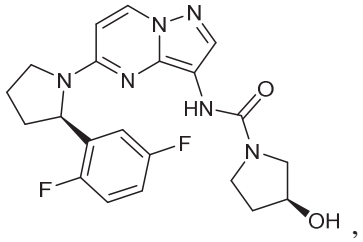
WO 2010/048314 discloses in Example 14A a hydrogen sulfate salt of (S)-N-(5-((R)-2-(2,5-difluorophenyl)-pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide. WO 2010/048314 does not disclose the particular form of the hydrogen sulfate salt described herein when prepared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

In one aspect, the present disclosure refers to a liquid formulation comprising: (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;

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 from 20 mg/mL to 30 mg/mL in the liquid formulation.

In some examples, the compound of formula **(I)**, a pharmaceutically acceptable salt thereof, or a combination thereof, is present in 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.%.

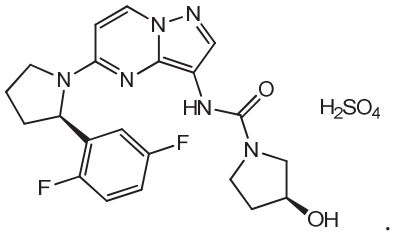
The liquid formulation can further include a bitterness masking agent. In some examples, the bitterness masking agent is present in the liquid formulation in an amount of about 0.01 wt.% to about 2 wt.%. For example, the bitterness masking agent can be present in the liquid formulation in an amount of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

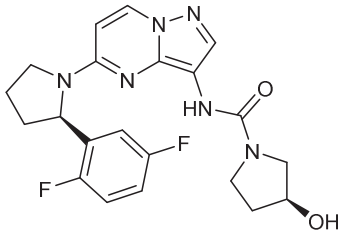
In some examples, the liquid formulation is prepared from a pharmaceutically acceptable salt of the compound of formula **(I)**. For example, the liquid formulation can be prepared from the hydrogen sulfate salt of the compound of formula **(I)**.

In some examples, the liquid formulation is prepared from a crystalline form of the compound of formula **(I)**. In some examples, the crystalline form has the formula **(I-HS)**:



I-HS

Also provided herein is a liquid formulation including (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)**:



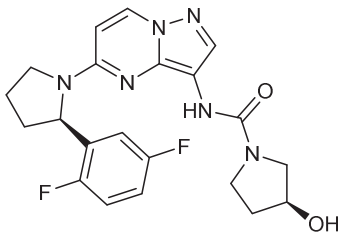
(I)

a pharmaceutically acceptable salt thereof, or a combination thereof. The liquid formulation also includes a solubilizing agent and a buffer. The liquid formulation has a pH of about 2.5 to about 5.5. The compound of formula (I), the pharmaceutically acceptable salt thereof, or the combination thereof, has a concentration of about 15 mg/mL to about 35 mg/mL in the liquid formulation.

In some examples, the liquid formulation has a pH of about 3 to about 4.

In some examples, the buffer includes sodium citrate dihydrate.

Also provided herein is a liquid formulation including (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)**:



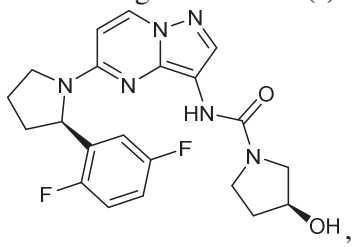
(I)

a pharmaceutically acceptable salt thereof, or a combination thereof. The liquid formulation

also includes a solubilizing agent and a base. The liquid formulation has a pH of about 2.5 to about 5.5. In some examples, the base includes a citrate (e.g., sodium citrate). The compound of formula (I), the pharmaceutically acceptable salt thereof, or the combination thereof, has a concentration of about 15 mg/mL to about 35 mg/mL in the liquid formulation.

In one aspect, the present disclosure refers to a liquid formulation comprising:

(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 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:

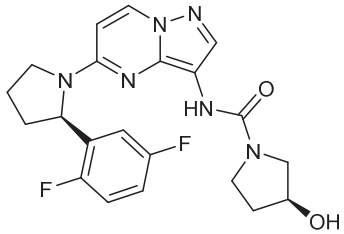
the formulation has a pH of 2.5 to 5.5; and

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 some examples, the liquid formulation has a pH of about 3 to about 4.

In some examples, the base includes sodium citrate dihydrate.

