, wherein the autoimmune disease is chosen from lupus (*e.g.*, systemic lupus erythematosus, cutaneous lupus, discoid lupus), Sjogren's syndrome, inflammatory arthritis, systemic sclerosis (SSc), morphea, psoriasis, lichen planus, dermatomyositis, lichen sclerosus, and cutaneous graft-versus-host disease (GVHD), adrenergic drug resistance, alopecia areata, ankylosing spondylitis, antiphospholipid syndrome, autoimmune Addison's disease, autoimmune diseases of the adrenal gland, allergic encephalomyelitis, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inflammatory eye disease, autoimmune neonatal thrombocytopenia,

autoimmune neutropenia, autoimmune oophoritis and orchitis, autoimmune thrombocytopenia, autoimmune thyroiditis, Behcet's disease, bullous pemphigoid, cardiomyopathy, cardiotomy syndrome, celiac sprue-dermatitis, chronic active hepatitis, chronic fatigue immune dysfunction syndrome (CFIDS), chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, cicatricial pemphigoid, CREST syndrome, cold agglutinin disease, Crohn's disease, dense deposit disease, essential mixed cryoglobulinemia, fibromyalgia-fibromyositis, glomerulonephritis (e.g., IgA nephropathy), gluten-sensitive enteropathy, Goodpasture's syndrome, Graves' disease, Guillain-Barre, hyperthyroidism (i.e., Hashimoto's thyroiditis), idiopathic pulmonary fibrosis, idiopathic Addison's disease, idiopathic thrombocytopenia purpura (ITP), IgA neuropathy, juvenile arthritis, Ménière's disease, mixed connective tissue disease, multiple sclerosis, Myasthenia Gravis, myocarditis, type 1 or immune-mediated diabetes mellitus, neuritis, other endocrine gland failure, pemphigus vulgaris, pernicious anemia, polyarteritis nodosa, polychondritis, polyendocrinopathies, polyglandular syndromes, polymyalgia rheumatica, polymyositis, post-MI, primary agammaglobulinemia, primary biliary cirrhosis, psoriatic arthritis, Raynaud's phenomenon, relapsing polychondritis, Reiter's syndrome, rheumatic heart disease, rheumatoid arthritis, sarcoidosis, stiff-man syndrome, takayasu arteritis, temporal arteritis/giant cell arteritis, ulcerative colitis, urticaria, uveitis, Uveitis Ophthalmia, vasculitides such as dermatitis herpetiformis vasculitis, vitiligo, and Wegener's granulomatosis.

[0156e] In another aspect, the disclosure provides use of the stable solution as disclosed herein or the formulation for intravenous injection as disclosed herein, in the manufacture of a medicament for treating or inhibiting solid tumors, optionally wherein the solid tumor is chosen from sarcomas, carcinomas, and lymphomas.

[0156f] In yet another aspect, the disclosure provides a vial containing the stable solution as disclosed herein or the formulation for intravenous injection as disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0157] **Figure 1A** provides DSC Data from the evaluations of stabilizing excipient detailed in Example 2.

[0158] **Figure 1B** provides DSC Data from the evaluations of stabilizing excipient detailed in Example 2.

Detailed Description

I. Definitions

[0159] As used herein, the terms "administering" and "administered" refer to the delivery of a composition into a subject by a method or route that results in at least partial localization of the composition at a desired site. A composition can be administered by any appropriate route that results in effective treatment in the subject, i.e., administration results in delivery to a desired location in the subject where at least a portion of the composition is delivered to the desired site for a period of time. Modes of administration include injection, infusion, instillation, or ingestion. "Injection" includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intraventricular, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, sub capsular, subarachnoid, intraspinal, intracerebrospinal, and intrasternal injection and infusion. In some examples, the route is intravenous.

[0160] As used herein, the term "agent" refers to any molecule, compound, and/or substance for use in the prevention, treatment, management and/or diagnosis of a disease, including the tagraxofusp disclosed herein.

[0161] As used herein, the term "buffer" or "buffering agent" refers to one or more components that can protect the variation in solution pH when added to an aqueous solution, when an acid or alkali is added, or diluted with a solvent. In addition to phosphate buffer,

What is Claimed is:

1. A stable solution ~~for lyophilization~~ in a pharmaceutically acceptable aqueous carrier comprising:

0.5 to 1.5 mg/mL of tagraxofusp;

2 to 10% w/v of at least one disaccharide sugar;

0.05 to 1.5% w/v of at least one surfactant;

at least one 5 to 25 mM buffering agent; and a pH 6.5-9.0

wherein the surfactant has no more than 3% peroxide.

