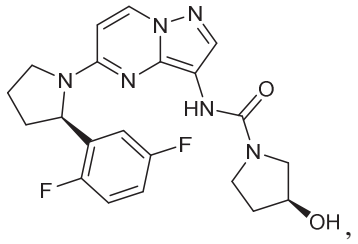
PCT Patent Publication Nos. WO 2010/033941, WO 2010/048314, WO 2011/006074, and WO 2011/146336 disclose compounds which exhibit Trk family protein tyrosine kinase inhibition, and which are useful in the treatment of pain, cancer, inflammation, neurodegenerative diseases and certain infectious diseases.

WO 2010/048314 discloses in Example 14A a hydrogen sulfate salt of (S)-N-(5-((R)-2-(2,5-difluorophenyl)-pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide. WO 2010/048314 does not disclose the particular form of the hydrogen sulfate salt described herein when prepared according to the method of Example 14A in that document. In particular, WO 2010/048314 does not disclose crystalline form (I-HS) as described below.

All documents, including scientific articles, patent publications and applications, and the like, referenced in the present disclosure are hereby incorporated by reference in their entirety.

SUMMARY

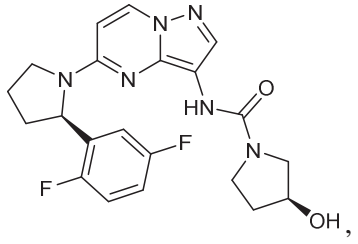
Provided herein are methods of treating a pediatric cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)-pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide having the formula **(I)**:



(I)

a pharmaceutically acceptable salt thereof, or combinations thereof.

In one aspect, the present disclosure refers to use of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide having the formula **(I)**:



(I)

a pharmaceutically acceptable salt thereof, or combinations thereof, in the manufacture of a liquid formulation for the treatment of a pediatric cancer in a subject in need thereof, wherein the liquid formulation comprises:

a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide, a pharmaceutically acceptable salt thereof, or combinations thereof;

hydroxypropyl-β-cyclodextrin;

sodium citrate; and

a sweetener;

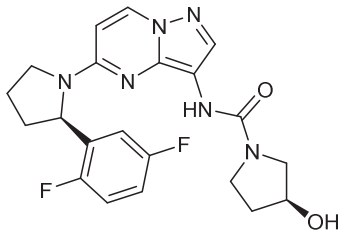
wherein:

the formulation has a pH of 2.5 to 5.5; and

the compound of formula **(I)**, the pharmaceutically acceptable salt thereof, or the combination thereof has a concentration of 20 mg/mL to 30 mg/mL in the liquid formulation.

In another aspect, the present disclosure refers to use of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide, a pharmaceutically acceptable salt thereof, or combinations thereof in the manufacture of a liquid formulation for treating a Trk-associated pediatric cancer in a subject in need thereof, wherein the liquid formulation comprises:

a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide having the formula **(I)**:



(I)

a pharmaceutically acceptable salt thereof, or a combination thereof;

hydroxypropyl-β-cyclodextrin present in an amount from 13 wt.% to 17 wt.%;

sodium citrate dihydrate present in an amount from 0.7 wt.% to 1.5 wt.%;

a sweetener that includes sucrose, glycerin, sorbitol, and flavoring, wherein the sweetener is buffered with citric acid and sodium phosphate, wherein the sweetener is preserved with methylparaben and potassium sorbate, and wherein the sweetener is present in an amount from 45 wt.% to 55 wt.%; and

a bitterness masking agent present in the liquid formulation in an amount from 0.2 wt.% to 0.5 wt.%;

wherein:

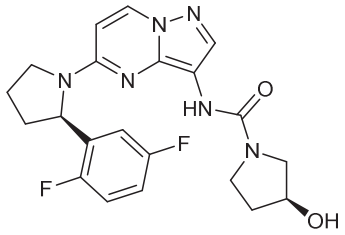
the formulation has a pH of 2.5 to 5.5; and

the compound of formula (I), the pharmaceutically acceptable salt thereof, or the combination thereof has a concentration of 20 mg/mL to 30 mg/mL in the liquid formulation.

In yet another aspect, the present disclosure refers to use of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide, a pharmaceutically acceptable salt thereof, or combinations thereof in the

manufacture of a liquid formulation for treating a Trk-associated pediatric cancer in a subject in need thereof, wherein the liquid formulation comprises:

a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide having the formula **(I)**:



(I)

a pharmaceutically acceptable salt thereof, or a combination thereof;

hydroxypropyl-β-cyclodextrin present in an amount from 13 wt.% to 17 wt.%;

sodium citrate dihydrate present in an amount from 0.7 wt.% to 1.5 wt.%;

a sweetener that includes sucralose; and

a flavoring agent present in an amount from 0.01 wt.% to 0.1 wt.%;

wherein:

the formulation has a pH of 2.5 to 5.5; and

the compound of formula (I), the pharmaceutically acceptable salt thereof, or the combination thereof has a concentration of 20 mg/mL to 30 mg/mL in the liquid formulation.

In some examples, the subject is an infant, child, or adolescent. For example, the subject is an infant.