Also provided herein is a liquid formulation including (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)**:



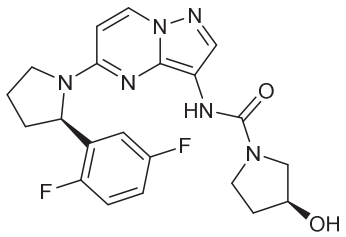
(I)

a pharmaceutically acceptable salt thereof, or a combination thereof. The liquid formulation includes a solubilizing agent, a buffer, a sweetener, a bitterness masking agent, and a flavoring agent. The liquid formulation has a pH of about 3 to about 4. The compound of formula (I), the pharmaceutically acceptable salt thereof, or the combination thereof, has a concentration of about 15 mg/mL to about 35 mg/mL in the liquid formulation.

In some examples, the buffer includes sodium citrate dihydrate.

In some examples, the sweetener includes sucrose.

Also provided herein is a liquid formulation including (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)**:



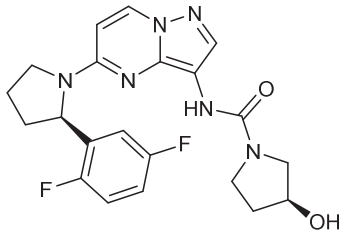
(I)

a pharmaceutically acceptable salt thereof, or a combination thereof. The liquid formulation

includes a solubilizing agent, a base, a sweetener, a bitterness masking agent, and a flavoring agent. The liquid formulation has a pH of about 3 to about 4. In some examples, the base includes a citrate (e.g., sodium citrate). The compound of formula (I), the pharmaceutically acceptable salt thereof, or the combination thereof, has a concentration of about 15 mg/mL to about 35 mg/mL in the liquid formulation.

In one aspect, the present disclosure refers to a liquid formulation comprising:

(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 in an amount from 13 wt.% to 17 wt.%;

sodium citrate dihydrate 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:

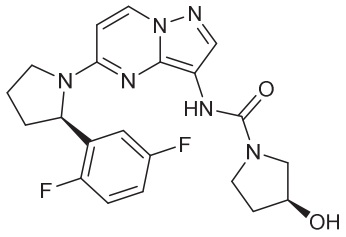
the formulation has a pH of 3 to 4; and

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 base includes sodium citrate dihydrate.

In some examples, the sweetener includes sucrose.

Also provided herein is a liquid formulation including (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)**:

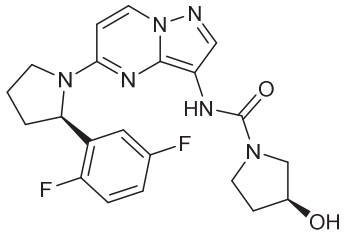


(I)

a pharmaceutically acceptable salt thereof, or a combination thereof. The liquid formulation includes a solubilizing agent present in an amount of about 5 wt.% to about 35 wt.% and a buffer present in an amount of about 0.1 wt.% to about 5 wt.%. The liquid formulation has a pH of about 2.5 to about 5.5. The compound of formula (I), the pharmaceutically acceptable salt thereof, or the combination thereof, has a concentration of about 20 mg/mL to about 30 mg/mL in the liquid formulation.

In one example, there is provided a liquid formulation comprising:

(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;

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

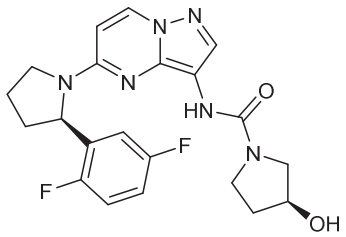
a base present in an amount of about 0.1 wt.% to about 5 wt.%;

wherein:

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

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

Also provided herein is a liquid formulation including (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)**:

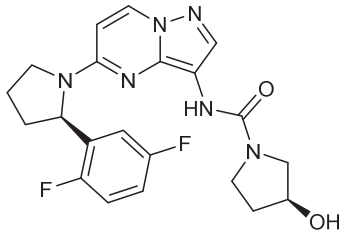


(I)

a pharmaceutically acceptable salt thereof, or a combination thereof. The liquid formulation

includes 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.%. The liquid formulation has a pH of about 2.5 to about 5.5. The compound of formula (I), the pharmaceutically acceptable salt thereof, or the combination thereof, has a concentration of about 20 mg/mL to about 30 mg/mL in the liquid formulation.