2. The stable ~~lyophilization~~ solution of claim 1, ~~wherein the lyophilization solution~~ further comprising ~~comprises~~ 2 to 10% w/v of at least one bulking agent.

3. The stable ~~lyophilization~~ solution of any of the preceding claims, comprising 0.6 to 1.4 mg/mL of tagraxofusp, or, 0.7 to 1.3 mg/mL of tagraxofusp, or 0.8 to 1.2 mg/mL of tagraxofusp, or 1 mg/mL of tagraxofusp.

4. The stable ~~lyophilization~~ solution of any of the preceding claims, wherein the surfactant is present in an amount from 0.07 to 1.5% w/v, or from 0.1 to 1.3% w/v, or from 0.15 to 1.2% w/v, or from 0.25 to 1% w/v, or from 0.24 to 0.26% w/v.

5. The stable ~~lyophilization~~ solution of any of the preceding claims, wherein the surfactant is chosen from polysorbates or poloxamers, or wherein the surfactant is poloxamer 188, poloxamer 168, poloxamer 144, polysorbate 20, polysorbate 60, or polysorbate 80, or wherein the surfactant is polysorbate 80.

6. The stable ~~lyophilization~~ solution of any of the preceding claims, wherein the disaccharide sugar is present in an amount from 2 to 8% w/v, or 2 to 6% w/v, or 2 to 4% w/v, or 2 to 3% w/v, or 2.45 to 2.55% w/v.

7. The stable ~~lyophilization~~ solution of any of the preceding claims, wherein the disaccharide sugar is chosen from trehalose, lactose, and sucrose, or wherein the disaccharide sugar is sucrose.

8. The stable ~~lyophilization~~ solution of any of the preceding claims, further comprising a ~~wherein the~~ bulking agent ~~is~~ present in an amount from 2 to 8% w/v, or from 2 to 6% w/v, or 2 to 4% w/v, or 2 to 3% w/v, or 2.45 to 2.55% w/v.

9. The stable ~~lyophilization~~ solution of ~~any of the preceding claims~~claim 2 or 8, wherein the bulking agent is chosen from glycine, maltose, glucose, mannitol, and sorbitol, or wherein the bulking agent is mannitol.

10. The stable ~~lyophilization~~ solution of any of the preceding claims, further comprising ~~wherein~~ at least one buffering agent ~~is~~ at a concentration of from 5 to 15 mM, or from 7 to 12 mM, or 10 mM.

11. The stable ~~lyophilization~~ solution of ~~any of the preceding claims~~claim 10, wherein the buffering agent is chosen from phosphate, arginine, histidine, and Tris HCl, or wherein the buffering agent is Tris HCl.

12. The stable ~~lyophilization~~ solution of any of the preceding claims, wherein the pH is from 6.5 to 8, or wherein the pH is from 7 to 8.

13. A stable ~~pharmaceutically acceptable lyophilization~~ solution in a pharmaceutically acceptable aqueous medium comprising:

0.5 to 1.5 mg/mL of tagraxofusp;

2 to 10% w/v of sucrose;

0.05 to 1.5% w/v of polysorbate 80;

5 to 25 mM Tris HCl; and

having a pH from 6.5 to 9;

wherein the polysorbate 80 has no more than 3% peroxide.

14. The stable ~~lyophilization~~ solution of claim 13, ~~wherein the lyophilization solution~~ further ~~comprises~~ comprising 2 to 10% w/v of mannitol.

15. The stable ~~lyophilization~~ solution of claim 13 or 14 comprising:

1 mg/mL of tagraxofusp;

2.45 to 2.55% w/v of sucrose;

2.45 to 2.55% w/v of mannitol;

0.24 to 0.26% w/v of polysorbate 80;

~~9~~ 5 to ~~11~~ 25 mM Tris HCl; and

having a pH from 6.5 to 9,

wherein the polysorbate 80 has no more than 3% peroxide.