In some examples, the pediatric cancer is a mesenchymal cancer. For example, the mesenchymal cancer can be selected from the group consisting of: pediatric nephroma, congenital fibrosarcoma (CFS), pediatric high-grade glioma (HGG), mesenchymal cancers (infant fibrosarcoma (IF), congenital mesoblastic nephroma, congenital infantile fibrosarcoma (CIFS); pilocytic astrocytoma, brain tumors, pediatic acute leukemia, Ph-like

acute lymphoblastic leukemia, cellular congenital mesoblastic nephroma (CMN); infantile fibrosarcoma, pediatric high-grade glioma (HGG), diffuse intrinsic pontine gliomas (DIPGs), non-brainstem HGGs (NBS-HGGs), anaplastic large cell lymphoma (ALCL), non-Hodgkin's lymphoma (NHL), pediatric papillary thyroid carcinoma, soft tissue sarcoma, spitzoid melanoma, pediatric hemangiopericytoma-like sarcoma, spindle cell sarcoma, NOS with myo/haemangiopericytic growth pattern, lung cancer, advanced pediatric solid tumors, neuroectodermal-derived tumors, pediatric colorectal cancer, adrenal neuroblastoma, and central nervous system tumors.

In some examples, the pediatric cancer is a fibrosarcoma such as infantile fibrosarcoma.

In some examples, the pediatric cancer is a glioma. For example, the pediatric cancer is selected from the group consisting of: pediatric high-grade glioma (HGG), diffuse intrinsic pontine gliomas (DIPGs), and on-brainstem HGGs (NBS-HGGs).

In some examples, the pediatric cancer is an extracranial solid tumor. For example, the pediatric cancer is selected from the group consisting of: neuroblastoma, nephroblastoma (e.g., Wilm's tumor), rhabdomyosarcoma and hepatoblastoma

In some examples, the cancer is mediated by TrkA. In some examples, the cancer is mediated by TrkB. In some examples, the cancer is mediated by TrkC. In some examples, the cancer is mediated by TrkA, TrkB, TrkC, or combinations thereof.

In some examples, surgical resection has failed to inhibit progression of the fibrosarcoma in the subject. In some examples, chemotherapy has failed to inhibit tumor progression in the subject. In some such examples, the chemotherapy comprises administering at least one of vincristine, actinomycin-D, cyclophosphamide, ifosfamide, etoposide, or doxorubicin. For example, the chemotherapy including administering vincristine, actinomycin-D, and cyclophosphamide has failed to inhibit tumor progression in the subject. In some examples, the chemotherapy including administering ifosfamide and doxorubicin has failed to inhibit tumor progression in the subject.

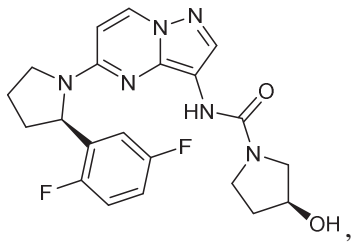
In some examples, the subject has a cancer that is ETV6-NTRK3 fusion positive.

In some examples, the methods provided herein further include performing a morphological diagnosis, molecular testing, or both prior to administering the compound of formula **(I)**, a pharmaceutically acceptable salt thereof, or a combination thereof.

Also provided herein is a method of treating an infantile fibrosarcoma, the method comprising administering to the subject a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)-pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-

hydroxypyrrolidine-1-carboxamide

having the formula **(I)**:

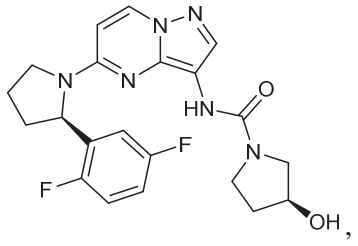


(I)

a pharmaceutically acceptable salt thereof, or a combination thereof.

Disclosed herein is use of a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

having the formula **(I)**:

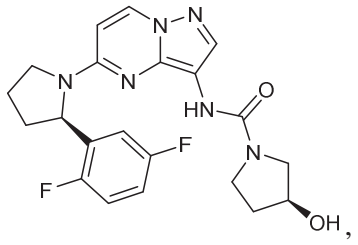


(I)

a pharmaceutically acceptable salt thereof, or a combination thereof, in the manufacture of a medicament for the treatment of an infantile fibrosarcoma.

Further provided herein is a method of treating a subject diagnosed or identified as having a Trk-associated pediatric cancer, the method comprising administering to the subject a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)-pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

having the formula **(I)**:

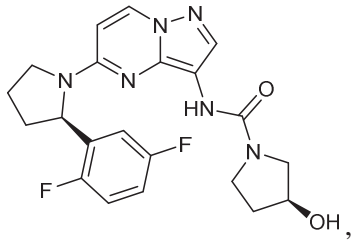


(I)

a pharmaceutically acceptable salt thereof, or a combination thereof.

Disclosed herein is use of a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

having the formula **(I)**:



(I)

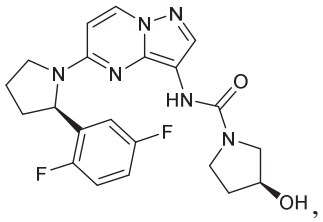
a pharmaceutically acceptable salt thereof, or a combination thereof, in the manufacture of a medicament for the treatment of a subject diagnosed or identified as having a Trk-associated pediatric cancer.

This disclosure also provides a method for treating a pediatric cancer in a subject in need thereof, the method comprising:

(a) determining if the cancer is associated with one or more of overexpression, activation, amplification, and mutation of a Trk kinase; and

(b) if the cancer is determined to be associated with one or more of overexpression, activation, amplification, and mutation of a Trk kinase, administering to the subject a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)-pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

having the formula **(I)**:

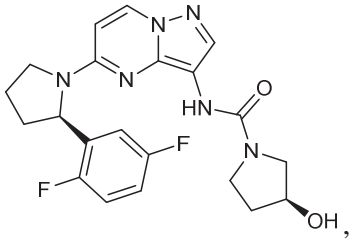


(I)

a pharmaceutically acceptable salt thereof, or a combination thereof.