Also provided herein is a liquid formulation including (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)**:

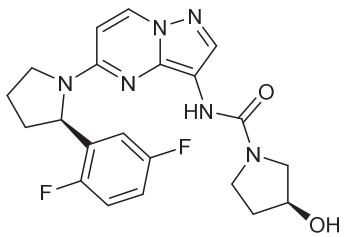


(I)

a pharmaceutically acceptable salt thereof, or a combination thereof. The liquid formulation includes 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.%. The liquid formulation has a pH of about 2.5 to about 5.5. The compound of formula (I), the pharmaceutically acceptable salt thereof, or the combination thereof, has a concentration of about 20 mg/mL to about 30 mg/mL in the liquid formulation.

In one example, there is provided a liquid formulation comprising:

(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)**:

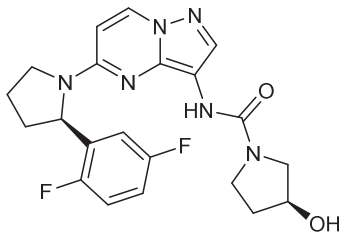


(I)

(I)

a pharmaceutically acceptable salt thereof, or a combination thereof. The liquid formulation includes a solubilizing agent present in an amount of about 5 wt.% to about 35 wt.%. The liquid formulation also includes a buffer including sodium citrate dihydrate present in an amount of about 0.1 wt.% to about 5 wt.%. The liquid formulation also includes a sweetener including sucrose present in an amount of about 30 wt.% to about 70 wt.%. The liquid formulation also includes a bitterness masking agent is present in an amount of about 0.2 wt.% to about 0.5 wt.%. The liquid formulation also includes a flavoring agent present in an amount of about 0.01 wt.% to about 2 wt.%. The liquid formulation has a pH of about 3 to about 4. The compound of formula (I), the pharmaceutically acceptable salt thereof, or the combination thereof, has a concentration of about 20 mg/mL to about 30 mg/mL in the liquid formulation.

Also provided herein is a liquid formulation including (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)**:

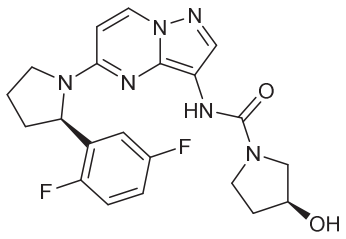


(I)

a pharmaceutically acceptable salt thereof, or a combination thereof. The liquid formulation includes a solubilizing agent present in an amount of about 5 wt.% to about 35 wt.%. The liquid formulation also includes a base including sodium citrate dihydrate present in an amount of about 0.1 wt.% to about 5 wt.%. The liquid formulation also includes a sweetener including sucrose present in an amount of about 30 wt.% to about 70 wt.%. The liquid formulation also includes a bitterness masking agent is present in an amount of about 0.2 wt.% to about 0.5 wt.%. The liquid formulation also includes a flavoring agent present in an amount of about 0.01 wt.% to about 2 wt.%. The liquid formulation has a pH of about 3 to about 4. The compound of formula (I), the pharmaceutically acceptable salt thereof, or the combination thereof, has a concentration of about 20 mg/mL to about 30 mg/mL in the liquid formulation.

In one example, there is provided a liquid formulation comprising:

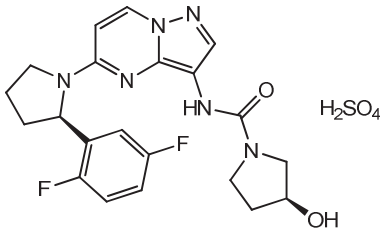
difluorophenyl)-pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide having the formula **(I)**:



(I)

a pharmaceutically acceptable salt thereof, or a combination thereof. The liquid formulation includes a solubilizing agent present in an amount of about 5 wt.% to about 35 wt.%. The liquid formulation also includes sodium citrate dihydrate present in an amount of about 0.1 wt.% to about 5 wt.%. The liquid formulation also includes a sweetener including sucrose present in an amount of about 30 wt.% to about 70 wt.%. The liquid formulation also includes a bitterness masking agent is present in an amount of about 0.2 wt.% to about 0.5 wt.%. The liquid formulation also includes a flavoring agent present in an amount of about 0.01 wt.% to about 2 wt.%. The liquid formulation has a pH of about 3 to about 4. The compound of formula (I), the pharmaceutically acceptable salt thereof, or the combination thereof, has a concentration of about 20 mg/mL to about 30 mg/mL in the liquid formulation.

The liquid formulations provided herein can be prepared from a crystalline form of the compound of formula **(I)** having the formula (I-HS):



I-HS

In some examples, the crystalline form can be 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.