~~16. A lyophile prepared from the lyophilization solution of any of the preceding claims.~~

~~17. The lyophile of claim 16, wherein:~~

~~(a) the relative percent abundance of an oxidized species of tagraxofusp will increase to no more than 2%, or to no more than 1%, over 12 to 36 months, or wherein the relative percent abundance of an oxidized species of tagraxofusp will increase to no more than 2%, or to no more than 1%, over 18 to 24 months;.~~

~~(b) the relative percent abundance of an acidic species of tagraxofusp will increase less than the relative percent abundance of the same acidic species of tagraxofusp in a liquid tagraxofusp formulation during storage for 18, 24 or 36 months;~~

~~(c) the formulation provides for the required dose of 1 to 1.5 mg on dry weight basis;~~

~~(d) the lyophilized dry product is stable at storage temperatures from 2°C to 8°C for at least 24 months, or wherein the lyophilized dry product is stable in storage temperatures from 2°C to 8°C for 24 months to 5 years; and/or~~

~~(e) an oxidation impurity is at or below 2%, or is at or below 1%, as determined by reversed-phase ultrahigh performance chromatography (RP-UPLC), and/or wherein the oxidation impurity is measurable as a single peak in mass spectral analysis +16 Da from a tagraxofusp peak, and/or wherein in a RP-UPLC analysis the oxidation impurity elutes before tagraxofusp and the oxidation impurity peak on the RP-UPLC chromatogram is the peak closest to the tagraxofusp peak.~~

~~18. A stable lyophile comprising:~~

~~1 mg of tagraxofusp;~~

~~25 mg of at least one disaccharide sugar;~~

25 mg of at least one surfactant; and

2.4 mg of at least one buffering agent,

wherein, the lyophile has no more than 2% oxidation impurity as determined by reversed-phase ultrahigh performance chromatography (RP-UPLC) for at least 24 months.

19. The stable lyophile of claim 18,

(a) further comprising 25 mg of at least one bulking agent; and/or

(b) wherein the relative percent abundance of an oxidized species of tagraxofusp will increase to no more than 2%, or to no more than 1%, over 18 to 24 months.

20. A method of preparing a tagraxofusp lyophile comprising:

a) providing the lyophilization solution of any one of claims 1 to 15 and
b) lyophilizing the solution to form a lyophile.

21. The method of claim 20, wherein the lyophilization occurs at a temperature from -40°C to 25°C over a period of 2 to 7 days, and/or

wherein the lyophilization comprises a loading step, at least one freezing step, at least one annealing step, and at least one drying step, and/or

wherein the lyophilization comprises a loading step, at least two freezing steps, at least two annealing steps, and at least one drying step, and/or

wherein the lyophilization comprises a loading step, at least two freezing steps, and at least two annealing steps that occur over a period of no more than one day; and at least one drying step that occurs over a period of one to five days.

22. The method of claim 20 or 21, wherein the lyophilization comprises the following lyophilization cycle:

a) loading a sample comprising the lyophilization solution into a lyophilizer, wherein the sample is pre-chilled by lowering the lyophilizer temperature to 10°C for 10 minutes at ambient lyophilizer pressure;

b) freezing the sample in a first freezing step, wherein the temperature of the lyophilizer is changed from 10°C to -40°C over a period of 180 minutes at ambient lyophilizer pressure;

c) freezing the sample in a second freezing step, wherein the temperature of the lyophilizer is held at -40°C for 60 minutes at ambient lyophilizer pressure;

d) annealing the sample in a first annealing step, wherein the temperature of the lyophilizer is changed from -40°C to -15°C over a period of 60 minutes at ambient lyophilizer pressure;

e) annealing the sample in a second annealing step, wherein the temperature of the lyophilizer is held at -15°C for 60 minutes at ambient lyophilizer pressure;

f) annealing the sample in a third annealing step, wherein the temperature of the lyophilizer changes from -15°C to -40°C over a period of 60 minutes at ambient lyophilizer pressure;

g) annealing the sample in a fourth annealing step by holding the temperature of the lyophilizer at -40°C for about 60 minutes at ambient lyophilizer pressure;

h) drying the sample in a first primary drying step, wherein the lyophilizer temperature is held at -40°C and the lyophilizer pressure is held at 0.133 mBar for 10 minutes;

i) drying the sample in a second primary drying step, wherein the temperature of the lyophilizer is changed from -40°C to -25°C and the lyophilizer pressure is held at 0.133 mBar over a period of 60 minutes;

j) drying the sample in a third primary drying step, wherein the lyophilizer temperature is held at -25°C and the lyophilizer pressure is held at 0.133 mBar for 2400 minutes;

k) drying the sample in a fourth primary drying step, wherein the temperature of the lyophilizer is changed from -25°C to 25°C and the lyophilizer pressure is held at 0.133 mBar over a period of 840 minutes; and

l) drying the sample in a secondary drying step, wherein the lyophilizer temperature is held at 25°C and the lyophilizer pressure is held at 0.133 mBar for 1390 minutes.