Disclosed herein is use of a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

having the formula **(I)**:



(I)

a pharmaceutically acceptable salt thereof, or a combination thereof, in the manufacture of a medicament for the treatment of a pediatric cancer in a subject in need thereof,

wherein the cancer is determined to be associated with one or more of overexpression, activation, amplification, and mutation of a Trk kinase.

This disclosure also provides a method for treating a pediatric cancer in a subject in need thereof, the method comprising:

(a) identifying the cancer as associated with one or more of overexpression, activation, amplification, and mutation of a Trk kinase; and

(b) administering to the subject a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)-pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

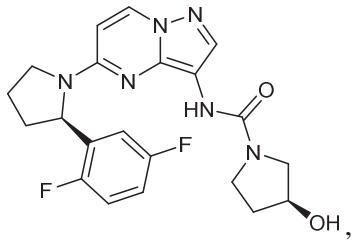
having the formula **(I)**:

(I)

a pharmaceutically acceptable salt thereof, or a combination thereof.

Disclosed herein is use of a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

having the formula **(I)**:



(I)

a pharmaceutically acceptable salt thereof, or a combination thereof, in the manufacture of a medicament for the treatment of a pediatric cancer in a subject in need thereof,

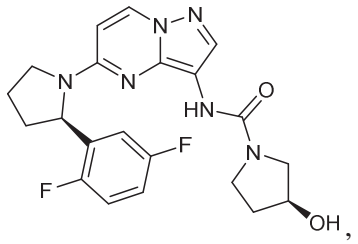
wherein the cancer is determined to be mediated by a Trk kinase.

Further provided herein are methods for treating a pediatric cancer in a subject in need thereof, the method comprising:

(a) identifying the cancer as mediated by a Trk kinase; and

(b) administering to the subject a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)-pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

having the formula **(I)**:



(I)

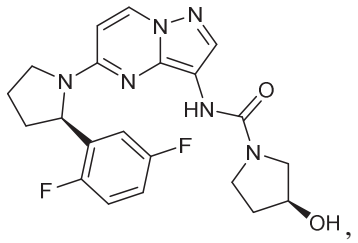
a pharmaceutically acceptable salt thereof, or a combination thereof.

Also provided herein are methods of treating a pediatric subject comprising:

(a) performing an assay on a sample obtained from the subject to determine whether the subject has dysregulation of a NTRK gene, a Trk protein, or expression or level of the same; and

(b) administering to a subject determined to have dysregulation of a NTRK gene, a Trk protein, or expression or activity, or level of the same a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)-pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

having the formula **(I)**:

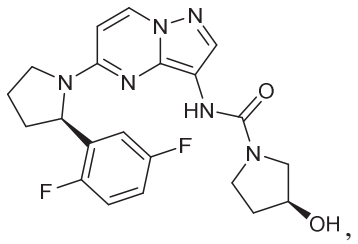


(I)

a pharmaceutically acceptable salt thereof, or a combination thereof.

Disclosed herein is use of a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

having the formula **(I)**:



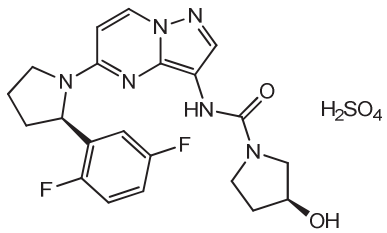
(I)

a pharmaceutically acceptable salt thereof, or a combination thereof, in the manufacture of a medicament for the treatment of a pediatric subject, wherein the subject is determined to have dysregulation of a NTRK gene, a Trk protein, or expression or activity, or level of the same, based on an assay performed on a sample obtained from the subject to determine whether the subject has dysregulation of a NTRK gene, a Trk protein, or expression or level of the same.

In some examples, the dysregulation of a NTRK gene, a Trk protein, or expression or level of the same is a chromosome translation that results in the translation of a Trk fusion protein. For example,

the Trk fusion protein can be NTRK3-ETV6. In some examples, the dyregulation of a NTRK gene, a Trk protein, or expression or activity of the same is one or more point mutation in the gene.

In some examples provided herein, the compound of formula **(I)** is a pharmaceutically acceptable salt. For example, the compound of formula **(I)** can be a hydrogen sulfate salt. In some examples, the compound of formula **(I)** is provided as a crystalline form. For example, the crystalline form can have the formula **(I-HS)**:



I-HS

In some examples, the compound of formula **(I)**, a pharmaceutically acceptable salt thereof, or a combination thereof, is provided as a liquid formulation.

In some examples, the compound of formula **(I)**, a pharmaceutically acceptable salt thereof, or a combination thereof, is present in the liquid formulation an amount from about 0.5 wt.% to about 7 wt.%. For example, the compound of formula **(I)**, a pharmaceutically acceptable salt thereof, or a combination thereof can be present in the liquid formulation in an amount of about 1.5 wt.% to about 2.5 wt.%.

In some examples, the compound of formula **(I)**, the pharmaceutically acceptable salt thereof, or the combination thereof, has a concentration of about 5 mg/mL to about 50 mg/mL in the liquid formulation. For example, the compound of formula **(I)**, the pharmaceutically acceptable salt thereof, or the combination thereof, can have a concentration of about 15 mg/mL to about 35 mg/mL in the liquid formulation. In some examples, the compound of formula **(I)**, the pharmaceutically acceptable salt thereof, or the combination thereof, has a concentration of about 20 mg/mL in the liquid formulation.