Also provided herein is a method of treating a cancer in a patient in need thereof. The method includes identifying a patient in need thereof having dysphagia and administering to the patient a therapeutically effective amount of a liquid formulation provided herein.

In one example, there is provided use of a therapeutically effective amount of the liquid formulation as described herein in the manufacture of a medicament for treating a cancer in a patient in need thereof, wherein the patient in need thereof has been identified as one having dysphagia. 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, a pharmaceutically acceptable salt thereof, or a combination thereof, in the manufacture of a liquid formulation as described herein for treating a cancer mediated by a Trk kinase in a patient in need thereof.

Also provided herein is a method of treating a cancer in a patient in need thereof, which includes identifying a patient in need thereof having dysphagia, determining if the cancer is mediated by a Trk kinase and if the cancer is determined to be mediated by a Trk kinase, administering to the patient a therapeutically effective amount of a liquid formulation provided herein. In one example, there is provided use of a therapeutically effective amount of the liquid formulation as described herein in the manufacture of a medicament for treating a cancer in a patient in need thereof, wherein: the patient in need thereof has been identified as one having dysphagia; and the cancer has been determined to be mediated by a Trk kinase. Also provided herein is a method of treating a cancer in a patient in need thereof, which includes identifying a patient in need thereof having dysphagia, identifying that the cancer is mediated by a Trk kinase administering to the patient a therapeutically effective amount of a liquid formulation provided herein.

Also provided herein is a method of treating cancer in a patient in need thereof, which includes administering to the patient a therapeutically effective amount of a liquid formulation as provided herein. In one example, there is provided use of a therapeutically effective amount of the liquid formulation as described herein in the manufacture of a medicament for treating cancer in a patient in need thereof.

In some examples, the cancer is selected from the group consisting of a head and neck cancer, a throat cancer, an esophageal cancer, or combinations thereof.

In some examples, the patient is an infant, a child, an adolescent, or an elderly patient.

Also provided herein is a method for treating cancer in a subject in need thereof. The method includes determining if the cancer is associated with and/or exhibits one or more of overexpression, activation, amplification, and mutation of a Trk kinase and if the cancer is determined to be associated with and/or exhibits one or more of overexpression, activation, amplification, and mutation of a Trk kinase, administering to the subject a therapeutically effective amount of a liquid formulation as provided herein. In one example, there is provided use of a therapeutically effective amount of a liquid formulation as described herein in the manufacture of a medicament for treating 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. Also provided herein is a method for treating cancer in a subject in need thereof. The method includes identifying that the cancer is associated with and/or exhibits one or more of overexpression, activation, amplification, and mutation of a Trk kinase and administering to the subject a therapeutically effective amount of a liquid formulation as provided herein.

Also provided herein is a method for treating cancer in a subject in need thereof, which includes determining if the cancer is mediated by a Trk kinase, and if the cancer is determined to be mediated by a Trk kinase, administering to the subject a therapeutically

effective amount of a liquid formulation as provided herein. In one example, there is provided use of a therapeutically effective amount of a liquid formulation as described herein in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer is determined to be mediated by a Trk kinase. Also provided herein is a method for treating cancer in a subject in need thereof, which includes identifying the cancer as mediated by a Trk kinase, and administering to the subject a therapeutically effective amount of a liquid formulation as provided herein.

Also provided herein is a method of treating a subject. The method includes performing an assay on a sample obtained from the subject to determine whether the subject has a dysregulation of a NTRK gene, a Trk protein, or expression or level of the same. The method also includes administering to a subject determined to have a dysregulation of a NTRK gene, a Trk protein, or expression or activity, or level of the same a therapeutically effective amount of a liquid formulation as provided herein. In one example, there is provided use of a therapeutically effective amount of a liquid formulation as described herein in the manufacture of a medicament for treating a 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 that has been 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. The Trk fusion protein can be selected from the group consisting of: TP53-TrkA, LMNA-TrkA, CD74-TrkA, TFG-TrkA, TPM3-TrkA, NFASC-TrkA, BCAN-TrkA, MPRIP-TrkA, TPR-TrkA, RFWD2-TrkA, IRF2BP2-TrkA, SQSTM1-TrkA, SSBP2-TrkA, RABGAP1L-TrkA, C18ORF8-TrkA, RNF213-TrkA, TBC1D22A-TrkA, C20ORF112-TrkA, DNER-TrkA, ARHGEF2-TrkA, CHTOP-TrkA, PPL-TrkA, PLEKHA6-TrkA, PEAR1-TrkA, MRPL24-TrkA, MDM4-TrkA, LRRC71-TrkA, GRIPAP1-TrkA, EPS15-TrkA, DYNC2H1-TrkA, CEL-TrkA, EPHB2-TrkA, TGF-TrkA, NACC2-TrkB, QKI-TrkB, AFAP1-TrkB, PAN3-TrkB, SQSTM1-TrkB, TRIM24-TrkB, VCL-TrkB, AGBL4-TrkB, DAB2IP-TrkB, ETV6-TrkC, BTBD1-TrkC, LYN-TrkC, RBPMS-TrkC, EML4-TrkC, HOMER2-TrkC, TFG-TrkC, FAT1-TrkC, and TEL-TrkC.