~~23. A pharmaceutically acceptable formulation reconstituted in an aqueous medium for intravenous injection comprising:~~

~~0.5 to 1.5 mg/mL of tagraxofusp;~~

~~2 to 10% w/v of at least one disaccharide sugar;~~

~~0.05 to 1.5% w/v of at least one surfactant; and~~

~~at least one 5 to 25 mM buffering agent.~~

~~24. The reconstituted formulation for intravenous injection of claim 23, wherein~~

~~(a) the relative percent abundance of an oxidized species of tagraxofusp will increase to no more than 2%, or to no more than 1%, over 18 to 24 months;~~

~~(b) the lyophilization solution further comprises 2 to 10% w/v of at least one bulking agent;~~

~~(c) the formulation comprises 0.5 to 1.5 mg/mL of tagraxofusp, or 0.6 to 1.4 mg/mL of tagraxofusp, or 0.7 to 1.3 mg/mL of tagraxofusp, 0.8 to 1.2 mg/mL of tagraxofusp, or 1 mg/mL of tagraxofusp;~~

~~(d) the surfactant is present in an amount from 0.07 to 1.5% w/v, or from 0.1 to 1.3% w/v, or from 0.15 to 1.2% w/v, or from 0.25 to 1.0% w/v, or from 0.24 to 0.26% w/v;~~

~~(e) the surfactant is chosen from polysorbates or poloxamers, or wherein the surfactant is poloxamer 188, poloxamer 168, poloxamer 144, polysorbate 20, polysorbate 60, or polysorbate 80, or wherein the surfactant is polysorbate 80;~~

~~(f) the disaccharide sugar is present in an amount from 2 to 8% w/v, or from 2 to 6% w/v, or from 2 to 4% w/v, or from 2 to 3% w/v, or from 2.45 to 2.55% w/v;~~

~~(g) the disaccharide sugar is chosen from trehalose, lactose, and sucrose, or wherein the disaccharide sugar is sucrose;~~

~~(h) . the bulking agent is present in an amount from 2 to 8% w/v, or from 2 to 6% w/v, or from 2 to 4% w/v, or from 2 to 3% w/v, or from 2.45 to 2.55% w/v; (i) the bulking agent is chosen from glycine, maltose, glucose, mannitol, and sorbitol, or wherein the bulking agent is mannitol;~~

~~(j) at least one 5 to 15 mM, or 7 to 12 mM, or 9 to 11 mM, or 10 mM, buffering agent is added;~~

~~(k) the buffering agent is chosen from phosphate, arginine, histidine, and Tris HCl, or wherein the buffering agent is Tris HCl; and/or~~

~~(l) the pH is from 6.5 to 9, or wherein the pH is from 7 to 8.~~

~~25. The reconstituted formulation for intravenous injection of claim 23 or 24 comprising:~~

~~0.5 to 1.5 mg/mL of tagraxofusp;~~
~~2 to 10% w/v of sucrose;~~
~~0.05 to 1.5% w/v of polysorbate 80;~~
~~5 to 25 mM Tris HCl; and~~
~~having a pH from 6.5 to 9,~~
~~wherein the aqueous medium is water for injection (WFI).~~

~~26. The reconstituted formulation of claim 25, wherein the reconstituted formulation further comprises 2 to 10% w/v of mannitol.~~

~~27. The reconstituted formulation for intravenous injection of any one of claims 23 to 26 comprising:~~

~~0.9 to 1.1 mg/mL of tagraxofusp;~~
~~2.45 to 2.55% w/v of sucrose;~~
~~2.45 to 2.55% w/v of mannitol;~~
~~0.24 to 0.26% w/v of polysorbate 80;~~
~~9 to 11 mM Tris HCl; and~~
~~having a pH from 6.5 to 9.~~

16. The stable solution of any of the preceding claims, wherein the stable solution is frozen.

17. The stable solution of any of the preceding claims, wherein the stable solution is at a temperature of less than 0°C.

~~28~~18. The stable solution of any one of claims 1 to 17~~reconstituted formulation for intravenous injection of any one of claims 23 to 27~~, which upon dilution into an infusion fluid bag provides a fluid in the infusion fluid bag that is substantially free of particulate matter.

19. A formulation for intravenous injection comprising the stable solution of any one of claims 1 to 18.

20. The formulation for intravenous injection of claim 19, wherein the formulation comprises 1 part of the stable solution of any one of claims 1 to 18 to 50 parts water for injection in an infusion fluid bag.

21. The formulation for intravenous injection of claim 19 or 20, wherein the formulation is essentially free of particulate matter and further wherein the water for injection in the infusion fluid bag includes normal saline or Dextrose 5% (w/v).