The solubilizing agent can be selected from the group consisting of a cyclodextrin, a glycol, a glycerol, and combinations thereof. In some examples, the solubilizing agent includes a cyclodextrin. For example, the solubilizing agent can be selected from the group consisting of a β-cyclodextrin derivative, a γ-cyclodextrin, and combinations thereof. In some examples, the solubilizing agent includes a hydroxy alkyl-γ-cyclodextrin. The solubilizing agent can include a β-cyclodextrin selected from the group consisting of a

hydroxy alkyl-β-cyclodextrin, a sulfoalkyl ether-β-cyclodextrin, and combinations thereof. In some examples, the solubilizing agent includes hydroxypropyl-β-cyclodextrin.

In some examples, the solubilizing agent is present in the liquid formulation in an amount of about 5 wt.% to about 35 wt.%. For example, the solubilizing agent can be present in the liquid formulation in an amount of about 13 wt.% to about 17 wt.%.

The liquid formulation can further include a buffer. In some examples, the buffer includes at least one of a citrate buffer, a lactate buffer, a phosphate buffer, a maleate buffer, a tartarate buffer, a succinate buffer, or an acetate buffer. In some examples, the buffer includes at least one of lithium lactate, sodium lactate, potassium lactate, calcium lactate, lithium phosphate, sodium phosphate, potassium phosphate, calcium phosphate, lithium maleate, sodium maleate, potassium maleate, calcium maleate, lithium tartarate, sodium tartarate, potassium tartarate, calcium tartarate, lithium succinate, sodium succinate, potassium succinate, calcium succinate, lithium acetate, sodium acetate, potassium acetate, or calcium acetate. The buffer can be a citrate buffer. The citrate buffer can inlcude at least one of lithium citrate monohydrate, sodium citrate monohydrate, potassium citrate monohydrate, calcium citrate monohydrate, lithium citrate dihydrate, sodium citrate dihydrate, potassium citrate dihydrate, calcium citrate dihydrate, lithium citrate trihydrate, sodium citrate trihydrate, potassium citrate trihydrate, calcium citrate trihydrate, lithium citrate tetrahydrate, sodium citrate tetrahydrate, potassium citrate tetrahydrate, calcium citrate tetrahydrate, lithium citrate pentahydrate, sodium citrate pentahydrate, potassium citrate pentahydrate, calcium citrate pentahydrate, lithium citrate hexahydrate, sodium citrate hexahydrate, potassium citrate hexahydrate, calcium citrate hexahydrate, lithium citrate heptahydrate, sodium citrate heptahydrate, potassium citrate heptahydrate, or calcium citrate heptahydrate. In some examples, the buffer includes at least one of sodium citrate monohydrate, potassium citrate monohydrate, calcium citrate monohydrate, sodium citrate dihydrate, potassium citrate dihydrate, calcium citrate dihydrate, sodium citrate trihydrate, potassium citrate trihydrate, calcium citrate trihydrate, sodium citrate tetrahydrate, potassium citrate tetrahydrate, calcium citrate tetrahydrate, sodium citrate pentahydrate, potassium citrate pentahydrate, calcium citrate pentahydrate, sodium citrate hexahydrate, potassium citrate hexahydrate, calcium citrate hexahydrate, sodium citrate heptahydrate, potassium citrate heptahydrate, or calcium citrate heptahydrate.

In some examples, the buffer includes sodium citrate dihydrate.

The buffer can be present in the liquid formulation in an amount of about 0.1 wt.% to about 5 wt.%.

In some examples, the formulation has a pH of about 2 to about 7. For example, the formulation can have a pH of about 3 to about 4. In some examples, the formulation has a pH of about 3.5.

In some examples, the pH of the liquid formulation is adjusted. In some such examples, the formulation includes a base. For example, the base can include one or more of a citrate, a lactate, a phosphate, a maleate, a tartarate, a succinate, an acetate, a carbonate, and a hydroxide. In some examples, the formulation includes at least one of lithium lactate, sodium lactate, potassium lactate, calcium lactate, lithium phosphate, sodium phosphate, potassium phosphate, calcium phosphate, lithium maleate, sodium maleate, potassium maleate, calcium maleate, lithium tartarate, sodium tartarate, potassium tartarate, calcium tartarate, lithium succinate, sodium succinate, potassium succinate, calcium succinate, lithium acetate, sodium acetate, potassium acetate, calcium acetate, sodium carbonate, potassium carbonate, calcium carbonate, sodium bicarbonate, potassium bicarbonate, calcium bicarbonate, sodium hydroxide, potassium hydroxide, calcium hydroxide, or combinations thereof. In some examples, the base includes a citrate. The citrate can include at least one of lithium citrate monohydrate, sodium citrate monohydrate, potassium citrate monohydrate, calcium citrate monohydrate, lithium citrate dihydrate, sodium citrate dihydrate, potassium citrate dihydrate, calcium citrate dihydrate, lithium citrate trihydrate, sodium citrate trihydrate, potassium citrate trihydrate, calcium citrate trihydrate, lithium citrate tetrahydrate, sodium citrate tetrahydrate, potassium citrate tetrahydrate, calcium citrate tetrahydrate, lithium citrate pentahydrate, sodium citrate pentahydrate, potassium citrate pentahydrate, calcium citrate pentahydrate, lithium citrate hexahydrate, sodium citrate hexahydrate, potassium citrate hexahydrate, calcium citrate hexahydrate, lithium citrate heptahydrate, sodium citrate heptahydrate, potassium citrate heptahydrate, or calcium citrate heptahydrate. In some examples, the liquid formulation includes at least one of sodium citrate monohydrate, potassium citrate monohydrate, calcium citrate monohydrate, sodium citrate dihydrate, potassium citrate dihydrate, calcium citrate dihydrate, sodium citrate trihydrate, potassium citrate trihydrate, calcium citrate trihydrate, sodium citrate tetrahydrate, potassium citrate tetrahydrate, calcium citrate tetrahydrate, sodium citrate pentahydrate, potassium citrate pentahydrate, calcium citrate pentahydrate, sodium citrate hexahydrate, potassium citrate hexahydrate, calcium citrate hexahydrate, sodium citrate heptahydrate, potassium citrate heptahydrate, or calcium citrate heptahydrate.