In some examples, the dysregulation of a NTRK gene, a Trk protein, or expression or activity of the same is one or more point mutation in the gene. The NTRK gene can be a NTRK1 gene, and the one or more point mutations in the NTRK1 gene can result in the translation of a TrkA protein having substitutions are one or more of the following amino acid positions: 33, 336, 337, 324, 420, 444, 517, 538, 649, 682, 683, 702, and 1879.

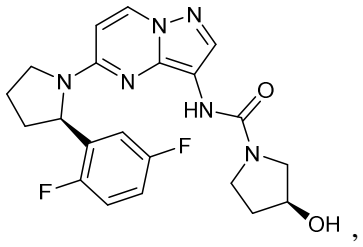
In some examples, the one or more point mutations in the NTRK1 gene results in the translation of a TrkA protein having one or more of the following amino acid substitutions: R33W, A336E, A337T, R324Q, R324W, V420M, R444Q, R444W, G517R, G517V, K538A, R649W, R649L, R682S, V683G, R702C, and C1879T.

The features and advantages described in this summary and the following detailed description are not all-inclusive. Many additional features and advantages will be apparent to one of ordinary skill in the art in view of the drawings, specification, and claims hereof.

What is claimed:

1. A liquid formulation comprising:

(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;

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 from 20 mg/mL to 30 mg/mL in the liquid formulation.

2. The liquid formulation of claim 1, wherein the hydroxypropyl-β-cyclodextrin is present in an amount of 13 wt.% to 17 wt.%.

3. The liquid formulation of any one of claims 1 or 2, wherein hydroxypropyl-β-cyclodextrin is present in an amount of about 15 wt.%.

4. The liquid formulation of any one of claims 1-3, wherein the sodium citrate comprises at least one of sodium citrate monohydrate and sodium citrate dihydrate.

5. The liquid formulation of any one of claims 1-4, wherein the sodium citrate comprises sodium citrate dihydrate.

6. The liquid formulation of any one of claims 4 or 5, wherein the sodium citrate dihydrate is present in an amount of 0.7 wt.% to 1.5 wt.%.

7. The liquid formulation of any one of claims 4-6, wherein sodium citrate dihydrate is present in an amount of about 1.1 wt.%.

8. The liquid formulation of any one of claims 1-7, wherein the sweetener comprises sucrose, glycerin, sorbitol, and flavoring.

9. The liquid formulation of claim 8, wherein the sweetener further includes citric acid and sodium phosphate.

10. The liquid formulation of claim 9, wherein the sweetener further includes methylparaben and potassium sorbate.

11. The liquid formulation of any one of claims 8-10, wherein the sweetener is present in an amount of 45 wt.% to 55 wt.%.

12. The liquid formulation of any one of claims 8-11, wherein the sweetener is present in the liquid formulation in an amount of about 50 wt.%.

13. The liquid formulation of any one of claims 8-12, wherein the liquid formulation further comprises a bitterness masking agent.

14. The liquid formulation of any one of claims 8-13, wherein the bitterness masking agent is present in an amount of 0.2 wt.% to 0.5 wt.%.

15. The liquid formulation of any one of claims 1-7, wherein the sweetener includes sucralose.

16. The liquid formulation of claim 15, wherein the formulation further comprises a flavoring agent.

17. The liquid formulation of claim 16, wherein the flavoring agent comprises a natural berry flavoring agent.

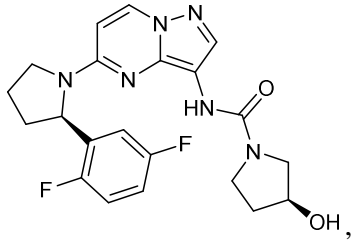
18. The liquid formulation of any one of claims 16 or 17, wherein the flavoring agent is present in an amount of 0.01 wt.% to 0.1 wt.%.