~~29~~22. Use of the stable solution of any one of claims 1 to 18 or the formulation for intravenous injection of any one of claims 19 to 21, in the manufacture of a medicament ~~A method~~ for treating a disease ~~comprising administering to a subject in need thereof an effective amount of the reconstituted formulation for intravenous injection of any one of claims 23 to 28~~, wherein the disease is

a) a myeloproliferative neoplasm (MPN) with monocytosis,

b) a myeloproliferative neoplasm (MPN), wherein the MPN is polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis (MF), chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia, chronic eosinophilic leukemia, systemic mastocytosis (SM), symptomatic hypereosinophilic disorder, or other bone marrow disorder that causes the production of excess red blood cells, white blood cells, and/or platelets, or a primary eosinophilic disorder (PED)

c) acute myeloid leukemia (AML),

d) chronic myelomonocytic leukemia (CMML),

e) myelodysplastic syndrome (MDS),

f) multiple myeloma,

g) blastic plasmacytoid dendritic cell neoplasm (BPDCN),

h) an autoimmune disease,

i) an autoimmune disease, wherein the autoimmune disease is chosen from lupus (*e.g.*, systemic lupus erythematosus, cutaneous lupus, discoid lupus), Sjogren's syndrome, inflammatory arthritis, systemic sclerosis (SSc), morphea, psoriasis, lichen planus, dermatomyositis, lichen sclerosus, and cutaneous graft-versus-host disease (GVHD), adrenergic drug resistance, alopecia areata, ankylosing spondylitis, antiphospholipid syndrome, autoimmune Addison's disease, autoimmune diseases of the adrenal gland, allergic encephalomyelitis, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inflammatory eye disease, autoimmune neonatal thrombocytopenia, autoimmune neutropenia, autoimmune oophoritis and orchitis, autoimmune thrombocytopenia, autoimmune thyroiditis, Behcet's disease, bullous pemphigoid, cardiomyopathy, cardiotomy syndrome, celiac sprue-dermatitis, chronic active hepatitis, chronic fatigue immune dysfunction syndrome (CFIDS), chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, cicatricial pemphigoid, CREST syndrome, cold agglutinin disease, Crohn's disease, dense deposit disease, essential mixed cryoglobulinemia, fibromyalgia-fibromyositis, glomerulonephritis (e.g., IgA nephropathy), gluten-sensitive enteropathy, Goodpasture's syndrome, Graves' disease, Guillain-Barre, hyperthyroidism (i.e., Hashimoto's thyroiditis), idiopathic pulmonary fibrosis, idiopathic Addison's disease, idiopathic thrombocytopenia purpura (ITP), IgA neuropathy, juvenile arthritis, Ménière's disease, mixed connective tissue disease, multiple sclerosis, Myasthenia Gravis, myocarditis, type 1 or immune-mediated diabetes mellitus, neuritis, other endocrine gland failure, pemphigus vulgaris, pernicious anemia, polyarteritis nodosa, polychondritis, polyendocrinopathies, polyglandular syndromes, polymyalgia rheumatica, polymyositis, post-MI, primary agammaglobulinemia, primary biliary cirrhosis, psoriatic arthritis, Raynaud's phenomenon, relapsing polychondritis, Reiter's syndrome, rheumatic heart disease, rheumatoid arthritis, sarcoidosis, stiff-man syndrome, takayasu arteritis, temporal arteritis/giant cell arteritis, ulcerative colitis, urticaria, uveitis, Uveitis Ophthalmia, vasculitides such as dermatitis herpetiformis vasculitis, vitiligo, and Wegener's granulomatosis.

~~30~~23. Use of the stable solution of any one of claims 1 to 18 or the formulation for intravenous injection of any one of claims 19 to 21, in the manufacture of a medicament ~~A method~~ for

treating or inhibiting solid tumors ~~comprising administering to a subject in need thereof an effective amount of the reconstituted formulation for intravenous injection of any one of claims 23 to 28~~, optionally wherein the solid tumor is chosen from sarcomas, carcinomas, and lymphomas.

~~31. The stable pharmaceutically acceptable lyophilization solution of any one of claims 1 to 15 in a vial.~~

~~32. The lyophile of any one of claims 16 to 19 in a vial.~~

~~33~~24. A vial containing the stable solution of any one of claims 1 to 18 or the formulation for intravenous injection of claim 19~~a reconstituted solution of any one of claims 23 to 28~~.

~~34~~25. The ~~solution, lyophile or~~ vial of ~~any one of claims 31 to 33~~claim 24, wherein the vial is a 2 mL or a 3 mL vial.