In some examples, the base includes sodium citrate dihydrate.

In some examples, the formulation includes about 0.1 wt.% to about 5 wt.% of a

base such as citrate (e.g., sodium citrate dihydrate).

The liquid formulation can further include a sweetener. In some examples, the sweetener includes a sugar. The sugar can include sucrose. In some examples, the sweetener includes an intense sweetener. The intense sweetener can include sucralose.

In some examples, the sweetener is present in the liquid formulation in an amount of about 30 wt.% to about 70 wt.%. For example, the sweetener can be present in the liquid formulation in an amount of about 45 wt.% to about 55 wt.%.

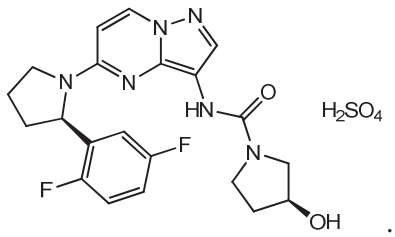
The liquid formulation can further include a bitterness masking agent. In some examples, the bitterness masking agent is present in the liquid formulation in an amount of about 0.01 wt.% to about 2 wt.%. For example, the bitterness masking agent can be present in the liquid formulation in an amount of about 0.2 wt.% to about 0.5 wt.%.

The liquid formulation can further include a flavoring agent. The flavoring agent can include at least one of a natural flavoring agent, a natural fruit flavoring agent, an artificial flavoring agent, an artificial fruit flavoring agent, or a flavor enhancer. In some examples, the flavoring agent is present in the liquid formulation in an amount of about 0.01 wt.% to about 2 wt.%. For example, the flavoring agent can be present in the liquid formulation in an amount of about 0.01 wt.% to about 0.1 wt.%.

In some examples, the liquid formulation further includes a coloring agent.

In some examples, the liquid formulation is prepared from a pharmaceutically acceptable salt of the compound of formula **(I)**. For example, the liquid formulation can be prepared from the hydrogen sulfate salt of the compound of formula **(I)**.

A liquid formulation as provided herein can be prepared from a pharmaceutically acceptable salt of the compound of formula **(I)** such as the hydrogen sulfate salt. In some examples, the liquid formulation is prepared from a crystalline form of the compound of formula **(I)**. For example, the crystalline form can have the formula **(I-HS)**:



I-HS

In some examples, the crystalline form is characterized by having XRPD diffraction peaks (2θ degrees) at 18.4±0.2, 20.7±0.2, 23.1±0.2, and 24.0±0.2. In some examples, the crystalline form is characterized by having XRPD diffraction peaks (2θ degrees) at 10.7±0.2,

18.4±0.2, 20.7±0.2, 23.1±0.2, and 24.0±0.2. In some examples,the crystalline form is characterized by having XRPD diffraction peaks (2θ degrees) at 10.7±0.2, 18.4±0.2, 19.2±0.2, 20.2±0.2, 20.7±0.2, 21.5±0.2, 23.1±0.2, and 24.0±0.2. In some examples, the crystalline form is characterized by having XRPD diffraction peaks (2θ degrees) at 10.7±0.2, 15.3±0.2, 16.5±0.2, 18.4±0.2, 19.2±0.2, 19.9±0.2, 20.2±0.2, 20.7±0.2, 21.5±0.2, 22.1±0.2, 23.1±0.2, 24.0±0.2. 24.4±0.2, 25.6±0.2, 26.5±0.2, 27.6±0.2, 28.2±0.2, 28.7±0.2, 30.8±0.2, and 38.5±0.2.

In some examples, the liquid formulation comprises a compound of formula **(I)**, a pharmaceutically acceptable salt thereof, or a combination thereof;

a solubilizing agent; and

a buffer;

wherein:

the formulation has a pH of about 2.5 to about 5.5; and

the compound of formula (I) has a concentration of about 15 mg/mL to about 35 mg/mL in the liquid formulation.

In some examples, the formulation has a pH of about 3 to about 4. In some examples, the buffer comprises sodium citrate dihydrate.

In some examples, the liquid formulation comprises a compound of formula **(I)**, a pharmaceutically acceptable salt thereof, or a combination thereof;

a solubilizing agent; and

a base;

wherein:

the formulation has a pH of about 2.5 to about 5.5; and

the compound of formula (I) has a concentration of about 15 mg/mL to about 35 mg/mL in the liquid formulation.

In some examples, the formulation has a pH of about 3 to about 4. In some examples, the base comprises sodium citrate dihydrate.

In some examples, the liquid formulation comprises a compound of formula **(I)**, a pharmaceutically acceptable salt thereof, or a combination thereof;

a solubilizing agent;

a buffer;

a sweetener;

a bitterness masking agent; and

a flavoring agent,

wherein:

the formulation has a pH of about 3 to about 4; and

the compound of formula (I) has a concentration of about 15 mg/mL to about 35 mg/mL in the liquid formulation. In some examples, the buffer comprises sodium citrate dihydrate. In some examples, the sweetener comprises sucrose.