19. The liquid formulation of any one of claims 1-18, wherein the liquid formulation is prepared from a pharmaceutically acceptable salt of the compound of formula **(I)**.

20. The liquid formulation of any one of claims 1-19, wherein the liquid formulation is prepared from the hydrogen sulfate salt of the compound of formula **(I)**.

21. A liquid formulation comprising:

(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 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.

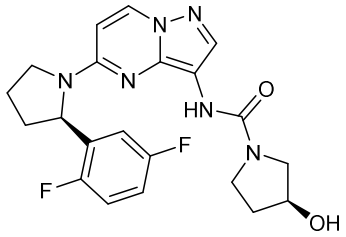
22. The liquid formulation of claim 21, wherein hydroxypropyl-β-cyclodextrin is present in the liquid formulation in an amount of about 15 wt.%.

23. The liquid formulation of any one of claims 21 or 22, wherein sodium citrate dihydrate is present in an amount of about 1.1 wt.%.

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

25. A liquid formulation comprising:

(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 in an amount from 13 wt.% to 17 wt.%;

sodium citrate dihydrate 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 3 to 4; 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.

26. The liquid formulation of claim 25, wherein hydroxypropyl-β-cyclodextrin is present in the liquid formulation in an amount of about 15 wt.%.

27. The liquid formulation of any one of claims 25 or 26, wherein sodium citrate dihydrate is present in an amount of about 1.1 wt.%.

28. 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 a combination thereof, in the manufacture of a liquid formulation of any one of claims 1-27 for treating a cancer mediated by a Trk kinase in a patient in need thereof.

29. The use of claim 28, wherein the cancer is associated with one or more of overexpression, activation, amplification, and mutation of a Trk kinase.

30. The use of claim 28, wherein the cancer is determined to have a dysregulation of a NTRK gene, a Trk protein, or expression or level of the same.

31. The use of claim 30, wherein the dysregulation of a NTRK gene, a Trk protein, or expression or level of the same is a chromosome translocation that results in the translation of a Trk fusion protein.

32. The use of claim 31, wherein the Trk fusion protein is selected from the group consisting of: TP53-TrkA, LMNA-TrkA, CD74-TrkA, TFG-TrkA, TPM3-TrkA, NFASC-TrkA, BCAN-TrkA, MPRIP-TrkA, TPR-TrkA, RFWD2-TrkA, IRF2BP2-TrkA, SQSTM1-TrkA, SSBP2-TrkA, RABGAP1L-TrkA, C18ORF8-TrkA, RNF213-TrkA, TBC1D22A-TrkA, C20ORF112-TrkA, DNER-TrkA, ARHGEF2-TrkA, CHTOP-TrkA, PPL-TrkA, PLEKHA6-TrkA, PEAR1-TrkA, MRPL24-TrkA, MDM4-TrkA, LRRC71-TrkA, GRIPAP1-TrkA, EPS15-TrkA, DYNC2H1-TrkA, CEL-TrkA, EPHB2-TrkA, TGF-TrkA, NACC2-TrkB, QKI-TrkB, AFAP1-TrkB, PAN3-TrkB, SQSTM1-TrkB, TRIM24-TrkB, VCL-TrkB, AGBL4-TrkB, DAB2IP-TrkB, ETV6-TrkC, BTBD1-TrkC, LYN-TrkC, RBPMS-TrkC, EML4-TrkC, HOMER2-TrkC, TFG-TrkC, FAT1-TrkC, and TEL-TrkC.

33. The use of claim 30, wherein the dysregulation of a NTRK gene, a Trk protein, or expression or activity of the same is one or more point mutation in the gene.

34. The use of claim 33, wherein the one or more point mutations in the NTRK gene results in the translation of a TrkA protein having one or more of the following amino acid

substitutions: R33W, A336E, A337T, R324Q, R324W, V420M, R444Q, R444W, G517R, G517V, K538A, R649W, R649L, R682S, V683G, R702C, and C1879T.

35. The use of claim 33, wherein the one or more point mutations in the NTRK gene results in the translation of a TrkB protein having one or more of the following amino acid substitutions: A13T, E142K, R136H, V619M, F663L, G639R, G709C, G709S, and G709S.

36. The use of claim 33, wherein the one or more point mutations in the NTRK gene results in the translation of TrkC protein having one or more of the following amino acid substitutions: V603M, F617L, G623R, G696C, G696A, or G696S.