In some examples, the liquid formulation comprises a compound of formula **(I)**, a pharmaceutically acceptable salt thereof, or a combination thereof;

a solubilizing agent;

a base;

a sweetener;

a bitterness masking agent; and

a flavoring agent,

wherein:

the formulation has a pH of about 3 to about 4; and

the compound of formula (I) has a concentration of about 15 mg/mL to about 35 mg/mL in the liquid formulation. In some examples, the base comprises sodium citrate dihydrate. In some examples, the sweetener comprises sucrose.

In some examples, the liquid formulation comprises a compound of formula (I), a pharmaceutically acceptable salt thereof, or a combination thereof;

a solubilizing agent present in an amount of about 5 wt.% to about 35 wt.%;

a buffer present in an amount of about 0.1 wt.% to about 5 wt.% ;

wherein:

the formulation has a pH of about 2.5 to about 5.5; and

the compound of formula (I) has a concentration of about 20 mg/mL to about 30 mg/mL in the liquid formulation.

In some examples, the liquid formulation comprises a compound of formula (I), a pharmaceutically acceptable salt thereof, or a combination thereof;

a solubilizing agent present in an amount of about 5 wt.% to about 35 wt.%;

a base present in an amount of about 0.1 wt.% to about 5 wt.% ;

wherein:

the formulation has a pH of about 2.5 to about 5.5; and

the compound of formula (I) has a concentration of about 20 mg/mL to about 30 mg/mL in the liquid formulation.

In some examples, the liquid formulation comprises a compound of formula **(I)**, a

pharmaceutically acceptable salt thereof, or a combination thereof;

a solubilizing agent present in an amount of about 5 wt.% to about 35 wt.%;

a buffer present in an amount of about 0.1 wt.% to about 5 wt.% ;

a sweetener present in an amount of about 30 wt.% to about 70 wt.%;

a bitterness masking agent present in an amount of about 0.2 wt.% to about 0.5 wt.%; and

a flavoring agent present in an amount of about 0.01 wt.% to about 2 wt.%,

wherein:

the formulation has a pH of about 2.5 to about 5.5; and

the compound of formula (I) has a concentration of about 20 mg/mL to about 30 mg/mL in the liquid formulation.

In some examples, the liquid formulation comprises a compound of formula **(I)**, a pharmaceutically acceptable salt thereof, or a combination thereof;

a solubilizing agent present in an amount of about 5 wt.% to about 35 wt.%;

a base present in an amount of about 0.1 wt.% to about 5 wt.% ;

a sweetener present in an amount of about 30 wt.% to about 70 wt.%;

a bitterness masking agent present in an amount of about 0.2 wt.% to about 0.5 wt.%; and

a flavoring agent present in an amount of about 0.01 wt.% to about 2 wt.%,

wherein:

the formulation has a pH of about 2.5 to about 5.5; and

the compound of formula (I) has a concentration of about 20 mg/mL to about 30 mg/mL in the liquid formulation.

In some examples, the liquid formulation comprises a compound of formula **(I)**, a pharmaceutically acceptable salt thereof, or a combination thereof;

a solubilizing agent present in an amount of about 5 wt.% to about 35 wt.%;

a buffer comprising sodium citrate dihydrate present in an amount of about 0.1 wt.% to about 5 wt.% ;

a sweetener comprising sucrose present in an amount of about 30 wt.% to about 70 wt.%;

a bitterness masking agent is present in an amount of about 0.2 wt.% to about 0.5 wt.%; and

a flavoring agent present in an amount of about 0.01 wt.% to about 2 wt.%,

wherein:

the formulation has a pH of about 3 to about 4; and

the compound of formula (I) has a concentration of about 20 mg/mL to about 30 mg/mL in the liquid formulation.

In some examples, the liquid formulation comprises a compound of formula **(I)**, a pharmaceutically acceptable salt thereof, or a combination thereof;

a solubilizing agent present in an amount of about 5 wt.% to about 35 wt.%;

a base comprising sodium citrate dihydrate present in an amount of about 0.1 wt.% to about 5 wt.%;

a sweetener comprising sucrose present in an amount of about 30 wt.% to about 70 wt.%;

a bitterness masking agent is present in an amount of about 0.2 wt.% to about 0.5 wt.%; and

a flavoring agent present in an amount of about 0.01 wt.% to about 2 wt.%,

wherein:

the formulation has a pH of about 3 to about 4; and

the compound of formula (I) has a concentration of about 20 mg/mL to about 30 mg/mL in the liquid formulation.

In some examples, the liquid formulation comprises a compound of formula **(I)**, a pharmaceutically acceptable salt thereof, or a combination thereof;

a cyclodextrin present in an amount of about 5 wt.% to about 35 wt.%;

sodium citrate dihydrate present in an amount of about 0.1 wt.% to about 5 wt.%;

a sweetener comprising sucrose or a high intensity sweetener present in an amount of about 30 wt.% to about 70 wt.%;

a bitterness masking agent is present in an amount of about 0.2 wt.% to about 0.5 wt.%; and

a flavoring agent present in an amount of about 0.01 wt.% to about 2 wt.%,

wherein:

the formulation has a pH of about 3 to about 4; and

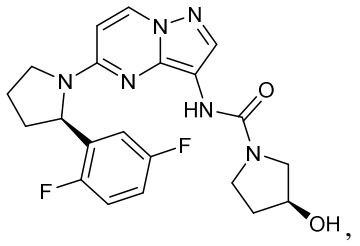
the compound of formula (I) has a concentration of about 20 mg/mL to about 30 mg/mL in the liquid formulation.

In some examples, the liquid formulation is an oral liquid formulation.

In some examples, the compound of formula **(I)**, a pharmaceutically acceptable salt thereof, or a combination thereof, is administered in 28-day cycles. In some examples, the compound is administered in a dosage calculated to be equal to the

What is claimed:

1. Use of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide having the formula **(I)**:



(I)

a pharmaceutically acceptable salt thereof, or combinations thereof, in the manufacture of a liquid formulation for the treatment of a pediatric cancer in a subject in need thereof, wherein the liquid formulation comprises:

a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide, a pharmaceutically acceptable salt thereof, or combinations thereof;

hydroxypropyl-β-cyclodextrin;

sodium citrate; and

a sweetener;

wherein:

the formulation has a pH of 2.5 to 5.5; and

the compound of formula **(I)**, the pharmaceutically acceptable salt thereof, or the combination thereof has a concentration of 20 mg/mL to 30 mg/mL in the liquid formulation.

2. The use of claim 1, wherein the subject is an infant, child, or adolescent.

3. The use of claim 1, wherein the subject is an infant.

4. The use of any one of claims 1-3, wherein the pediatric cancer is a mesenchymal cancer.

5. The use of claim 4, wherein the mesenchymal cancer is selected from the group consisting of: pediatric nephroma, congenital fibrosarcoma (CFS), pediatric high-grade glioma (HGG), infant fibrosarcoma (IF), congenital mesoblastic nephroma, congenital infantile fibrosarcoma (CIFS); pilocytic astrocytoma, brain tumors, pediatic acute leukemia,

Ph-like acute lymphoblastic leukemia, cellular congenital mesoblastic nephroma (CMN); infantile fibrosarcoma, pediatric high-grade glioma (HGG), diffuse intrinsic pontine gliomas (DIPGs), non-brainstem HGGs (NBS-HGGs), anaplastic large cell lymphoma (ALCL), non-Hodgkin's lymphoma (NHL), pediatric papillary thyroid carcinoma, soft tissue sarcoma, spitzoid melanoma, pediatric hemangiopericytoma-like sarcoma, spindle cell sarcoma, NOS with myo/haemangiopericytic growth pattern, lung cancer, advanced pediatric solid tumors, neuroectodermal-derived tumors, pediatric colorectal cancer, adrenal neuroblastoma, and central nervous system tumors.

6. The use of any one of claims 1-3, wherein the pediatric cancer is a fibrosarcoma.

7. The use of any one of claims 1-3, wherein the pediatric cancer is infantile fibrosarcoma.

8. The use of any one of claims 1-7, wherein the compound of formula **(I)** is a pharmaceutically acceptable salt.

9. The use of any one of claims 1-8, wherein the compound of formula **(I)** is a hydrogen sulfate salt.

10. The use of any one of claims 1-9, wherein the hydroxypropyl-β-cyclodextrin is present in an amount of 13 wt.% to 17 wt.%.

11. The use of any one of claims 1-10, wherein hydroxypropyl-β-cyclodextrin is present in an amount of about 15 wt.%.

12. The use of any one of claims 1-11, wherein the sodium citrate comprises at least one of sodium citrate monohydrate and sodium citrate dihydrate.

13. The use of any one of claims 1-12, wherein the sodium citrate comprises sodium citrate dihydrate.

14. The use of any one of claims 12 or 13, wherein the sodium citrate dihydrate is present in the liquid formulation in an amount of 0.1 wt.% to 5 wt.%.

15. The use of any one of claims 12-14, wherein sodium citrate dihydrate is present in the liquid formulation in an amount of about 1.1 wt.%

16. The use of any one of claims 1-15, wherein the sweetener comprises sucrose, glycerin, sorbitol, and flavoring.

17. The use of claim 16, wherein the sweetener further includes citric acid and sodium phosphate.

18. The use of claim 17, wherein the sweetener further includes methylparaben and potassium sorbate.

19. The use of any one of claims 16-18, wherein the sweetener is present in an amount of 45 wt.% to 55 wt.%.

20. The use of any one of claims 16-19, wherein the sweetener is present in the liquid formulation in an amount of about 50 wt.%.

21. The use of any one of claims 16-20, wherein the liquid formulation further comprises a bitterness masking agent.

22. The use of claim 21, wherein the bitterness masking agent is present in an amount of 0.2 wt.% to 0.5 wt.%.

23. The use of any one of claims 21 or 22, wherein the bitterness masking agent is present in the liquid formulation in an amount of about 0.4 wt.%.

24. The use of any one of claims 1-15, wherein the sweetener includes sucralose.

25. The use of claim 24, wherein the formulation further comprises a flavoring agent.

26. The use of claim 25, wherein the flavoring agent comprises a natural berry flavoring agent.

27. The use of any one of claims 24 or 25, wherein the flavoring agent is present in an amount of 0.01 wt.% to 0.1 wt.%.

28. The use of any one of claims 1-27, wherein the pediatric cancer is associated with or having a dysregulation of a NTRK gene, a Trk protein, or expression, or activity, or level of the same.

29. The use of claim 28, wherein the dysregulation of a NTRK gene, a Trk protein, or expression, or activity, or level of the same is a chromosome translocation that results in the translation of a Trk fusion protein.

30. The use of claim 29, wherein the Trk fusion protein is selected from the group consisting of ETV6-NTRK3, RET/NTRK1, TPM3-NTRK1, BTBD1-NTRK3, VCL-NTRK2, AGBL4-NTRK2, LMNA-NTRK1, TFG-NTRK1, QKI-NTRK2, NACC2-NTRK2, TPR-NTRK1, RABGAP1L-NTRK1, MPRIP-NTRK1, SQSTM1-NTRK1, EML4-NTRK3, and AFAP1-NTRK2.

31. The use of claim 29, wherein the Trk fusion protein is ETV6-NTRK3.

32. The use of claim 28, wherein the dysregulation of a NTRK gene, a Trk protein, or expression or activity, or level of the same is one or more point mutations in the gene.

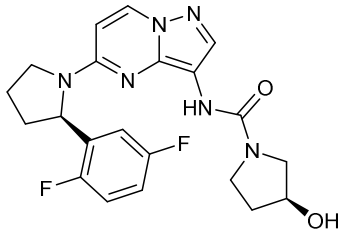
33. The use of claim 32, wherein the one or more point mutations in the gene results in translation of a TrkA protein having one or more amino acid substitutions selected from the group consisting of C6773T, C7232T, C7301T, R33W, A336E, A337T, R324Q, R324W, V420M, R444Q, R444W, G517R, G517V, K538A, V573M, F589L, G595R, G667C, F598L, R649W, R649L, R682S, V683G, R702C, Q627X, Q597X, and Q633X.

34. The use of claim 32, wherein the one or more point mutations in the gene results in translation of a TrkB protein having one or more amino acid substitutions selected from the group consisting of A13T, E142K, R136H, V619M, F633L, G639R, G709C, G709A, and G709S.

35. The use of claim 32, wherein the one or more point mutations in the gene results in translation of a TrkC protein having one or more amino acid substitutions selected from the group consisting of V603M, F617L, G623R, G696C, G696A, and G696S.

36. Use of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide, a pharmaceutically acceptable salt thereof, or combinations thereof in the manufacture of a liquid formulation for treating a Trk-associated pediatric cancer in a subject in need thereof, wherein the liquid formulation comprises:

a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide having the formula **(I)**:



(I)

a pharmaceutically acceptable salt thereof, or a combination thereof;

hydroxypropyl-β-cyclodextrin present in an amount from 13 wt.% to 17 wt.%;

sodium citrate dihydrate present in an amount from 0.7 wt.% to 1.5 wt.%;

a sweetener that includes sucrose, glycerin, sorbitol, and flavoring, wherein the sweetener is buffered with citric acid and sodium phosphate, wherein the sweetener is preserved with methylparaben and potassium sorbate, and wherein the sweetener is present in an amount from 45 wt.% to 55 wt.%; and

a bitterness masking agent present in the liquid formulation in an amount from 0.2 wt.% to 0.5 wt.%;

wherein:

the formulation has a pH of 2.5 to 5.5; and

the compound of formula (I), the pharmaceutically acceptable salt thereof, or the combination thereof has a concentration of 20 mg/mL to 30 mg/mL in the liquid formulation.

37. The use of claim 36, wherein the Trk-associated pediatric cancer is selected from the

group consisting of: congenital mesoblastic nephroma, Ph-like acute lymphoblastic leukemia, infantile fibrosarcoma, pediatric high-grade glioma (HGG), diffuse intrinsic pontine gliomas (DIPGs), pediatric papillary thyroid carcinoma, soft tissue sarcoma, and spindle cell sarcoma.

38. The use of any one of claims 36 or 37, wherein hydroxypropyl-β-cyclodextrin is present in the liquid formulation in an amount of about 15 wt.%.

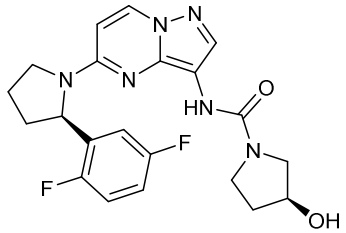
39. The use of any one of claims 36-38, wherein sodium citrate dihydrate is present in the liquid formulation in an amount of about 1.1 wt.%.

40. The use of any one of claims 36-39, wherein the sweetener is present in the liquid formulation in an amount of about 50 wt.%.

41. The use of any one of claims 36-40, wherein the bitterness masking agent is present in the liquid formulation in an amount of about 0.4 wt.%.

42. Use of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide, a pharmaceutically acceptable salt thereof, or combinations thereof in the manufacture of a liquid formulation for treating a Trk-associated pediatric cancer in a subject in need thereof, wherein the liquid formulation comprises:

a therapeutically effective amount of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide having the formula **(I)**:



(I)

a pharmaceutically acceptable salt thereof, or a combination thereof;

hydroxypropyl-β-cyclodextrin present in an amount from 13 wt.% to 17 wt.%;

sodium citrate dihydrate present in an amount from 0.7 wt.% to 1.5 wt.%;

a sweetener that includes sucralose; and

a flavoring agent present in an amount from 0.01 wt.% to 0.1 wt.%;

wherein:

the formulation has a pH of 2.5 to 5.5; and

the compound of formula (I), the pharmaceutically acceptable salt thereof, or the combination thereof has a concentration of 20 mg/mL to 30 mg/mL in the liquid formulation.

43. The use of claim 42, wherein the Trk-associated pediatric cancer is selected from the group consisting of: congenital mesoblastic nephroma, Ph-like acute lymphoblastic leukemia, infantile fibrosarcoma, pediatric high-grade glioma (HGG), diffuse intrinsic pontine gliomas (DIPGs), pediatric papillary thyroid carcinoma, soft tissue sarcoma, and spindle cell sarcoma.

44. The use of any one of claims 42 or 43, wherein hydroxypropyl-β-cyclodextrin is present in the liquid formulation in an amount of about 15 wt.%.

45. The use of any one of claims 42-44, wherein sodium citrate dihydrate is present in the liquid formulation in an amount of about 1.1 wt.%.